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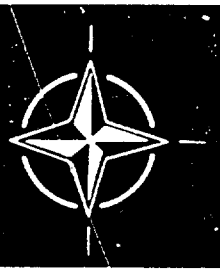

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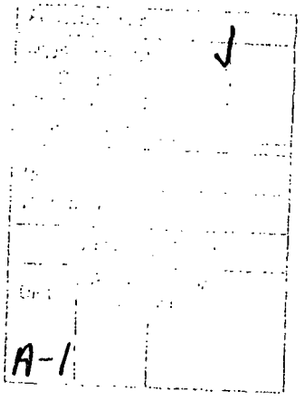
ADVISORY GROUP FOR AEROSPACE RESEARCH AND DEVELOPMENT

(ORGANISATION DU TRAITE DE L'ATLANTIQUE NORD)

AGARD Conference Proceedings No.432

ELECTRIC AND MAGNETIC ACTIVITY OF THE CENTRAL NERVOUS SYSTEM: RESEARCH AND CLINICAL APPLICATIONS IN AEROSPACE MEDICINE



Papers presented at the Aerospace Medical Panel Symposium held in Trondheim, Norway from 25 to 29 May 1987.

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PREFACE

The cockpit of each new generation of fighter aircraft is becoming more and more cluttered, and the workload imposed on the aircrew more and more formidable. Heavy loads of information from the different aircraft sensors must be assimilated and managed in a timely and efficient manner. Severe physiological stresses are imposed by the environment of rapid onset, high sustained-G-accelerations in which the aircraft operate.Such heavy demands may well limit the ability of aircrew to perform their required tasks. As a result, there is a compelling need to obtain more objective measures of the effects of such factors as workload, fatigue, physiological stress, drugs and diseases on operator effectiveness in the high stress environment of the future cockpit, if performance is to be meaningfully assessed. A variety of new or upgraded techniques for studying the function of the central nervous system (CNS) is now available; they may allow the objective assessment of aircrew in terms of selection, performance, training and medical care. Many of these techniques rely on extracting and interpreting the electrical potentials and magnetic fields that can be recorded from the brain with scalp sensors. The purpose of this Symposium was to examine the value of these CNS measures in understanding human performance in individuals exposed to the variety of stresses that are associated with the aerospace environment.

Experts from both civilian and military institutions were drawn together to address a broad spectrum of topics related to the research and clinical use of these electromagnetic measurements in aerospace operations. These include:

- Computer-aided dynamic brain imaging, using the multi-electrode scalp recording of electrical potentials — electroencephalogram (EEG) and event-related potentials (ERPs) — in combination with good signal enhancement and feature extraction methodologies;
- the implications and expectations of recording multi-sensor brain magnetic fields in behavioural and clinical research;
- the functional significance of using ERP components, such as P300 and CNV, and EEG events as indices of cognition, workload and fatigue;
- the application of physiological measures for indexing operator effectiveness during demanding aircraft and simulator flight missions;
- the effects of acceleration on CNS activity, and its use in the assessment of human performance;
- the changes in EEG and ERP patterns to CNS-modifying drugs, and their implication to brain status;
- the relationship between abnormal EEGs and aircraft incidents/accidents; and
- the "neurometric" approach to diagnosing disease states.

The issues dealt with in this Symposium are broad and complex, and are often of a tentative nature. They reflect that there is a continuing need for further research into the relationship between CNS electromagnetic activity, and behaviour and clinical diagnoses. The fact that this is a growing field in the brain sciences with direct application to aerospace medicine should recommend these Proceedings to those involved in the health care of aircrew.

RESUME

Les postes de pilotage des nouvelles générations d'avions de chasse deviennent de plus en plus encombrés et la charge de travail imposée aux équipages ne cesse de s'accroître. Les quantités élevées d'informations transmises au pilote par les différents capteurs embarqués doivent être assimilées et exploitées de façon rapide et efficace. L'environnement opérationnel des chasseurs, qui est caractérisé par des forces d'accélération élevées et soutenues, appliquées de façon brusque, impose un stress physiologique intense au pilote. Dans de telles conditions, la capacité de l'équipage à accomplir les tâches qui lui sont allouées se trouve souvent limitée. Par conséquent, toute évaluation valable de l'efficacité opérationnelle des pilotes passe nécessairement par l'obtention de mesures plus objectives des effets de certains facteurs, tels que: la charge de travail, la fatigue, le stress physiologique, les drogues et les maladies infectieuses sur l'efficacité de l'opérateur, dans l'environnement à haut niveau de stress que représente le poste de pilotage futur. Le corps médical dispose d'un large éventail de techniques, nouvelles ou améliorées, pour l'étude du système nerveux central; elles devraient permettre un évaluation objective de l'équipage du point de vue la sélection, des performances, de la formation et des soins médicaux. Bon nombre de ces techniques ont pour principe le captage et l'analyse des potentiels électriques et des champs magnétiques du cerveau, enregistrés à l'aide de capteurs crâniens. L'objet du symposium était d'étudier l'intérêt de ces mesures pour la compréhension des actions humaines chez des individus soumis à différents types de stress liés à l'environnement aérospatial.

Le symposium a réuni des experts de différents organismes civils et militaires dans le but d'étudier toute une gamme de sujets liés à la recherche et à l'exploitation de ces mesures électromagnétiques par des médecins dans le contexte aérospatial, à savoir:

- l'imagerie dynamique du cerveau assistée par ordinateur, avec l'enregistrement des potentiels électriques à l'aide de capteurs crâniens à multi-électrodes, des électroencéphalogrammes (EEG) et des potentiels liés à des événements (ERP) associés à des méthodologies performantes d'amélioration de la qualité du signal et d'extrapolation des caractéristiques.

- les conséquences possibles et les résulats attendus de l'enregistrement des champs magnétiques du cerveau à l'aide de capteurs crâniens dans le domaine de la recherche médicale et des sciences du comportement.
- l'intérêt pratique de l'emploi de composants ERP tels que le P300 et la variation contingente négative (CNV) ainsi que des évènements EEG, comme des indicateurs de la cognition, de la charge de travail et de la fatigue.
- l'application des mesures physiologiques à la détermination de l'efficacité de l'opérateur lors des mission aériennes réelles ou simulées, de nature stressante.
- l'incidence des accélérations sur l'activité du système nerveux central (CNV) et son emploi éventuel pour l'évaluation des actions humaines.
- l'évolution des traces EEG et ERP en fonction de l'absorption de drogues ayant pour effet de modifier le CNS, et leur incidence sur l'état de l'activité cérébrale.
- le rapport entre les EEG anormaux et les accidents/incidents d'avion.
- l'approche "neurométrique" au diagnostic de la maladie.

Les questions examinées lors du symposium couvrent un vaste domaine; elles sont complexes et revêtent souvent un caractère expérimental. Elles témoignent du besoin permanent de recherche en ce qui concerne le rapport qui existe entre l'activité électromagnétique, le comportement des sujets et le diagnostic médical. Le présent compte-rendu de symposium est le reflet d'une activité croissante de recherche dans un secteur des neuro-sciences qui trouve des applications directes dans les techniques de la médecine aérospatiale, et devrait, par conséquent, intéresser tous ceux qui sont resposables des soins médicaux dispensés aux équipages.

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TECHNICAL EVALUATION REPORT

by

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1. INTRODUCTION

The Aerospace Medical Panel held a symposium on "Electric and Magnetic Activity of the Central Nervous System: Research and Clinical Applications in Aerospace Medicine" at the Nye Sentrum Hotell in Trondheim, Norway from May 25 to 29, 1987. Thirty-seven papers and an invited Keynote Address were given by authors from ten NATO countries.

2. THEME

At its 41st Business Meeting, the Aerospace Medical Panel decided that several proposals for symposia submitted by the four Panel Committees (Behavioural Sciences, Biodynamics, Special Clinical and Physiological Problems, and Special Senses) should be combined and integrated into a proposal for one symposium. Its theme was to be a review of the modern techniques, both neuroelectric and neuromagnetic, which can be used for assessing the function of the central nervous system (CNS), both at rest and in the military aviation environment. The increasingly heavy physiological and cognitive demands that will be imposed by new and future high performance combat aircraft may well limit aircrew effectiveness. Thus, the ability to obtain objective measurements of the function and state of the CNS under a variety of physical and mental stresses, and the correct interpretation of these measurements could well provide a basis from which operator effectiveness during combined stresses can be quantified and assessed. Research and clinical papers were selected which addressed the value of measurements of electromagnetic activity of the CNS as indices of task performance and cognition in aircrew exposed to the stresses of the military aviation environment, and in the selection and medical care of aircrew.

3. PURPOSE AND SCOPE

In recent years, a variety of new techniques for studying CNS function have become available. The development of methods for studying a variety of evoked (EPs) or event-related potentials (ERPs), the new technique of magnetoencephalography as well as improvements in the analysis and understanding of the electroencephalogram (EEG) offer considerable promise for evaluating the human condition and performance in a variety of special environments. The application of modern computer-aided analytical methods to the information obtained by these techniques can provide objective measurements of the effects of different factors on CNS function. The purpose of the symposium was to review these techniques and to discuss the potential value of such CNS measurements in assessing the performance and abilities of individuals exposed to the stresses of modern military aviation environments.

The scope of the symposium was broad, covering important interests in most of the current research thrusts in aerospace medicine; viz., the behavioural sciences, biodynamics the special senses, physiology and clinical research. The electric and magnetic activity of the CNS was first discussed in terms of signal extraction, enhancement, and display techniques. Topics discussed under research and clinical applications included the effects of factors such as workload, fatigue, and physiological stress on CNS activity; the relationship between such CNS activity and cognition and performance; and the use of specific neurophysiological indices of the electromagnetic activity in the assessment of CNS disorders, the effects of drugs and other metabolic substances, G-induced loss of consciousness (G-LOC) and other accelerative effects, and sensory function. The participants included military and civilian experts in experimental psychology, the neurosciences, neuropsychiatry and psychopathology, research clinicians, vision scientists, ear specialists, human factors and biomedical engineers, physicists, statisticians, mathematicians, and defence research scientists. Presentations were drawn from defence and civilian institutes of aviation and environmental medicine, medical centres, brain research institutes, universities, and technical institutions.

4. SYMPOSIUM PROGRAM

The symposium consisted of a Keynote Address and six scientific sessions which addressed a continuum of topics, starting with state-of-the-art techniques for extracting CNS electromagnetic activity, continuing on with discussions on specific neurophysiological indices for assessing normal and abnormal brain function, and closing with a series of papers that considered the applicability of these measurements in both research and clinical aerospace medicine.

The Keynote Address provided a brief overview of new trends in exploring CNS electromagnetic activity in terms of research, instrumentation, and application. The major part of the Keynote Address related to the development and use of multi-channel magnetometers as a tool in cognitive neuroscience research.

The first session of six papers, Brain Function Monitoring: Signal Extraction Techniques, emphasised the importance of conducting proper EEG recording techniques in combination with good computer-aided analysis. The focus was on multi-electrode scalp recording, dynamic topographic and other colour displays of brain activity, and signal enhancement and feature extraction methodologies.

The five papers that made up the second session, Neuromagnetic Activity: Techniques & Applications, addressed the topic of magnetoencephalography, one of the most promising new techniques for the non-invasive study of brain function. The session focused on multi-sensor instrumentation and dipole source localization.

Session III, Cognition, Workload and Fatigue: Neurophysiological Indices - Research Considerations, explored the usefulness of some psychophysiological electromagnetic measures in the assessment of cognitive workload, fatigue and reaction time. Seven papers were included in the session.

The five papers of the fourth session, Cognition, Workload and Fatigue: Neurophysiological Indices - Human Performance Assessment, discussed the application of psychophysiological measures of CNS activity in quantifying performance and fatigue in operational scenarios. The emphasis was on the value of such measures in assessing performance during airborne and simulator missions, and for the selection of aircrew.

Session V, Neuroelectric Activity: Studies on the Effects of Acceleration, consisted of five papers that dealt with the use of EEG's and evoked responses to detect and/or assess a variety of accelerative effects. The focus was on the use of indices of this CNS activity for determining G-LOC and other associative effects of high-G forces, and in studying injury thresholds during linear impact accelerations. The session concluded with two papers that described the nature and utility of the vestibular evoked potential.

The sixth session, Neuroelectric Activity: Research and Clinical Applications, was made up of eight papers. Three papers discussed the effects of drugs on cerebral activity; two demonstrated a correlation between abnormal EEGs and aircraft accidents; one described the use of auditory evoked responses in assessing fatigue in aircrew; one described the concomitant EEG changes that are associated with prolonged low blood glucose levels; and one described a clinical technique using the visual evoked response to detect optic nerve lesions.

5. TECHNICAL EVALUATION

(For quick reference, some fundamental terms, definitions and concepts that are pertinent to this technical evaluation and/or the papers and discussions in these Proceedings, are provided in the APPENDIX to this report.)

5.1 Brain Function Monitoring: Signal Extraction Techniques

Improvements in the analysis, understanding, and presentation of the EEG to various stressors form the body of work in Paper #1 (Itil). The authors have developed a microprocessor-based system which records and analyzes EEG data on-line in real time from 19 electrodes simultaneously. The software has been designed to support both clinical analysis and research use. For basic clinical analysis, it allows frequency analysis of the EEG for each 2.5-, 5-, 10-, and 20-second epoch, from which the percentages of delta, theta, alpha and beta activities are determined and updated in real time. EEG amplitude and frequency averages are also obtained. A high-resolution colour monitor, on which up to 27 different types of topographic dynamic brain "maps" can be displayed, is used to study brain function. Such maps are particularly useful for simultaneously studying the clinically relevant features at each electrode site of the activities in one or more of the four fundamental frequency bands. Artifact rejection routines are also included in the software. Power spectral and period analyses make up the software for research purposes. Through a series of colour montages, the authors demonstrate the utility of the system for studying EEG activity under different psychological and drug conditions.

The second paper (Gevins), describes a sophisticated "neurocognitive pattern analysis system" that was developed in the authors' EEG Systems Laboratory in San Fransico in order to analyze and display the spatiotemporal brain state changes which occur during the performance of complex behavioural tasks. The current (fourth-generation) version records up to 64 channels of brain wave activity and processes them by means of a series of "expert knowledge" subsystems which employ operator feedback to enhance hypothesis testing. A novel feature of the system is an automated classifier-directed artifact rejection subsystem. It consists of five parallel detectors which are employed to distinguish between "clean" and five different types of contaminated data. The system utilizes the Laplacian spatial transform operator, a signal enhancement technique that corrects for the volume conduction distortion resulting from electrical potential transmission from the brain to the scalp surface. Single-trial brain wave activity is quantified by determining the crosscovariances for the different signal lag times between different electrode pairs. The functional interdependencies of the neural networks subserved by the different electrode sites are established when there is waveform congruence; i.e., when the associated crosscovariance is at its maximum value. The results are displayed on a graphics screen in colour as scalp distributions in three-dimensional perspectives. The system has been used to assess human performance during high-workload (Paper #22) and visuomotor-judgement (Paper #25) tasks. To establish plausible dipole brain sources, the authors intend to combine the results obtained from the joint analysis of event-related electric and magnetic activities, and relate them to anatomical data derived from the subject's brain structures as imaged by the technique of nuclear magnetic resonance (NMR).

Electroencephalographers differ in their ability to assess neurological disorders from visual inspection of the EEG. The authors of the third paper (John) have developed methods, called "neurometrics", which they feel not only increase the likelihood of identifying clinical neurological disorders but can also be used in assessing cognitive impairments and psychiatric disorders from the EEG. Neurometrics entails the computerized extraction of some 1200 neurophysiological features from artifact-free brain activity. After multivariate statistical analysis, the diagnostically-significant observations are presented topographically as colour-coded displays suitable for ease of clinical interpretation. Data from over 750 subjects between 6 and 90 years, who underwent extensive psychiatric and neurological examinations, make up the normative data base against which diagnostic comparisons are to be made. Features such as absolute and relative power, coherence, and symmetry of activity in delta, theta, alpha and beta bands were among those determined for each of 19 electrodes positioned according to the 10 - 20 International Electrode Placement System. The features from the normative data were first transformed mathematically to correct for skewness and enable Gaussian-distribution significance testing to be done. The neurometric features were then described by a series of normative regression equations across the age span from 6 to 90 years that were culture-fair and independent of ethnic background. These equations detected few abnormal values in healthy individuals. A high proportion of abnormal values were

found in patients with neurological, psychiatric and cognitive disorders. These equations were augmented by cluster-analysis methods to improve the discriminant classification of brain dysfunction. The authors demonstrate the applicability of the technique for differentiating between patients with different brain cerebrovascular incidents and/or psychiatric disorders.

The authors of Papers #4 (Wright) and #5 (Bachen), described methods for detecting non-stationarities in EEG epochs. The paper by Wright and her colleagues evaluated several methods for identifying non-stationarities associated with three levels of arousal: alert wakefulness, drowsy sleep and a transitional state between alertness and drowsiness. By their very nature, these three states are of variable length; therefore, the techniques adopted were chosen for their ability to correctly assess the state of drowsiness under such conditions. The methods employed included: (a) an evolutionary power spectrum (which determines the instantaneous local power-frequency distribution), (b) autoregressive modelling, and (c) the autocorrelation function. For comparative purposes, these EEG epochs were also analyzed by methods that relied on fixed-length data as follows: (a) Fourier analysis, (b) Hjorth's descriptors (which measure mean power, mean frequency, and waveshape deviation from a sinusoid), and zero-crossing analysis. The method based on the evolutionary power spectrum was the most effective one for detecting non-stationarities in the EEG. This method was able to distinguish the high frequency components superimposed on the low frequency activity that is characteristic of these transition states. Fixed-length methods tended to underestimate periods of continuous alpha (alertness) or theta (drowsiness) activity. The authors contend that methods of analysis which employ variable-length epochs may be useful in detecting short EEG periods that are associated with changes in the state of alertness in tasks requiring vigilance. The paper by Bachen describes a statistical technique for enhancing the detection of evoked responses in the EEG. Since the accepted method of ensemble averaging may not sufficiently enhance the presence of the evoked response over that of the background "noise" (the EEG) in certain clinical situations, the author recommends supplementing it. The method involves comparing the phase angles of the Fourier-transformed poststimulus activity with those in the EEG spectrum. In the absence of evoked activity, the phase angles are assumed to be uniformly distributed (the null hypothesis); for evoked activity, a nonuniform distribution results. The problem is reduced to testing the null-hypothesis assumption of uniformity by using a Kolmogorov-Smirnov type of statistic. The technique is quite sensitive and has clinical diagnostic value for detecting the presence or absence of evoked activity in certain critical situations; e.g., in diagnosing suspected cases of "brain death".

The final paper of the session (#6, Regan) describes a new steady-state EP technique that shows great promise as a clinical tool for "dissecting" sensory nerve pathways in specialized areas of the brain. Using novel Fast Fourier Transform (FFT) techniques, the method entails measuring the nonlinear interactions that occur in an EP waveform when two sensory stimuli are presented at the same time. For example, when a subject views a sinewave grating that is counterphase-modulated at F1 Hz and superimposed on a second grating counterphase-modulated at F2 Hz, the EP frequency components are comprised of discrete spikes of less than 0.004 Hz bandwidth, which appear at frequencies of $(nF1 \pm mF2)$ Hz $(n,m = 0,1,\ldots)$. The method rests on the premise that such nonlinear interactions can only occur if the neurons generating the EP respond to both stimuli at the same time; i.e., for whatever reason, the brain must be "tuned" to see both stimuli at once. The method may lend itself to mapping specialized brain areas that respond to both individual and combined visual, auditory and somatosensory stimuli, for both normal and pathological conditions. Brain areas in which such information processing would be important are those areas that respond asymmetrically to certain stimuli; e.g., to changes in contrast, motion or pitch. The difficult problem of locating and identifying EP source generators may be aided by combining a method such as this with evoked neuromagnetic methods, and imaging techniques such as positron emission tomography (PET) or NMR.

5.2 Neuromagnetic Activity: Techniques and Applications

Neuromagnetics, the study of the magnetic activity of the nervous system, is a relatively new science. The application of this technology shows great promise as a clinical diagnostic tool for investigating brain physiology and pathology, and in cognitive research for studying human performance during stress. The introduction of the cryogenic sensor, the Superconducting Quantum Interference Device (SQUID) into neuromagnetic methodology has enabled the measurement of very weak fields, that are several orders of magnitude less than Earth's magnetic field, in good noise rejection environments. Much current work has used SQUID technology for modelling the sources or generators of brain magnetic activity that are associated with the cognitive and physiological processing of specific sensory stimuli; and this is reflected in some of the papers presented at this Symposium (Kaufman [Keynote Address] and Hoke [#1] to auditory stimuli; Weinberg [#12] to separate and combined auditory and tactile stimuli; and Weinberg [#13] to visual stimuli). Although much current and past work was associated with shallow brain sources such as those in the cerebral cortex, there are practical reasons for believing that the neuromagnetic activity from deep brain and brain stem sources can also be mapped as equivalent current dipole sources.

The mapping of neuromagnetic fields of the brain has been done mainly with a single sensor which must be moved many times over the head in order to obtain a complete localization of each dipole source in the brain. Of course, a single sensor channel is useless when there is a need to simultaneously measure the magnetic activity of many equivalent dipole sources in the brain. Efforts are now underway to use multiple sensors for source localization of these magnetic field generators. Kaufman described isofield contour maps obtained from the auditory cortex to selective attention using a 5-channel system that was recently constructed for the Neuromagnetism Laboratory at New York University. Romani (Paper #7) discussed the instrumental problems of recording with 100 magnetic sensors which, unlike NMR imaging, should provide three-dimensional, real-time brain function imaging.

Chapman and his colleagues (Paper #10), and others have argued the case for combining both electric and magnetic recording in brain function studies. Each method contributes different and unique information. The magnetoencephalogram (MEG) is a non-invasive technique requiring sensors that do not touch the head. Traditionally, the spatial resolution of the EEG has been poor, since the electrical potentials that are recorded on the scalp are modified by the different resistivities of the hard and soft tissues of the head. However, there are now available Laplacian "deblurring" techniques which are used to improve the estimation of source localization of EEG equivalent current dipoles (e.g., see Gevins — Paper

#2). MEG generators, of course, are not affected by the different resistivities of the head; consequently, the magnetic field flux does not need to be recorded relative to a reference level as is the case with EEGs (where reference levels of "linked" ears, nose, etc. are routinely used). This ability to provide a real baseline level of neuromagnetic activity is a decided advantage over EEG methods when a stable and indifferent reference is required.

Weinberg and his colleagues used both EEG and MEG measurements to locate dipole sources in the brain (Papers #12 & #13). In the first of these papers (#12), the authors make a strong case for a 40-Hz resonance response to the interaction of independent auditory and tactile sensory stimulation in thalamo-cortical sites. In their second paper, EEG and MEG measurements were used to identify the properties of cortical generators for binocular vision. The next step in this particular study is to assess how factors such as fatigue and other stressors break down stereoptic performance well before there are other tangible signs of the effects of stress on performance.

Two papers scheduled for this session in the Symposium were not presented. These were Paper No. 8, which was to adddress MEG measurements of deep sources in the brain, and Paper No. 9, which was to discuss the effect of visual stimulus complexity on the distribution of visual evoked romagnetic fields.

5.3 Cognition, Workload and Fatigue: Neurophysiological Indices - Research Considerations

P300 is an ERP, the amplitude of which reflects cognitive attentional demands to task-relevant, rare-event stimuli. The functional significance of P300 as an index of mental workload is the topic of the paper by Kramer and his colleagues (Paper #14). The authors applied the P300 technique to two operational problems: (a) the assessment of pilot workload during flight missions in a fixed-base flight simulator for single- and dual-task ERP paradigms; and (b) as a "biocybernetic" communications link between man and machine. Preliminary results from the pilot workload experiment, strongly suggest that P300 amplitude can be used to distinguish between single and dual tasks, and between two versions of the flight mission. If P300 is truly sensitive to such cognitive demands, then it may well serve as a neurophysiological index to complement some of the less rigorous techniques that are now being utilized as subjective and performance-based measures for assessing workload. The results of the experiment in which P300 amplitude was used as a communications channel are more clear-cut. The authors constructed a paradigm which signaled a P300 response whenever an item in an array of items was being actively processed. P300s were not evoked by unattended items. The experiment demonstrated that P300 amplitude could be employed as an effective binary switch to toggle a choice reaction according to operator demands. The method may have applicability in constructing a biocybernetic communications channel for motor-nerve-impaired patients.

Paper No. 15 was to discuss some data which showed that different subcomponents of the P300 complex index (through amplitude and/or latency changes) different aspects of learning, but it was withdrawn from the Symposium.

The authors of the sixteenth paper (Fowler) make a case for P300 latency as a measure of the effects of hypoxia on cognitive performance. Hypoxia increased both the behavioural (reaction time) and the electrophysiological (P300 latency) manifestations of performance in a dose-related manner. In contrast, the P300 amplitude was not influenced by the hypoxic conditions.

In an excellent theoretical paper, Gaillard (#17) outlined the differences between exogenous and endogenous ERPs, and discussed the use of endogenous components to study psychological information processing. Exogenous components are directly related to the stimulus; they are dependent on the physical characteristics of the stimulus (e.g., pitch, colour, duration, and intensity) and the state of the organism. They are reflected reliably in the peaks and troughs of the waveform. The whole waveform is rather fixed and predictable in amplitude, latency, and topographical distribution. Endogenous components, however, may be induced by the stimulus or even in the absence of a stimulus. They are related to psychological processes and, as such, depend on task demands and the instructions given to the subject. Most importantly, there is a large variability in the form, latency, and topographical distribution of these components. Since exogenous components remain fixed between experimental conditions for the same task, endogenous components can be obtained by subtracting ERP waveforms from each other. Gaillard's central thesis is that the endogenous components can only be used as indices of cognition and workload after their psychological significance has been established. He argues for a better definition of what entails an endogenous component. He further reflected on the ambiguity amongst investigators regarding the way their measurements have been taken. Apparently, there appear to be as many components as there are paradigms, and as many paradigms as there are investigators. He argues for strict rules for establishing a taxonomy of tasks in order to make it possible to use ERP techniques as unobtrusive measures of cognitive processing.

The gist of the eighteenth paper (Stern) is that workload and attention can be effectively evaluated using the physiological measures of ERP, heart rate and eye blink activity. The experimental paradigm used was a variant of the Sternborg memory-scanning task in which CUE, MEMORY, and TEST demands were asked of the subjects. A CUE (alerting) stimulus is first presented which provides information on the nature of an upcoming set of items that are to be committed to memory. The MEMORY stimulus, which usually consists of a set of letters follows. The final stimulus, the TEST set, is a member of the MEMORY set in one-half the trials. For fixed times during the CUE and MEMORY task intervals, a "probe" stimulus -- a diffuse light flash that is irrelevant to the assigned task — was introduced and the ERP changes noted. The "Task-ERPs" are differentially affected by information storage and retrieval requirements: the P300 amplitude increased with increasing storage demands, and decreased with an increasing demand for information retrieval. "Probe-ERPs" are exogenous (or early) components that appear to index selective attention. Heart rate changes are related to both expectancy and task difficulty. Eye blink activity monitors both attention and difficulty in processing information. This study shows that, taken together, these three physiological measures index complementary combinations of cognitive activity. EEG, heart rate and eye blink activity are used to examine pilot performance during airborne and simulated fighter missions in Paper #23 (Skelly). Such an approach should dispel some of the criticisms that have been

levelled at the individual use of these components for studying cognitive workload.

The author of Paper #19 (Abraham) quite simply asks whether or not the amplitude of the contingent negative variation (CNV) — an ERP component — can be used to predict demanding task ability? Abraham raised this question when he noted the dubious findings in CNVs in controlled experiments with subjects firing the shoulder-mounted surface-to-air missile launcher "Blowpipe". The literature had indicated that the firing of this weapon would not be unlike a CNV-generating situation. Increased CNV amplitudes are associated with timely, ordered, and attentive responses; whereas, decreased CNV amplitudes are related to distractive and disordered mental functioning. His surprising findings that poor performance in Blowpipe operation was associated with either high or low CNV amplitude led him to conclude that personnel should be selected on the basis of job performance and not on the basis of CNV. Perhaps, there is merit in this message for other instances in which such performance measurements are to be used.

Papers #20 and #21 (Pigeau) describe the successful use of EEG measures to index different cognitive processes. The first paper (#20) addresses two research issues. Firstly, the hypothesis is advanced that individual differences in producing endogenous alpha activity account for the EEG hemispheric asymmetries that are observed during cognitive tasks which presumably induce such asymmetries in the first place. Results indicated that this was the case. Subjects ranked as low alpha generators (according to their eyes-closed ability to generate endogenous alpha activity) did not exhibit such EEG asymmetries; whereas, middle and high alpha generators demonstrated a definite relationship. Secondly, it was established that frontal theta activity indexes attentional demands. The second paper (#21) describes some novel methods using EEG measures to index "drowsiness" as an indicator of mental fatigue in sleep deprivation. Drowsiness in terms of a so-called EEG Drowsiness Index was determined during a 4 minute eyes-closed relaxation period which was embedded once every hour in a multi-hour sleep deprivation experiment. (The Drowsiness Index takes into account the fact that alpha activity is reduced, and theta and delta activities are increased during transition from the awake stage to Stage 1 sleep.) A second metric, the autoFFT (analogous to autoregressive smoothing in the time domain), was used to provide three-dimensional time/frequency plots of the EEG characteristics during sleep onset. (The autoFFT entailed performing Fast Fourier Transforms to "windows" of data that are successively lagged in the time-domain sense.) The EEG methods described in the study appear to be quite sensitive indicators of mental fatigue as indexed by drowsiness. These two studies demonstrate the fact that tightly-controlled experimentation combined with the judicious processing of EEG activity is a necessary requirement if cognitive processes are to be reliably indexed.

5.4 Cognition, Workload and Fatigue: Neurophysiological Indices - Human Performance Assessments

The physiological significance of EEG, heart rate and eye measurements (blink frequency and duration) as unobtrusive and continuous measures of pilot performance was discussed by Skelly and her associates (Paper #23). At the Armstrong Aerospace Medical Research Laboratories in Ohio, using these measures, they undertook the difficult task of recording pilot responses to comparable 90-minute A-7 aircraft and simulator training missions. A battle area interdiction mission consisting of takeoff, fast-flight, high-G manoeuvres, weapons delivery, threat evasion, low-level navigation, and landing was selected in order to study the effects of cognitive demands on human performance in an operational environment. The authors concluded that all physiological measures used in the study provided meaningful information on pilot workload. The EEG data discriminated quite well the changes in workload that were specific to each of the different mission demands. It was suggested that EEG changes appear to index overall workload; i.e., they reflect on both cognitive and physical demands. The EEG and eye blink duration are more sensitive to G-stress than is heart rate. Heart rate and EEG discriminated well between airborne and simulator missions, reflecting on the greater attentional demands imposed by a real-flight environment. Eye blink duration seems to be a sensitive indicator of attentional demands with eye blink durations decreasing as mental workload increases and vice versa. Blink rate data were difficult to interpret.

The attempt to relate ERPs and slow potentials to varying levels of mental workload while performing visual tracking tasks is the subject of Paper #24 by McCallum and his colleagues from the Burden Neurological Institute in Bristol. The authors contend that, although the CNV amplitude is usually associated with task-involved preparatory phenomena, it has been investigated only for short preparatory intervals, lasting at most for a few seconds. They argue convincingly that comparable negative slow potential shifts may extend over considerably longer periods for longer-duration tasks, thereby reflecting a continuum of different mental processes at work. Experiments were conducted in which the level of difficulty of the visual tracking task was varied in a systematic way. In some experiments, a secondary task was introduced in order to study further the relationship of cerebral processing to workload. The results indicated that such slow potentials extend over tens of seconds, that they are robust and consistent, and that they are CNV-like in their preparatory character, but that they also index the level of workload. There was an increased negative shift in slow potential when the secondary task was added to the primary task, thereby reflecting the sensitivity of this potential to increasing task demands. The authors further conjectured that a reduction in amplitude of the late ERP components during tracking (compared to control values) after the secondary task was added constituted an example of resource reciprocity (i.e., a drop in amplitude as resources are withdrawn and an increased amplitude as additional resources are deployed to meet increasing demands). In the authors' opinion, these negative slow potential shifts may be strongly associated with focal awareness; i.e., high-demand cerebral processing at the most conscious level.

Paper No. 25 (Gevins) is a discourse on the discovery that "preparatory sets", consisting of specific CNS electrical activity patterns, precede accurate visuomotor tasks. Using an expanded scalp electrode system, on right-handed males, the authors compared signal-enhanced brain electrical patterns associated with the preparation and execution of precise right- and left-handed finger actions in response to numerical visual stimuli. Significantly, when comparing similarities in wave shape (covariance pattern of the CNV), the precursory electrical patterns in individuals performing accurate visuomotor tasks were substantially different from those performing inaccurate ones. At least three distinct CNV components were found to be involved in the preparatory sets preceding accurate visuomotor performance: a cognitive component from the left frontal cortex, that is hand-invariant; a hand-specific parieto-central

somasthetic-motor component; and an integrative motor component from the midline and antero-central sites for left-handed actions. Degraded or inappropriate preparatory sets were associated with inaccurate performances. There were relatively weaker and fewer CNV covariances preceding inaccurate right-handed performances than there were in the comparable left-handed conditions. Moreover, the left-handed inaccuracies were characterized by strong, complex and widely distributed CNV patterns, suggesting that inaccurate performances by the non-dominant hand of strongly right-handed subjects may result from disordered preparatory sets. Similar studies on left-handed and ambidextrous subjects may clarify the importance of the dominant hand in performing complex visuomotor tasks. It is possible that consideration of hand-dominance may be required in the design of future aircraft and weapon control systems, and even in the selection of aircrew candidates, if maximum performance is to be achieved.

Investigators from the EEG Systems Laboratory, in collaboration with those in other US medical research laboratories, have used event-related covariances of EEG data to assess cognitive and perceptuomotor functions in US Air Force pilots during conditions of full alert, incipient fatigue and full fatigue (Gevins, Paper #22). Preliminary results would seem to indicate that the exogenous stages of visual processing during perceptuomotor tasks are relatively unaffected by fatigue. However, neural systems associated with higher cognitive functions such as working memory rehearsals, preparation, and motor inhibition are selectively compromised, even during the incipient stages of fatigue. The method shows promise for predicting signs of impaired or degraded cognition well before it becomes obvious from performance. Such results, should they stand up under further scrutiny, would have clear implications in the selection of personnel for employment in high stress situations that require both mental work and automated perceptuomotor activity, as is the case with air traffic controllers.

Paper #26 (Stanny) focuses on some preliminary considerations for using sensory evoked components in the evaluation and selection of naval personnel for aviation duty. The authors felt that the early results were encouraging; however, it was pointed out in the ensuing discussion that the method employed was too loose, and unlikely to reflect on the cognitive requirements for aircrew duty. It was further suggested that attention should be focussed on the late components and slow potentials; and it should be determined how these interact with task variables that relate more strictly to on-job performance (e.g., such as those in Paper #24 — McCallum).

5.5 Neuroelectric Activity: Studies on the Effects of Acceleration

Paper #27, which was to discuss the use of ERPs to stimuli in non-volitional "cognitive" paradigms with patients in the early stages of recovery from traumatic head injury, was not presented at the Symposium.

Paper #28 (Matson) reports one aspect of a number of tests in a continuing program at the Naval Biodynamics Laboratory, in New Orleans, to investigate impairment and injury thresholds for exposure to -X direction acceleration with the head unrestrained in primates. Neurophysiological impairment due to impact in rhesus macaques was objectively measured through changes in latency of components of the somato-sensory evoked potential (SEP). The SEP is a characteristic response measured at the cerebral cortex after stimulation of sensory nerve tracts in the spinal cord. The authors show that both slow and fast components of the SEP are delayed after impacts above 56 G, which is well below the threshold (82 G) for visible injury for similar -X impacts in this animal. These results indicate: (a) that stress on the occipital-cervical junction determines the lowest threshold of sensory performance impairment in this animal in this particular impact environment, and (b) that the SEP method can be used to assess potential impairment as a result of non-injurious impact exposure in humans. (This avenue has been pursued at the authors' laboratory already.) The results described in this paper should be complemented by those of an analysis of the head-neck kinematic data from the same tests, which would determine the deformations of the critical tissues of the brain stem which accompany the SEP latency changes. These data would allow comparisons with the results obtained from humans in order to determine whether or not there are size-independent strain thresholds for functional impairment of neural tissue at this level. Such thresholds, if they existed, could be used to define the limits on human head motions during impact which would not impair perception and cognition. This would have obvious value in the design of protective systems.

The authors of Paper #29 (Lewis) set out to assess the utility of the EEG as an indicator of state of consciousness in subjects exposed to rapid onset (6 Gz/s), high-G centrifugation (+7 Gz). Their preliminary results confirm earlier findings in the literature that there is a pronounced shift to high-amplitude delta activity during unconsciousness. In the ensuing discussion, it was felt that the prognosis for recording EEG and ERP data during centrifuge runs was good provided that appropriate steps are taken to minimize the effects of artifacts.

Matched filtering is a technique by which a filter is designed to "match" the signal in such a way that the peak signal-to-noise (S/N) ratio is maximized. The authors of the thirtieth paper (Nelson) used the technique in an attempt to enhance detection of the steady-state visual evoked response (VER) (signal) in the EEG (background noise) as an objective measure for determining visual function degradation during high +Gz acceleration runs in a human centrifuge. During exposure to progressively-higher G accelerations in a centrifuge, subjects experience a progression of visual symptoms - starting with decreasing visual sensitivity, then diminution of visual field, followed by peripheral (gray-out) and central (blackout) light-losses before culminating in a total loss of consciousness (G-LOC) as blood circulation to the eyes and brain is compromised. The authors reasoned that real-time monitoring of the VER might provide a rapid means of detecting degradation of visual function (within three seconds of initiation) during high-G centrifuge runs. (Experiments in the human centrifuge at the authors' Naval Air Development Center in Pennsylvania had earlier shown that the VER progressively decreases with G, disappearing at blackout.) In static experiments, matched filtering on appropriately-weighted data gave an S/N ratio improvement of about 33 dB over that obtained from "raw" VERs. However, an additional improvement of 5 to 6 dB is required before the technique can be considered as showing promise as a reliable measure of impending G-LOC. The technique still needs to be improved, and its effectiveness as an end-point measure must be evaluated against other methods (e.g., the peripheral-vision light bar) in dynamic centrifuge test experiments. The technique may also have clinical applications as an enhanced means of monitoring evoked responses during brain surgery.

Paper #31 (Sterman) is a review of a very extensive on-going study which sets out to evaluate the efficacy of using EEG measures as indices of pilot performance during laboratory-simulator and in-flight task-related missions. In the experiments reported on, the EEG was recorded by scalp electrodes according to the 10-20 International Electrode Placement System from visual and sensorimotor cortical areas while subjects were performing visuomotor tasks associated with aircraft control. For the in-flight studies, a portable EEG recording system was devised, comprised of: (a) a custom-made flight helmet liner containing scalp electrodes (appropriately-placed for the requisite cortical recording), miniature pre-amplifiers and associated electrical cabling for connecting to flight-vest components; (b) a mesh cranial cap for covering the helmet-liner ensemble; (c) a pre-molded flight helmet; and (d) a specially-designed flight vest containing a data filter module, amplifier unit, miniature 4-channel FM tape recorder, and a battery pack. In order to study the interplay between visual and sensorimotor cortical activity, a power spectral analysis was conducted on the EEG, the spectral estimates were sorted into seven consecutive 4-Hz wide frequency bands, and statistical comparisons were made on the processed data. Some preliminary results based on two in-flight and two simulator visuomotor performance experiments are characteristic and consistent. During competent performance of the visuomotor task, there is a significant discrepancy in the amount of 8 - 15 Hz activity between the left and right hemispheres in the sensorimotor cortex. The activity was greater in the left hemisphere than in the right. This discrepancy was independent of hand dominance and age of subject. It disappeared as flight-related performance degraded, and it did not occur if the subject was not operating the controls. The temporal modulation of this activity also reflected these changes. For high-G acceleration manoeuvres (4 - 5 G), power at frequencies below 8 Hz increased significantly in a non-specific manner. However, if competent performance was manifested during such G manoeuvres, then the left-hemispheric dominance of 8 - 15 Hz activity continued to be a feature of the data. During the ensuing discussion, it was suggested that these observations are typical of the phenomenon of desynchronization, wherein there is increased beta activity concomitant with a decrease in alpha activity (which can occur asymmetrically) during conditions that require the pilot to be alert. The authors are continuing to analyse the data.

Papers #32 (Wilson) and #33 (Fraser) describe the brain potentials that are presumably evoked by vestibular stimuli. In Paper #32, subjects were rotated into left- and right-side down positions from seated-upright positions at a roll acceleration of about 45 degrees/s centred on an axis passing through the nose. Such stimulation generates both semicircular-canal and otolithic neuronal activity, and, possibly also, somatosensory evoked activity. The effects of three different levels of mild hypoxia on the long-latency vestibular evoked response was addressed in Paper No. 33. The authors found an appreciable reduction in vertex responses, compared to air control levels, with breathing gas mixtures (12.7 & 16.6 $\%O_2$) that provided the mildest hypoxic levels tested. However, for the most severely hypoxic gas mixture (14.6 $\%O_2$), there was a reversal of effect, and no appreciable difference from air controls was detected. An analogous biphasic response had been noted earlier in studies on standing steadiness, and serial choice reaction times in subjects exposed to similar levels of mild hypoxia. By way of an explanation, the authors suggest that mild hypoxia increases the rate of brain dopamine excretion, while the higher hypoxic levels cause it to return to normal; thus, accounting for the biphasic response.

5.6 Neuroelectric Activity: Research and Clinical Applications

Papers #34 (Frauendorf) and #35 (Johnson) are attempts to classify drug action according to VER-component projections in a factor space. The method entails observing the mode of drug action on the VERs to multi-channel stimulation of the visual system; viz., the brightness (to full-field flash stimuli), contrast (to checkerboard reversals), and colour (to colour changes) channels. Following a Fast Fourier analysis of the digitized raw data, latency changes were measured from the delta, theta, alpha and beta components to form coefficients of activation (latency decreases) and attenuation (latency increases). These coefficients were used as variables in a factor analysis that employed a varimax-rotation procedure to provide a set of principal factors appropriately oriented in space to best define a specific mode of drug action. (The varimax procedure entails rotating a set of principal factors in a factor space in such a way that the amount of variance derived from each successive principal factor is maximized. No more than three factors were required to account for most of the variances of the VERs in these two studies.) The method, which has now been tried on five antidepressants, a nootropic drug and three cardiovascular agents shows promise as a clinical tool, but work is required to prepare the results in a manner comprehensive enough to aid in interpretation.

The Centre d'Etude et de Recherches de Médecine Aérospatiale (CERMA) in Paris is active in research dealing with the pharmacological control of states of vigilance, in the context of maximizing the operational value of combat arms personnel. As part of this research, a study was conducted on the effects of three psychostimulant substances on brain electrical activity in the rhesus monkey by Legarde and Milhaud (Paper #36) from CERMA. The prime objective of these experiments was to obtain a data base of EEG properties and the changes caused by well-known psychostimulants at different dosages; and compare them to the EEG modifications induced by experimental psychotropic drugs. The authors used the power spectral density to analyze EEG data into different frequency bands for caffeine, d-amphetamine sulfate and the experimental drug CRL 40476. In general, the results showed that caffeine caused a significant increase in delta activity, some decrease in the theta and alpha bands, and variable decreases in the beta band. Amphetamine produced an increase in delta and alpha activities, relative stability with signs towards an increase in theta activity, and a clear decrease in beta activity. CRL 40476 caused important increases in delta activity, no changes in theta and alpha activity, and some decrease in the level of beta activity. This work is not unlike that of Itil and his colleagues (Paper #1) who have much more extensive data bases of the EEG profiles of both healthy subjects and patients to CNS-modifying drugs which they use in deriving the therapeutic properties of experimental drugs. Of significance was the finding by Itil's group that psychotropic drugs with equivalent therapeutic properties exhibit similar EEG profiles, whereas therapeutically unequivalent properties produce different EEG effects.

A reduced tolerance to +Gz accelerations resulting from low blood sugar levels has been reported to be responsible for several fatal aircraft accidents. The authors of the thirty-seventh paper (Porcu) investigated the quantitative EEG changes that occurred in normal individuals who were made hypoglycemic through the use of an artificial pancreas which employed a glucose clamp technique. Human insulin was intravenously administered until a constant level of 43 mg% blood glucose was reached. The study showed

that, with such hypoglycemic levels, there is a slowing of alpha activity; in particular, in the frontal brain regions (cf. with Itil — Paper #1). Hyperventilation (which causes cerebral hypoxia due to hypocapnia) in combination with the hypoglycemic state did not act synergistically with respect to EEG changes. In fact, hyperventilation appears to counteract the slowing of the alpha activity caused by low blood sugar. The authors caution that the significance of neuroglycopenia — glucose deficiency in neurons — secondary to hypoglycemia as a factor in aircraft accidents needs examination.

The Snellen acuity test is the standard measure for determining the resolving power of the eye. It evaluates the ability to accurately recognize progressively smaller black letters on a high contrast background — a white chart. Visual contrast sensitivity can also be measured by using sinewave gratings of alternate dark and bright bars at different "spatial frequencies" as test targets. This method has the advantage that visual sensitivity to fine, intermediate and coarse details can be separately assessed. Sinewave gratings are used clinically to detect visual pathway disorders that are not necessarily evident in Snellen testing. Abnormal VEPs to checkerboard pattern reversals have also been used to diagnose neurological disorders. In particular, the use of VEP techniques for the differential diagnosis of multiple sclerosis (MS) is quite a common practice, even though there is evidence that pattern VEP latency correlates poorly with visual function in patients with MS. In an attempt to resolve this predicament, the authors of the thirty-eighth paper (Regan) combined techniques; and used high- and low-contrast Snellen tests, sinewave gratings, and VEP methods to large- and small-check patterns in an attempt to detect the full range of visual loss in patients having a variety of diseases. Their results led them to believe that, provided that stimuli are of comparable sizes (e.g., grating of low spatial frequency vs large checks), then there is good correspondence between contrast sensitivity and VEP amplitude. To further improve the specificity of their tests to MS, the authors experimentally-induced visual fatigue in their patients. Preliminary results indicate that abnormal VEP attenuation to the fatigue test may help to differentiate demyelinating diseases from other visual pathway disorders. The specificity is not complete, however, because fatigue tests do not differentiate between MS and ocular hypertension. VEP latency would appear to be a nonspecific indicator of visual pathway disorders. Clearly, the method shows promise as a clinical tool.

Papers #39 (Stavropoulos) and #40 (Merry) are studies of the correlation of EEG activity with aircraft accidents. The first of these papers (#39) is a ten-year follow-up relating abnormal EEG activity with aircraft accidents due to pilot error in student fighter pilots who entered the Hellenic Air Force in 1975-76. EEG activity was considered abnormal if: (a) the wakefulness EEG showed a "sharp-type" form having a hemispheric preponderance with/without a concomitant increased activity following some EEG activation procedure (e.g., by photic stimulation, hyperventilation, sleep deprivation), and/or (b) the drug-induced sleep EEG showed sharp discharge activity with hemispheric preponderance. Of the pilots classified as having normal EEGs, only about 6% were subsequently involved in aircraft accidents that occurred because of pilot error; whereas, 46% of those classified as having abnormal EEGs were subsequently involved in these kinds of accidents. Thus, pilots with abnormal EEG activity seem to be more predisposed to multiple involvement in aircraft accidents than the others. The second paper argues in favour of using the wakefulness EEG with photic stimulation for screening aircrew with a latent predisposition to epilepsy. In reviewing the literature, Merry concludes that there is a clear-cut relationship between epileptic seizure (or other causes of sudden loss of consciousness) and an aircraft crash. His arguments in support of EEG testing are based on the fact that there is a strong correlation between clinical epileptic seizures and focal spike wave paroxysms in the EEG. Apparently, there is a cumulative incidence of epileptic seizures varying from 2 to 5% in formerly healthy individuals showing abnormal paroxysmal spike activity.

Paper No. 41, which was to discuss the use of the auditory evoked response in audiometry, was not presented at the Symposium.

The final paper of the Symposium (#42, Castelo Branco) argues for the use of cluster analysis and multivariate analysis for distinguishing the differences between brain stem evoked potentials (BAERs) from control and study conditions. The method was applied to compare pre-flight BAERs in military pilots with those that occurred following operator fatigue due to a stressful flight.

6. CONCLUSIONS

6.1 The electric and magnetic activity of the central nervous system that can be recorded with scalp sensors is being studied in particular detail. The papers presented, from both military and civilian institutions, addressed the merit of employing such brain measurements both in the prediction of human performance, and for the detection and qualification of clinical disorders.

6.2 Methods for extracting signals from the "noisy" EEG and ERP are well advanced. Many laboratories have systems employing computer-aided signal enhancement and feature extraction methodologies on multi-electrode scalp recordings which provide dynamic three-dimensional colour display maps of brain function. The EEG and ERP have good temporal resolution (in ms). However, their spatial resolution is poor because the recorded scalp potentials are modified by the different resistivities of the "tissues" of the head; and, accordingly, are influenced by the choice of reference electrode (e.g., single ear, "linked" ear, nose tip, etc.). A Laplacian spatial transformation can now be applied to these scalp potentials, thereby removing the influence of the chosen reference and providing improved estimates of the "sources" of the EEG potentials. Methods of controlling or rejecting unwanted eye movements, muscle potentials and other artifacts continue to be improved and developed.

6.3 The neurometric or quantitative approach to diagnosing abnormal EEG/ERP data with reference to a normative data base that is age dependant but "culture- and ethnic-origin-free" deserves to be developed further and assessed against known methods of determining neurological, psychiatric and cognitive disorders. For the method to be truly effective in an adjuvant diagnostic screening role, the cooperation of many laboratories would be required in order to conduct comparative studies, to evolve (as required) and standardize the methodology, and to increase the sample sizes of the data bases (both normative and abnormal).

6.4 The "two-input" technique is a novel Fast Fourier method for evaluating sensory nerve pathways and brain areas that respond to two stimuli simultaneously. The method has a clear clinical application for delimiting common brain areas that respond asymmetrically to certain stimuli (e.g., motions in two different directions), or to two different sensory modalities (e.g., to visual and auditory stimuli).

6.5 Rapid developments are occurring in the field of neuromagnetometry. The MEG is a non-contact method which has a good capability for spatial resolution since it does not suffer from the "reference" problem that hinders the EEG. (Magnetic fields are not affected by the different "tissue" resistivities of the head.) To improve spatial resolution, investigators are now conceptualizing MEG systems of 100 - 120 sensors which should provide the capability for real-time brain function imaging to further both clinical diagnostic and behavioural research.

6.6 Perhaps a more useful system for monitoring brain function is one which combines the real-time imaging of EEG and MEG with the imaging of NMR and PET. Combined with the PET scan, which identifies the areas of the brain that are metabolizing organic molecules such as labelled glucose, it should be possible to relate changes in energy consumption to changes in EEG/MEG activity of specific brain sources and provide some new insights into sensory and cognitive processing. NMR can further reveal the location of cortical fissures and sulci, cerebral ventricles, and other fluid-filled anatomic "spaces" in the brain.

6.7 The use of physiological measures to augment performance-based measures and subjective ratings in quantifying human information processing during task performance shows great promise. Physiological measures such as heart rate, eye blinks, ERP and EEG are relatively unobtrusive, continuous, and appear to index complementary combinations of cognitive activity during stress-task protocols. There is now a sizable body of research demonstrating that the ERP components of P300 and CNV are sensitive and reliable measures of cognitive processing in tightly controlled laboratory situations. Nevertheless, there is still some doubt as to their true psychological significance in the workplace. There are strong arguments for developing and standardizing a "taxonomy of tasks" whereby specific task characteristics are related to specific ERP components and their constituent features — latency, amplitude, topographical scalp distribution, etc.

6.8 Methods for obtaining physiological responses during airborne and simulator missions should continue to be developed, not only for their value in comparing crew performances during workload in different operational environments, but also for their ability to index physiological and behavioural responses to unforseen events.

6.9 The concept that different brain "preparatory sets" precede accurate and inaccurate task-related visuomotor performances in right-handed individuals is intriguing. Consideration of hand-dominance may be a requirement in the design of future aircraft and weapon control systems, and even in the selection of aircrew candidates, if maximum performance is to be achieved.

6.10 Evoked-potential methods for determining pre-injury modes in animals undergoing linear impact accelerations should allow the development of criteria for exposing human volunteers to acceptable levels of linear G-forces.

6.11 EEG and EP methods for predicting pilot G-LOC look promising, but are in a very early stage of development and require much further study. In particular, the use of adaptive filters to monitor the visual evoked response may be a practical alternative to the peripheral-vision light bar in human centrifuge studies.

6.12 The definitive experiment to determine whether or not there is a true vestibular evoked response still needs to be done.

6.13 Good progress is being made in the development of data bases consisting of the parameters obtained through the quantitative assessment of multi-lead EEG/ERP activity from both healthy subjects and patients of different ages in response to different CNS-modifying drugs. Much more extensive data bases will be required if the therapeutic effects of a broad range of experimental drugs are to be established with any degree of confidence. The observation that psychotropic drugs with different therapeutic effects also produce different EEG profiles is a major step towards establishing suitable performance effectiveness measures with which to assess drug effects.

6.14 There is a clear-cut relationship between aircraft incident/accident and epileptic seizure. Although imperfect, the standard "wakefulness EEG" with photic stimulation should be part of the medical examination of candidate military aircrew. If focal or generalized spikewave paroxysms are detected, then the student pilot should be considered at risk for epilepsy and disqualified from flight duty.

7. RECOMMENDATIONS

7.1 The topics discussed in this Symposium are of fundamental importance if progress is to be made in improving human performance and reducing pilot workload at the man-machine interface in the cockpit. Many of the studies that were presented are part of on-going programs that will take several years to complete. By all accounts, however, the study of brain activity, whether through EEG or MEG techniques, is a growing field of scientific endeavour. In order that these methodologies may become part of the armamentaria of measures and techniques that Aerospace Medical Research Institutes use in evaluating human performance, it will be necessary for the AGARD Aerospace Medical Panel to continue monitoring the activities of workers in the field. Accordingly, a second Symposium should be held, in about five-years' time, in order to assess the degree to which these techniques have been adapted to the problems of, and practices in, aerospace medicine.

7.2 The psychological significance of the physiological components and their constituent parts in relation to mental performance in operational situations remains more or less putative. It would seem that physiological signals such as the EEG/MEG, the ERP and magneto-evoked activity, eye blinks and other ocular activity, heart rate and other cardio-respiratory indices, the galvanic skin response (GSR), the

electromyogram (EMG), head movements, etc. provide a rich source of information with which to assess psychological processing. Yet the question remains: How best can these measures augment performance-based measures and subjective ratings as indices of human performance in a flight simulator and in the aircraft cockpit? It is recommended that a Working Group of experts be constituted in the near future under the auspices of the AGARD Aerospace Medical Panel with the objective of producing an Advisory Report that addresses this issue. The experts would review the available information on the nature of these components in regard to indexing the different aspects of mental performance, and identify which of these different components can best be applied to field situations and under what conditions.

8. ACKNOWLEDGEMENTS

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DCIEM Report No 87-R-36.

9. APPENDIX

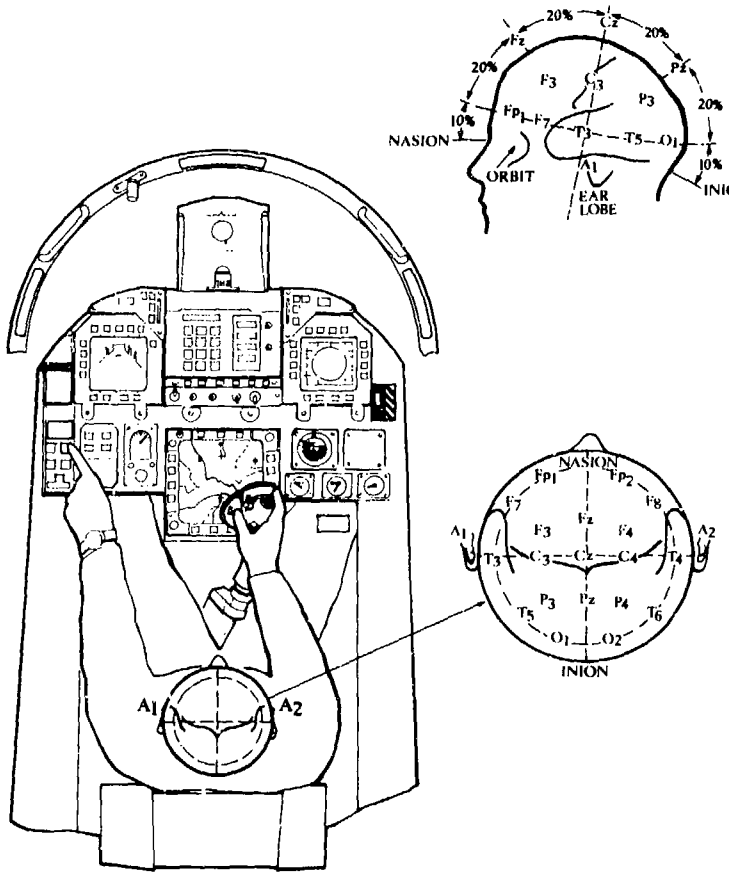

Figure 1. Man in modern cockpit. These lateral and superior views of the skull indicate all of the electrode positions according to the 10 - 20 International Electrode Placement System (adapted from Jasper, H.J. Electroenceph. clin. Neurophysiol., 10:370 - 375, 1958). Designations are: Frontal pole (Fp), Frontal (F), Central (C), Vertex (Cz), Temporal (T), Parietal (P), Occipital (O), and Ears (A_1, A_2).

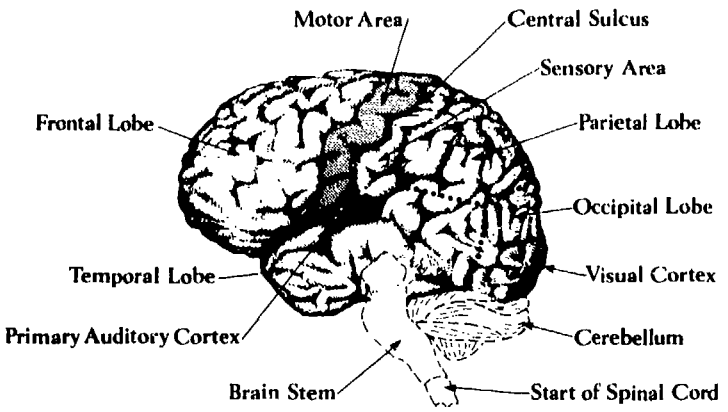

Figure 2. The major parts of the central nervous system, to which many of the papers in the Symposium make reference. The cerebral cortex, which is associated with higher perceptual, cognitive and motor functions, is divided into four anatomically distinct regions: the frontal, parietal, temporal, and occipital lobes. The central sulcus is one of the most prominent grooves in the cortex. Cortical areas associated with vision, audition, and motor actions are indicated. Also shown are the cerebellum, the brain stem, and the beginning of the spinal cord.

The background electrical activity recorded with surface electrodes, the EEG, is characterized by the following four frequency bands:

- delta (0.5 - 4 Hz),
- theta (4 - 8 Hz),
- alpha (8 - 12 Hz), and
- beta (12 - 30 Hz).

The term evoked potential (EP) was originally used to define the computer-averaged transient responses of the CNS to sensory stimulation. The term event-related potential (ERP) is now more commonly used in behavioural studies. Evoked or "exogenous" components are stimulus-dependent and can be recorded from many levels of the afferent pathways. Event-related or "endogenous" components are those components which occur independently of the external stimulus. The paper by Gaillard (#17) further delineates the differences between exogenous and endogenous components. Figure 3 illustrates both types of components.

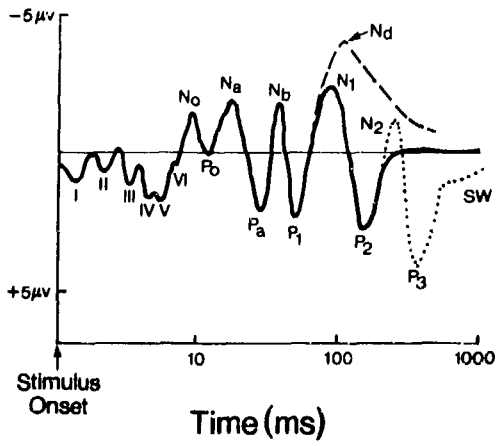

Figure 3. The auditory exogenous (solid line) and endogenous (dashed and dotted lines) components in response to a "click". Shown are brain stem (waves I to VI; up to 10 ms), mid-latency (N_o to N_b; 10 - 50 ms), and long-latency (P_1 to N_2; over 50 ms) exogenous components. N_d and the P_3 - SW complex represent endogenous components associated with different modes of processing (after Hillyard, S.A. TINS, 8:399 - 405, 1985).

Three ERP components that appear more often than others in the papers or the DISCUSSIONs in this Symposium are the following:

(a) the P300 (see Figure 4);
(b) the contingent negative variation (CNV -- see Figure 5); and
(c) the readiness potential (also called Bereitschaftspotential -- see Figure 6).

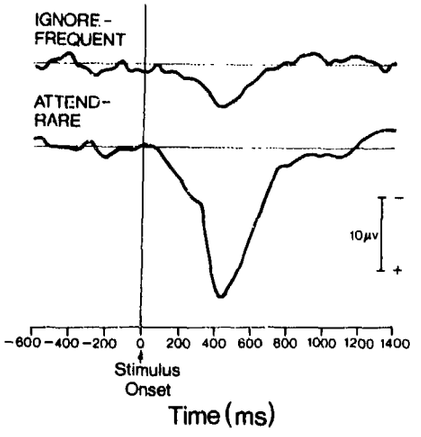

Figure 4. Shown is the P300 waveform which occurs as a positive wave in the EEG between 300 and 500 ms following certain kinds of events. In the classic "oddball" paradigm, two kinds of events are presented to the subject. The subject is asked to pay attention to one kind of event (usually the rarer one, hence the terminology oddball), and to ignore the other. The figure illustrates the marked difference in P300 amplitude between ERPs elicited by rare attentive events (bottom) and frequent unattentive events (top). P300 is commonly associated with perception (adaptad from Donchin, E. In: Gomer, F.E. Biocybernetic Applications for Military Systems; pp 69 - 100, 1980, Rept. MDCE2191, McDonald Douglas Corp.).

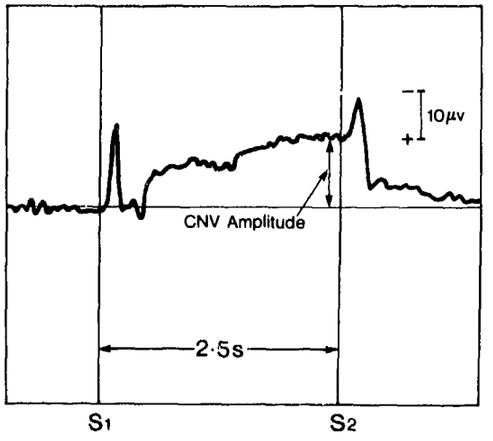

Figure 5. The CNV is a slow negative shift in the EEG baseline which develops between a warning stimulus (S_1) and an imperative stimulus (S_2) which demands a response. The CNV is related to expectancy (adapted from Denoth, F. et al. Ann. N.Y. Acad. Sci. 425:177 - 187, 1984).

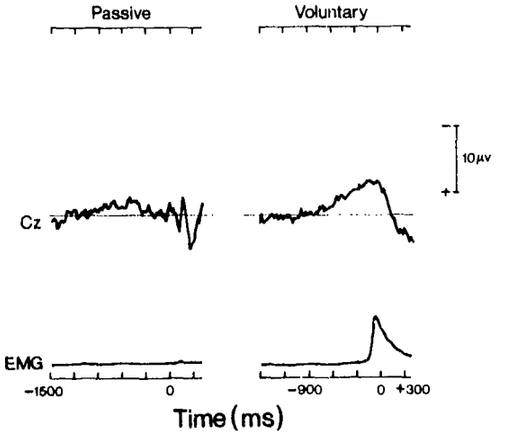

Figure 6. The readiness potential is a slow negative scalp potential which precedes the actual execution of a voluntary movement by several hundred milliseconds. The figures show the vertex response (Cz) and EMG to passive and voluntary movements. Volitional response is preceded by a slowly increasing negativity. The readiness potential is related to intention (adapted from Shibaski et al. Electroenceph. clin. Neurophysiol. 50:201 - 213, 1980).

STUDIES OF THE INTACT HUMAN BRAIN: IMPLICATIONS FOR PERFORMANCE

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Introduction

The performance of a human in running a marathon can be measured directly. A world class youthful runner can complete the 26 miles in slightly more than 2 hours, while a competent middle aged runner can complete the race in something less than 4 hours. Thus, despite wide age differences, championship performance is only a factor of 2 better than mediochre performance. Furthermore, we know if a runner's capacity his been exceeded. He may falter, start walking and even withdraw from the race. In addition, the history of the runner in terms of past performance, the types and frequencies of past injuries, and other factors as well, are good predictors of performance. What is true of this and other types of athletic performance may even be true of certain kinds of mental work, and the results used to predict performance that depends upon that knowledge.

Methodology provides a unifying theme for this conference. Many of the papers deal with electrical potentials and magnetic fields recorded at the scalp as well as with advances in methods for analyzing these recordings. Psychological states and cognitive processes are directly related to the activity of the brain. It is precisely these states and processes that make it so very difficult to define highly skilled performances and to predict their outcomes. Hence, some of the papers attempt to find links between brain measures and perrormance. But the types of performance of concern are essentially different from running or test taking. Instead, drowsiness, disorientation (which may or may not be related to drugs), mental workload, the deployment of attention, and access to memories are assumed to be related to the performance of intricate tasks. drowsy drivers may fall asleep at the wheel, locomotive engineers under the influence of some kinds of drugs are more likely to have accidents, and pilots overloaded with information may make the wrong decision as to whether or not to engage in a dogfight. Despite this common wisdom it is an easy matter to predict performance from self-reports of fatigue, information overload, and so on. Also, the precise effects of strategies for deploying attention in some situations probably do not predict performance in other more complicated situations. Performance in real life situations may not be predictable even if we know that the subject suffers from mild hypoxia or low levels of intoxication, partly because the events we want to predict may have a low probability of occurrence, and partly because they are influenced by many other factors. So some of us have turned to the brain. Is it possible that measures of the activity of the brain can significantly complement behavioral measures, self-reports, and chemical tests of the blood in predciting performance? We would be remiss if we did not study brain activity if we hope to understand performance of tasks involving cognitive processes as well as acquired intricate motor skills.

The study of brain activity is an increasingly valuable adjunctive medical procedure. It also shows signs of becoming useful in "diagnosing" subclinical disorders, e.g., dyslexia, although there are still grounds for some reservations. Moreover, studies of the activity of the intact human brain promise to help us to define momentary states that could contribute to variability in both mental and physical task performance. This optimistic assessment is admittedly largely subjective, but some of the advances described at this meeting tend to justify the optimism.

It is important to note that cognitive neuroscience is not a young discipline, but it is teribly immature. We cannot say with confidence that a particular normal individual will almost certainly place his aircraft at risk because of some properties of his EEG. In fact, cognitive neuroscience is still at a descriptive level of development. we are still trying to decide what various physiological and psychological stressors do to the brain activity we measure. We want to further our understanding of brain events known to be associated with particular tasks and events associated with those tasks. Truly, remarkable beginnings have been made. We know that P300 is related to perceptual processing of rare events and to the transfer of information between long term and short term memory. We even know some-

thing about the place in the brain that contributes to the P300 wave detectable at the scalp. However, we know very little about the neural events that precede P300 and are causally related to it. Clearly, sensory processes are not necessary events in that sequence, because P300 occurs when an expected event does not occur. N100 is modulated by selective attention, and, unlike P300, sensory pathways seem to play a very important role, but we shall have more to say about that later. N400 seems to be associated with semantic incongruity, and the readiness potential may well teach us much about the accuracy of responses in choice reaction experiments. Moreover, we are beginning to learn to identify unusual patterns and sequences of activity in the ongoing EEG that could reflect important but otherwise unobservable inner processes. We believe that much can be learned from neuropathology, which may display on a grander scale subtler subclinical processes that are now difficult to detect in the "noise" of the ongoing and seemingly normal EEG.

Of course our ideas about performance and workload must also be refined. The racing analogy is largely inapplicable to cognition. Measures of mental work and its quality are not the same as those for physical work. Moreover, by now we are all disenchanted with the originally seductive idea that the answer lies in information theory. Humans are not simple transmitters of information. Some of us "chunk" information and handle large amounts of it with seeming ease, while in other circumstances the same persons may be unable to process very little information. However, we are becoming more sophisticated here too. For example, "structural information theory" is coming to replace the now outmoded direct application of information theory to the problem of defining perceptual "simplicity", and, by inference its inverse, "complexity". If this is true of relatively passive perceptual organization, why should simple definitions of "workload" or of "performance" apply to human activities of all types? Clearly, the conjoint study of cognitive psychology and of cognitive neuroscience can lead to progress that may not be so readily achieved from within either discipline alone.

New physical methods for the study of brain activity represent remarkable advances over those available just a few years ago, and promise to make it easier to perform experiments that are more obviously related to cognitive processes. These new methods include improved techniques for measuring the brain's magnetic field, particularly the advent of multichannel recording. I shall have more to say about this and its implication later. But let us not neglect the marvelous progress in the technology associated with measuring regional cerebral blood flow, using materials that have half-lives on the order of 2 minutes. While cyclotrons are still needed to produce such materials, the results obtained to data promise to reveal much about the functions of various portions of the brain. Also, the application of increasingly sophisticated techniques to EEG recording promises to make us free at last of restricting our attention primarily to activity that is time-locked to particular events. It may now be possible to distinguish reliably between states of alertness and drowsiness by employing advanced quantitiative methods in analyzing the ongoing EEG. Similarly, different portions of the EEG spectra and hemispheric asymmetries may well be related to the level of sustained attention. Correct and incorrect decisions in choice reaction times seem to be preceded by differential activity in the frontal areas of the two hemispheres, and so on.

The study of time-locked activity is still important and uninformative. One relatively recent advance is activity that is time-locked to vestibular stimulation. This promises to teach us much about spatial orientation perception, as well as about the effects of environmental factors on this vital capacity. Also, we are learning to study interactions among time-locked brain responses to different stimuli, and this tool lends itself to the determination of which perceptual or cognitive functions involve common, overlapping or fully shared capacities or resources of the CNS.

In the time permitted me, I cannot give you a detailed overview of what is to be presented at this conference. However, the topics I have mentioned are not not isolated instances. The world of cognitive neuroscience is becoming far richer in content and method than many of us could have predicted a few years ago. In the remaining time I would like to cover the work of our group at New York University, since I feel that what my colleagues and I have been doing is one of the more exciting developoments. I should add that this work is not the product of our laboratory alone. Many groups throughout the world have contributed to the rapid advances in this area, and I want to take this opportunity to thank all of them for openness in sharing information, and for the collaborative work that has gone on across laboratories. In particular, I want to mention the group in Finland (Riita Hari and her colleagues), Italy (G.-L. Romani and his colleagues), West Germany (S. Erne' and also T. Blum and their colleagues), Canada (H. Weinberg and his colleagues), and the United States (J. Beatty; E. Flynn; J. Wikswo; C. Hatzell; D. Cohen; and all of their colleagues, who are really too numerous to mention). I also want to express our gratitude to colleagues working with event related potentials. They been extremely supportive of our work, particularly in the days when what we were doing

was not quite respectable. These include E. Donchin, S. Hillyard, T.Picton, D. M. Regan, I. Bodis-Wollner, R. Naatanen, and others whom I would like to mention if time were available. If it weren't for these and other friends and colleagues, none of us would be where we are today. That is why I mention these people in the body of my paper rather than in obscure and easily ignored footnotes.

Although the mood of this paper is suitable for a keynote address, this audience is undoubtedly interested in a substantive technical presentation as well. Therefore, the remaining portion of the paper will be devoted to recent work done in our laboratory. I shall focus on three main areas. The first is the development and testing of multi-channel neuromagentometers, since it now seems evident that such instruments stand the best chance of giving us the information we need about the activity of the brain. I will briefly discuss the relationship between the numbers of sensing channels and the background noise. Also, I shall provide a brief acount of some of the analytical methods we have been applying to neuromagnetic data. This will be illustrated in the context of a specific experiment dealing with selective attention.

Instrumentation

1. Background

Before beginning this section, it is important to stress the fact that the work I am about to describe is the result of a team effort, and credit should be given to colleagues who have worked with us at various times over the past 15 years. Naturally, Samuel J. Williamson, who is my co-director of the Neuromagnetism Laboratory, played a major role in all of the work we have accpmlished. Drs. Douglas Brenner, Y. Okada, M. Pellizone, R. Ilmoniemi, P. Costa Ribiera, and B. Schwartz ali made important contributions. Dr. Rodolfo Llinas, who led the effort to found the CNM at Bellevue deserves a special acknowledgement. Our current and past graduate students also played important roles in many of the projects we have undertaken. In particular I want to single out Sarah T. Curtis who collaborated with us in the study of selective attention to be described at the end of this paper.

The first studies of extracranial magnetic field patterns, or magnetoencephalogram (MEG) made use of a single-channel instrument in a magnetically shielded room (7). Such high-sensitivity studies were made possible by a cryogenic device known as the SQUID (Superconducting QUantum Interference Device). This senses the field of interest by means of a detection coil, and the probe containing this system is suspended within a vacuum-insulated container (dewar) filled with liquid helium. Our own first instrument made use of a detection coil having the geometry of a second-order gradiometer. This type of detection coil discriminates against noise sources that are far away because they produce spatially uniform fields, to which the gradiometer is insensitive. To improve the rejection of amibient fields, small superconducting tabs placed near the coil were adjusted by rods extending through the top of the dewar so that, in effect, the areas outlined by the individual turns of wire in the coil could be matched. This adjustment is called "field balancing". Our first such instrument (8) employed an rf-SQUID which permitted us to detect fields that were as weak as one billionth the strength of the earth's steady field without shielding in a normal laboratory environment. Ultimately the rf-SQUID was replaced by an even more sensitive dc-SQUID, so that the limiting factor at low frequencies was no longer SQUID sensitivity but the residual ambient magnetic noise.

2. Multiple Channel Neuromagnetometers

Fields originating in sources in the primary sensory areas tend to be quite stable over time for any given subject. However, by definition, labile sources, those affected by states of attention or arousal, are not stable over time. Thus, to study "event-related fields" it is necessary to avoid the assumption of stationarity. One way to do this is to measure the field at several places outside the head at the same time. Replications of measurements at or near some of these places while measuring the field at more distant places enable one to determine if the source of the observed field is indeed the same from one trial to the next.

There is still another justification for multiple-channel instruments. It simply takes too long to collect enough data to allow the construction of accurate maps of the field radial to the head. Such maps are needed if we are to compute the location, orientation and strength of the underlying source of the field.

It should be noted that it is also essential that the position and orientation of the head relative to the sensors be known is equally important to the accurate description of the underlying source. We will not discuss the latter problem here except to say that new methods have already been developed which enable us to automatically record the head's position and orientation relative to the detection coils within the dewar. Completed tests of these methods demonstrate their feasibil-

ity. A fuller technical discussion of this subject will become available in the near future.

Returning to the topic at hand, we collaborated with Biomagnetic Technologies, Inc. (BTi) in developing and constructing a 5-channel system (11). The individual coils of the five second-order gradiometers in this system are 1.5 cm in diameter with the end sets separated from the middle set by 4 cm (the "baseline" of the gradiometer). The bottom coils ("pick-up coils") of the gradiometers have a center-to-center separation of 2 cm from each other, with the axes of the outer four coils tipped by 10 deg from the dewar axis so that each coil points to a common position 9 cm below the bottom of the dewar. While we relied upon the mechanical positioning of superconducting tabs to obtain field balance in our single-sensor system, as did Romani et al. (12) for a 4-sensor system, we adopted a totally new procedure in this system. Instead we incorporated three rf-SQUID magnetometers for monitoring the field in three orthogonal directions just above the detection coils and a simple first-order gradiometer for monitoring the field gradient along the axis of the dewar. The outputs of these ancillary devices are given empirically determined weights, and then subtracted from the outputs of each of the five signal channels. This "electronic" field balancing yields results comparable to those obtained with the mechanical field balancing for the single-channel instrument. The noise level above about 4 Hz in each channel, after subtracting the weighted outputs of the references, is about 20 femtotesla (fT) per root Hz of bandwidth. However, at lower frequencies the noise amplitude increases at a rate that is slightly faster than the inverse of the frequency. This effect of ambient magnetic noise is pervasive, and it seriously restricts our ability to measure very slowly changing fields. Excess noise at power line frequencies is largely removed by comb filters.

Our experience with this system convinced us that it is indeed possible to place a large number of channels in close proximity to each other within a single dewar, i.e., the "cross talk" between channels was less than 1 %. Since we were also thinking in terms of clinical applications, it became increasingly obvious that it will ultimately be necessary to monitor the field over the entire scalp at once. Although many technical problems remain, we consider it feasible to construct a system composed of about 100 channels within a single dewar. As an intermediate step, BTi is now producing 7-channel neuromagnetometers similar to the 5-channel system described above. A pair of these instruments is now installed at Bellevue Hospital where a Center For Neuromagnetism (CNM) was established within the Department of Physiology and Biophysics at NYU.

It is becoming clear, however, that even with electronic balancing for field and its second-order gradient (the method in use in more advanced 7-channel systems, such as those installed at Bellevue and at UCLA) the low-frequency noise level may not be acceptable for all state-of-the-art neuromagnetic measurements. For instance, there is increasing interest in slowly varying phenomena related to higher levels of brain function, such as cognition. It appears that these can be studied most effectively in a clinical or laboratory setting through use of a magnetically shielded room to better reduce low frequency magnetic noise. Several types of rooms have been described in the literature for use in noisy environments (13,14), although simpler ones may suffice in clinics and laboratories in suburban or rural areas.

3. Implications of Multiple Measurements

While work is progressing along several different lines toward the goal of resolving and locating sources of neuromagnetic fields, in this section we shall focus on the implications of using multiple sensors for source localization. Our motivation for employing 14 sensors (7 in each of two dewars) at the CNM at Bellevue is perhaps best explained by considering the precision with which field measurements can locate the simplest neural source: a confined region of activity that can be modeled by an equivalent current dipole. Such a dipole is characterized by 5 parameters: the strength Q of its moment tangential to the scalp (the normal component is magnetically silent); transverse position x and y in the tangent plane; depth D beneath the scalp; and orientation PSI in the tangent plane. Therefore, in principle, our 5-sensor probe is sufficient to determine the parameters with simultaneous measurements at a single, appropriate position. Computations for the case where the probe is centered on one of the two field extrema show that while this is indeed true, the presence of a typical level of magnetic noise introduces considerable uncertainty in the values of these parameters (15). Table 1 illustrates this in comparison with the uncertainties for systems with a single 7-sensor probe and a pair of 7-sensor probes similar to those installed at Bellevue, since these are the most advanced available systems. With a noise level of only 10% the uncertainties in strength and depth exceed 30% for both 5- and 7-sensor probes, although the latter provides a significant advantage in determining the lateral position and orientation. By comparison a 14-sensor system provides a marked advantage in the precision of all parameters, with less than 16% uncertainty in strength and depth, 2 mm uncer-

tainty in lateral coordinates, and 3 deg in orientation. We hasten to add that these computations are for a favorable situation where the dipole is relatively shallow, i.e., when its depth is comparable to the distance separating the detection coils within a given probe. For deeper sources the uncertainties will be greater. Furthermore, this illustration is based on a simplified spherical model of the cranium where the electrical conductivity is assumed to depend on radial but not angular position (the external magnetic field pattern then being independent of the exact functional description). Nevertheless, the results shown in Table 1 clearly display the relative advantage of using a large array of sensors.

It is worth noting that similar considerations apply to determining the position, orientation and strength of a equivalent current dipole source from potential measurements. However, in this case at least 7 electrodes are required to fully characterize a single dipole source - and that is true only when the noise level is negligible. In the EEG the background activity is generally larger an amplitude than is that encountered in the MEG (where ambient noise and not "brain noise" is the limiting factor. Therefore, many more than 7 electrodes are required if one is to even attempt to deal with more than one source at a time.

TABLE 1

Uncertainties in best-fitting current dipole parameters for various levels of noise, expressed as a percentage of the dipole field sensed at a field extremum. The dipole is located at a depth of 2 cm in a spherical head of 9-cm radius. For the 5- and 7-sensor systems, the probe was centered on one of the field extrema; the 14-sensor system consists of two 7-sensor probes which were centered on the two extrema.

PROBE	NOISE (%)	_Q/Q (%)	_D/D (%)	_x (mm)	_z (mm)	_PSI (deg)
5-sensor	5	21	16	4.6	13.6	40
	10	42	31	6.7	20.0	64
7-sensor	5	20	15	1.2	4.0	12
	10	44	31	2.6	8.1	14
14-sensor	5	8	6	0.4	1.0	3
	10	16	11	0.8	1.9	6

4. Remarks on Sensory Evoked Fields

One of the principal advantages of neuromagnetic methods is the possibility of locating sources of neural activity by a relatively simple procedure (1,16). The procedure does not require knowledge of the exact shape of the head, but merely the sphere that best fits the relevant region of the head. Recently it was argued that the sphere fitting the inner surface of the skull nearest the source is most appropriate (5,17). In any event, if the source is sufficiently confined to allow it to be reasonably well modeled as an equivalent current dipole in a spherical head, the resulting pattern across the scalp of the radial component of the field is always the similar: there is one region of outward field and another of inward field. This universality is due to the fact that only the tangential component of the dipole contributes to the field outside the head - the radial component is magnetically "silent". Magnetic field lines form closed loops around the dipole, and the extrema indicate where the loops are most dense where they emerge from and enter the scalp. To determine the lateral position and depth of the current dipole, it is only necessary to locate the positions of the maximum outward and inward radial field. The dipole is located midway between these extrema, and it is oriented perpendicular to a line joining the extrema, in the sense given by the right-hand rule of electromagnetism. Its depth is determined by the ratio of the distance between the extrema to the radius of the sphere. The strength of the dipole (the current dipole moment) is proportional to the value of the maximum field and related to the depth of the dipole.

To exploit this ability to locate sources of fields, Romani et al. (20,21) studied the steady-state response to a tone whose amplitude was sinusoidally modulated at a rate of 32/sec. Mapping the field patterns for tones having different

carrier frequencies showed that the depth of the source increased monotonically with frequency, with the cumulative distance across the auditory cortex within the Sylvian fissure from one source to the next varying as the logarithm of the frequency. This demonstrated the existence of a tone map across the auditory cortex which extends over a distance of about 2 cm for the range 100 - 5000 Hz. Thus, using a simple sphere model we were able to demonstrate the tonotopic organization of a portion of the human auditory cortex (Figure 1).

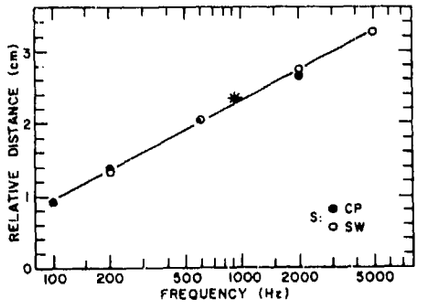

Figure 1. Tonotopic organization of activity across auditory cortex represented by locations of the equivalent current dipole sources, for steady state responses to amplitude modulated tones of the indicated frequencies. The star indicates the position of the response to click stimuli presented at 32/sec whose power spectrum peaks at 900 Hz.

The potencial evoked by a long tone burst contains four major components commonly referred to as P50 (latency of about 45 ms), N100 (90 ms), P200 (160 ms) and a steady potential (SP). It is now agreed that one source of the N100-P200 complex (21,23,24) lies in the auditory cortex. However, variations in amplitudes at different electrodes suggest that the complex should be modeled by more than one equivalent current dipole (21,26,27).

These findings are nicely complemented by auditory evoked field studies. First, however, we should mention the convention of affixing an "m" after the symbol for an evoked potential component to indicate that we are discussing a neuromagnetic correlate of that component. Thus, "N100m" is the neuromagnetic counterpart to the potential referred to as "N100", and the "m" emphasizes that the magnetic and electric components may not in general be attributable to identical sources.

The first observations of the auditory evoked field components P50m and N100m were made over the temporal area by Reite et al. (28) for click stimuli, but Farrell et al. (29) were the first to note an anterior-posterior polarity reversal for P50m which implied that the position of its source was in or near the primary auditory cortex. Elberling et al. (30) studied responses to tone bursts of long duration and found a polarity reversal for N100m suggesting that its source lay in the same general area. Hari et al. (31) also reported a reversal of polarity of N100m and P200m, as well as the steady field (SF), where the positions of the extrema were consistent with dipole sources in or near primary auditory cortex with moments oriented perpendicular to the lateral sulcus. Thus, all of these major components of the transient auditory response, viz. P50m, N100m, P200m and SF, seem to originate in the vicinity of the auditory cortex.

As already indicated, electrical potential data suggest that N100 may well reflect the activity of more than one source. This is confirmed by a study (32) in which the amplitudes of N100m and the vertex-recorded N100 were compared as the interstimulus interval (ISI) was increased. It was found that N100 and N100m do not grow at the same rates with ISI. This is but one example of how the neuromagnetic and electrical measures may complement each other, since the former is primarily sensitive to sources that are tangential to the scalp while the latter is sensitive to both tangential and to radial sources. Moreover, sources at distant cerebral positions may well contribute to electrical potential differences, while this is far less likely to happen in magnetic recordings (33). However, one caveat is in order. Hari et al. measured N100 using a vertex electrode which was affected by electrical activity originating in both hemispheres. Her complementary magnetic measurements were made over the left hemisphere in all subjects. It is possible that there was a asymmetry in the effect of ISI on N100, with it saturating after longer ISIs in the

right hemisphere than in the left. If this hypothesis is confirmed, it could reduce the need to postulate sources that affect N100 but are silent with regard to their effect on N100m.

Assuming that the sources contributing to N100 are not identical to those that contribute to N100m, it is also interesting that the sources of N100m and of P200m are not in precisely the same place on the auditory cortex (34). These components may differ functionally as well, but this has yet to be determined.

Arthur et al. (36) examined the field patterns associated with P100m, N100m, P200m and SF where the stimuli were 500-ms tone bursts of 250 and 2500 Hz. The sources of all of these components for a given subject lie within a spherical volume of 2 cm radius in the vicinity of primary auditory cortex. Pelizzone et al. (35) found that the sources of the N100m and P200m components for tone bursts having an abrupt onset were not selectively affected by frequency. However, Hoke et al. report tonotopicity in the locations of sources of N100m (this conference).

It is highly relevant to the purpose of this conference that some components of the auditory response are strongly affected by attention or other cognitive states of the subject. In particular, the classic electrical N100 and P200 show strong effects of selective attention, and these and other components of the ERP or ERF cannot be fully understood if the subject passively listens to tones or looks at changing visual displays. We now turn to some of these effects of attention.

5. Modulation of Activity of the Auditory Cortex by Attention

5.1. Background

Various filter theories of attention based on behavioral experiments, e.g., dichotic listening tasks, are well known (51, 37, 38, 39). The earliest of these theories resemble the so-called single resource models of human information processing while later thinkers suggest that there may be multiple resources ("channels"), and activity attended to in one of these channels need not result in the depletion of the capacity to attend to activity drawing upon other independent pools of resources (cf 53).

While a detailed discussion of the concept of "channels" transcends the scope of this paper, it should be pointed out that this concept is often used quite ambiguously. Thus, for example, a channel has been defined according to the sensory modality involved, the ear to which a message is delivered, the direction from which a message appears to come, and other physical features that make a particular message distinctive. These definitions of channels were usually made on an ad hoc basis. The issue was further complicated by the finding that differences in semantic content of two concurrent messages could well affect the subjects' ability to attend to one of them selectively. Thus, physical features alone need not govern the ability to keep attention focussed on one of several concurrently ongoing events (39, 40, 41).

The notion of an early filter (prior to perception) can be avoided by by assuming that ignored messages are evaluated, but if the message ingause the competing message is being shadowed. When a forgotten (42). Thus, the filtering is due to the limited capacity of the motor system which is active during shadowing. Hence, the "filter" is not active at a level prior to conscious perception. This idea is also consistent with the observation that ignored messages may be processed to a level higher than that of simple physical features without postulating an early attenuation of signals having particular physical characteristics (41).

Liberman's (54) motor theory implicated the speech producing apparatus in the perception of speech. Thus, it bears some resemblance to the theory of Deutsch and Deutsch (42). Most current thinkers reject the idea that perception depends upon overt motor activity, and some suggested that it does depend upon the calling up of programs for motor responses even if these are never actually executed (55,56). Similar considerations led others (57,58,59,60) to assume an active participation by the perceiver in which neural programs of motor action may be coupled with active "covert" testing of hypotheses as to the future course of a message. This "testing" is an essential element of attention. Neisser's analysis-by-synthesis" theory adopts the latter intepretation of attention, and does not consider such a process to belong in the category of filter theories. Even so, this aproach allows for analysis of both shadowed and unshadowed messages up to the phonemic level during a dichotic listening task, but only the shadowed message is being matched against a "speech plan" or schema (cf. 59). Only then is it encoded into verbal structures, which are stored and remembered. The ignored message is forgotten because it is

never encoded. The attended message is perceived because it is responded to.

Thus, we are left with three general approaches to attention. One is employs the concept of a filter, but it places the filter prior to conscious awareness. The second is also a filter theory, but it postulates selection based upon a limited capacity to respond to a message after it is perceived. Finally, the third approach is that of identifying attention with an ongoing process of matching a message against expectations. Can measures of the electrical activity of the brain cast any light on these issues?

The event related potential (ERP) is useful in determining if there is any change in the electrical activity of the brain that reflects an attenuation of physiological events related to an ignored message. Such an attenuation, which could result from a reduction in neural activity at a particular place, or a shift in the position of the neural activity in the brain, could represent the action of a filtering mechanism. By the same token, the enhancement of a physiological event associated with a stimulus to which attention is being paid may represent the action of an analyzing mechanism tuned to respond preferentially to that particular event. What is more, subject to some caveats to be reviewed later, the timing of either enhancement or attenuation related to attention may indicate the levels at which such filtering operations occur.

It was suggested that selective attention effectively gates the input from the ignored stimulus at the level of the receptor organ itself (44). However, this turned out to be incorrect for a number of reasons (47, 43).

Even so, attenuation of activity due to selective attention does occur early, as in a dichotic listening experiment by Hillyard, Hink, Schwent and Picton (45) who found that the amplitude of the N100 component of the ERP (peak latency 80-110 msec after stimulus onset but beginning to show an effect about 50 msec after stimulus onset) was larger than the corresponding component of the averaged response to the ignored stimuli. In subsequent studies (62,63,64) it was found that the magnitude of this effect of attention on N100 was greater when stimuli were presented at rapid rates and also when the stimuli were difficult to detect (49). This suggested that the difference in amplitude of N100 with attention reflected the selection or rejection of stimuli on the basis of their channel (ear) of entry. It was also found found that either pitch cues or spatial location cues alone provided sufficient "channel separation" (49, p. 320) to elicit changes in the N100 component as attention is shifted among channels.

Hillyard et al. (45) also subtracted the ERPs associated with the ignored stimuli from those associated with the attended stimuli. This resulted in the generation of the so-called "negativity difference wave" (Nd) since it revealed a consistent negative shift in the baseline of the ERP beginning about 70 msec after stimulus onset (prior to the peak of N100) and extended for as long as 500 msec. The authors inferred that Nd is also a sign of early selection related to stimulus set (Broadbent, 40).

Hansen and Hillyard (65) suggested that Nd is largely endogenous in origin (also see Hillyard and Munte, 66), and while this may be correct, we shall not be concerned with Nd here. Rather, we shall focus on N100 and whether or not it in particular is modulated by attention. Naatanen and Mitchie (67) proposed that the modulation of the N100 does not reflect changes in the activity of an N100 generator located in primary sensory cortex, but involved the superposition of a temporally overlapping "endogenous" component on N100. This endogenous component could coincide with the early phase of Nd. Hansen and Hillyard (65) proposed that this early portion of Nd reflects a modulation of the N100 generator, corresponding to the activation of a filtering mechanism as described in the Broadbent/Treisman model. Alternatives have also been proposed, e.g., Picton (68) suggested that endogenous activity in the frontal cortex may well contribute to the effect of attention on the scalp-detected N100.

One of the reasons for uncertainty as to the source or sources of the N100 phenomenon stems from the fact that most ERP studies use relatively few electrodes. As pointed out above, this makes it virtually impossible to determine the properties of even a single current dipole source of an observed scalp potential. The problem is compounded further when one attempts to characterize more than one source of an observed field or potential. Clearly, the usual string of a few midline electrodes is simply incapable of leading to unambiguous conclusions vise vis the numbers of sources underlying observed potentials. Hence, we must regard prior ERP studies that focus on effects of selective attention on N100 (and even on Nd) as being largely inconclusive about the numbers and locations of sources contributing to N100.

Before turning to the experimental portions of this paper, it is worth noting that little effort has been devoted to the study of effects of attention on P200. Early studies (c.f. Spong Haider and Lindsley, 46) described effects of attention on both N100 and P200. Despite flaws in such studies (47,48), it does appear that P200 is affected by attention in the same way as is N100. Thus, a secondary objective of this paper is to determine how P200m is affected by selective listening.

5.2. Methods

In an experiment conducted with S. Curtis and S.J. Williamson we made use of a dichotic listening task which, in certain respects, was similar to that employed by Hillyard et al. (45).

The acoustic stimuli were tone bursts of either 1000 Hz or 1050 Hz, presented to one ear, and tone bursts of 3000 Hz or 3050 Hz presented to the other ear. The lowest frequency tone bursts had a repetition rate of 3/sec per sec, while those of higher pitch had a repetition rate of 3.5/sec. The duration of each tone burst was 100 msec, and they were separated by periods of silence.

The two trains of tone bursts were applied separately to the two ears. Thus, one ear received tones of either 1050 or 1000 Hz, while the other ear received tones of either 3050 or 3000 Hz. Prior to the beginning of each session the subject listened to the two series of stimuli and instructed the experimenter to adjust the loudness of one until it appeared to match that of the other. Except in the case of one control experiment, in which the loudness of one ear's stimulus was reduced by 20 dB, the intensities of both stimuli were at an approximate level of 70 dB SPL.

The 1000 and 1050 Hz bursts had equal probabilities of occurrence, as did the bursts at 3000 and 3050 Hz. However, each random sequence had a finite length and was then repeated. The average length of such a sequence was about 30 tone bursts. The subject was instructed to listen one of these two sequences and determine how many tone bursts occurred before the entire sequence was repeated. Thus, while attending to the 3/sec stimulus, the subject ignored the 3.5/sec stimulus, and vice versa. After the run the subject was asked to tell the experimenter the total number of high and low pitch tones in the repeating pattern. Formal data collection did not begin until the subject was able to perform this task with an accuracy approaching 95%. On the next run the subject was told to switch his attention to the previously ignored ear. Thus, the stimulus from one run to the next was essentially the same, except that the instruction to attend to one ear or the other was varied. Introspective reports by the subjects and by the experimenters who listened to the stimuli suggested that attention was sharply focussed on the train of stimuli that was being followed to determine the length of its pattern, while the listener was completely unaware of the pattern of the ignored stimulus. The experience was not unlike that of shadowing a spoken message presented to one ear while ignoring a message presented to the other ear during the classic dichotic listening task.

The activity of the brain was monitored on only one side of the head during a run. Thus, for example, the subject lay on his left side with the 3/sec stimulus presented to his left ear and the 3.5/sec stimulus to his right ear. The magnetic sensing system was positioned over the right side of the subject's head where it was kept while the subject attended to the stimulus to the left ear, and also when he ignored that stimulus and attended instead to the stimulus to the right ear. The sensors were then moved to another position on the right side of the head and the entire procedure repeated (using independently selected pseudorandom sequences) several times. The 3/sec stimulus was always presented to the ear contralateral to the side of the head being examined. Then the subject was moved so that the sensors could be placed over the left side of the head where the procedure was once again repeated many times, with attention deployed first to one ear and then to the other. Thus, for each position of the sensors there were two conditions: attend 3/sec and attend 3.5/sec. Two to six runs were recorded at each position, with the larger number of runs conducted with the sensors placed at locations over the scalp that provided the strongest responses of the brain.

In an additional condition, subjects were presented with the 1000 Hz tone bursts and the ISI was increased and made to vary at random from 1000 to 1500 msec, and the subject was instructed to listen passively to the tone bursts. This permitted the collection of classic transient ERFs so that we could check on whether or not known components in the ERF (N100m and P200m in particular) corresponded to deflections in the waveforms of the responses of the main experiment. This was done to insure that the standard transient N100-P200 complex had the same source as did the sources of the peaks occurring at about the same times in the quasi-steady state conditions of our experiment. It turned out that we could find no significant

differences in the locations of the sources of these components, whether associated with transient stimuli or those presented with short ISIs.

Also, the stimuli were made markedly different in loudness, with one ear's stimulus attenuated 20 dB below the level at which it appeared to match the other stimulus in loudness. Then the subject attended to either the louder or softer of the two stimuli to determine if any of the effects to be reported below were possibly due to uncontrolled differences in loudness of the stimuli. The results obtained here were not essentially different from those of our main experiment, and we had to conclude that apparent differences in loudness could not account for the phenomena to be described below.

Finally, the two trains of tone bursts were applied to one ear piece of the headset used to present the stimuli. This required the subject to follow one of the two trains when both of them were presented to but one ear. In this case pitch alone was the cue used by the subject to keep the two trains separated in attention.

Since the repetition rates of 3/sec and 3.5/sec are not integer multiples of each other, it is only the 6th harmonic of the latter rate and the 7th of the former that are coherent. Hence, activity of the brain at 3 Hz (the fundamental frequency component of the 3/sec repetition rate) or its higher harmonics up to the 7th would be due strictly to the 3/sec stimulus, while activity at 3.5 Hz and its next five harmonics would be due to the 3.5/sec stimulus. This makes it possible to detect average responses due to one stimulus without those responses being contaminated by responses to some other concurrently presented stimulus.

Average transient responses from all 5 channels were computed and the responses were found to contain prominent peaks that apparently correspond to the classic N100 and P200 components of the ERP. The amplitudes of these peaks in femtotesla (fT) were plotted as a function of position on the scalp. A computer program based on a program known as GRID 3 was employed to fit the data obtained at many different positions about the scalp by contours representing fields of equal strength. These contour plots were made in rectangular coordinates in which distance between the ear canal and the outer canthus of the eye is represented along the X-axis, and vertical distance from this line toward the midline is represented along the Y-axis. The interpolation and smoothing routines incorporated in the program made it possible to estimate the coordinates associated with the two field extrema in isofield contour plots of data representing the amplitudes of the fields occurring at the peaks of N100m and of P200m. Knowing these coordinates and the amplitudes at these coordinates, we then measured the actual distances between them on the scalps of our subjects. We also measured the diameters of their heads in several directions, and computed a mean radius for each of them. This information sufficed for us to define the characteristics of the equivalent current dipole source that would produce the best fitting dipolar field pattern. These characteristics include the location of the tangential current dipole and its orientation as well as its strength. This procedure was used with the transient ERF data, and also with the responses related to the 3/sec and 3.5/sec repetition rate stimuli which also contained two peaks that correspond to what we have labeled N100m and P200m. In addition, the amplitudes of the Fourier components of the average responses were also computed to determine if harmonics higher that the second or third contributed to any effect of selective attention.

Most of the useful information in the isofield contour maps is in the vicinity of the field extrema. Thus, for example, shifts in the locations of these extrema signify changes in the position and orientation of the underlying source. Data collected in the vicinity of the extrema readily indicate such changes. If the position or orientation of the source in the tangential plane does not change significantly, then changes in the magnitudes of the extrema signify a change in the amount of underlying neural activity. Since we obtained many independent measurements of the field in the vicinity of the extrema, it was possible to examine the statistical significance of the effects of various treatments on the strengths of the fields and, by inference, on the amount of underlying neural activity. Since some of the measurements were repetitions of prior measurements taken at the same positions, they were averaged to give us a single measurement per position. In all, we used 5 measurements from the vicinities of each of the observed extrema over both hemispheres, making a total of 20 measurements per subject in an ANOVA. This enabled us to examine the effects of instruction (to attend or ignore), the repetition rates of the stimuli, the components of the response (N100m and P200m), the channels used to detect the fields (position), the hemisphere over which the measurements were taken, and whether the sensors were positioned over the anterior or posterior field extrema.

5.3. Results

Responses to stimuli presented at a 3/sec repetition rate and recorded from the left hemisphere of one of the three subjects are shown in Figure 2. The dark waveforms on the left are responses obtained while the subject attended to the stimuli, while the dashed lines were responses obtained at the same positions at the scalp but when the stimuli were being ignored. On the right side of the figure are reponses obtained using the 3.5/sec repetition rate stimulus. Here the dark waveforms represent responses to ignored stimuli, and the dashed lines responses to stimuli to which attention was being paid. The responses obtained during attention are clearly larger in amplitude, and contain two pronounced peaks, one at about 100 msec and the other about 225 msec after stimulus onset.

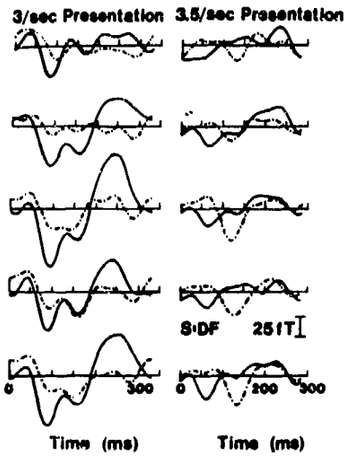

Figure 2. Typical responses to tonal stimuli (see text) presented at repetition rates of 3/sec and 3.5/sec. The dark lines on the left are average responses to stimuli to which attention was paid, while the dashed lines are responses to ignored stimuli. On the right the dark lines represent average responses to ignored stimuli. The five tracings are responses as detected simultaneously by the five sensors in the multichannel instrument.

The first peak in the waveforms of Figure 2 occurs at about the same times as does the N100m component of the the transient AEF. However, the second peak occurs about 25 to 50 msec earlier than the P200m. Because of this as well as the difference in ISI between the periodically presented stimuli of this experiment and that used in the typical transient response study, the peaks found in this experiment may not have the same sources as do the more frequently studied N100m and P200m. Therefore, as already indicated, we recorded transient AEFs from two of our subjects. The subjects were given no special instructions except that they were to simply listen to the tone bursts. Comparisons of the computed source locations of the components of the transient and quasi-steady state responses indicated that their sources were in the same positions.

An isofield contour plot made for N100m obtained while one subject (DS) was attending to the 3/sec stimulus is shown in Figure 3. A similar plot, based on data obtained when the same subject was ignoring the stimuli is shown in Figure 4. Note that the amplitudes at the extrema are smaller than those obtained when the subject was attending to the stimuli. It is clear that the sources of the responses to the ignored stimuli were in the same locations as the sources of the responses to the stimuli to which attention was being paid.

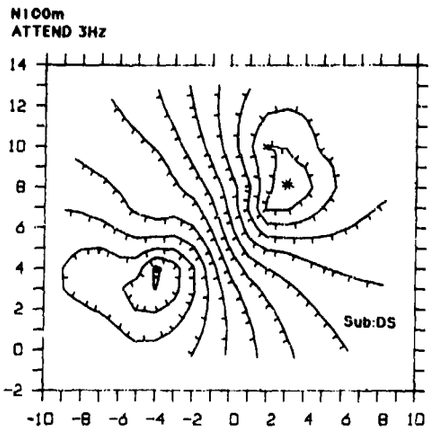

Figure 3. Isofield contours representing the way in which the amplitude of the radial field (about 100 msec after stimulus onset) varies with position about the side of the head of one subject attending to a 3/sec stimulus. This is a typical dipolar pattern and the position, orientation and depth of the equivalent current dipole source can be computed from these data.

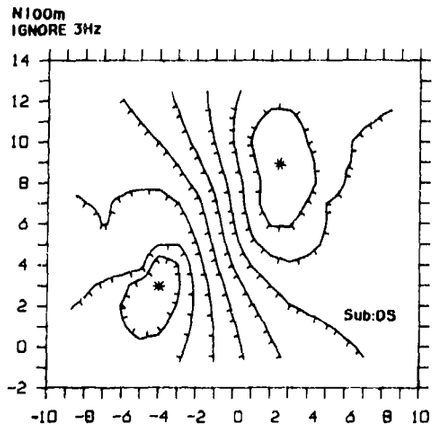

Figure 4. Isofield contours similar to those shown in Figure 3, except that the stimulus train was being ignored. The fact that the density of contours is less than that in Figure 3 is due to the fact that the fields were weaker. Superimposing the two patterns shows that the position of the source did not change significantly.

The ANOVA was performed using the field amplitudes measured at 20 different positions outside the scalps of all 3 subjects. The positions were those at which responses significantly greater than background noise were measured. Since the ANOVA included a test for the significance of differences in the amplitudes of N100m and P200m, two different amplitudes at each of the 20 positions furnished the data for analysis.

No significant differences were found between the amplitudes of N100m and P200m. Moreover, we found no consistent hemispheric differences. There were significant differences among the amplitudes of the components measured at different positions, but this is to be expected as the different positions were at different distances from the field extrema. The most important finding was that the effect of instruction to attend to a stimulus (and, by implication, ignore the alternative stimulus) was significant with $p = .028$.

It is noteworthy that all of the variance due to instruction was due to the first two harmonics of the Fourier analyzed responses. This may have some significance for bandwidth selection in future experiments.

In addition to comparing the field strengths obtained when the subject paid attention to the stimuli with those obtained when the stimuli were ignored, the positions of their equivalent dipole sources were computed from the locations of the extrema on the subjects' scalps. In all cases the sources of both N100m and P200m were located in or near the auditory cortex. This was consistent with the location of the point on the scalp that bisected the field extrema, and also with the depths of the sources.

Let us consider the locations and strengths of the sources of N100m and of P200m when attention was paid to the stimulus. For the 3/sec stimulus, the average depth of N100m (for 3 subjects) in the left hemisphere was 2.8 cm. The average current dipole moments for these same subjects was 3.1 nA-m. The average depth of the source of P200m for the same subjects was 3 cm, and the current dipole moment was 5.2 nA-m. The corresponding values for the same sources when the stimuli were ignored were 2.8 cm deep for N100m and 2.9 cm for P200m. The dipole moment was about 2.5 nA-m. Thus, the source strength was weaker for responses to ignored stimuli, and not just field strength. Similar results were obtained for the right hemisphere. The main point is that source location did not change, and source strength was affected by instruction. This has never been shown for the corresponding components of the ERP, where changes in potential could be due equally to changes in source location or orientation as well as amount of neural activity. Of course, we cannot determine from these data if the relative enhancement of activity during attention is due to the recruitment of more neurons, or if it is due to an increase in the amount of activity in a fixed population of neurons.

Another implication of these results is that no nearby additional source was activated during attention, for otherwise the apparent position or orientation of the equivalent current dipole source would have changed. Moreover, measurements were taken from positions that sampled most of the scalp, and there was no indication at all of the presence of additional sources.

The main conclusion to be drawn from these results is that activity originating in the auditory cortex is modulated by attention. There is no sign at all of the presence of other non-specific sources that contribute to the auditory N100m and P200m. While we cannot rule out the possibility that other non-specific sources may contribute to the effect of attention on the electrical N100 and P200, the magnitude of our effect suggests that such additional sources would add very little to the modality specific effect of attention. Moreover, we needn't postulate an effect of Nd on N100m to account for our results. The bandpass of our experiment precludes any addition of slow activity from another source to faster activity arising in the auditory cortex.

In view of other studies cited above, it is clear that N100m and P200m originate in the auditory cortex, and their sources are quite close to the primary receiving area. The fact that tissue in such close proximity to regions of very early cortical processing of acoustic information is affected by attention provides us with an important problem for future consideration. This result suggests at least two possible hypotheses. The first of these is that the "filter" is located prior to conscious perception, and is activated when a task is performed with a set to select from among different stimuli. The second possibility is that the selection is first completed at some much later stage of processing, and feedback from this stage results in attenuation (or enhancement). This leads to the prediction that if responses could be recovered without signal averaging, then the first responses to ignored stimuli would be as strong as those to attended stimuli. However, as further

stimuli are provided, responses to those that are ignored will become increasingly attenuated. Hence, we cannot completely rule out a theory which places the filtering operation at some later stage. Our new magnetically shielded rooms will make it possible to obtain responses with very little signal averaging. Hence, it should be possible to test this hypothesis. Even so, on the average, the relatively attenuated response to ignored stimuli is reflected in activity of the auditory cortex. It is also important to note that P200m displays the same type of response change as does N100m. It remains a problem as to whether or not the separated source of P200m has some specialized functions of its own.

6. Conclusion

Experiments of the type described above do not provide final answers, but they show promise of our ultimately discovering mechanisms that underly cognitive processes like selective attention. We have been pursuing work in visual atention, and while it is too early to describe the results here, it is apparent that the effects are somewhat different than they are in auditory attention. Moreover, it is now seems that attentional effects are modality-specific, and are not related to any currently observable general or non-specific neural center. This is probably not true of other endogenous components of ERPs or of ERFs. Also, we find that we can adapt some of our procedures to the study of the properties of different kinds of memory, and this will occupy much of our time in the immediate future. However, the main task with which we have yet to deal is that of relating the processes we are just beginning to learn how to study to the predicition of human performance. This is the enticing challenge of the future.

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CEEG DYNAMIC BRAIN MAPPING, A NEW METHOD TO EVALUATE BRAIN FUNCTION IN DIFFERENT PSYCHOLOGICAL AND DRUG CONDITIONS

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Abstract

The electroencephalogram (EEG), discovered more than half a century ago, is still the only non-invasive, simple and objective method to continuously and repetitively study brain function, and has recently gained new significance since quantification by microprocessors was developed. Quantification of single-lead EEG proved to be of significant value in psychotropic drug development. Discoveries of the psychotropic properties of drugs and the determination of the bioavailability of CNS-active compounds validated this method. They demonstrated that the brain's bioelectrical activity, even recorded in only one area of the brain, can represent brain function and is closely associated with human behavior. A newly-developed brain function monitoring system using multi-lead, broad frequency spectrum computer-analyzed EEG (CEEG) with Dynamic Brain Mapping seems to be a very promising methodology to study human behavior and to monitor its changes due to external and internal factors.

Introduction

In spite of the fact that the scalp-recorded EEG is still the only simple, non-invasive method to continuously monitor human brain function and, therefore, can offer an enormous amount of information, it is grossly underutilized. Undiagnosed brain dysfunction, lacking either serious neurological symptoms or life-threatening course (lapses in consciousness, subnarcoleptic attacks, uncontrollable episodes of drowsiness or sleepiness), can still pose a grave risk to the public if it occurs in individuals in certain professions. Some are obvious, such as pilots, public transportation drivers and conductors, air traffic controllers, nuclear reactor technicians and operators of heavy machinery or radar. In addition, consider the risk if an executive, politicians, public servants or even law enforcement officials suffer from memory deficits, lack of attention, concentration and/or impaired judgement.

These types of central nervous system (CNS) dysfunctions can occur in abnormal clinical conditions or as a result of metabolic changes (hypoglycemia or hypoxia), or simply due to certain physiological conditions. They may also be caused or accentuated by consumption of alcohol, illicit drugs, CNS-effective drugs used to treat certain psychiatric conditions (depression, anxiety, insomnia, etc.) and even medical conditions (antihypertensive drugs, anti-allergic drugs, or simple cough or cold medicines). The serial monitoring of brain function can provide significant insight about the patient's behavior in all of these conditions so that a serious incident might be averted.

However, brain function evaluation using neurophysiology like EEG, and Evoked Potential (EP), and neuropsychology (psychometric and cognitive) testing which could provide life-saving information, are not performed systematically, routinely, and repetitively, even in accident-prone persons who perform critical jobs. One of the major excuses for the underutilization of brain function examinations is that they are time-consuming or impractical, lacking objectivity and offering results with a high degree of variability.

In order to objectively evaluate brain function, we have been utilizing computer-analysis of EEG (CEEG™) for more than two decades (1,2,3,4). The results are already impressive, especially with regard to determination of effects of drugs on the CNS. However, the early computer systems and procedures that we developed were extremely costly, complicated, and could analyze only one area of the brain (single occipital-lead analysis) at a time.

Thanks to improved electronic and computer technology, we have now developed a sophisticated system to record and analyze EEG from 19 leads simultaneously (5). This state-of-the-art high-technology hardware/software system, which is a compact yet more powerful version of our previous systems, has a significantly improved signal/noise ratio, is practical, fast, accurate, and extremely cost-effective. The outputs include a standard EEG strip chart, report, raw data for each epoch, and 27 different color topographic Dynamic Brain Maps for each 2.5, 5, 10 or 20 second epoch and even entire sample means. These maps can be displayed either statically (the mean of an entire EEG run) or continuously by a dynamic, moving display of each single epoch to study the dynamic processes of brain function.

In this report, the application of CEEG Dynamic Brain Mapping in different psychological conditions and before and after intake of a variety of drugs will be presented.

Methods of Brain Function Evaluation:

HZI's Brain Function Monitoring (BFM) System™ includes three objective brain function tests utilizing the same basic high-technology hardware. These are: CEEG and Dynamic Brain Mapping, EP and topographic brain mapping, and interactive neuropsychological tests (Figure 1).

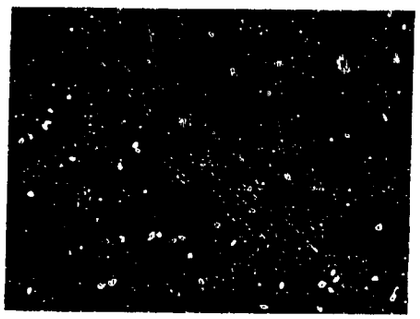

Fig. 1

Fig. 2

In this presentation, we will limit ourselves to the CEEG and Dynamic Brain Mapping components of the BFM System. For the neuropsychological tests and EP, the reader is referred to our previous publication (5).

Hardware:
CEEG analysis and Dynamic Brain Mapping hardware includes (Figure 2):

1. IBM-PC/AT with 512K memory (or, most recently, the IBM-AT Model 80 with Intel 80386 chip) (no clones) and peripheral equipment including printer, A-D board and interface, analog RGB monitor, high-resolution color board;
2. HZI-QPEEG interface for filtering, calibration, and system diagnostics;
3. Standard 8-16 channel EEG or polygraph equipment;
4. An instant hard copy system.

The same hardware is used for each of the different CEEG software programs.

For the Evoked Potential (EP), in addition to the hardware outlined above, either a polygraph or special amplifiers, a stimulus-generator, and a stimulus trigger-systems unit are required.

For neuropsychological testing, a seperate station with an additional microprocessor are interfaced with the IBM central microcomputer.

Software:
More than 200 CEEG software packages, developed over the past 20 years, were regrouped into four major software packages:

1. Power Spectrum Analysis:
This software performs 4-16 channel on-line real-time Fast Fourier Transformation (FFT) analysis in up to 20 distinct frequency bands and various types of Dynamic Brain Mapping. EEG analysis is integrated into a data base package, creating enormous flexibility to modify sample size, define variables, and change montage structure. Mean and sigma values of FFT data for each channel after every recording are available for statistical evaluation. This type of analysis is commonly applied in both human and animal research settings.

2. A Special Time-Domain Analysis for Clinical EEG:
This analysis simulates the "reading" of an electroencephalographer for clinical purposes. It includes artifacting procedures, and an automatically generated clinical report. It includes 4 standard frequency bands (alpha, theta, delta, beta) in addition to average frequency and average absolute amplitude and is compatible for basic electroencephalographic interpretation.

3. CEEG Analysis Using Time-Domain Analysis or Power Spectrum, Simultaneously or Separately:
This also generates instant printed reports and Dynamic Brain Mapping based on 4 standard frequency bands (alpha, theta, delta, beta) but analyzes and stores EEG data for research purposes based on 20 different frequency bands. It offers great flexibility to modify the sample size, number of variables, frequency bands, or mapping and statistics. Two different artifacting capabilities (manual and automatic) are included. CEEG analysis software is integrated in a database and data management software package affording options for statistical evaluation of the data and graphic demonstration.

4. CEEG Analysis Using Separate or Simultaneous Time-Domain Analysis, Period Analysis And Power Spectrum Analysis:
This is based on our previously tested and validated psychopharmacology Quantitative Pharmaco-EEG (QPEEG) programs for drug development. It is integrated in database and data management packages and provides clinically useful data with instant printed reports and Dynamic Brain Mapping, and also sophisticated research outputs. Two simultaneous analyses with zero-cross and power spectrum or period analysis and power spectrum can be conducted. It is specifically designed for both QPEEG research and clinical settings to provide immediate information on drug effects, discrimination from placebo, time- and dose-related CNS effects, and CEEG profiles of different drug dosages in different areas of the brain.

Method of CEEG Investigations:
For the studies to be presented here, CEEG recordings were done from 19 leads selected according to the International 10-20 Electrode Placement System. The length of the EEG recordings was an average minimum of 10 minutes' artifact-free recording. From each unipolar and bipolar recordings, time samples (pre-drug and 1 hour, 2 hour, 3 hour, 4 hours, etc. post-drug recordings) were taken for QPEEG trials and bioavailability studies. To determine physiologically-induced changes in brain function such as drowsiness or blood sugar alterations, or to determine the onset and duration of CNS effects of antihistamines and analgesic drugs, CEEG recordings were conducted up to several hours continuously. To establish the acute effects of pain, acoustic stimuli or hypnosis, individual 5-second recording samples were used to correlate the CNS effects.

Material:
Groups of a minimum of 10-12 subjects (healthy or patient populations) were studied to test the CNS effects of psychotropic drugs. In these studies, both group-response and individual subject response were demonstrated.

Research Design:
Studies were conducted double-blind crossover with placebo and active controls.

Results:

CEEG Data Base:
Although in studying CEEG in different psychological and drug conditions, symptomatic and asymptomatic subjects are used as their own controls, a scientifically collected data base of healthy subjects with different age groups is still an important prerequisite to conduct scientifically reliable studies. Using both Power Spectrum and time-domain analyses over the past two decades, we developed a CEEG computer data base of more than 1100 healthy subjects and computer EEG (CEEG) profiles of 149 CNS effective drugs (9,10,11). Unfortunately the majority of the data collected were only from two EEG leads (right occipital to left ear and left occipital to right ear) because of the time-consuming procedure and expenses involved with our previous CEEG Analysis system.

In the past two and one-half years, using our newly-developed Brain Function Monitoring System, we have stored in our data base multi-lead (up to 19 leads according to the International 10-20 System) CEEG data of more than 700 healthy males and females and more than 2000 patients in the age range of 5-92 years. As Figure 2 illustrates, the delta activity ranges from 1.6 percent in the parietal leads and up to 5 percent in the anterior leads. The theta activity shows a steady decrease from the frontal (32 percent) to occipital (20 percent). The mean alpha activity ranges from 40 percent in the anterior up to 57 percent in the posterior area. The mean beta activity ranges from 19 to 22 percent. Thus, our preliminary data base values support well-known and published material concerning the increase of alpha activity from the anterior to posterior area, the lower percentage of alpha activity in the left hemisphere of the right-handed population, decreased theta activity from frontal to occipital leads and insignificant delta activity in healthy adults.

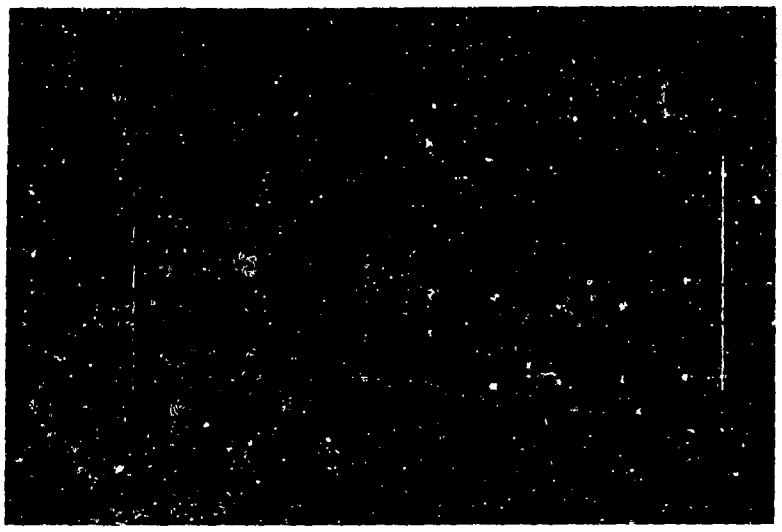

Figure 3

In contrast to the young healthy (male) population, the elderly patients (N= 87; age range 45-89 years) without significant clinical symptomology show significantly less alpha activity (a mean alpha range from 29 percent in the frontal left up to 38 percent in the occipital right) and the delta activity is significantly higher (7 percent in the right occipital up to 12 percent in the left frontal area (Figure 4). Also, theta activity is significantly higher in the elderly (mean of 8 leads in elderly 34 percent, in young males 26 percent).

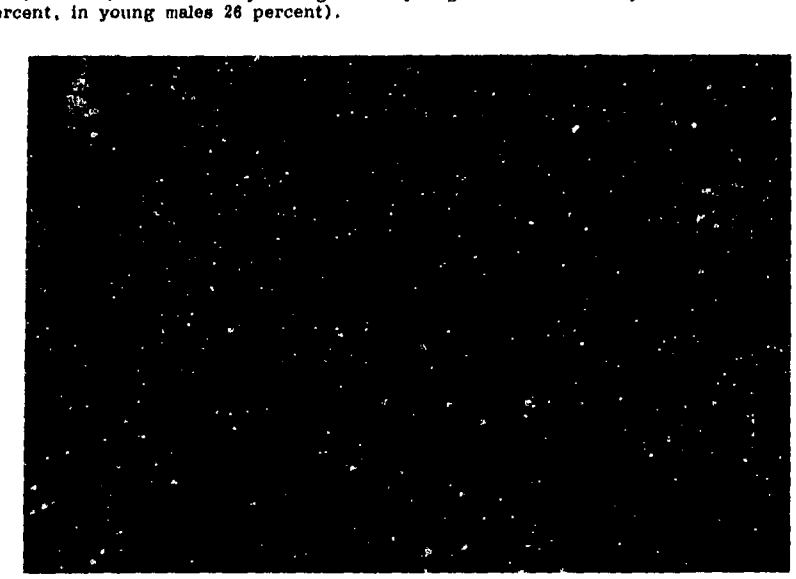

Figure 4

While collecting this data we incurred the following difficulties:

1. Definition of "Healthy" subjects particularly in elderly is very difficult. We have established a variety of physical findings and neuropsychiatric symptoms in so-called healthy asymptomatic patients.

2. Compared to visual ("eyeball") evaluation of EEG records, using time-domain analysis, CEEG shows more low voltage slow waves. By visual inspection electroencephalographers usually tend to ignore low voltage slowing as baseline sway, eye movement or eye lead artifacts. Our comparative studies between computer evaluation and two electroencephalographers' readings indicated that time domain analysis and electroencephalographers are more in agreement than the electroencephalographers and Power Spectrum Analysis.

CNS Effects of Psychotropics:

It is well-established that drugs which induce significant effects on human behavior (psychotropics) also exert significant effects on scalp-recorded human CEEGs, even after only one single oral dose has been administered (12).

It was further established that drugs with similar therapeutic effects (all antidepressants or antipsychotics or anxiolytics) exert similar changes on the CEEG (profiles) whereas drugs with different therapeutic properties (i.e. antidepressants versus antipsychotics) have different CEEG profiles (13,14,15) (Figure 5).

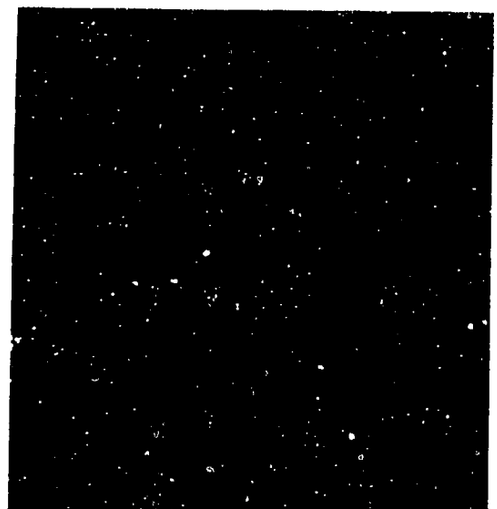

Figure 5

These findings, established using only single-lead CEEG analysis, were confirmed and expanded by the multi-lead CEEG Dynamic Brain Mapping method.

CEEG Brain Mapping of Anxiolytics:

In a recent study in a group of 10 asymptomatic male volunteers (aged 22-41 years, mean = 29.8 years), it was established that CEEG changes induced by Valium^{R} (diazepam) a potent anxiolytic, are characterized by an increase of fast beta activity as previously reported (16,17). No changes were seen after saline (as placebo). However, in contrast to previous findings, very early onset of CNS effects (two to three minutes after I.V. and 25 to 30 minutes after oral administration) was established in the anterior area of the brain (18). The peak of the CNS effects of Valium^{R} were established within 5 to 10 minutes after 5mg I.V.$_{R}$ and 35 to 40 minutes after 10mg oral administration. When the peak CNS effects after 5mg Valium^{R} I.V. on the individual subjects were studied, it was observed that three of the ten subjects did not show any significant CNS effects. The effects in three others were marked. In one subject a noticeable effect was detected only in one hemisphere, and in three others in only one quadrant of the brain. Whereas it was established that the subjects who showed extreme CEEG effects or no CNS effects have some behavioral correlations (pronounced sedation versus none), the clinical therapeutic meaning of these inter-individual differences has not yet been systematically investigated.

CEEG Dynamic Brain Mapping of Antidepressants:

The classic CEEG profiles of antidepressant drugs are characterized by decreased alpha and increased slow and fast activities, and are based on the recording and analysis of the CEEG in a single occipital lead (19,20). In a recent study (24 male subjects in the age range of 19-39 years, mean age = 27.8 years), we were able to demonstrate that Sinequan® (doxepin), a potent tricyclic antidepressant, has potent effects on all areas of the brain (21). As we previously predicted (22,23), the most characteristic CEEG activity useful as a "bio-assay" in bioavailability studies of antidepressants, was 7.5-13.0 Hz (alpha) activity. A marked decrease of alpha activity was observed within an hour after oral administration of 50mg and 100mg Sinequan and lasted up to six hours. According to a pharmacodynamic model (area under the curve), the CNS effects of Sinequan®, in both 50 and 100mg doses, were significantly different than those after administration of placebo (Figure 6).

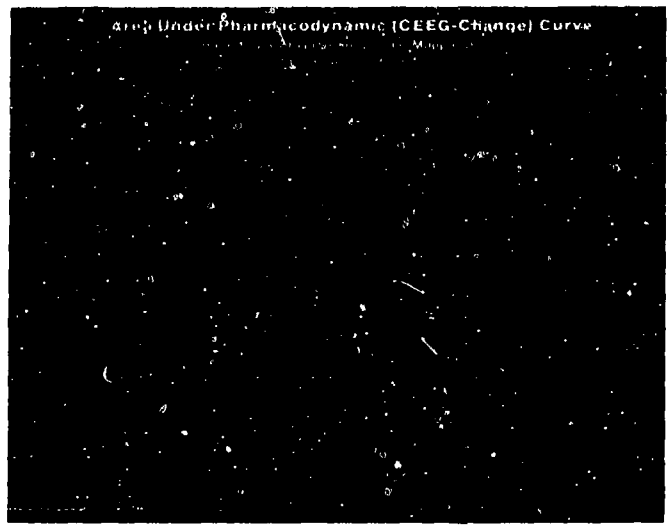

Figure 6

When we investigated the inter-individual differences during the peak time of the CNS effects, it was established that the majority of the subjects showed marked effects with 50mg Sinequan®. However, some subjects did not show any significant changes.

CEEG Dynamic Brain Mapping of Antipsychotics (Neuroleptics):

According to single-lead analysis, the CEEG profiles of neuroleptics were characterized by increased slow waves and decreased fast activity (14,15,24,25,26). However, in our previous studies, the CEEG profiles of different neuroleptics could not be established as consistently as anxiolytic and antidepressant drugs. Our CEEG Drug Data Base generally classified neuroleptics with lower similarity coefficients than those of antidepressant, anxiolytic of psychostimulant compounds (27,9,11).

In a recent study, the CNS effects of Navane® (thiothixene), a potent neuroleptic, were investigated in a group of 24 asymptomatic male volunteers (18-40 years of age, mean 27.2 years). The results of this extensive study clearly confirm the previous findings (22,23) that 1.3-3.5 Hz (delta) activity significantly increases after Navane and that this frequency band can be applied as pharmaco-dynamic "bio-assay" for this neuroleptic (28). The most surpising finding was that the CNS effects of Navane start within four hours but did not peak before 8 hours after oral administration of either 5 or 10mg single-doses (Figure 7).

This study was helpful to explain the inconsistant results of our previous CEEG studies with neuroleptics and their poorer classification relative to other therapeutic classes. In all previous investigations, we usually only conducted CEEG recordings up to six hours after oral administration. Thus, it is apparent that we did not evaluate CNS effects of neuroleptics during their peak. Another surprising result with Navane® was that its CNS effects start predominately in the occipital area of the brain and spread first to the temporal and later to the frontal regions. In addition, we noted a significant difference in the peak plasma level (+ 1.3 hours) versus peak CNS effects (8 hours) as defined by both CEEG and side effects ratings, which themselves were well-correlated.

Figure 7

In the present study, it was also established that there were significant inter-individual differences in CNS response. Although 8 subjects showed maximum effects, there were 5 subjects who showed very little or no CNS response.

CEEG Brain Mapping of "Anti-geriatric" Drugs:

According to our previous studies, drugs with psychostimulant properties induced significant effects on human brain function (14,26). CEEG profiles of psychostimulants are characterized by increased 7.5 to 13.0 Hz (alpha) activity. In recent studies, we further established that so-called cognitive-activating compounds (anti-geriatric drugs), either with or without vigilance-enhancing properties, also cause a marked increase in alpha activity in human EEG (7,29,30,31). In a study (12 symptomatic male patients with dysthymic disorder [DSM-III: 300.40] in the age range of 21-47 years, with a mean age of 32.5 years) the percentage of alpha activity is significantly increased and delta activity decreased after administration of a new cognitive-activator, oxiracetam, in comparison to placebo. It was found that the onset of CEEG effects of oxiracetam started after 3 hours and lasted at least 8 hours. Maximum effects were observed at 6-8 hours after oral drug administration.

The Effects of Physiological Changes in Brain Function Using Dynamic Brain Mapping Methods

The significant changes in brain function due to spontaneous drowsiness and natural sleep have been described extensively. Using single-lead CEEG, we demonstrated that the sleep stages can be classified objectively and all-night sleep recording can be quantatively evaluated (32,33,34). We also established that the CEEG sleep prints (35,36,37,38,39,40) are characteristic for each individual and can deviate significantly when someone suffers from sleep disturbances attributable to psychological or organic causes. Using multi-lead Dynamic Brain Mapping, we can now classify the sleep stages according to 16 areas of the brain.

The percentage distribution of different frequency bands in different sleep stages is shown in Figure 8. As expected, the delta activity increased in deep sleep stages (2 and 3). We observed that there is significant variance in the onset and the depth of the sleep stages in different areas of the brain. Based on previous experience with single-lead CEEG, we expect to have the most interesting results when we amass more data during all night sleep and particularly during dream periods. Our preliminary investigations suggest that the topographic quantification of the EEG patterns, particularily during REM periods, may provide us with significant correlations between behavior and EEG.

Figure 8

It is well-known that during hypoglycemic states slow waves increase and alpha activity decreases. Dynamic Brain Mapping enabled us to establish that the slowing is predominately in the anterior area of the brain in a hypoglycemic patient (5). Subsequent to glucose administration, dramatic change was observed in EEG with an increase of alpha and decrease of slowing. However, the glucose-induced normalization of CEEG lasted only approximately one hour and the abnormal pattern in the anterior brain area recurred.

CEEG Alterations During Different Psychophysiological Conditions:

In order to replicate the previous findings and possibly contribute additional information, a series of exploratory investigations were conducted in different psychophysiological conditions.

The following is a presentation of some of the preliminary results:

Dynamic Brain Mapping made it possible to note and observe CEEG changes throughout the brain both in the induction phase as well as during deep hypnosis.

As might be expected, we have also observed significant changes after pain stimuli (ice water). Slight but generalized slowing in the CEEG of a subject decreased significantly, and was replaced by an increase of alpha activity within five seconds when the right hand was in ice water. Within fifteen seconds after the painful stimulus was terminated, the alpha activity was again replaced by theta waves in all brain areas except in the occipital leads. When the left hand was put in the ice water, slow wave activity again disappeared and was replaced by alpha activity.

The Effects of Non-Psychotropic Drugs on Human Brain Function:

Whereas CEEG has already sufficiently illustrated changes in brain function due to the (pharmacological) effects of psychotropic drugs, even with only single-lead analysis, detection of CNS effects of substances without classic psychotropic properties was more difficult. Dynamic Brain Mapping was recently applied in some preliminary investigations with several non-psychotropic substances.

The existence of psychotropic properties of aspirin has been reported by several investigators. Two hours after oral administration of 1000mg aspirin, a decrease of alpha and even beta activity and increase of slow potentials was observed (Figure 9a).

Chlor-Trimeton^{R} (chlorpheniramine maleate), a sedative antihistamine, was also noted for having CNS effects but to a lesser degree than aspirin. According to our preliminary investigations using Dynamic Brain Mapping, it was possible to demonstrate a slight increase of slowing within one hour after 8 mg Chlor-Trimeton (Figure 9b).

Propranolol, a beta blocker with antihypertensive and antiarrythmia properties, was previously described as having significant CNS effects (41). Using Dynamic Brain Mapping, we demonstrated that 40mg propranolol induced significant increase of delta activity within one hour after administration (Figure 9c). After two hours, slowing effects of propanolol decreased significantly. Alpha activity reoccurred. There was even a "rebound" noted whereby the relative percentage of alpha activity was seen to increase beyond pre-administration levels.

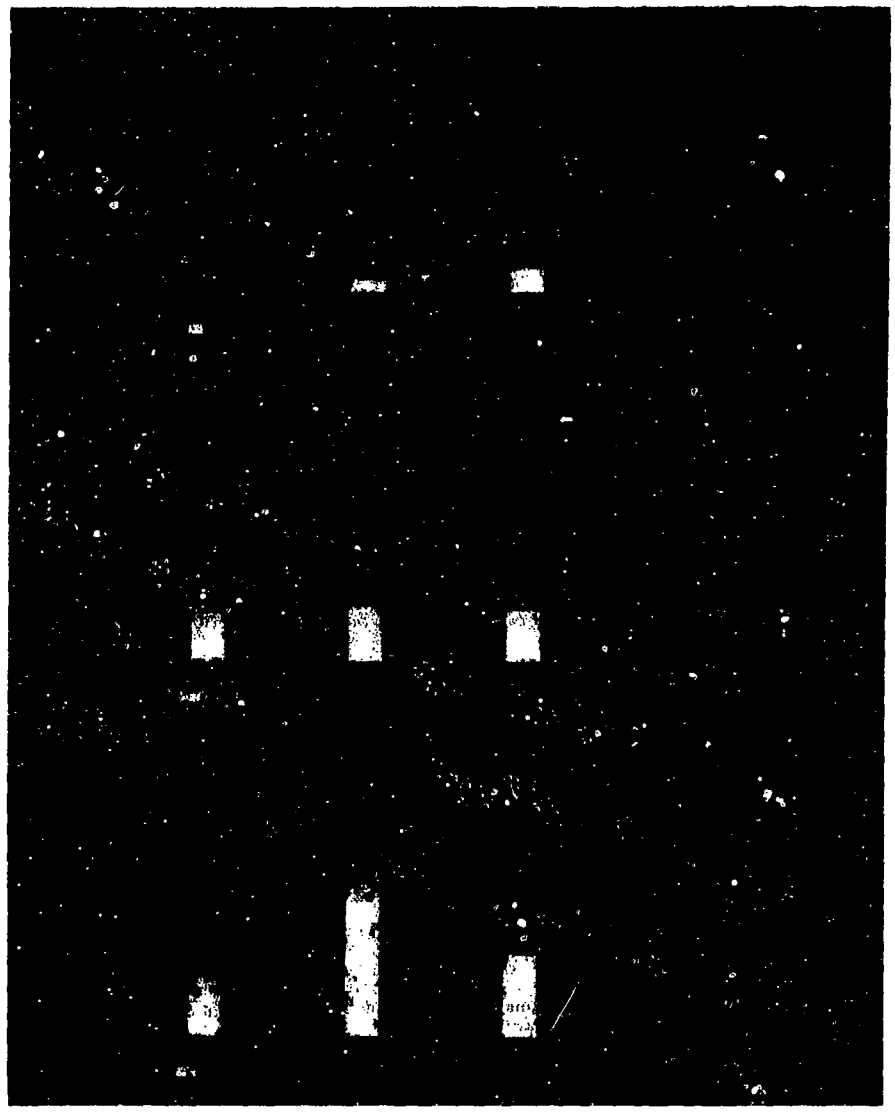

Figure 9

Summary and Conclusion:

Single-lead computer analysis of EEG demonstrated that this method is very unique in both its objectivity and efficiency to determine the existence of CNS effects of drugs and classify and predict their psychotropic properties. Furthermore and most importantly, that there are known correlations between behavior and EEG makes this method a clinically useful tool in psychiatry and psychology. The replicability of the findings through statistical analysis of the quantitative data are scientific validation of the reliability of the results. In spite of these and other findings, EEG has still not been accepted as a method of choice for most behavioral scientists or practicing clinicians.

Persons in professions such as air traffic controllers, nuclear reactor technicians, airplane pilots and others whose vigilance or coordination play a critical role in the performance of their duties, which in turn can have an impact on numerous people, are frequently examined with respect to physical condition. Yet it is rare and certainly not routine that these same individuals ever undergo any examinations that monitor the functioning of their brain. Even accident-prone persons who, according to literature, frequently exhibit periods of impaired alpha activity in EEG indicating temporary changes in vigilance or consciousness, could possibly be helped by such testing.

As this presentation has demonstrated, quantification of EEG can pinpoint a marked decrease of alpha and an increase of slow wave activity indicating impairment of vigilance. For example, when a person takes two aspirin for a headache, an antihistamine for allergies, or a beta blocker for hypertension, such changes in vigilance can take place. When the same person then consumes alcohol, the EEG changes are likely to be potentiated significantly resulting in disturbed psychomotor function, hazardous to both the person and their environment. Not only "classic" psychotropics but also hypnotics, antiepileptics, some antiallergics, antihypertensives, cough medicines, analgesics, and even some of the antiulcer drugs can induce significant vigilance, consciousness and psychomotor changes that are potentiated by alcohol, illicit drugs and tranquilisers. Quantified EEG can provide significant information on the status of brain function and its changes relative to a variety of internal and external conditions.

In spite of the challenges encountered by quantification of EEG from only one area of the brain (left or right occipital), due largely to the extrordinary cost and relatively limited storage and slow data processing capabilities, we were nonetheless able to generate substantial findings that demonstrate both the actual and potential utility of computer-analyzed EEG (CEEG) in behavior research, psychiatry and psychopharmacology:

1. CEEG can assist in the determination of the existence of organicity in psychotic patients. Thus, psychotropic drug treatment can be modified to achieve the best therapeutic effect (42,43).

2. There are close correlations between EEG and behavior. CEEG has been useful in the monitoring of psychotropic drug treatment and was applied during drug treatment with antipsychotics (44,45,46,47,48,49,50,51,52,53,54,55,56), anxiolytics (17,57,58,59,60), "antigeriatrics" (61,62,63,64,65), "anti-agressives" (66,67,68), and antidepressants (19). CEEG has also been used to monitor and determine the best combined drug treatment (69,70,71). CEEG has furthermore been applied to predict the therapeutic outcome before or during treatment of acute schizophrenics (72,73,74), (drug) therapy-resistant schizophrenics (75,76,77,78,79), depressive patients (80,81), and behaviorally disturbed children (82).

3. CEEG can be used as a pharmacodynamic parameter to determine bioavailability and bioequivalency, or lack thereof, of psychotropic drugs (22,23,28,101,129,130,131). We demonstrated that a generic psychotropic can have significantly different quantitative and qualitative effects on the CNS than its ethical competitor, although the peripheral blood levels may be acceptable according to conventional pharmacokinetic standards (129).

4. CEEG studies demonstrated that therapeutically equivalent psychotropics induce similar, even characteristic alterations in EEG patterns, called profiles, whereas therapeutically unequal compounds generate different CEEG profiles. CEEG has and still is being used in the development of antipsychotics (55,84,85,86,87,88,89,90), antidepressants (19,20,38,91, 92,93,94,95,96,97,98), anxiolytics (16,17,57,59,99,100,101,102,103), "antigeriatrics" (29,30,31,62,63,64,104,105,106), "anti-aggressives" (107,108), "antimanic" drugs (109,110), hypnotics (111,112) and cerebrovascular compounds (31,41,62,106,113).

   CEEG's utility in psychotropic drug development was indisputably validated by the discovery of the psychotropic properties of a series of compounds. Based solely on their CEEG profiles, the antidepressant properties of three compounds were discovered: mesterolone, a male hormone (114), estradiol valerate, a female hormone (115,116), and mianserin, an antihistamine (117,118). From among these, mianserin is now marketed as an antidepressant. Antianxiety properties of two substances were discovered: cyproterone acetate, an anti-androgen (116,120), and l-norgestrel, a progestational compound (121,122,123). "Antigeriatric" and even alcohol-blocking properties of lisuride, a potent antiserotonergic compound, were also predicted, again based solely on its CEEG profile (104,124,125,126,127,128).

5. CEEG can illustrate systematic and statistically significant effects of a variety of compounds not considered to be CNS-effective in the classic sense. Among others, strong anticholinergics (132), fenfluramine (133), antimigraine compounds (134), caffeine and Coca-Cola® (135), cinanserin (136), nicotine (137,138), beta-blockers (41), antihistamines and analgesics (Itil et al, In Press) exert noticeable effects on CEEG which have significant behavioral correlations.

6. Single dosages of psychotropic drugs induce significant alterations in CEEG within hours after administration. The bioavailability of a psychotropic is determinable according to its pharmacodynamic effects on the target organ, the brain. Therefore, a technique called Test-Dose was developed to assist in the "tailoring" of the most bioavailable, and thus effective, drug treatment for each individual patient. Preliminary studies in schizophrenia (79) and anxiety neurosis (60,83) suggest the value of CEEG to predict the right drug for the right patient.

Until recent years, the quantification of EEG using computers was a complicated, time-consuming and expensive procedure. The development of microprocessors and newer software for fast, economical computer analysis of EEG will significantly enhance its practical application in behavioral research and clinical settings. As we have shown here utilizing the CEEG Dynamic Brain Mapping system that we developed, quantification can be achieved on-line, real time, generating statistical results and vivid topographic maps with different types of analyses (Power Spectrum, Zero Crossing, time domain, etc.). The expenses of the hardware and software are minimal. The cost of the analysis per minute is a fraction of the cost of just a few years ago. Thanks to the power of hardware and availability of software packages, we have already been able to develop a significant data base to enhance the practical use of the system and to correlate with other data. Although it still operates using the old type of EEG machines, this newer technology can provide a variety of frequency spectra of the EEG in addition to classic alpha, beta, theta, and delta frequency bands. Thus, the recording and analysis of the wide spectrum of brain electrical activity sensitizes the standard four frequency band EEG.

Multi-lead, on-line, real-time computer analysis of EEG will further enhance the research and clinical applications of this method. Our preliminary investigations demonstrate multi-lead analysis is significantly superior to single-lead EEG quantification as, for example, in the studies of the bioavailability and bioequivalency of psychotropic drugs. We were able to discriminate between two seemingly similar anxiolytics, two different dosages of neuroleptics, and even the CNS effects of a generic from a brand-name psychotropic drug based even on just four frequency bands (129). We predict that multi-lead, multi-frequency quantification will assist both scientists as well as practitioners in understanding human behavior and its correlations with brain bioelectrical phenomena.

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DISCUSSION

JOHN, US: You mentioned the ability to map spikes, i.e., to find them. We have been doing that for some years with our spike detection algorithm. If we take a population of normal subjects and a population of epileptics from our data base and pass their EEGs through our spike detector, we find the same number of spikes in both. How do you know that you are detecting spikes and not the same kind of sharp event that would be displayed in a normal EEG? What is your criteria?

ERALP, US: We scan the EEG looking for any high voltage, fast activity that has a certain shape. When we graph the spike activity on the spike plot, we only do that to draw attention to the sample of EEG that has the spike, or so-called spike, so that someone can determine whether it is an artifact or a true spike. We do not indicate that it is definitely a spike; we only want to draw attention to it so that it can be further evaluated.

JOHN, US: Have you ever done that with a population of normals?

ERALP, US: We haven't done that; but I've noticed that in all of our records we have a certain threshold spike level which varies from 2 to 10 spikes per EEG sample, some of which is due to muscle artifact. Sometimes, certain high-frequency alpha activity is picked up with our methods. Above a certain threshold there is definitely abnormal spiking.

FOURTH GENERATION NEUROCOGNITIVE PATTERN ANALYSIS SYSTEM

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SUMMARY

We use the generic term "Neurocognitive Pattern (NCP) Analysis" to refer to procedures being developed to extract spatiotemporal neurocognitive patterns from the unrelated neuroelectric "noise" of the brain. Recordings with up to 64 scalp channels during highly controlled tasks are now routine in our laboratory, as is the extended signal processing sequence required to extract minute neurocognitive signals from gigabyte sets of single-trial data. More robust measures of the degree of "functional interdependency" between electrodes have been developed and applied to several visuomotor and high-load cognitive tasks. The results are clear-cut and consistent with prior neuropsychological models of the rapidly shifting cortical network accompanying expectancy, stimulus registration and feature extraction, response preparation and execution, and "updating" to feedback about response accuracy. These results suggest that it is possible to characterize "functional interdependencies" of event-related processing between local neural areas by measuring the wave congruence and lag time of appropriately preprocessed low-frequency brain waves. Determining the distributed functional network of specialized areas of the brain producing the observed patterns is a formidable problem which is being attacked on a number of fronts: use of magnetic resonance images to relate the scalp electrode positions to underlying brain structures; use of spatial filters to remove the "blurring" effect of conduction of brain potentials through skull and scalp; and incorporation of multichannel magnetoencephalogram data.

INTRODUCTION

Here we describe some of our developments in signal processing and computer science, and some of the results they have made possible.

The generic term "Neurocognitive Pattern Analysis" (NCP Analysis) describes the signal processing procedures we developed to extract task-related spatiotemporal patterns from the unrelated electrical activity of the brain. In the past 10 years, we have applied these procedures towards one underlying goal: to resolve spatially and temporally overlapping, task-related mass neural processes. Since such processes are complex, we are concerned with spatiotemporal task-related activity recorded by many (currently up to 64) scalp electrodes in many (currently about 25) time intervals spanning a 4-6 second period extending from before a cue, through stimulus and response, to presentation of feedback about performance accuracy. In order to quantify the similarity of activity and time dependencies between channels, we developed the method of event-related covariance (ERC).

NEUROPHYSIOLOGICAL BASIS OF MEASUREMENTS

We are investigating whether the summed dendritic activity of a large number of neurons in a structure is sensitive to the rapid changes in brain state associated with performance of complex behavioral tasks. Our studies in humans [1-8], and preliminary studies in monkeys indicate that appropriate measures of correlation or covariance between channels can reveal "functional interdependencies" between different parts of the brain that are rapidly changing (in fractions of a second) and are spatially specific. While the scalp functional interdependency patterns have been consistent with the known functional neuroanatomy of the cerebral cortex as determined by other lines of evidence, the source of these patterns is, in fact, unknown. The major thrust of our research program is to determine their sources.

Our method is based on prior studies suggesting that there is a consistent morphology and timing of macropotentials from functionally related brain regions. More than a decade ago, Elul [9] concluded that extracellularly recorded cortical macropotentials result from summation of dendritic activity of the synchronized portion of a neuronal population. Recently, Petsche et al [10] have demonstrated with their "micro-EEG" approach the importance of the close relation between macropotentials and local cortical architectonics. Although the extracellular field of potential (dependent as it is on the local neuronal topology) is a complex superposition of multiple closed and open fields, the far field projection at the scalp, to a first approximation, is only due to the resultant dipole of the active open fields [11-12].

The idea that functional relation between two populations is reflected in their co-synchronization (possibly with delay) was originally studied with behavioral conditioning experiments [13-15]. Dumenko [16] found in dogs that correlation between extracellular potentials of visual and motor cortices increased with conditioning to a visual stimulus and was highest at the time of the conditioned stimulus and response. The finding that high correlation was specific to particular regions of motor and visual cortices was similar to the observation of Bressler [17,18] that high correlation between olfactory bulb and cortex in rabbits was specific to particular regions of each. Measures of similarity between field potentials have also been applied to averaged event-related potentials. John et al. [19] measured the relatedness of waveforms recorded from different conditioned responses and demonstrated differential generalization of neural activity based on waveform similarity.

The theoretical framework for the study of field potentials comes from the pioneering work of Freeman [20], who discovered a systematic order between pulse probability of individual neurons and the phase of extracellular field potentials. Beyond this, his recent work has suggested that a fundamental property of macropotentials is the emergence of dynamic self-organizing order from chaotic macroscopic states, lasting from tens to hundreds of milliseconds [21]. In this context, we expect event-related potentials to reflect the emergence of a rapidly-shifting, widely distributed functional aggregate of neuronal populations.

These studies were important in laying the foundation for our current NCP Analysis. Using modern recording and signal processing technologies, our aim is to improve the spatial, temporal and behavioral specificity of event-related potential studies. In the spatial domain, we seek to expand the number of simultaneously recorded brain structures, on the scalp, as well as cortically and subcortically in neurosurgery patients and in monkeys. Temporally, our goal is to measure shifts in the timing of event-related potentials on the order of tens of milliseconds. Behaviorally, our approach is directly in line with that of single-neuron experimenters, with Mountcastle's [22] notion of a "combined experiment." Basically, we select a behavior believed on other grounds to involve the regions of the brain under study, and train a person, or animal, to produce that behavior. As with the recording of single neurons, the interpretation of our results depends on correlating neural activity with that behavior. Other lines of evidence are used to impute cause from correlation.

NEUROCOGNITIVE PATTERN ANALYSIS AND THE ADIEEG-IV ANALYSIS SYSTEM

First Generation

Thus far, there have been four generations of NCP analysis. The first measured background EEG spectral intensities while people performed complex tasks, such as arithmetic problems lasting up to one minute. Complex perceptuomotor and cognitive activities like these produce unique, spatially differentiated scalp EEG spectral patterns. These patterns had sufficient specificity to identify the type of tasks being performed [1-3]. These results agreed with previous reports of hemispheric lateralization of "spatial" and "linguistic" processing. But when the tasks were controlled for stimulus, response and performance-related factors, they had identical, spatially diffuse EEG spectral scalp distributions [4] (Figure 1). Since no patterns of hemispheric lateralization were found, this suggested that previous and most current reports of EEG hemispheric lateralization may have confounded electrical activity related to limb and eye movements and arousal with those of mental activity.

Second Generation

The second generation of NCP analysis measured crosscorrelations between 91 pairwise combinations of 15 electrodes recorded during performance of simple tasks. These split-second tasks, controlled so that only the type of judgment varied, were associated with complex, rapidly-shifting event-related correlation patterns [5] (Figure 2). By extracting differences between similar spatial tasks, rapidly shifting focal patterns were found that were in agreement with the known functional neuroanatomy of the cerebral cortex [6,7] (Figure 3). From these results, it was clear that it was possible to measure salient aspects of the rapidly shifting, complex mass neural processes that are associated with the successive information processing stages of simple visuomotor judgment tasks.

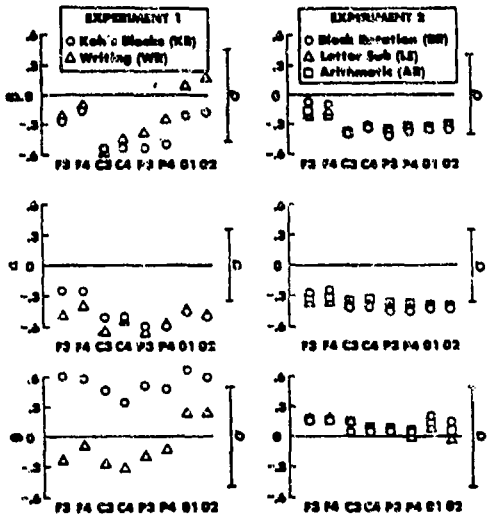

Figure 1. Results of experiments designed to assess EEG correlates of higher cognitive functions. (Left) Tasks of Experiment 1 were one minute long and involved limb movements and uncontrolled differences in stimulus characteristics and performance-related factors. (Right) Tasks of Experiment 2 were less than 15 seconds long and required no motion of the limbs; stimulus characteristics and performance-related factors were also relatively controlled. The graphs display means over all subjects of standard scores of EEG spectral intensities (expressed as changes from visual fixation values for clarity of display) recorded during performance of two tasks in Experiment 1 and three tasks in Experiment 2. Upper, middle and lower sets of graphs are for spectral intensities in the theta, alpha, and beta bands. The abscissae show scalp electrode placements: F3, left frontal; F4, right frontal; C3, left central; C4, right central; P3, left parietal; P4, right parietal; 01, left occipital; and 02, right occipital. Standard deviations, which differed only slightly between electrode placements, are indicated at the right of each graph. Although there are prominent EEG differences between the uncontrolled tasks of Experiment 1, EEG differences between the relatively controlled tasks of Experiment 2 are lacking. Each of the controlled tasks is, however, associated with a remarkably similar bilateral reduction in alpha and beta spectral intensity over occipital, parietal, and central regions [3].

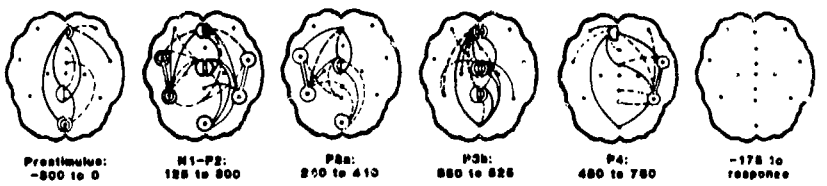

Figure 2. Spatiotemporal brain potential differences between two split-second tasks, one requiring a spatial judgment and the other a numeric judgment, are shown in each of six intervals from just before the stimulus to just before the response. A pressure of the right index finger was required in both cases. The most significantly differing electrodes, their significance level, and the most prominent correlations with other electrodes are shown. A solid line between two electrodes indicates that the correlation between the electrodes was higher in the spatial task, while a dotted line indicates higher numeric task correlations. Note the contrasts between the spatial and numeric tasks in the prestimulus interval, a finding that might be interpreted as evidence of a "preparatory set." Also, the lack of contrast in the preresponse interval may be interpreted as the completion of task-specific perceptual processing [5].

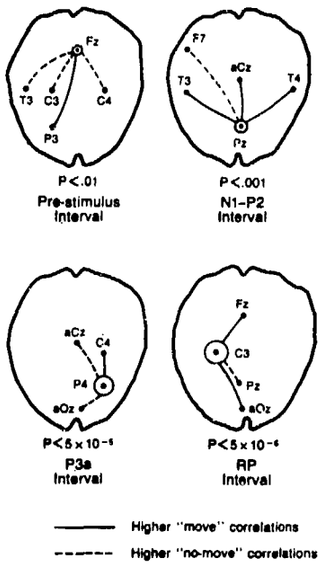

Figure 3. Spatiotemporal brain potential differences between two split-second spatial tasks in each of four intervals from just before the stimulus to just before the response. The "Move" task required a pressure of the right index finger, while the "No-Move" task required withholding the response. The size of the circle in each interval is proportional to the significance of between-task differences at the most significant electrode in that interval (i.e., Fz<.01, Pz<.001, P4<.00005, C3<.000005). A solid line between two electrodes indicates that the correlation was higher in the "Move" task, while a dotted line indicates higher "No-Move" task correlations. The midline frontal (F2) electrode focus in the prestimulus interval suggests a differential preparatory set; the midline parietal (P2) focus in the interval centered on the N1 and P2 evoked potential peaks suggests task-specific feature extraction and pattern recognition; the right parietal (P4) focus in the interval centered on the P3a evoked potential peak suggests differential spatial judgments between the "Move" and the "No-Move" tasks, while the left-centered (C3) focus in the preresponse interval is suggestive of preparation of the right index finger response in the "Move" task [6,7].

Third and Fourth Generations

The third generation was improved to operate on up to 64 channels recorded during a controlled sequence of stimuli in which a person prepared for, and executed, perceptual judgment and motor response tasks, and received performance feedback. The fourth and latest version of NCP Analysis and the ADIEEG-IV system includes many significant operational improvements (Figure 4) [23]. It has a greatly expanded capacity and its operation is automated by an AI expert system. It is designed for up to 256 channels, and is implemented on a 32-bit multiprocessor system which currently has 3 computing nodes, a 6-MFLOP floating point capability and a 3500 megabyte on-line disk capacity.

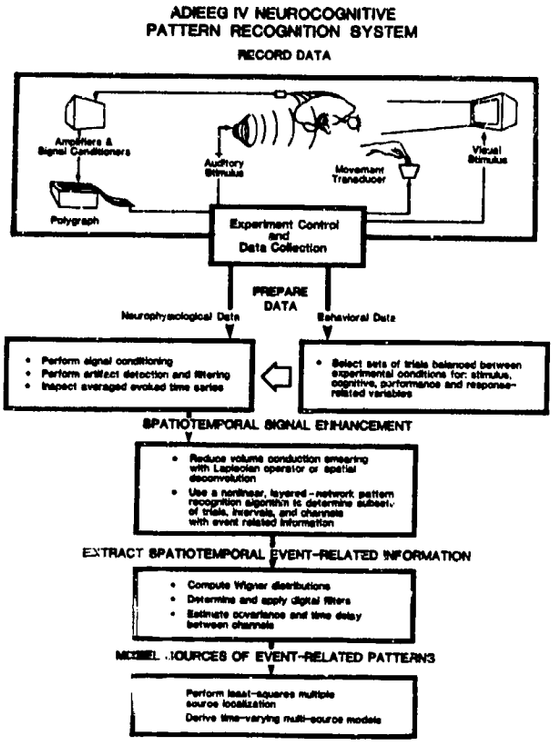

Figure 4. ADIEEG-IV system for quantification of event-related brain signals. Separate subsystems perform on-line experimental control and data collection, data selection and evaluation, signal processing and pattern recognition. Current capacity is 128 channels. Spherical-head spatial deblurring modules have been implemented, and multiple source modeling algorithms are being developed. Digital tapes of magnetic resonance images or of electrophysiological data from other laboratories are converted into the ADIEEG data format using gateway programs; they are then processed using the same program modules as data collected in the EEG Systems Laboratory.

The data acquisition system is capable of sampling up to 256 channels at up to 2 kHz sampling rates per channel. (Current amplification capabilities are 128 channels.) Trial presentation is automatically delayed until eye blinks, amplifier settling from eye blinks, and gross body movements have all died down. Up to 64 channels of EEG and non-EEG channels are monitored at a time on a color graphics screen for electrode problems. Other channels are bank-switchable to the monitor. Channels that are not currently on-screen are nonetheless automatically monitored to detect serious problems such as channels going dead or saturating. Additionally, other artifacts such as eye movement and muscle contamination are automatically marked by on-line pattern classification programs (Figure 5) [24]. These programs use a combination of time domain and frequency domain features for classification by multiple, 3-layered neural network pattern classifiers. Averages can also be viewed on-line to check for event-registered artifacts.

CLASSIFIER-DIRECTED ARTIFACT DETECTION

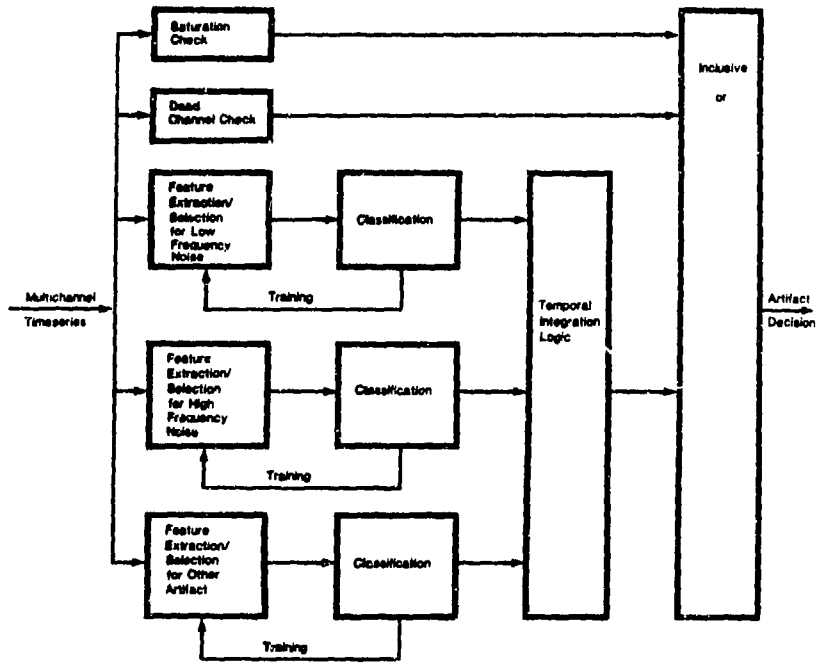

Figure 5. Classifier-directed artifact rejection. A system consisting of five parallel detectors is used to find contaminants. Three of the detectors incorporate layered-network classifiers to choose and weight feature combinations. In this way, a precise automated procedure replaces sole reliance on ad hoc waveform detectors and manually set thresholds.

Off-line, an interactive graphics trial editing program is used by an operator to check the decisions of the automatic on-line classifiers. In practice, editors have become sufficiently skilled to check the single trials of an experiment in roughly the time that it takes to run the experiment. (This represents a speed-up of 10-15 times over previous manual procedures.) Algorithms are under development to recover trials with non-saturating artifacts. Eye blinks or eye movements, for example, can be removed using least squares noise cancellation given EOG reference electrodes near the eyes.

The system then automatically calculates the optimum (largest) subset of trials that behaviorally balance for a requested set of variables on each split of the data required to test an experimental hypothesis (e.g., between low and high accuracy trials). This is followed by a manual check of the split distributions, along with corrections in exceptional cases. This is speeded up by a convenient, window-oriented user interface.

A Laplacian spatial transformation can be applied using precise measurements of electrode position to remove the effect of choice of reference channel and reduce spatial blur [25,26]. Additionally, a pathway has been built for detailed structural information via reconstruction of actual scalp, skull, and brain geometries using MRI (Figure 6). This information is used to deblur average event-related potential waveforms to estimated currents leaving the brain (actually, a smooth hypothetical surface surrounding the brain).

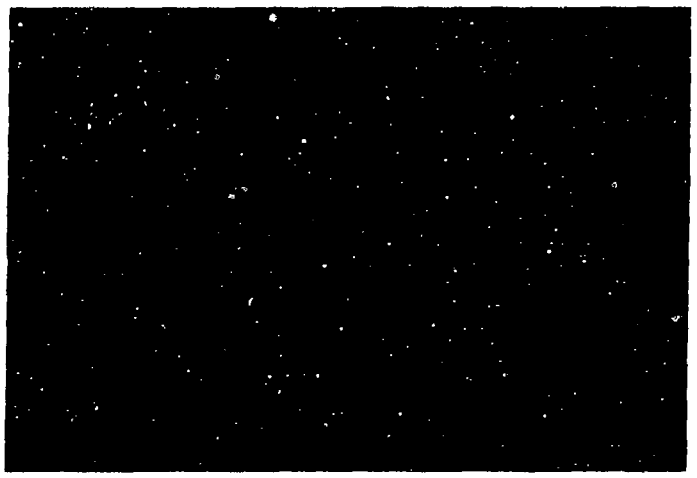

Figure 6. Magnetic Resonance Image of mid-sagittal section of subject's cranium with EEG electrodes mathematically superimposed.

The resulting sets of purified and selected EEG (or MEG, for imported data) trials are then entered into one of a number of possible single-trial or average event-related potential analyses. Averaging, filtering, time-varying spectral analysis, modeling, ERC measures, and multivariate pattern recognition are all supported under this system. Finally, two- and three-dimensional perspective plots are available to view the results of these analyses.

Each off-line step of the analysis is requested by the user without having to maintain knowledge of file names or directory locations. This is done by maintaining a fast associative memory of file locations indexed by fields of variables relevant to experimental analysis (e.g., experiment, person, session, condition) . A backward-chained reasoning system generates a tree of requests to the associative memory given a type of requested analysis. Because of these features, the user also does not need to consider whether a particular analysis result has been computed or not. If it has, the user is presented with the result immediately. If it has not yet been computed, the system traces antecedents and computes the result. If this takes a significant amount of time, the user is informed that the job has been batched.

COMPUTING EVENT-RELATED COVARIANCES (ERCS) BETWEEN CHANNELS

A number of steps are currently performed in computing ERCs. Because of the size of the single-trial data sets (up to 500 megabytes for each person), a large on-line disk capacity is required. The first pass reduces spatial smearing and then selects intervals and trials with task-related information to enhance the signal-to-noise ratio and reduce the amount of data prior to measuring ERCs. The second pass measures ERCs on band-pass-filtered, enhanced (optional), averages from the reduced data set.

The following steps are required:

1. Preparation: Record a sufficient amount of data using as many electrodes as possible. Apply the Laplacian operator to the potential distribution of each non-peripheral scalp electrode location. Remove data with artifact contamination [24].

2. Enhance average ERPs: Find trials with consistent event-related signals and compute an enhanced average from these trials [27]. Graph ERPs, make amplitude distribution maps ("BEAMS") at selected time points, and compute Wigner Distributions [28].

3. Compute ERCs: Select digital bandpass filters and intervals for measurement by examining ERPS and amplitude distribution maps. Compute multilag crosscovariance functions between all pairwise channel combinations of the enhanced (optional), filtered and decimated averages in each selected analysis window. Use the magnitude of the maximum crosscovariance function and its lag time as features characterizing the ERC [8,29-31].

4. Estimate significance of ERCs: Estimating the significance of ERCs requires an estimate of the standard deviation of the "noise" ERC. It is obtained as follows: (1) Random intervals in each single trial of the ensemble are averaged. (2) ERC analysis is performed on a filtered and decimated version of the resulting "noise" averages, yielding a distribution of "noise" ERCs. (3) Multiple comparisons are accounted for with a Duncan procedure.

5. Graph: The most significant ERCs in each interval are graphed.

6. Compare ERC maps between conditions: Test the difference in means of significant ERCs between conditions with an ANOVA and post-hoc t-tests. Measure similarity between multivariate ERC maps with an estimate of the correlation between them. Calculate these estimates using a distribution-independent "bootstrap" Monte Carlo procedure [32], which generates an ensemble of correlation values from randomly selected choices of the repeated measures. This will also yield a confidence interval for the estimates.

MEASUREMENTS OF HIGHER BRAIN FUNCTIONS

Four-Second, Bimanual, Visuomotor Judgment Task

The fourth generation NCP Analysis has been applied to data recorded from seven right-handed men during preparation and execution of precise right- and left-hand finger pressures contingent upon a visually presented stimulus [8,29,30]. Twenty-six EEG channels were recorded from which 16 current source density (CSD) Laplacian derivations were computed. Detailed analyses were made of a series of 187- or 387-msec-wide intervals throughout the four-second visuomotor task from cued preparation, through post-stimulus perceptual and cognitive processing, response preparation and execution, to the "updating" associated with feedback about performance accuracy.

Several significant results were obtained:

a. Evidence was found of a hand-specific "preparatory set" in pre-stimulus ERC patterns during the "late CNV" wave. Different ERC patterns were found for trials that subsequently had accurate or inaccurate performance [33]. These predictive patterns were complex and time-varying and differed between hand. Strong ERC patterns of the left prefrontal electrode with other electrodes characterized subsequently accurate performance by either hand.

b. ERC patterns for left- and right-tilted stimuli were similar during the interval centered at 62 msec after the numeric stimulus. Midline posterior parietal electrode ERCs led midline anterior parietal, which led midline premotor electrode ERCs. When the direction of tilt of the numeric stimulus was opposite that of the cue, no finger pressure was to be made. These were "catch" trials that occurred at random, approximately 20 percent of the time. During an interval centered 312 msec after the numeric stimulus on a catch trial, the midline premotor electrode lagged the left and right prefrontal electrodes, as well as a midline parietal electrode. This pattern may be a sign of motor inhibition.

c. Covariance patterns for movement-registered timeseries closely corresponded to prior functional neuroanatomical knowledge (see [33]). The anterior midline precentral electrode that overlies the premotor and supplementary motor cortices was the focus of all movement-related ERC patterns. The pattern for the Motor Potential clearly reflected the sharply focused current sources and sinks spanning the hand areas of motor cortex.

d. Feedback-registered ERC patterns and averaged current source density timeseries reflected different degrees of updating of neural systems when a subject is given

information about response accuracy. Feedback for accurate responses elicited a larger amplitude "early P300", while feedback for inaccurate responses elicited a larger amplitude in the later P300. The ERC pattern in the interval spanning these waves was more complex for inaccurate trials, involving foci of lagging ERCs over left, midline and right dorsolateral prefrontal areas.

High-Load, Visuomotor Memory Task

Fourth Generation NCP analysis has just been applied to recordings with 51 scalp channels from 5 U.S. Air Force test pilots performing a battery of tasks during four 6-8 hour experimental sessions over a 4-day period [34]. The results showed that, while neural systems responsible for perceptual processes were not affected by incipient fatigue, systems associated with preparation, and maintaining working memory, and motor inhibition were differentially affected.

Monkey Data

ERC analysis was also applied to recordings from intracerebral electrodes in a primate model [35]. Cynomologus monkeys were trained to perform a delayed-response discrimination task similar to those used to study the Contingent Negative Variation in humans. Preliminary results suggest that intracerebral ERCs merit further study, and may eventually supplement the use of unit recordings to characterize the temporal evolution of spatially distributed processes responsible for goal-directed behaviors.

CONCLUSION

Our Neurocognitive Pattern (NCP) Analysis and Event-Related Covariance (ERC) Analysis should be distinguished from brain electrical activity maps [36], which are attractive color displays of the individual time points of 16-20 channels of averaged ERPs or EEG spectra, or the difference between such measures and a set of normative data. We use extensive signal processing and pattern recognition algorithms to reduce volume conduction effects and to extract minute event-related signals from unrelated background noise of the brain, compute between-channel ERC patterns, and display their scalp distribution in 3-D perspective graphics of the head and brain. Subtle aspects of neurocognitive function, such as the measurement of preparatory sets that precede accurate performance, are revealed by these ERC patterns but are not apparent on topographic maps [8,33].

By combining EEG and MEG recordings, and using anatomical information from MRI scans, we hope to be able to compute plausible multiple-equivalent-dipole, 3-dimensional source configuration models.

It is a testimony to the ingenuity of cognitive psychologists and psychophysiologists that so much has been learned about the timing of neurocognitive processes using very modest recording equipment and analysis techniques. It is, therefore, certain that when they are equipped with more advanced recording methods and more powerful analytic tools, cognitive psychologists and psychophysiologists will make rapid advances in understanding human higher brain functions.

ACKNOWLEDGMENTS

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DISCUSSION

LANDOLT, CA: In the pictures that you presented, how many channels of EEG information had been treated with the Laplacian "deblurring" technique?

GEVINS, US: Fifty-one.

LANDOLT, CA: Do you see any upper limit to the number of scalp recording electrodes beyond which more electrodes would be superfluous for data collection?

GEVINS, US: The closest electrode spacing that I have achieved is a 3-mm spacing, and even then it is possible to discern differences in the waveform. As a practical matter, I think that 128 channels is a good number to strive for in the next few years.

LANDOLT, CA: Do you think that the results that you alluded to for the visuomotor judgement task would change if you went to 128 channels?

GEVINS, US: You would see more detail in the field patterns. When one solves for multiple sources and there is independence between measurements, then nuances will appear in the localized differences, as projected onto the scalp, that you would not see with fewer electrodes.

PRICE, US: Could you explain the occipital localized pattern?

GEVINS, US: This occurred as the result of applying the Laplacian transformation to the 51 EEG channels. This produced a beautifully oriented dipole, having a maximum anterior to the central sulcus and a minimum posterior to it. It looked exactly like a MEG map, except that it was rotated 90 degrees.

KAUFMAN, US: If it looks exactly like a MEG map, which can be explained by an equivalent current dipole, then why do you make the statement that there are no current dipoles? The current dipole is a fundamental building block in electrophysiology. Clearly, the source distribution will change over time. Yet you talk about magnetic waves without the current dipole as the fundamental building block.

GEVINS, US: I must have misstated what I meant to say. When the patterns became so complicated that I couldn't conceive of accounting for them with a single source, then I used more than one dipole to explain them.

OFFENLOCH, GE: You showed pattern changes to right-handed finger movements on the left side and vice versa. Was the analysis done on the basis of averaged multipotentials or as frequency changes in the EEG?

GEVINS, US: It was a combination of both. The data were time locked to the onset of finger movement and the time window used extended for approximately 1/6 second from the onset of movement. This could be called the N_2 component of the movement potential (according to Vaughan). The time series, though, were filtered in the theta band (approximately 4-7 Hz).

KRAMER, US: Your preference seems to be to discard eye-movement contaminative voltages, rather than filter them out. There has been much recent work by John Stern and others on the relationship between eye movements, blinks, etc., and cognition. If we are interested in studying the EEG or its changes during such eye movements, then we will no longer be able to look at these relationships if we discard the data.

GEVINS, US: There is no such thing as cognition without eye movement. In designing an experiment to examine changes in mental activity, the experimental design must take into account eye movements, as an a posteriori means of checking the data. I would rather not resort to filtering to remove eye-movement contaminants from the EEG because that brings in subtle issues such as the neural control of eye movements themselves. It is possible to produce an experiment having a strong visual-fixation presentation of a simple visual stimulus that subtends a very small visual angle for a very short time. Then, with proper training of the subject, data can be obtained in which there are no saccades during the short interval of time when this stimulus is being processed and a decision is being made. Therefore, through proper experimental design and careful checking, it is possible to select only data in which there are no contaminative voltages. Of course, if there are sufficient data, then one can discard the contaminative portion.

WEINBERG, CA: What you are saying in effect is that there are times when you present a stimulus for which you do not get an evoked potential, or there may be times when the response is not perceivable by any systematic event-related potential. Those are the ones that you discard and I agree that this should be done. However, does that imply that the evoked potential does not need to occur preceding the response output or following stimulus input? Does it imply that you can have processing of information without an evoked potential?

GEVINS, US: The brain has many ways of producing the same behaviour. One explanation for the fact that about 1/3 of my experimental trials have no discernible event-related signals may be that the subjects are using a more automated way of performing their tasks. For example, an experienced driver can have his attention and mind on other matters and still perform perfectly well.

WEINBERG, CA: Let me word it in a slightly different form. You are saying that there are times when you are measuring some distribution of electrical activity in the brain and that there is nothing systematic which precedes an event or an output, or nothing systematic which follows from an input. Those are the data that you are discarding. Is there no way to identify systematic events which are preceding or following inputs or outputs?

GEVINS, US: Some "things" are fairly hard-wired. The earliest processing of an auditory stimulus will go through certain brain stem nuclei and will produce very clear-cut peaks if you average several thousand trials. We call that the brain stem evoked potential. Visual feature extraction in areas 17, 18, and 19

of the visual cortex are also fairly hard-wired, although this becomes less certain as one leaves the primary visual cortex. The kinds of behaviour that we use in our experiments, in which we present some sort of stimulus, require some sort of judgement -- usually fairly trivial -- leading to some sort of response — which is also more-or-less trivial. These types of goal-directed behaviours become more and more automated. For example, I may wish to make a MEG recording to a simple task consisting of the presentation of a visual stimulus requiring a discrimination leading to a response. If I need 100 trials per sensor position for a 5 to 7 channel machine, I would have to present the stimulus from 500 to 1000 times; in other words, over and over again. There is no way that a human being doing something this simple and boring over and over again will pay full attention unless there is some reward for responding correctly to the stimulus and the response. It may be advantageous that there is not an evoked response in every trial; that fact may be telling us something important.

Normative Developmental Equations for the EEG and their Sensitivity to Neurological and Psychiatric Disorders

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Although the electroencephalogram (EEG) is altered by many brain dysfunctions, its clinical utility has been severely limited by reliance upon visual pattern recognition and subjective interpretation. Not only is the concordance poor between electroencephalographers and the test-retest reliability low, but many changes due to more subtle dysfunctions are simply not apparent by visual inspection. Accordingly, there has been increasing interest in developing methods for objective computer extraction of quantitative features with diagnostic utility from brain electrical activity.

Our laboratories have been engaged in this endeavor since 1973. Our goal has been not only to replace subjective judgements by objective quantification, but to extend the utility of electrophysiological examinations beyond their traditional role in the detection of neurological disorders to the assessment of cognitive impairments and the evaluation of psychiatric patients. In many disorders, similar behavioral symptoms may be displayed for quite different underlying reasons. For example, learning disabilities may be due to motivational or psychosocial factors, or to sensory deficits or brain dysfunctions. An elderly person may display problems with recent memory because of a sense of lack of purpose or because of organic changes caused by Alzheimer's disease or multiple infarcts. Depression may be a reaction to the disintegration of personal relationships or reflect inbalance in neurotransmitters. A victim of head injury may report inability to concentrate because of the desire to receive compensation benefits or because of significant brain damage. Even when behavioral symptoms are caused by brain dysfunctions, there may be a variety of brain dysfunctions capable of producing the same behavioral outcomes but requiring drastically different treatments.

Our initial studies, supported by the RANN program (Research Applied to National Needs) of the National Science Foundation, were focussed on the problem of learning disabilities in children. As our techniques evolved, we applied them successfully to the assessment of pediatric neurological patients, to adult patients with mild head injury, cerebrovascular disease including transient ischemic attacks, alcoholism, cognitive impairment due to senile dementia, affective disorders and psychoses. The method which we have developed for these purposes, called "Neurometrics", is based upon the computerized extraction of a wide variety of objective indices of brain function as reflected in electrophysiological activity, the multivariate statistical evaluation of these quantitative measures, and the display of diagnostically significant findings in color coded topographic maps easily interpretable by the clinician without extensive specialized training.

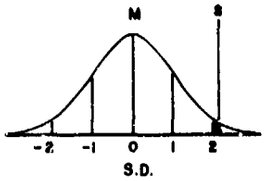
Methodological Considerations

Before presenting the clinical results which we have obtained with these methods, several basic methodological issues must be raised. Although this discussion may seem unnecessarily detailed to some of you, failure to consider these problems considerably weakens the clinical utility of many of the functional imaging devices which are now becoming commercially available.

Quantitative analysis of electrophysiological data yields a massive amount of numerical features. Numerous commercial devices now produce brilliantly colored topographic maps of such features. No matter how objective these measurements may be or how pretty the topographic maps, their clinical interpretation remains subjective and tentative unless they can be referred to a normative data base and statistical evaluation. This raises the difficult question of how to define 'normal'. Because our particular interest was in cognitive dysfunctions and psychiatric disorders, the instruments used to define our normal subjects included a psychiatric as well as neurological examination, an extensive psychometric and neuropsychological test battery, achievement tests and determination of lateral cerebral dominance. Medical and psychosocial histories, current and past school and work records were also evaluated. Subjects with significant abnormal findings or antecedents which placed them at risk were excluded. Additional exclusion criteria included current use of prescription drugs, a history of convulsions, head injury or loss of consciousness, or any previous EEG or neurological examination. Our normative data base includes over 750 subjects between 6 and 90 years old, collected from six sites using standardized methods.

We use the Z-transform (see Fig. 1) to quantify the probability that any quantitative EEG or EP feature is abnormal, a method now adopted by most workers in this field. The precision of this estimate depends upon satisfying the requirement that the distribution of the feature is Gaussian or 'bell-shaped'.

'Z' - TRANSFORM



$$Z = \frac{\text{SUBJECT VALUE} - \text{MEAN VALUE OF SAMPLE}}{\text{STANDARD DEVIATION OF SAMPLE}}$$

Z ≈ PROBABILITY THAT SUBJECT VALUE LIES WITHIN 'NORMAL' RANGE

Figure 1: A Gaussian distribution, M denotes the mean value of the distribution, S the observed value in a subject. The Z-transformation expresses the distance between the population mean and the individual observed value in S.D. units, a Z-score. The area under the curve that lies beyond the mean (+ or -) and the observed Z-score is equal to the probability that the observed value lies within the normal range.

We routinely now extract over 1200 quantitative features from a 60 second long sample of resting eyes closed EEG, collected using an on-line artifact rejection algorithm. Unless adequate on-line artifact rejection or skilled visual editing precedes quantitative analysis, data can be seriously contaminated by a wide variety of artifacts. These features include measures of absolute power, relative or % power, coherence (synchronization) and symmetry in the delta, theta, alpha and beta frequency bands in the 19 electrodes of the 10/20 International Electrode Placement System.

We found the distribution of most of these features in our normative population to be markedly non-Gaussian. We constructed various transforms to achieve Gaussianity for all of them, many of which have since been confirmed by other workers [1]. Failure to make such corrections of skewed distributions results in an asymmetrical statistical bias, with increased false positives on one side of the mean value and increased false negatives on the other side. Many of these features also show significant correlations with age. Reliance upon mean values and standard deviations for such a variable will yield false positives which increase with deviation from the center of the age range, as well as false negatives because of the inflated estimate of variance. Each of our 1200 neurometric EEG features has therefore been described by polynomial age-regression equations from age 6 to 90. These equations have recently been published [2].

The issues thus far raised are not merely puristic academic concerns. Compare the data on the left side of Figure 2, with transforms for Gaussianity and age dependence, with the data on the right side, without correction for these biases. False positives occur at the chance level and the detection of pathology is markedly increased when legitimate statistical procedures are followed.

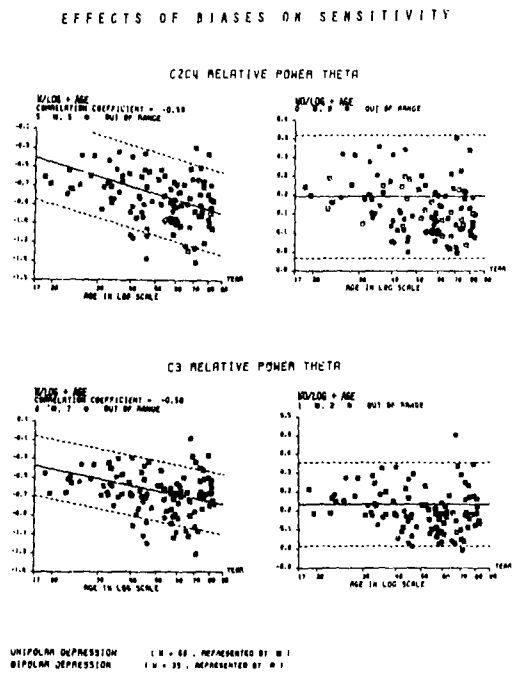


Figure 2: Scatterplots for C_2C_4 relative power in theta (top) and C_3 relative power in theta (bottom) for depressed patients. Left panels with age regression and log transform, right panels without either. Dotted lines show plus and minus two standard deviations from mean (solid line) [3].

The functional organization of the brain is based upon complex relationships among its regions. Quantitative analyses restricted to the topographic mapping of local features, even if they are statistically valid, often yields little insight into subtle changes in organization which may be brought about by pathology. For this reason, we augmented our set of local or 'univariate' features by a set of regional and systemic composite features. We have normed the covariance structure of relationships among features within a region or across features between regions, quantifying the changes from normal relationships by the 'Mahalanobis distance'.

For example, consider the two univariate features, percentage power in the alpha band and in the beta band, in the left parieto-occipital region, shown in Figure 3 below. If one considers these feature to be independent, the locus of values significant at the 0.05 level, for the 2-dimensional composite features 'left parieto-occipital alpha and beta power', is defined by the circle representing the square root of the sum of the squares of their separate Z-scores. If the high covariance normally found between these two features is taken into account, the 5% significance level of the composite feature is bounded by the ellipse.

Note how few false positives (3.3%) among an independent sample of normal subjects lie outside the ellipse seen on the left side of Figure 3. The data on the right side demonstrate the great increase in sensitivity to brain dysfunction achieved by taking explicit account of the normal covariation between features. Only the patients outside the circle would be identified as abnormal if independence were assumed between these two measures (19.8%). When departure from normal covariance is considered, the patients outside the ellipse can be identified as abnormal (46.3%) even though a high proportion of them lie inside the circle.

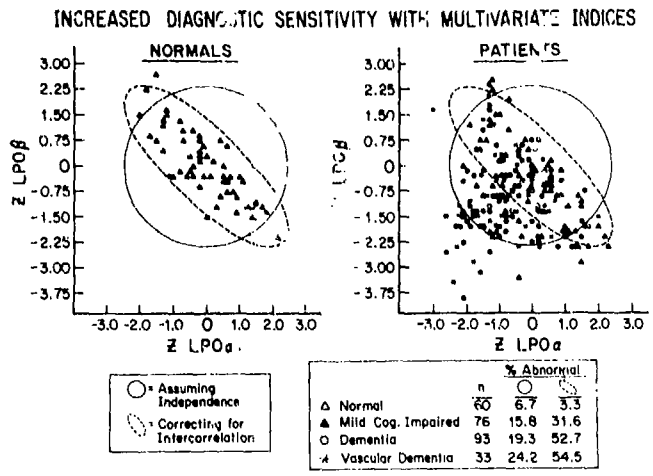


Figure 3: Univariate scatter plot for Z-values of relative power in alpha and beta bands in LPO region for normals (left panel) and psychiatric patients (right panel). The 95% confidence region is a circle if the composite feature is computed as the square root of the sum of the squared Z values, and an ellipse if it is computed as the Mahalanobis distance.

Clinical Results

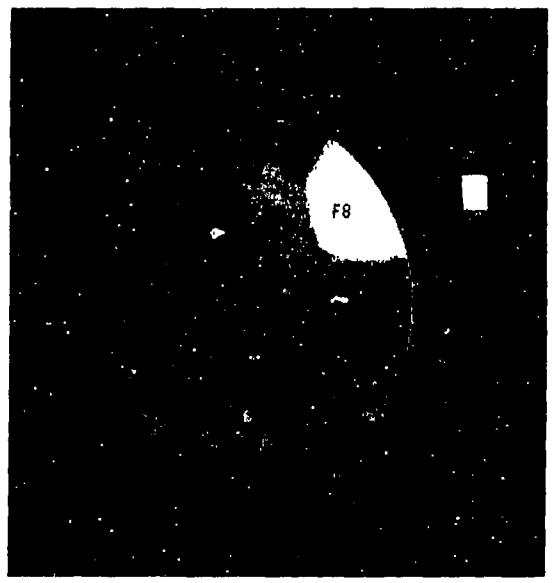


Figure 4: Topographic map of relative (%) power in delta band in a patient shortly after infarct of right middle cerebral artery. The greater the percentage of delta the brighter the map (note upper right quadrant).

Figure 4 is the topographic map, face upward, of relative (%) power in the delta frequency band in a patient who was left hemiplegic after thrombosis of the right middle cerebral artery. Increased power in the delta band, indicated by brighter colors in the map, reflects decreased regional cerebral blood flow (rCBF) in the underlying brain. Symptomatic patients who have suffered cerebrovascular accidents usually show abnormal rCBF and focal slowing of the EEG which is well detected by univariate features such as relative power (%) in delta at the corresponding electrode placement.

Table I

DETECTION OF CEREBRAL ISCHEMIA
USING ^{133}XE rCBF AND
NEUROMETRIC EVALUATION OF THE EEG

Group	n	rCBF	Nx
CS	11	82	91
PNS	43	70	91
RIND	15	53	93
TIA	25	38	88
AVERAGE		61	91

(rCBF = regional blood flow; Nx = neurometric EEG analysis; CS = completed stroke; PNS = persisting neurological symptoms; RIND = reversed ischemic neurological deficit; TIA = transient ischemic attack)

However, this is not always the case, as seen in Table I for data obtained in collaboration with Drs. Poortvliet and Jonkman in Holland [4]. In the cerebrovascular patients, in Groups CS and PNS, who displayed persistent neurological symptoms, a high proportion of abnormal findings were obtained by ^{133}Xenon measures of rCBF and also by the EEG multivariate feature 'Overall All Frequencies' which quantifies the relationships among the power spectra observed in all derivations. In the asymptomatic patients in Groups RIND and TIA, the detection of abnormalities by ^{133}Xenon rCBF was much lower. However, the Mahalanobis distance across all frequencies in all leads detected abnormalities in most of these patients, although few had focal EEG slowing. Visual inspection of conventional EEGs found abnormalities in only 57% of the total set of patients. Thus, multivariate neurometric analysis may provide a sensitive indicator of cerebral ischemia in asymptomatic patients, which might identify individuals at risk for stroke.

We have found that different categories of psychiatric patients display distinctive profiles of abnormality [5,6]. The magnitude of abnormalities in these profiles correlate well with clinical severity, and can be used as an objective criterion for the evolution of dysfunction or to evaluate treatment. Multiple discriminant functions have been constructed and subjected to independent replication, which accurately classify patients suffering from alcoholism, mild head injury, cognitive impairments, senile dementia, and major affective disorders, and distinguish them from normals. Promising preliminary successes have been obtained with vascular dementia and schizophrenia and are awaiting replication with independent samples. Multivariate features play an essential role in most of these discriminations. Certain aspects of our findings indicate that currently asymptomatic individuals who have previously displayed symptoms of particular disorders may often be correctly classified, suggesting that some Neurometric trait or vulnerability marker may exist.

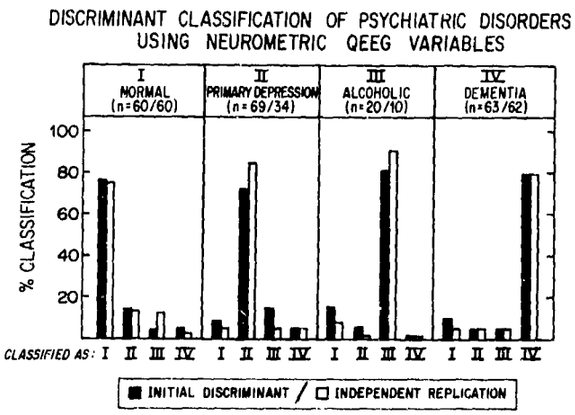


Figure 5: Discriminant classification of normal (I) and psychiatric disorders [primary depression (II), alcoholism (III), dementia (IV)]. Initial discriminant is represented by black bars and independent replication by white bars.

Figure 5 presents the accuracy of a multiple discriminant function classifying normals, primary depressed, alcoholic and dementia patients. Black bars show accuracy in the training sample and white bars show the accuracy of independent replication on a new test sample. Overall mean accuracy was 79%.

Table II

DISCRIMINANT CLASSIFICATION OF DEPRESSION SUBTYPES USING NEUROMETRIC QEEG VARIABLES

		INITIAL DISCRIMINANT Classification (%)	
Actual Group	n	I	II
I Unipolar Depression	(34)	85	15
II Bipolar Depression	(20)	15	85

		INDEPENDENT REPLICATION Classification (%)	
Actual Group	n	I	II
I Unipolar Depression	(34)	85	15
II Bipolar Depression	(15)	13	87

Patients with major affective disorders have been discriminated from normals with better than 90% accuracy. Neurometric profiles corresponding to depressive subtypes can also be identified. Table II shows the accuracy of separation of unipolar versus bipolar depressed patients. Overall initial accuracy was 85%, with independent replication at 86% [3].

CONCLUSION

Accurate differential discrimination between psychiatric disorders can be achieved if multivariate statistical analyses are performed on carefully constructed neurometric EEG features. Once the discriminating variables have been identified, topographic mapping of the appropriate univariate features (selected from the large set of mappable variables) reveals patterns which are commonly encountered within patients with the same disorder. However, such maps are not unique and may also be encountered in patients with other disorders.

Neurometric EEG analysis and topographic mapping, in conjunction with discriminant classification techniques, offer a powerful adjunct to the clinical diagnosis and treatment of patients with a wide variety of subtle brain dysfunctions. This technology may help to identify trait markers of vulnerability to certain disorders and may eventually permit early detection and intervention in vulnerable individuals. Since aerospace personnel, like all of us, are potentially susceptible to these conditions, neurometric evaluations may also play a useful role in assessing the suitability of such personnel for particularly critical tasks.

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DISCUSSION

PRICE, US: The only diagnostic category in which you included mild cases, or lets say marginal cases, was in dementia, but certainly you must have had some in the other categories also. How did these fare in your multivariate analysis?

JOHN, US: Dementia is the one disease that is the most elaborately developed because we have a 4-hour multidisciplinary assessment of those patients, which goes well beyond what we have in other categories. As a rule of thumb, if you think of the neurometric measurement as an n-dimensional space with a different direction for each class of measurements, then a vector from the origin out into this space has an orientation which is a specific disease. The longer the vector, the more serious is the disease. So we can represent the patient as an orientation in space, and the different orientations are the vectors of patients with different diseases. When you have the ability to correlate the intensity of state with neurometric measurements, then these correlations are always positive. The more abnormal the neurometric measurement, the more severe is the clinical condition. For example, I've tracked patients following traumatic head injury in terms of both their Z-values and their Glasgow Coma Scale (GCS) ratings. (For a GCS from 0 to 4, the prediction is that the patient will probably die. From 10 and up, the patient will probably live, and between 5 and 10 the patient's prognosis is indeterminate.) Patients with a GCS of 4 to 5 may have Z's of 10, 12, or 14 which have a probability of 10^{-10} of being in the normal range. As you track these patients, you see no changes in their GCS as the Z-value starts to go down. When the Z-value intersects the normal value for a given brain region (Z=2.5, P level = 0.01), then the function that is normally associated with that particular brain region will return. In other words, electrical changes always precede clinical changes. The patient who is going to recover may show no clinical changes but the electrophysiological measures show a positive trend.

JOHNSON, GE: I have two questions that relate to the limitations of the technique. How well can you discriminate between pre-senile and senile dementia? How well can you differentiate between Alzheimer's patients and normal senile patients?

JOHN, US: We can separate individuals with a Global Deterioration Scale (GDS) (Alzheimer's Disease, B. Reisberg, Free Press, Glencoe, Illinois, 1983) of 2 (mild cognitive impairment) from 3 and 4 (moderate) and from 5 and 6 (severe). We identify individuals with a GDS of 2 in the range of 50 to 55 years as having pre-senile dementia. Our separations are on the order of 80% in these three categories. The Alzheimer's patient; frankly, I am not comfortable with that terminology because there is a tendency to label all elderly individuals with cognitive impairments as Alzheimer's patients. We have done three different cluster analyses each on 100 to 120 ostensibly Alzheimer's patients; and in each analysis we found 3 major and 3 minor clusters with different pathophysiological profiles, i.e., they were not clustering on the basis of severity of disease. Interestingly, only one of these clusters gives a picture of diffuse cerebral ischemia; i.e., showing a widespread excess of delta or theta activity. There is an extremely intriguing group of patients which shows no signs of cerebral ischemia but demonstrates some interesting features when you do a P300 paradigm — an oddball paradigm. Using the 10-20 International Electrode Placement System, you compute the coherence of the event-related potentials for latencies from 200 to 300 ms, determine the average value (call this R) from the left to the right side for a homologous lead, and then find the sum of R^2 across all homologous pairs to estimate interhemispheric coherence. If you do that, you can separate normal patients from a class of Alzheimer's patients or a class of demented patients who have no signs of cerebral ischemia. These patients also have perfectly symmetrical and coherent primary (shorter-latency) evoked potentials. This is quite a large sub-group of patients, who other people call Alzheimer's patients, who have no signs of frontal hypometabolism, no signs of frontal theta or delta activity, no indications of primary pathway transmission inadequacy but the outflow of the diffuse projection pathways (perhaps norepinephrine/serotonin dependent pathways) is absolutely not functioning properly. It's as if the retrieval of the significance of a symbol is different in the two hemispheres in these patients. It's very important to do cluster analysis of these patterns and to assume that if you can clearly see distinct clusters of pathophysiological variables, then you are looking at different diseases that produce similar symptoms. For example, we have tentatively defined a number of different patterns of neurometric profiles for schizophrenia, according to the DSN-III diagnostic catagory (Standard Psychiatric Diagnostic Manual). Incidently, in our studies of pharmaceutical intervention in the different subgroups of Alzheimer's patients or demented patients, it is our impression that drugs like the calcium channel blockers or the nootropic agents tend to affect members of one cluster if they have any affect at all, and not at all in the other clusters. So an advantage of cluster analysis of these clinically homogeneous but pathophysiologically heterogeneous populations may be the fact that you can begin to understand why it is that some drugs help some people with the disease and not others who apparently have, behaviourally at least, the same disease.

BROOKS, CA: Should we still be using the EEG as a medical screen in the initial selection of our aircrew?

JOHN, US: I think the EEG and the computerized EEG look at totally different aspects of brain function. The EEG is superior to the computerized EEG in the detection of paroxysmal phenomena. I'm not satisified with my spike detector because it gives too many false positives. I think visual inspection of the EEG ought to be done, but it is totally inadequate to identify subtle pathological conditions of the brain. To not take the EEG data and analyze it quantitatively by a computer, with proper artifact rejection capability, when it is there for the taking is a great loss of valuable information.

KRIEBEL, GE: I think that the routine EEG is still necessary for aircrew selection. For example, during the past year, we detected abnormal spike wave activity in two young patients who had never had seizures. In one of them, we detected a meningioma from the focal delta activity. We rely on visual inspection of the EEG without benefit of computerized quantification. The few problems that we encounter are well worth the effort.

JOHN, US: I am not implying that the conventional EEG should be abandoned. I just think that it is better to not even think of the standard visual inspection of the EEG and the computerized EEG as two variations of the same measurements. All they have in common is that both look at the electrical activity of the brain. They are very different from each other; and they provide very different types of information.

THE APPLICATION OF NON-STATIONARY DATA ANALYSIS TECHNIQUES IN THE IDENTIFICATION OF CHANGES IN THE ELECTROENCEPHALOGRAM ASSOCIATED WITH THE ONSET OF DROWSINESS

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The electrical activity of the brain was analysed using techniques to detect the occurrence of non-stationarities associated with transitional states between alert wakefulness and sleep. Eight minutes of resting eyes closed data were used in the analysis. A visual inspection was carried out to classify the record into epochs of varying lengths according to the different states of arousal. Three states were defined, alert wakefulness, drowsy sleep and a transitional state. Non-stationary data analysis techniques were used to identify these changes automatically.

The techniques used were autoregressive modelling, in which the prediction error was used as a criterion to detect change, and evolutionary power spectrum analysis, where a spectral ratio was defined to detect differences between short epochs of the signal. In addition, the autocorrelation function was calculated for a limited number of lags, and changes in the function with reference to previous epochs used to identify the onset of change.

These techniques were compared with methods of analysis based on a pre-defined epoch length, to determine the most efficient method of detecting changes associated with the transition between alertness and drowsiness.

A discriminant function was calculated for each of the three visually classified states to define a classification rule, which was then used to allocate the segments produced by each of the automatic analysis techniques to one of the three states of alertness. Finally, the performance of each technique was assessed in terms of its ability to correctly classify segments of data.

Introduction

The change from alertness to drowsy sleep in an eyes closed recording involves a decrease in alpha activity and the appearance of theta waves. Prior to the appearance of drowsiness, most subjects pass through a transitional stage, where the statistical characteristics of the EEG show greater moment-to-moment variability - the signal contains more non-stationarities. These changes may be abrupt, with distinct boundaries, such as seen with short duration alpha bursts, or gradual, with amplitude and/or frequency characteristics changing slowly.

The purpose of this study is to present methodology for detecting these types of non-stationarities, in order to identify the onset of drowsiness. The detection of changing statistical characteristics of the signal leads to segmentation of the record into stationary epochs of varying length (adaptive segmentation, (1)). The methodology is compared with the results of analyses based on a fixed duration epoch in terms of ability to classify segments according to the state of arousal.

Methodology

Eight minutes of occipital EEG recorded from a healthy male subject resting quietly with eyes closed were used in all analyses. The recording included periods containing non-stationarities, and also times when the statistical characteristics of the signal were relatively stable.

In order to provide a basis for defining the required sensitivity of the techniques for determining non-stationarities, three states were defined by visual inspection according to the level of arousal. These were alert wakefulness (state A), consisting of high amplitude, continuous alpha activity, a transitional state (state B) where alpha activity was reduced with some theta activity present, and drowsy sleep (state C) consisting of continuous theta activity (Fig 1).

Boundaries between these states were placed by visual inspection (Fig 2). Non-stationary data analysis techniques were then used to identify changes in the characteristics of the signal, with the computer analysis positioning boundaries, indicating where possible changes in state may have occurred. This resulted in the EEG being split into variable length epochs.

The analysis techniques used were

1) evolutionary power spectra, which expresses the local power-frequency distribution for a given instant in time at a specified time resolution (2). The technique is used to describe time-varying signals, and can therefore indicate the onset of change in the EEG by computing a spectral ratio involving

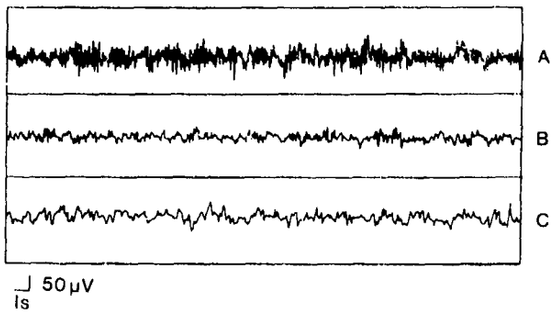
FIG 1

DEFINITION OF STATES

A : alertness, continuous alpha activity

B : transition, reduced alpha mixed with theta

C : drowsy sleep, continuous theta activity



a specific band of frequencies relating the spectral content of the current epoch with previous epochs of data. In this study, a time resolution of 0.5s was required, resulting in 2 Hz resolution in the frequency domain.

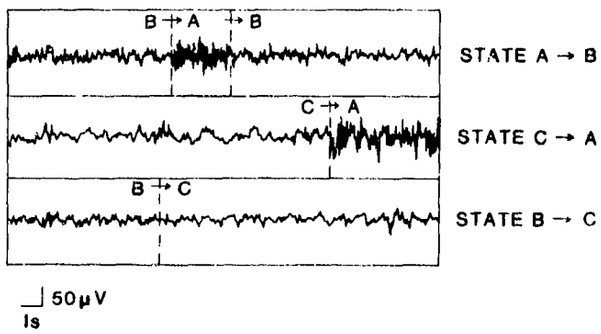
2) changes in the autocorrelation function: the three states of alertness have distinctly different autocorrelation functions, and therefore absolute differences in the autocorrelations at corresponding lags for the current epoch with reference to previous epochs can be used to determine onset of change in the signal (3). In this study, lags of up to 10 were used, based on an analysis epoch of 1s, and advancing at a rate of 0.5s.

3) the prediction error based on fitted autoregressive models: one-step-ahead prediction errors from a model fitted to 1s of data were estimated and summed over short (125ms) epochs. As the signal begins to change, the fitted model will no longer describe the signal adequately, resulting in structure appearing in the residuals. Identification of non-stationarities (or changes of state) involves determining a threshold criterion based on the prediction error. The summed residuals are a chi-square variable, and can be compared with the chi-square distribution to determine the onset of change (4).

FIG 2

CHANGES BETWEEN STATES

Visual classification



For each of the techniques, a reference window was defined at the start of the recording, and an advancing analysis window used to compare the current epoch with the reference epoch (1). Comparison with the previous epoch was also done. Each time a non-stationarity occurred, as determined by preset threshold criteria, a new reference epoch was set up consisting of the epoch immediately following the boundary. The process continued for the duration of the recording.

In addition to detecting non-stationarities, classification of segments according to level of arousal was required. A subset of the data from each of the three states was used as a training data set to calculate discriminant functions relating to each state. The variable-length segments were then classified as state A, B or C according to the discriminant functions. The proportion of time classified in agreement with the visual classification for each of the analysis methods was then calculated, together with an assessment of the success of each technique at detecting non-stationarities.

For comparative purposes, the recording was also analysed using methods based on epochs of fixed duration. These methods were fourier analysis, zero-crossing analysis, and Hjorth's method (5) which measures activity (total power), mobility (mean frequency) and complexity (wave shape in comparison with a sine wave). Each of these analyses was based on a 4s epoch. As before, discriminant functions were calculated corresponding to each state, and individual 4s epochs of the eight minute recording classified as state A, B or C based on the EEG measures derived from each analysis method. The proportion of time in each state classified by each computer technique based on agreement with the visual classification was then calculated for each method, and the results compared with the classifications from the analyses using varying length epochs.

Results

There were marked differences in the autocorrelation functions between each of the three states (Fig 3). The autocorrelation function for state A was typical of sinusoidal activity in which the frequency varies about a peak (corresponding to the width of the alpha peak in the power spectrum). The autocorrelation function was a decaying sinusoid indicating a cyclic component of about 10 Hz. For state B, the autocorrelation function indicated very low serial correlation in the signal, with the autocorrelation coefficients decaying to zero very rapidly. State C was characterized by an autocorrelation function decaying slowly to zero - greater than 60 lags were required to display the cyclic nature of the data.

For state A, the power spectrum showed a pronounced alpha peak, while for state B there were maxima in both the alpha and beta bands of approximately the same amplitude, as well as marked low frequency components (Fig 4). The spectrum for state C was characterized by low frequency activity, with only 8.9% of the power arising from activity greater than 8 Hz. The spectra for states B and C differed in their content above 8 Hz, together with lower theta activity for state B than C.

In the case of autoregressive models, the order was chosen by increasing the number of fitted parameters until the residual variance of the model decreased to a minimum. An order of 10 was selected as a compromise for all three states, although the residual variance continued to decrease by a small amount until orders as high as 16 were reached for states A and C. Based on a model of order 10, 89.4 and 94.7% of the variance was explained for states A and C respectively, while for state B only 62.3% was accounted for, and so the model fitted considerably less well in this state.

In terms of ability to detect the types of non-stationarities identified visually, the method based on evolutionary power spectra was more effective than the analyses used in the autocorrelation function and prediction residuals from fitted autoregressive models (Fig 5). This applied to the duration of the recording. All methods were able to detect changes between states A and C, but boundaries with state B were difficult to detect. In order to identify the required changes, the threshold criteria for the methods based on the autocorrelation function and autoregressive models had to be set at a low level, resulting in over-segmentation.

However, following segmentation of the recording into varying length epochs, computer classification into states A, B and C resulted in similar proportions of time classified in agreement with the visual classification - 400 , 412 and 414 s for the 480s long record for evolutionary power spectra, the autocorrelation function and autoregressive models respectively.

For the analysis based on epochs of fixed duration, the amount of time classified in agreement with the visual states was 366 , 361 and 356 s for fourier analysis, Hjorth's method and zero crossing analysis respectively. These methods tended to underestimate the proportion of time spent in states A and C.

FIG 3
THE AUTOCORRELATION FUNCTION
FOR EACH STATE

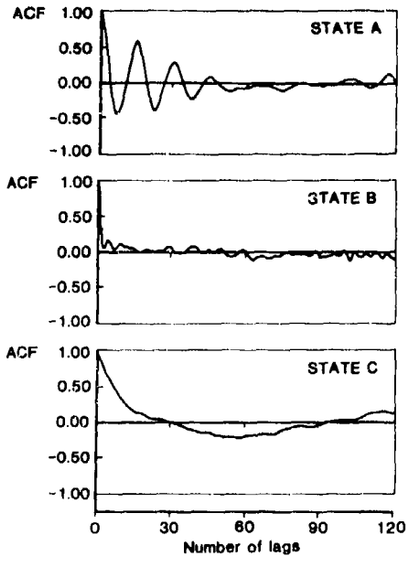
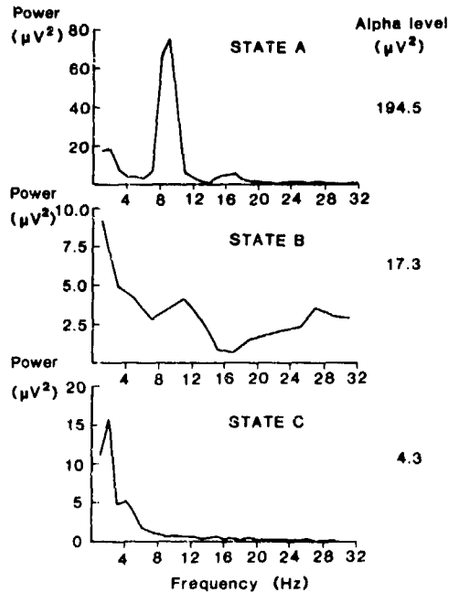


FIG 4
POWER SPECTRA FOR EACH STATE



Discussion

In terms of ability to detect non-stationarities identified visually, the method based on evolutionary power spectra was the most effective. In the case of other methods studied, the threshold criterion had to be set at a low level to detect changes of the type identified visually. This may have been because for a short duration epoch, evolutionary power spectra were able to distinguish the high frequency components superimposed on low frequency activity in the signals, which for example were characteristic of the difference between states B and C. In the case of the autocorrelation method, low frequency components in the signal would dominate the autocorrelation function, and thus gradual changes between states B and C would be more difficult to detect. In addition, the standard errors associated with autocorrelation functions based on 0.5 or 1s would be high - this was the lowest acceptable time resolution since some of the non-stationarities lasted only of the order of 1s. In the case of the prediction error, lack of fit of the autoregressive model for state B resulted in relatively high residuals during stationary periods leading to over-segmentation, and reduction in sensitivity of the method for detecting boundaries.

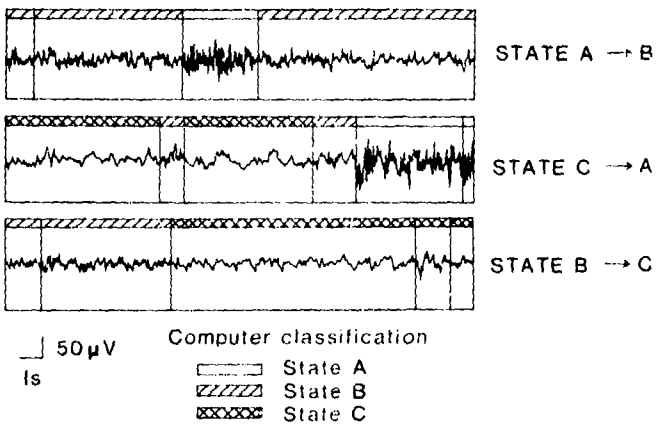
The methods based on analysis epochs of varying length compared with fixed length epochs gave a small advantage in terms of proportion of time identified as agreeing with the visual classification. The methods using fixed duration epochs tended to underestimate periods with continuous alpha (state A) and continuous theta (state C), and this is likely to have arisen because the boundaries between 4s epochs occurred when the characteristics of the EEG were changing.

However, the purpose of this study was to detect non-stationarities in the EEG, and the ability of evolutionary power spectra gives it an advantage over fixed length analyses, though the amount of time agreeing with the visual classification was not substantially greater. The frequency of non-stationarities can be determined, together with the lengths of the stationary periods, and these factors may themselves be important in the early detection of drowsiness.

FIG 5

CHANGES BETWEEN STATES

Computer detection based on evolutionary power spectra



In conclusion, methods based on analysis epochs of variable length are likely to be of importance where the temporal characteristics of the EEG within a short recording are of interest, for example, the occurrence of specific events such as alpha bursts or microsleeps. As such, these methods may be useful in the detection of short periods of drowsiness in the EEG in an eyes closed recording performed in studies of irregular or extended periods of work, and in measurement of sedation produced by drugs such as hypnotics. The occurrence of these types of events may also be important in the context of individuals performing vigilance tasks, since their presence may indicate the onset of reduced alertness and therefore increased likelihood of missing critical events.

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A STATISTICAL PROCEDURE FOR THE EVALUATION OF PRESENCE/NON-PRESENCE OF STIMULUS-RELATED EEG ACTIVITY

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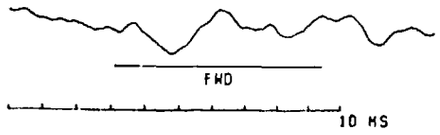
SUMMARY

Averaging of a sufficient number of stimulus-related sample functions is a commonly applied method for the demonstration of evoked activity in the electroencephalogram (EEG). However, problems may arise in the visual evaluation of averaged waveforms when the signal-to-noise ratio is low, such as for instance in certain cerebral disease conditions, or when the intensity of the stimuli is low (threshold studies). In such situations the question of presence or not of evoked activity may be of material importance. Even experienced observers will find it difficult to give a reliable answer if their judgement has to depend only on visual assessment of the averaged waveforms obtained. A statistical test for the presence of evoked activity may be a guide to the correct decision in such cases.

This paper presents a statistical procedure based on phase value measurements of Fourier components in the post stimulus sample functions. The distribution of these phase values is uniform in the interval 0^o - 360^o when the EEG sample functions contain no evoked activity (the null hypothesis or control situation). On the other hand, an aggregation of phase values in a certain angular region and hence a non-uniform distribution is to be expected if evoked activity is present. A statistical procedure testing a null hypothesis of uniformity may thus be applied in the evaluation of presence/non-presence of stimulus-related activity in the critical situations mentioned above. In the present work a test of the Kolmogorov-Smirnov type, Kuiper's V_n test, was applied with satisfactory results.

INTRODUCTION

Stimulus-related signal averaging is a commonly employed method in evoked response studies. The efficiency of the method, however, is largely dependent on the level of noise. In unfavourable test conditions the response may be buried in noise to such an extent that idenfification becomes impossible when based on visual judgement of a stimulus-related average alone. False negative as well as false positive conclusions may occur.



SECTION FWD: NO SIGNIFICANT RESPONSE ACTIVITY (α=0.731)

Fig. 1 "False response". The trace represents the average of 500 epochs of equal length taken from an EEG recording during which no stimulation was performed ("non-stimulated EEG"). The average may give a false impression of stimulus-related activity. A significance test on the presence of evoked activity corresponding to the horisontal bar (FWD) underneath the trace was, however, negative.

An example of the latter situation is shown in Fig. 1. The waveform represents an average of 500 epochs taken from an EEG without stimulation ("non-stimulated EEG"). The average is seen to have a configuration giving the false impression of a latency time followed by a sequence of waveforms resembling evoked activity. The absence of the latter was, however, guaranteed in this experiment, a fact that is supported by the significance statement underneath the trace, resulting from a statistical test procedure. Significance tests may therefore be useful aids to the correct conclusion in evoked response experiments. Several statistical procedures have been suggested (1,2,3). Common to many of them is the choice of the phase angles of the Fourier harmonics in the post stimulus sample functions as a suitable random variable. The basic idea is that if the phase angle of a given Fourier harmonic is measured in each of the post stimulus sample functions, then this phase value will be a random variable which is uniformly distributed in the angular interval (0^o - 360^o), provided that the signal contains no evoked activity. In our case this corresponds to the "no response" or control situation. This assumption of uniformity in the non-stimulated EEG case may be confirmed experimentally. An example is given in Fig. 2. Denoting the random variable by θ, the probability d e n s i t y function of a uniformly distributed $\theta(0^o, 360^o)$ is $f(\theta) = 1/360$. The left part of Fig. 2 shows the corresponding cumulative probability distribution (DF), denoted as $F(\theta) = \theta/360$, a straight line extending from origin to the point (360,1). In our case $F(\theta)$ is the distribution specified by the null hypothesis. The right side of Fig. 2 is a graph of the s a m p l e

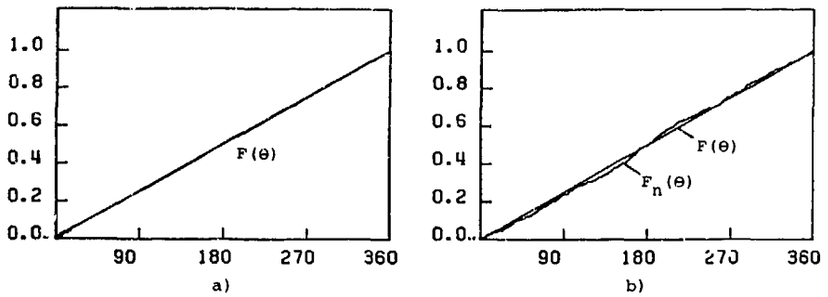


Fig. 2. a) The distribution function F(θ) of a random variable θ which is uniformly distributed in interval (0, 360). b) Sample DF $F_n(\theta)$ resulting from observing the phase values of one of the Fourier harmonics in 500 consecutive epochs taken from a nonstimulated EEG. $F_n(\theta)$ is seen to follow the superimposed F(θ) quite closely.

distribution function obtained from observing the phase values of one of the Fourier harmonics in 500 epochs taken from a nonstimulated EEG. The sample DF, $F_n(\theta)$ is seen to follow the straight line of the superimposed F(θ) quite closely.Contrary to this, when the post stimulus EEG epochs do contain stimulus-related activity, then the phase values of one or more of the observed Fourier harmonics would be expected to show a tendency towards aggregation in some angular regions, with resulting deviation from uniformity. This situation is illustrated in Fig. 3, which shows the sample DF $F_n(\theta)$ constructed from a sample of 500 phase values taken from an EEG during visual stimulation. $F_n(\theta)$ is seen to deviate quite strongly from the uniform distribution F(θ)specified by the null hypothesis.

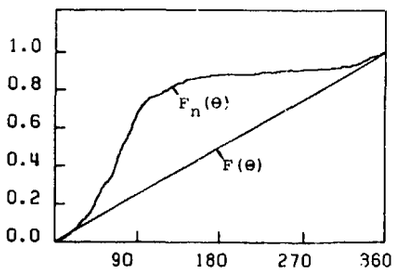


Fig. 3. Sample DF $F_n(\theta)$ obtained from a sample of size 500 of phase values belonging to a Fourier component in the post stimulus epochs taken from an EEG during visual stimulation. $F_n(\theta)$ is seen to deviate quite strongly from F(θ), indicating nonuniformity due to phase aggregation and presence of evoked activity.

From a statistical point of view it thus follows that a significance test on the presence of evoked activity becomes one of testing whether experimentally obtained sample distributions of phase values have a significant deviation from uniformity.

STATISTICAL TEST PROCEDURE

Concerning the choice of a suitable statistical procedure, however, there are certain precautions to be taken. It is important to realize that the random variable θ observed in our case represents directional data which are being measured relative to a fixed origin or zero direction. This concept is illustrated in Fig. 4. A given phase angle realization θ_i may be measured as the angle made by a unit vector with the positive x-axis in the anti-clockwise direction. The vector endpoint on the unit circle is then given by $(\cos\theta_i, \sin\theta_i)$, and hence our random variable may also be represented as points on the unit circle. Any point on this circle may be accepted as an origin for measurements. The same is true for the choice of the zero direction, which may be different from the positive x-axis selected in the present illustration. Many statistics commonly employed in measurements on the line, such as for instance the sample mean and standard deviation, will be dependent on the choice of origin for the measurements. Consider, for instance, a sample of size 2 and assume that the angles measured were 1^0 and 359^0. The

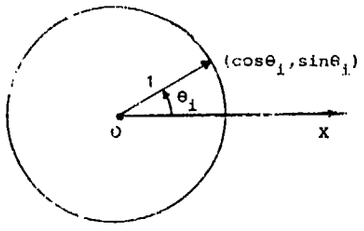


Fig. 4. Representation of a phase angle realization θ_i as the angle made by a unit vector with the positive x-axis in the anti-clockwise direction, and as a point $(\cos\theta_i, \sin\theta_i)$ on the unit circle.

arithmetic mean would become 180°. Intuitively, however, we would assume a mean direction near 0° in this case. It thus follows that the circular, modulo 360 nature of the data has to be accounted for, and fo the significance test we need a statistic that is invariant under the choice of origin. The V_n variable defined by Kuiper in 1960 (4) has the desired property. The measurement of this V_n variable is illustrated in Fig. 5. The step function $F_n(\theta)$ shown in the figure represents the cumulative sample DF obtained from a sample of n observations of the random variable θ. The V_n variable is measured as the sum of the maximum vertical deviation (A) of $F_n(\theta)$ above + the maximum deviation (B) below the continuous distribution $F(\theta)$ specified by the null hypothesis.

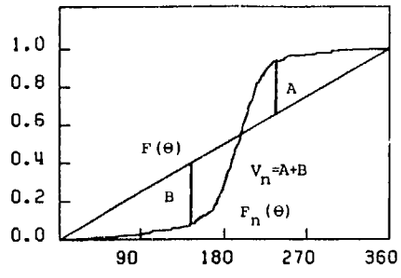


Fig. 5. The V_n value: V_n = A+B, i.e., the sum of the maximum vertical deviation of a sample distribution function $F_n(\theta)$ above and below a hypothetical distribution $F(\theta)$ specified by the null hypothesis. V_n does not depend on $F(\theta)$, and is also independent on the choice of origin for the random variable θ.

A high V_n obviously indicates a large deviation from $F(\theta)$, and would thus, in our case, lead to the rejection of the null hypothesis and the conclusion "response activity present". As shown by Kuiper, the statistic V_n has two important properties:

a) The V_n value does not depend on the choice of origin for the measurements.

b) The distribution of V_n, on the null hypothesis, is independent of $F(\theta)$.

The distributuion of V_n on the null hypothesis is known, and tables have been made, giving the percentage points or α values. However, the use of extensive tables may be avoided if the V_n value is modified according to the following formula suggested by Stephens in 1970 (5):

$$T = V_n(\sqrt{n} + 0.155 + 0.24/\sqrt{n}) \qquad (I)$$

Then, for a given value of T=Z the significance level α or $P(T \geq Z)$ in the upper tail of the V_n distribution may be approximated by the formula

$$\alpha = P(T \geq Z) = (8Z^2 - 2)\exp(-2Z^2) \qquad \text{(II)}$$

For samples of size $n \geq 8$ the approximation error is negligibly small, as shown by Stephens. In the present investigation Kuiper's V_n statistic was therefore found suitable for the problem at hand, i.e., testing the null hypothesis that a sample of size n comes from a population with a given distribution $F(\theta)$. Stephens formulas (Eq.(I) and (II)) were used for the estimation of the significance level.

The experimental situation may be described as follows. A sensory system is stimulated n times during simultaneous recording of neuroelectric activity. On each of the post stimulus sample functions a Fourier transform (FFT) is performed, and the phase values of the 10 first harmonics are observed, separately. The reason for limiting the phase measurements to only the first 10 is that higher harmonics are supposed to contribute little to the signal, representing noise rather than evoked activity in the transform lengths applied in this investigation. At the end of the experiment each of the observed harmonics will be represented by a phase value sample of size n. The null hypothesis is as follows.

H_0: The 10 observed phase variables are uniformly distributed in the interval (0,360) (no response, or control situation).

The alternative hypothesis is,

H_A: At least one of the phase variables has a nonuniform distribution (response present).

For a given harmonic, if the observed phase values (θ) are arranged in ascending order of magnitude $\theta_1 < \theta_2 < \ldots < \theta_n$, then the sample DF may be expressed as $F_n(\theta_i) = i/n$, and the corresponding V_n value may be computed as

$$V_n = \sup(i/n - F(\theta_i)) - \inf((i-1)/n - F(\theta_i)), \quad i = 1,2\ldots n$$

In our case a total of 10 V_n values will be available. Denoting the largest of these by V_{max}, the corresponding maximum T value may be found from Eq.(I) as

$$T_{max} = V_{max}(\sqrt{n} + 0.155 + 0.24/\sqrt{n}),$$

from which the probability

$$P(T \geq T_{max}) = (8T_{max}^2 - 2)\exp(-2T_{max}^2)$$

may be found, using Eq. (II). With reference to the formulation of H_A, the significance level of the experiment may be expressed as

$$\alpha = P(\text{"at least 1 of 10 T-values} \geq T_{max}\text{"})$$

An α value below a certain limit would lead to the rejection of H_0 and thus to the acceptance of H_A with the conclusion "response present". The estimation of the α level, however, needs some further elaboration. Let A_j (j = 1,2...10) denote the event that V_{max} and hence T_{max} was found for the j-th among the 10 observed phase variables. Then α may be expressed as the probability of a union of events A_j, i.e.,

$$\alpha = P(A_1 \cup A_2 \cup A_3 \ldots \cup A_{10})$$
$$= S_1 - S_2 + S_3 - \ldots - S_{10} \qquad \text{(III)}$$

in which $S_1 = \sum P(A_j)$, $S_2 = \sum P(A_j A_k)$, $S_3 = \sum P(A_j A_k A_m)$, ... , for $j<k<m \ldots \leq 10$. If statistical independence could be assumed between the 10 observed phase variables, then the events A_1, A_2 ... A_{10} in Eq.(III) above would be independent. In this case the expression for the significance level α would reduce to

$$\alpha = 1 - P(\text{all T-values} < T_{max})$$
$$= 1 - (P(T < T_{max}))^{10}$$
$$= 1 - (1 - P(T \geq T_{max}))^{10} \qquad \text{(IV)}$$

Zero correlation is a necessary (but not sufficient) condition for statistical independence. A test performed on the samples of phase variables during the non-stimulated EEG condition suggested a low degree of correlation between neighbouring harmonics. Apparently this contradicts the use of Eq.(IV) for estimating the α level. An alternative is then to use a Bonferroni inequality for estimating an upper α-bound, $\alpha' = S_1$ in Eq.(III) above, i.e.,

$$\alpha' = P(A_1) + P(A_2) + \ldots P(A_{10}) = S_1$$

which reduces to

$$\alpha' = 10 \cdot P(T \geq T_{max}), \qquad (V)$$

since, on the null hypothesis, $P(A_j)=P(T \geq T_{max})$ for all j=1,2, .. 10 in our case. Considering the expression for the true α value in Eq.(III), the upper α-bound α' is seen to be derived by dropping all terms except S_1. Then $\alpha \leq \alpha'$ is guaranteed, and the following Bonferroni inequality exists,

$$\alpha' - S_2 \leq \alpha \leq \alpha' ,$$

from which follows ,

$$- S_2 \leq \alpha - \alpha' \leq 0,$$

and hence,

$$|\alpha - \alpha'| \leq S_2 .$$

The last inequality thus states that α' approximates α with an error (true value minus approximation) which has the same sign as the first omitted term (S_2), and is smaller in absolute value.

In the present investigation α' in Eq.(V) was used as the upper α-bound. It should be noted, however, that the difference between α in Eq.(IV) and α' is rather small over a wide range of α' values.

SIGNAL RECORDING AND COMPUTING

Employing these statistical principles the evoked response detection program was implemented on a PDP 11/60 computer, using a high level language (FORTRAN IV). The neuroelectric signals were band-pass filtered and sampled at a rate well above the Nyquist frequency. Using a floating point algoritm, FFT was performed in each post stimulus sample function, on a section of fixed length and placement relative to the stimulus instant. Prior to each FFT these "Fourier windows" (FWD) were transformed to zero DC level and multiplied with a cosine bell (Hanning window) to reduce the effect of spectral leakage. The phase values for each of the 10 first harmonics were stored in separate arrays of length n (=number of stimuli delivered). The total storage requirement for the phase variables was thus n x 10. Due to restrictions in computer storage and addressing facilities, the maximum number of stimuli that could be processed by the computer program was 500. Although sufficient for many evoked response experiments, this number is rather small for recording low-voltage brain stem responses (BER), a problem which will be discussed later. At the end of the experiment (n stimuli presented) the phase values were arranged in ascending order of magnitude and the V_n value was computed for each of the harmonics separately. The modified statistic T_{max} for the l a r g e s t of the 10 V_n values and the corresponding probability $P(T \geq T_{max})$ were then computed. Finally the upper-bound value for the significance level was found, using Eq.(V)

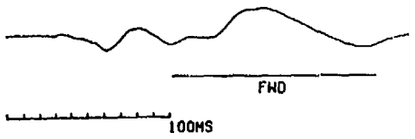
At the end of the experiment the analytical results were presented, comprising a plot of the averaged signal epochs with a statistical statement indicating the level of significance, and a plot of the phase sample DF $F_n(\theta)$ for which the highest V_n value was found. The plots of the averaged signal epochs were calibrated such that the maximum peak-to-peak value became of fixed length in any case, irrespective of the numerical value in the sampled waveform.

RESULTS

The efficiency of the detection program has so far been tested in visual (VER) and auditory BER experiments.

Fig. 6 illustrates the results obtained when testing for presence of VER in a normal person, using high intensity flash stimuli. The upper trace represents the average of 500 stimulus-related sample functions, and has the well-known configuration of an evoked response. The horisontal bar (FWD) below the trace indicates the post stimulus epoch (of length 128 ms) tested for presence of evoked activity in this experiment. The Fourier transform length was 64 sample points, corresponding to a fundamental harmonic frequency of 7.8 Hz. As indicated by the statement below the averaged trace, the statistical test resulted in rejection of H_0 on a high level of significance ($\alpha < 0.000001$), leading to the conclusion "significant response activity". The lower part of the figure represents a graph of the phase sample distribution function $F_1(\theta)$ belonging to Fourier harmonic no. 1, for which the highest V_n value (=0.61) was found in this case. The superimposed DF, $F(\theta)$, is the distribution of a continuous random variable which is uniform (0,360). $F_n(\theta)$ is seen to deviate quite strongly from $F(\theta)$, in accordance with the high level of significance.

Fig. 7 shows the effect of reducing the stimulus intensity such that the flashes became hardly visible, i.e., near threshold. The experimental procedure was otherwise the same as in the former test. The averaged waveform (upper trace) has noisy characteristics



SECTION FWD: SIGNIFICANT RESPONSE ACTIVITY ($\alpha \leq 0.000001$)

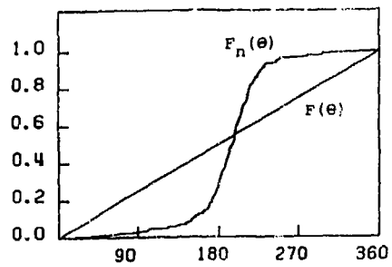
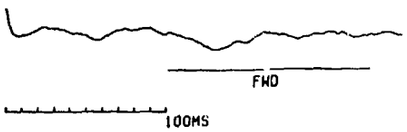


Fig. 6. VER experiment. Visual stimuli employed: Flashes of high intensity. The trace in the upper part of the figure is the average of 500 stimulus-related sample functions taken from the EEG of a normal person. Evoked activity is seen to be present in well-defined waveforms, and the statistical statement below the trace confirms this on a very high level of significance ($\alpha < 10^{-6}$). The post stimulus epoch is 128 ms, and is indicated by the horisontal bar (FWD) below the trace. Note the large deviation between the sample DF $F_n(\theta)$ and the uniform DF $F(\theta)$ in the lower part of the figure.



SECTION FWD: SIGNIFICANT RESPONSE ACTIVITY ($\alpha \leq 0.004931$)

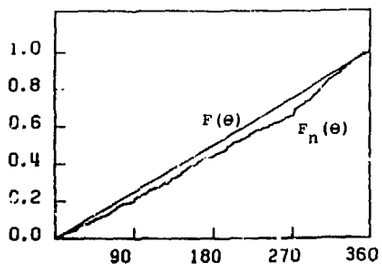
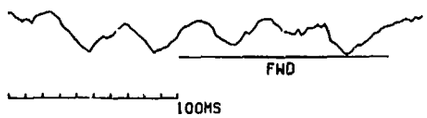


Fig. 7. VER experiment, employing flash stimuli of low intensity (hardly visible). Averaged waveform in upper part of the figure is rather inconclusive, but the statistical test result indicates presence of evoked activity in the epoch FWD, with a level of significance $\alpha < 0.004931$. Note the deviation between the sample DF $F_n(\theta)$ and $F(\theta)$ (much less than in Fig. 6).

and is rather inconclusive as to the presence or not of evoked activity. The statistical test, however, indicates presence of response on a rather high level of significance ($\alpha \leq 0.004931$, see statement below the trace). The highest V_n value (0.11) was found for the phase sample of the 2nd Fourier harmonic in this experiment. The sample DF $F_n(\theta)$ in the lower part of the figure is seen to deviate from the uniform $F(\theta)$, but much less than in the former experiment.

Fig. 8 is representing the results of an experiment in which 500 sample functions were taken from an EEG without simultaneous stimulation ("non-stimulated EEG"). The averaged waveform is noisy, as expected, and the statistical test procedure does not give any evidence for rejecting the null hypothesis in this case (upper α-bound = 0.438).



SECTION FWD: NO SIGNIFICANT RESPONSE ACTIVITY ($\alpha \leq 0.438$)

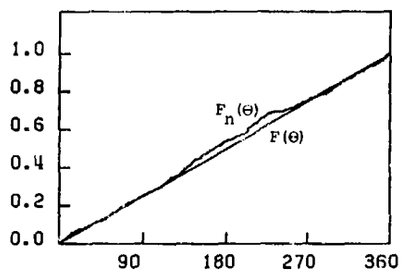
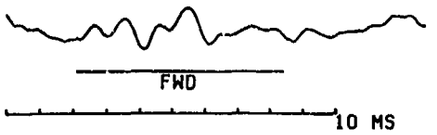


Fig. 8. Testing for evoked activity in a non-stimulated EEG. The statistical test resulted in a high upper α-bound, leading to the conclusion "no significant response activity".

Figs. 9 and 10 illustrate the results obtained in auditory brain-stem evoked response (BER) experiments, using 400 clicks of intensity 80 and 40 dB above sensory level (SL), respectively. In both experiments the Fourier transform length was 64 sample points, corresponding to a time length of 6.4 ms. The frequency of the fundamental harmonic was thus 156.25 Hz.

In the 80 dB experiment an evoked response is readily distinguished on visual inspection of the averaged waveform (Fig. 9, top), and the statistical test is highly significant ($\alpha \leq 0.000001$). The maximum V_n value (0.18) was found for the 7-th Fourier harmonic, and the corresponding $F_n(\theta)$ shows a substantial deviation from $F(\theta)$.

In the 40 dB case (Fig. 10) the upper α-bound was high (0.717), and hence the statistical test does not give any evidence for rejecting the null hypothesis. The highest V_n value was only 0.07 and belonged to the 9-th harmonic. $F_n(\theta)$ is seen to follow $F(\theta)$ quite closely, in accordance with the nonrejection of the null hypothesis. Contrary to the negative conslusion, however, an evoked response is normally expected when clicks of intensity 40 dB SL are applied. No definite evoked activity can be distinguished in the averaged waveform (top of figure), but nevertheless it has to be admitted that the test method failed to detect evoked activity in this case. The same result occurred when employing 500 stimuli, i.e., the maximum number that could be processed by the computer system. The problem will be discussed in more details later.



SECTION FWD: SIGNIFICANT RESPONSE ACTIVITY ($\alpha \leq 0.000001$)

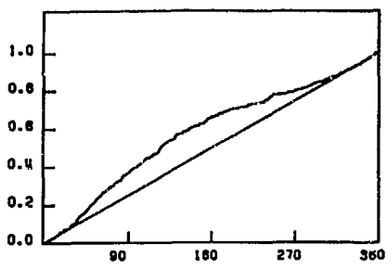
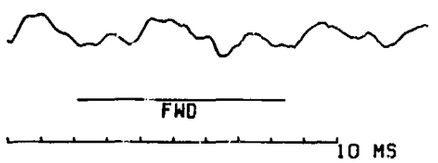


Fig. 9. BER experiment. Auditory stimuli: Clicks 80 dB above sensory level. The trace on top of figure is the average of 400 stimulus-related sample functions. Evoked activity is apparent on visual evaluation, and this is further supported by the statistical test which resulted in an upper α -bound of 0.000001. $F_\beta(\theta)$ belongs to the 7-th Fourier harmonic and is deviating quite strongly from $F(\theta)$. The post stimulus test window (FWD) is 6.4 ms and consists of 64 sample points.



SECTION FWD: NO SIGNIFICANT RESPONSE ACTIVITY ($\alpha \leq 0.717$)

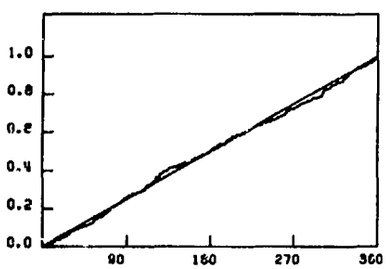


Fig. 10. BER experiment. Click stimuli, 40 dB above sensory level. Experimental procedure otherwise the same as in Fig. 9. Evoked activity is to be expected, but is not confirmed, neither by visual evaluation of the averaged waveform (top of figure), nor by the statistical test which resulted in a high upper α -bound (0.717).

DISCUSSION

A statistical method for the detection of evoked neuroelectric activity is to be considered useful mainly in situations when responses of low voltage are expected. Examples of the such situations are the studies dealing with the problem of estimating the minimum stimulus strength just capable of eliciting a distinguishable response (threshold examinations), moreover disease conditions affecting neuronal structures and reducing their response capability.

In the present investigation Kuiper's V_n test on the distribution of phase angles in stimulus-related sample functions appeared sensitive in detecting near-threshold visual evoked activity. In these cases presence of evoked activity could be statistically assessed with a rather high level of significance even when no response could be seen in the stimulus-related average. An explanation of this discrepancy is the fact that the averaged response may be hampered by just a few sample functions of bad quality, i.e., containing high-voltage artifacts or noise components, occurring during the recording procedure. Such events, however, are less destructive to a nonuniform trend in the phase sample measurements.

The efficiency of a statistical procedure is largely dependent on the sample size. This may be a plausible explanation of the failure in detecting BERs to medium or low intensity click stimuli. In the latter experimental situation the brain stem responses are in general of low voltage relative to the background activity, measuring only a few tenths of a microvolt. In conventional average evoked response recordings several thousand stimuli are commonly required in order to obtain a distinguishable response in such cases. The size of the phase samples in the present statistical analysis was equal to the number of stimuli, n . The maximum value of the latter was 500, due to restrictions in computing facilities mentioned previously. This number is probably too small for the statistical detection of nonuniformity in the phase samples during the low signal-to-noise conditions dealt with.

It follows that an improvement of the efficiency of the statistical procedure could be achieved by an extension of the number of stimulus-related sample functions. Another approach would be the employment of artifact rejection techniques, such as, for instance, template matching in order to reduce the effect of the noise component in the sampled epochs.

Finally, a comment should be made on the criterion used for rejecting the null hypothesis in this investigation. Referring to the formulation of H_A, H_0 is rejected only if one or more of the observed phase variables have a nonuniform distribution. Intuitively, however, one might imagine situations in which a certain number of the observed phase variables may show a deviation from uniformity which is moderate, but not large enough to allow rejection of H_0 with the present formulation of H_A. Such situations might indicate presence ofevoked activity, and hence indicate a reformulation of H_A as follows: H_A: At least m (=1,2...10) of the observed phase variables have a nonuniform distribution. This formulation, however, has effect on the estimation of the significance level and needs further elaboration from a mathematical-statistical point of view.

CONCLUSION

Kuiper's statistical V_n test on the distribution of phase angles of the Fourier harmonics in post stimulus sample functions appears to be rather sensitive for the detection of evoked activity. Satisfactory results were obtained in using the procedure for the detection of near-threshold visual stimuli, but failed in detecting brain stem responses when medium or low intensity clicks were used. A most probable reason for the failure is the relatively low number of stimuli applied in the experiments. The impression is that the efficiency of the statistical test could be improved by increasing the number of stimulus-related sample functions, a possibility that is readily achievable in modern computers with large storage and addressing capabilities. The results of the investigation therefore indicate that the statistical approach may be useful in diagnostic situations where presence/nonpresence of evoked activity is a question of material importance.

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"Dissecting" the visual and auditory pathways by means of the two-input technique

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SUMMARY

We describe an evoked potential technique for identifying the nonlinear characteristics of specialized sensory neural mechanisms in the human brain. For example, subjects viewed a grating pattern modulated at F_1 Hz superimposed on a second grating modulated at F_2 Hz. The VEP consisted of about 20 discrete frequency components, each of less than 0.004 Hz bandwidth. Most would be destroyed by conventional averaging, but could be measured by a zoom-FFT technique that gives 25,000 resolvable bins over DC-100 Hz. We have developed a mathematical treatment such that the pattern of behavior among these VEP components "fingerprints" the nonlinear processing. We report orientation tuning bandwidths (20 deg) and the spatial frequency tuning of a phase-independent visual mechanism; strong interactions between responses to orthogonal orientations; and a possible EP means of investigating the auditory hair cell transducer characteristic.

It has been clearly established by microelectrode recording that the visual and auditory pathways in primates contain many neurons with specialized properties that respond asymmetrically, for example to increase versus decrease of light intensity, increase versus decrease of pattern contrast, leftward versus rightward motion, receding versus approaching motion in depth, or auditory FM versus AM. Human equivalents of such neurons are presumably important for the special sensitivities of the human sensory pathways, e.g. those to contrast, motion and auditory pitch. We describe an EP technique for investigating the properties of such specialized neurons by measuring the nonlinear interactions between two simultaneously-presented stimuli.

The basic rationale can be understood in terms of the following illustration: We know that primate visual cortex contains neurons that respond to bars or gratings, and that many of these neurons prefer bars or gratings of a particular orientation. Suppose, for the sake of argument, that such an "orientation-tuned" neuron responds over a range of orientations on either side of the preferred orientation, and that the response falls to half-maximum when the bar or grating orientation departs by more than 10 deg from the preferred orientation. First we stimulate this neuron with a single grating to find the preferred orientation. Then we superimpose on the first grating a second stimulating grating with a different orientation. The crucial point is that a nonlinear interaction between the two grating responses can only occur if the neuron "sees" both gratings at once, in other words if they are both within its orientation tuning bandwidth.

If we can measure such a nonlinear interaction we can, in principle, measure the 20 deg orientation-tuning "bandwidth" of the neuron. This paper describes how that measurement can be made, and indicates the wider applicability of the technique to investigating the orientation and spatial frequency selectivities of cortical cells, to the exploration of auditory mechanisms and to the study of cutaneous receptive fields of somatosensory mechanisms.

EXPERIMENT 1: EVIDENCE THAT THE HUMAN VISUAL PATHWAY CONTAINS SPATIAL FREQUENCY ANALYZERS THAT ARE INDEPENDENT OF SPATIAL PHASE

Introduction

During the last 18 years a major theme in vision research has been the idea that, although at the first stage of retinal image analysis the photoreceptors sample on a point-by-point basis, at a later stage in the visual pathway the spatial aspects of the image are re-analyzed in terms of spatial frequency and orientation [1,2,3,4]. In a recent version of the hypothesis, every small patch of the retinal image is analyzed into a few (3-6) spatial frequency bands [5,6] and into about 4-8 bands of orientation [7]. At a functional level of description the hypothetical spatial frequency and orientation-selective analyzers are called "spatial frequency channels". The physiological basis of these functional subunits is widely assumed to be the spatial frequency selectivity and orientational selectivity that are well known characteristics of many cortical neurons [8].

In Experiments 1-3 we report an attempt to isolate and study the neural mechanisms tuned to orientation and spatial frequency that not only analyze the spatial aspects of the retinal image, but also subserve the spatial discriminations such as orientation discrimination and spatial frequency discrimination that are involved in recognizing objects.

Methods

We superimposed two vertical sinewave gratings, each of 5 cycles/deg spatial frequency on the face of a Joyce CRT of mean luminance 264 cd/m² with a white P4 phosphor. The fixed grating's contrast was 20%, and it was counterphase-modulated by an F_1 Hz sinewave (nominally 9 Hz). The variable grating's contrast was 40%, and it was counterphase-modulated by an F_2 Hz sinewave (nominally 7 Hz). The CRT's static calibration characteristic was linear to within 2% up to 85% contrast.

The steady-state EP consists of discrete frequency components, each of which can have very narrow bandwidths [9,10]. In practice, the optimum signal-to-noise ratio for any given component is obtained by matching the analyzer's frequency resolution to the bandwidth of the component. This was adequately achieved with a recording resolution of 0.0078 Hz. Therefore, the analysis was run with only 12,800 real frequency bins over DC-100 Hz and some of the extra resolution that could have been obtained with the 320-sec recording period was traded for frequency-domain averaging (N = 15). This technique is discussed in detail elsewhere [11].

Equipment was allowed at least 30 min to warm up, and the 7 Hz and 8 Hz signals were fed directly to the analyzer at the start of each session, thus calibrating frequency to within 0.0039 Hz. The computer then calculated the frequencies of all ($nF_1 \pm mF_2$) terms up to the fifth order (30 terms). Evoked potential components were only accepted if they agreed with calculation to an absolute accuracy of about one bin (i.e. 0.008 Hz). Recognition of high-order EP terms was limited by the long-term drift of electronic signal generators (say 0.1% over a day) rather than by the physiology. For this reason, several reproducible terms, presumably of high order, so far remain unidentified.

Although this ultra-high resolution analysis may seem unnaturally precise, it should be emphasized that it does not contravene Gabor's uncertainty principle or any other physical law. (Gabor's principle states that the best possible frequency resolution equals the reciprocal of recording duration. Thus, a 100-sec recording cannot give a better resolution than 0.01 Hz.) Our main result is the empirical finding that ultra-high frequency resolution reveals robustly-repeatable fine grain structure in the brain's responses, and this fine grain structure is invisible at lower resolution.

It is the noise level in the immediate neighborhood of an EP frequency component rather than overall noise level that determines the absolute signal-to-noise level of any component: It is important to note that the local noise level was quite different in different frequency ranges (e.g. 8 times less power/Hz at 32 Hz than at 8 Hz). Thus, for example, if 8 Hz flicker produces a 2 microvolt component at 8 Hz and a 0.5 microvolt component at 32 Hz, they will have roughly similar signal-to-noise ratios. Components of extremely small amplitude have excellent signal-to-noise levels in some frequency ranges. Signal level was calculated as the mean of the largest plus two adjacent lines (i.e. frequency bins) in Fig 1 minus the mean of the adjacent 10 lines, 5 on either side. (A signal-to-noise ratio measure gave similar results.)

Because the method may be unfamiliar, a brief explanation is appropriate. The discrete frequency components of a steady-state EP can be regarded as analogous to the components of an averaged transient EP. However, the number of clearly-resolvable frequency components can be larger and do not overlap. [We measured 20 in this study at signal-to-noise (power) ratios up to 140:1.] Most of the components of Fig 1 are irretrievably lost by averaging and cannot be regained by subjecting the average waveform to FFT. Our technique employs "zoom FFT" in a modified form that allows high zoom ratios to be combined with non-destructive analysis over a wide bandwidth [11].

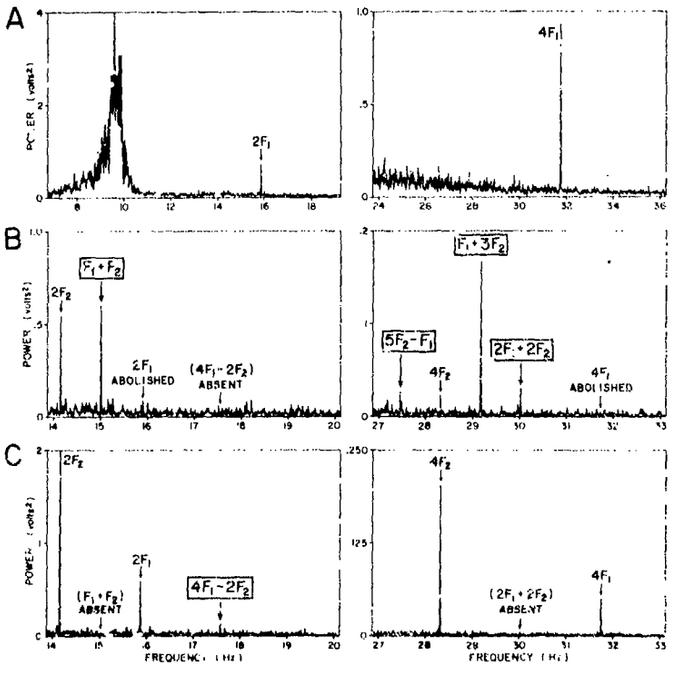

Figure 1. Discrete frequency components of the steady-state evoked potential. Two sections of the DC-100 power spectrum are shown at ultra-narrowband 0.0078 Hz resolution. A: The stimulus was a single grating that was counterphase-modulated at a nominal 8 Hz (actually 7.938 Hz). For comparison purposes the alpha region near 10 Hz is included in the spectrum. B: The grating in A was exactly superimposed on a second grating that was counterphase-modulated at a nominal 7 Hz (actually 7.080 Hz). C: The grating in A was superimposed on an unpatterned field flickering at 7.080 Hz. For any small retinal area the superimposed F_2 Hz grating in B was identical to the superimposed flicker in C. Thus, the terms boxed in B index nonlinear grating-grating interactions and are not explicable in terms of flicker processing or grating-flicker interactions. Ordinates are the dimensions of volts². Recording was between the inion and an electrode midway between inion and vertex with vertex grounded. Viewing was binocular.

Results and Discussion

First it was necessary to identify frequency components that were specific to spatial contrast rather than being explicable in terms of local flicker. Fig 1 illustrates the crucial control experiment.

Fig 1A shows two sections of the EEG power spectrum recorded during stimulation with a single grating that was counterphase-modulated at (nominally) F = 8 Hz. The response consisted of sharply-defined spikes at $2F_1$ = 16 Hz, $4F_1$ = 32 Hz and (not shown) other even harmonics of 8 Hz. Even at this ultra-high frequency resolution, VEP frequency components were often concentrated into a single 0.0078 Hz bin, implying, as noted previously [9,10], an amplitude and frequency stability that is quite remarkable for a physiological system. To put this in context, at the frequency resolution of Fig 1, the stability of the steady-state EP was not distinguishable from the stability of the electronic signal generators (Feedback model TWG-500 and Wavetek model 186) used to generate the stimuli.

Fig 1B shows two sections of the spectrum recorded when a second grating, counterphase-modulated at 7 Hz, was exactly superimposed on the Fig 1A grating with a relative spatial phase of zero. The $2F_1$ and $4F_1$ spikes were abolished, and several new terms appeared of frequency ($nF_1 \pm mF_2$). One of these cross-modulation terms, the (F_1+F_2) Hz component was larger than any other frequency component of the response. The terms that index a nonlinear interaction between responses to the two gratings are shown in boxes.

Four control experiments were then carried out. First, an instrumental control: A linear photocell was placed in front of the CRT and its output subjected to the same spectral analysis as that used in Fig 1. Nonlinear cross-modulation products were essentially zero, the largest having 0.02% of the power of the linear F_1 and F_2 signals). Then the EEG amplifier's linearity was tested: when fed with two equal-amplitude sinewaves, the largest cross-modulation term was 0.04% of the power of the two fundamental sinewave components at full drive. Next the sum of 7 and 8 Hz sinusoids was fed directly into the spectral analyzer. Cross-modulation terms were essentially zero (below 0.01% of the amplitude of the sinewave inputs). We conclude that the nonlinear terms, boxed in Fig 1B were not due to nonlinearity of the CRT, the EEG amplifier or the spectral analyzer.

The fourth control experiment was physiological. A uniform (unpatterned) field flickering sinusoidally at 7 Hz was superimposed on the Fig 1A grating. The flickering field had the same mean luminance as the F_2 Hz grating and the modulation depth was 40%. The rationale of this experiment was that if we consider any given small retinal area there is no difference whatsoever between the superimposed 7 Hz grating in Fig 1B and the superimposed homogeneous 7 Hz flicker in Fig 1C. Yet Fig 1C shows that this superimposed blank-field 7 Hz flicker produced a dramatically different effect to a superimposed 7 Hz counterphase-modulated grating. The nonlinear interaction terms boxed in Fig 1B were absent in Fig 1C, the Fig 1A $2F_1$ term that was abolished in Fig 1B is not abolished in Fig 1C. We conclude that the boxed terms in Fig 1B and the previously-reported suppression of $2F_1$ in B [12,13] reflect the processing of spatial pattern and cannot be explained in terms of flicker processing nor of interaction between pattern and flicker processing.

Having established that the (F_1+F_2), (F_1+3F_2), ($5F_2-F_1$) and ($2F_1+2F_2$) terms specifically index changes in retinal image contrast rather than the visual processing of local flicker we then asked whether any of these terms were determined by the spatial frequency power content of the stimulus independently of the particular pattern of light distribution in the retinal image. Our rationale was as follows. We varied the relative phase of the two superimposed gratings. This maneuver dramatically changed the luminance distribution in the retinal image while leaving the spatial frequency power content unaffected.

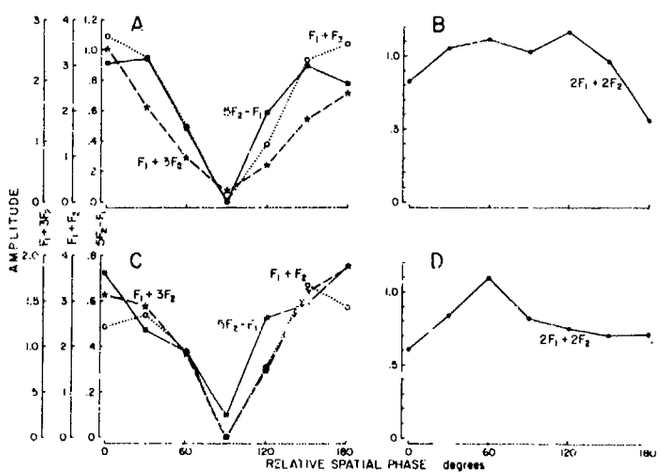

Figure 2. The effect of relative spatial phase on the amplitudes of nonlinear interactions between two superimposed gratings. As phase was changed from 0 deg to 180 deg, the light distribution across the retinal image changed considerably, but the spatial frequency power content remained constant. The interaction terms in A were strongly affected, but the ($2F_1+2F_2$) term in B was comparatively independent of relative phase. Panels C and D show similar results for a second subject. Amplitudes are in microvolts pk-pk. Other technical details as for Fig 1B.

Fig 2 shows the results of this manipulation for two subjects. Figs 2A and C show that several of the contrast-specific terms are strongly affected by the distribution of light in the retinal image. On the other hand, Figs 2B and D show that the contrast-specific ($2F_1+2F_2$) term is tolerably independent of the particular light distribution in the retinal image. Similar results were obtained for a third subject. We conclude that the ($2F_1+2F_2$) term indexes an interaction between responses to the two gratings that is rather independent of the particular light distribution in the retinal image [14].

The ($2F_1+2F_2$) term's insensitivity to spatial phase is intriguing in the context of Julesz's [15] psychophysical evidence that the phase spectrum is not used in preattentive texture discrimination.

At cellular level, the phase-independence of the ($2F_1+2F_2$) term in the human VEP parallels the phase-independence of complex cells in monkey visual cortex [16]. Furthermore, the nonlinear VEP properties of frequency doubling (Fig 1A) and the VEP interaction components boxed in Fig 1B can be modelled in terms of a compressive rectifier [17], thus providing a second parallel with the complex cell: De Valois et al [16] state that many complex cells in macaque give a frequency-doubled response to a counterphase-modulated grating (see Fig 1C) that is "virtually the same at every spatial phase", implying [18,19] that many rectifying subunits are distributed throughout the visual field.

EXPERIMENT 2: CAN THE VISUAL PROCESSING OF TWO-DIMENSIONAL PATTERNS BE EXPLAINED IN ONE-DIMENSIONAL TERMS?

Introduction

The hypothesis that human spatial vision can be described in one-dimensional spatial frequency terms [4] has created a substantial psychophysical and evoked potential (EP) literature. In its most recent version, the basic idea is that the spatial attributes of each small patch of the retinal image are analyzed by channels tuned to a limited number of discrete spatial frequencies (about six, according to Wilson and Gelb [6]), and also to orientation [3] - perhaps only a limited number (4-6) of discrete orientations [7]. These channels perform a kind of piecewise spatial Fourier Analysis [5]. At a physiological level, the responses of some neurons in monkey striate cortex evoked by two-dimensional checkerboard patterns can be explained in terms of the one-dimensional Fourier components of the pattern [20].

It is well known that a two-dimensional spatial pattern can be mathematically expressed as a linear sum of one-dimensional Fourier components, or as an integral [21,22]. It was soon realized that in some ways the spatial frequency approach is mathematically more convenient than the classical "point spread function" (Seidel aberration) approach to lens design and, following H.H. Hopkins' pioneering work in the 1950s, frequency domain analysis has become a standard procedure in optical engineering. But although, for a glass lens, the imaging of two-dimensional and one-dimensional targets are linearly related, this requisite cannot be assumed in physiological image processing. In particular, the application of one-dimensional Fourier methods to two-dimensional imaging assumes that there are no nonlinear interactions between responses to two simultaneously-presented gratings of different orientations. Here we report evidence that this assumption is substantially invalid for the human visual system.

Methods

A vertical sinewave grating of spatial frequency 5 cycles/deg was generated on a Joyce CRT and counterphase-modulated at frequency F1 (nominally 8 Hz). A second grating of spatial frequency 5.5 cycles/deg and variable orientation was generated on a second Joyce CRT and counterphase-modulated at frequency F2 (nominally 7 Hz). The two gratings were optically superimposed. Field size was 10 deg, contrast was 40% for each grating and mean luminance was 250 cd/m^2. Evoked potentials were analyzed in the frequency domain as described above.

Results and Discussion

The dashed line in Fig 3A plots the amplitude of a (2F1+2F2) cross-modulation response term as a function of the orientation difference between the gratings [23]. This cross-modulation term necessarily indicates a nonlinear interaction between visual responses to the fixed vertical grating and the variable-orientation grating, and is independent of spatial phase (see above). Fig 3A shows that the nonlinear interaction was large when the gratings were parallel and fell to a minimum when their orientations differed by about 30 deg. The half-height full bandwidth of the curve is about 12 deg, consistent with the bandwidths of sharply-tuned neurons in monkey striate cortex [24]. The frequency-doubled 2F1 Hz response produced by the fixed vertical grating was suppressed when the two gratings were parallel, but the second grating had comparatively little effect when grating orientations differed by about 30 deg. Similar results were obtained for a second (Fig 3) and third subject.

The observations reported above can be understood if the (2F1+2F2) term is generated by cortical neurons tuned to a narrow range of orientations. When the gratings orientations differ by more than about 30 deg, most of these neurons cannot encompass both gratings within their orientation bandwidths, and will therefore fail to generate an appreciable ($2F_1+2F_2$) term.

However, when we placed the two gratings at right angles (the fixed grating remaining vertical), the nonlinear cross-modulation term rose to a second maximum. For subject B this (2F1+2F2) term was as large for near-orthogonal gratings as for parallel gratings, and only a little less for subject A. The interaction term was largest at exactly 90 deg orientation difference for subject A but, curiously, peaked sharply just 5 deg from 90 deg for subject B.

This finding that there is a strong nonlinear interaction between responses to vertical and near-horizontal gratings can be understood if we assume that cortical neurons tuned to a narrow range of orientations around the vertical interact nonlinearly with cortical neurons tuned to a narrow range of orientations around the horizontal. It may be relevant that cortical neurons tuned to different orientations can inhibit each other when excited simultaneously [25,26], an effect that has been suggested as an explanation for the finding that some simple cells fail to respond to two-dimensional texture, even though they respond strongly to a one-dimensional pattern that is optically contained within the texture [27,28]. Complex cells, on the other hand, respond to both one- and two-dimensional patterns [27]. In this way, inhibition of simple cells by complex cells renders simple cells specifically sensitive to one-dimensional features such as edges [28].

If our findings can be generalized to other kinds of two-dimensional pattern, this would imply that human VEPs to two-dimensional patterns cannot entirely be explained in terms of VEPs to one-dimensional gratings. And, bearing in mind that psychophysical contrast threshold correlates with VEP amplitude for both one-dimensional gratings [29], and for two-dimensional checkerboards [10,30], our VEP findings may also point to the limits of applicability of one-dimensional Fourier methods in the psychophysics of two-dimensional spatial vision [23].

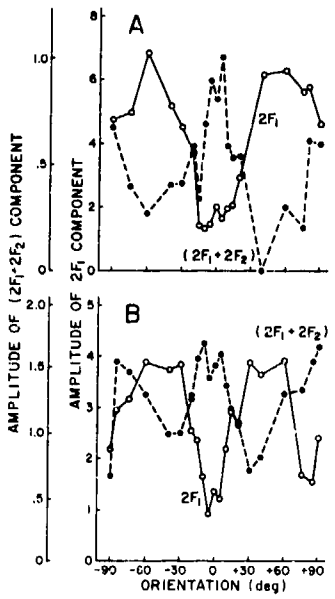

Figure 3. Nonlinear interactions between two gratings as a function of orientation difference. A vertical grating was counterphase-modulated at F1 Hz and a variable-orientation grating at F2 Hz. Filled symbols plot the amplitude of the nonlinear cross-modulation (2F1+2F2) Hz term in the evoked potential versus of the variable grating's orientation. Open symbols plot the frequency-doubled 2F1 Hz term. Results are shown for two subjects.

EXPERIMENT 3: SPATIAL FREQUENCY (SIZE) SELECTIVITY IN THE HUMAN VISUAL SYSTEM

Methods

A vertical 20% contrast grating was counterphase-modulated at F_1 = 8 Hz, and maintained at a constant spatial frequency of 5 cycles/deg. A second vertical grating of higher (40%) contrast was counterphase-modulated at 7 Hz, and its spatial frequency varied from 0 (blank field) to 21 cycles/deg. Evoked potentials were recorded with the two gratings superimposed.

Results and Discussion

Fig 1B confirms previous reports [12,13] that the $2F_1$ Hz component, characteristic of a single grating (Fig 1A), was attenuated when the F_2 grating had the same spatial frequency as the F_1 grating, but was comparatively little affected when the two spatial frequencies were very different. Fig 4 adds the new finding that the approximately phase-independent $(2F_1+2F_2)$ component rose to maximum power when the two gratings had the same spatial frequency.

Following our previous argument (see above), if one grating's spatial frequency falls inside a frequency-tuned mechanism's bandwidth and the other grating's spatial frequency is well outside, the mechanism "sees" only the first grating so that there can be no interaction. According to this argument, the attenuation of the $2F_1$ Hz component in Fig 4 indexes the spatial frequency tuning bandwidth of the mechanism that produces the $2F_1$ Hz response in Fig 1A. Note though, that the Fig 4 curve shape is for the specific temporal frequency F_2 = 7 Hz.

The $(2F_1+2F_2)$ curve in Fig 4 follows an approximately converse pattern to the $2F_1$ component, showing maximum interaction when the two spatial frequencies are equal though exact reciprocity cannot be expected because two rather than only one tuning bandwidth may be involved: the $(2F_1+2F_2)$ component may be produced by one tuned mechanism and/or by interaction between the frequency-doubled outputs of two mechanisms tuned to different spatial frequencies.

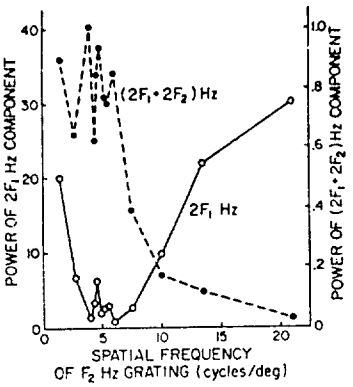

Figure 4. A vertical sinewave grating of 40% contrast, counterphase-modulated at F_2 = 7 Hz and of variable spatial frequency was superimposed on a second vertical grating of 20% contrast and fixed (5 cycles/deg) spatial frequency counterphase-modulated at F_1 = 7 Hz. The $2F_1$ Hz response to the second (reference) grating was virtually abolished when the variable grating had the same spatial frequency, and at the same time the phase-independent $(2F_1+2F_2)$ term rose to a maximum.

EXPERIMENT 4: AUDITION: THE FIRST STAGE OF PROCESSING IN THE INNER EAR

An amplitude-modulated (AM) tone, generated by multiplying a carrier sinusoid of frequency f_1 = 1048.50 Hz by a sinusoid of frequency F_1 = 20.886 Hz, was fed to the subject's left ear [31]. The potentials recorded between the right earlobe and vertex were amplified over a 1-200 Hz bandwidth and subjected to spectral analysis with a resolution of 0.0078 Hz, giving approximately 25,000 real frequency bins. Fig 5A is a segment of the spectrum that includes a response component of frequency $2F_1$ whose bandwidth was evidently less than 0.0078 Hz. This narrow bandwidth is consistent with very high stability of amplitude and phase over the 320-sec recording duration. The experiment was then repeated with the same f_1 Hz carrier modulated by a sinusoid of frequency F_2 = 21.778 Hz, and this stimulus produced a response at $2F_2$ Hz. Next, the F_1 Hz tone was fed to the left ear, and the F_2 tone to the right ear (dichotic situation). The only appreciable effect was a reduction of the left ear's $2F_1$ Hz response to about 60% of its power (i.e. approximately 20% amplitude reduction). In other words, the left ear's response was slightly attenuated by the input to the right ear and the right ear's $2F_2$ response could be recorded as well: no cross-modulation terms were recorded (Fig 5B).

Then the F_1 and F_2 Hz AM tones were electronically summed and fed to the same (left) ear. Fig 5C shows that the result was quite different to the dichotic case of Fig 5B. There was a strong nonlinear interaction that almost abolished the $2F_1$ and $2F_2$ components, and created a nonlinear cross-modulation term of frequency (F_1+F_2), i.e. (42.664 Hz) that had about twice the power of the $2F_1$ response to the F_1 Hz AM alone (compare C with A). Next, we used two carriers instead of one. The f_1 = 1048.50 Hz carrier was modulated by the F_1 = 20.886 Hz sinusoid as before, but this time the F_2 = 21.778 Hz sinusoid modulated an f_2 = 1048.49 Hz carrier. The two AM tones were summed and fed to the left ear. The (F_1+F_2) response was considerably diminished (about fourfold in power), and the $2F_1$ and $2F_2$ terms enhanced (about sixfold in power) so that the response pattern looked quite different to casual inspection (Fig 5D). More careful inspection at higher resolution showed an additional effect that may be just visible in panel D. The central spike had split into two components 0.02 Hz apart. (Remember that the two carriers differed by 0.01 Hz.) This split is quite clear in Fig 5E, where the carrier frequencies differed by 0.1 Hz, and the split terms (a and b) are 0.2 Hz apart. In Fig 5F the carriers differ by 0.25 Hz, and the split terms (a and b) are 0.5 Hz apart. In Fig 5G the carrier differ by 1.3 Hz and the split between a and b is so large (1.6 Hz) that a and b fall right outside the $2F_1$ and $2F_2$ terms.

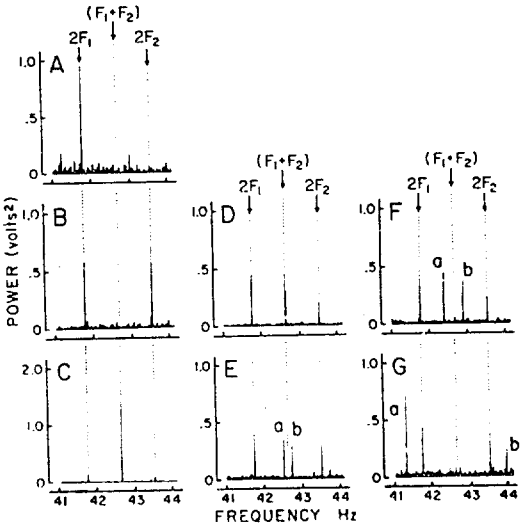

Figure 5. Response spectra recorded between the vertex and right earlobe. Three auditory waveforms were used: S1 - an f_1 Hz audio carrier amplitude-modulated at F_1 Hz; S2 - an f_1 Hz carrier modulated at F_2 Hz; S3 - an f_2 Hz carrier modulated at F_2 Hz. A: S1 to left ear. B: S1 to left ear, and S2 to right. C: S1 plus S2 to left ear. D-G: S1 plus S3 to left ear. D: (f_2-f_1) = 0.01 Hz. E: (f_2-f_1) = 0.1 Hz. F: (f_2-f_1) = 0.25 Hz. G: (f_2-f_1) = 1.3 Hz. Ordinates are power with the dimensions of volts². Signals were analyzed over a DC-200 Hz bandwidth using zoom-FFT by a Bruel and Kjaer model 2032 analyzer at 0.0078 Hz frequency resolution.

In brief, Figs 5D-G show the following two effects: (1) The (F_1+F_2) term is smaller (relative to the $2F_1$ and $2F_2$) terms) than in Fig 5C where there was only one carrier; (2) The (F_1+F_2) term splits into two parts whose separation equals $2(f_1-f_2)$ Hz. The effects were confirmed in two other subjects.

The sound stimulus was calibrated by placing a microphone in front of the earphone, and analyzing its output in the same way as the brain responses. Nonlinear terms were essentially zero.

A proposed explanation for these physiological findings is as follows. The responsible nonlinearity must lie before the signals from the two ears unite, because the dichotic case (Fig 5B) does not show these effects. We note that binaural convergence occurs already at the olivary nucleus. It is known that the transducer function of hair cells has the rectifier-like shape shown in Fig 6A [32]. An electronic circuit with a similar input-output characteristic (Fig 6B) was fed by the same AM signals used to generate the auditory stimuli used in Figs 1C-G. Fig 6C-J shows that this analog model of hair cell transduction produced all the effects observed in the physiological recordings of Fig 5C-G.

We tentatively suggest that the curious nonlinear behavior observed when one ear is stimulated with the sum of two AM tones is consistent with the characteristic shape of the transducer function of hair cells. Furthermore, the rectifier-like shape of the function explained why a single carrier modulated at F_1 Hz produces a $2F_1$ Hz response (Fig 5A), even though the sound wave contains no $2F_1$ or F_1 Hz Fourier component, or indeed any component within 1000 Hz of these frequencies [31].

Further developments of this approach and its formal mathematical treatment may enable variations of the shape of the hair cell transducer function to be investigated in the normal ear, and in ears affected by pathology or by toxic agents.

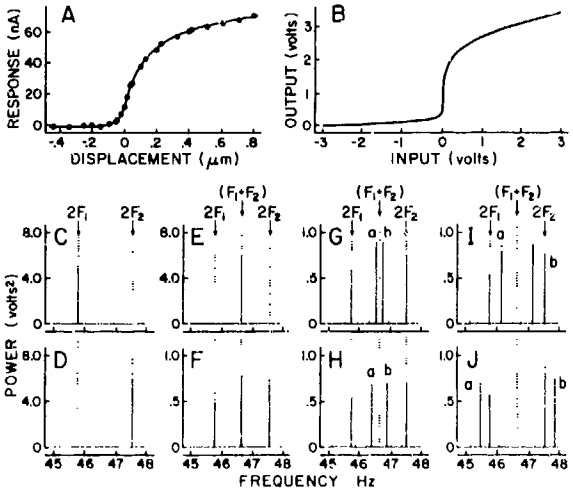

Figure 6. A: physiological transducer function for hair cells [32]. B: input-output transducer function for hardware model. C-J: response spectra for hardware model. C: as A in Fig 5. D: stimulus S2 only. E: as C in Fig 5. F: as D in Fig 5. G: as E in Fig 5. H: as F in Fig 5. J: as G in Fig 5. Analysis as in Fig 5. Input voltage 2.6 pk-pk maximum. Similar results were obtained for 0.5, 0.18 and 0.09 maximum volts pk-pk.

CONCLUSIONS

The frequency domain techniques previously developed for the analysis of steady-state EPs enable small signals to be extracted from a high noise background [9,10,33] or, alternatively, by means of such methods as "sweep EPs" or "EP feedback" [33,34,35,36], offer substantially shorter recording procedures (up to 30-fold speed increase compared with conventional time-domain averaging).

We describe here an additional development of steady-state EP recording that allows certain powerful mathematical techniques of nonlinear systems analysis to be generally applied to the investigation of visual, auditory and somatosensory processing in the human brain. (It should be noted that time-averaging techniques are quite inappropriate. Any averaging that is required must be carried out in the frequency domain rather than the time domain. This point is discussed in detail elsewhere; see references 9,10,11.)

FUTURE POSSIBILITIES

The use of the techniques described here in neuromagnetic investigations of visual, auditory and somatosensory pathways will add the greater precision of generator location offered by neuromagnetic recording to the analytic power illustrated here. (Because volume currents propagate large distances, both nearby and distant sources may contribute to the evoked potential recorded from any given electrode, but a SQUID magnetic sensor coil records nearby sources only.)

But there is a further, and more basic point. So far we have discussed the interpretation of results only in terms of qualitative commonsensical conclusions. Mathematics has been mentioned only in the purely technical context of signal recording, rather than as a tool for more profoundly probing central nervous system function and interpreting experimental results.

In general terms, nonlinear interactions between multiple sensory inputs can be regarded as basic to brain function in the everyday world. The brain is not a linear system that merely applies a scaling factor to the sensory inputs it receives; rather it manipulates the incoming sensory information, using strongly nonlinear processing in order to achieve goal-directed motor action. The nonlinear operations performed by the brain, it has been suggested, include multiplication [37,38], division [39,40] and logarithmic compression.

One of us (MPR) has developed a mathematical procedure, based on Bennett's [41] double Fourier integral approach, of calculating the nonlinear cross-modulation products of frequency ($nF_1 \pm mF_2$) produced when the sum of two sinewaves of frequencies F_1 and F_2 are fed to rectifiers of different kinds. Single rectifiers of linear, compressive (e.g. square root), accelerating (e.g. square law) characteristics, cascaded rectifiers and parallel cascaded rectifiers have been theoretically treated, and discrete components up to the fifth order calculated [the order is defined as (n+m)] [42]. The point of all this is that many neurons behave rather like rectifiers. For example, a neuron may respond to an increase but not a decrease of contrast. Our theoretical work suggests that the behavior of the discrete frequency components constitutes a kind of high-resolution "fingerprint" that characterizes different kinds of nonlinearity. This "fingerprint" is capable, for example, of identifying rectification-plus-multiplication or rectification-plus-compression.

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DISCUSSION

LANDOLT, CA: Have you tried to record intermodality interactions? For example, have you tried to record any visual-auditory or visual-vestibular interactions? Do you see the method's applicability in mapping out common brain areas responding to more than one sensory modality?

REGAN, CA: Yes, in principle, the method is capable of recording interactions between different sensory modalities. We have recorded visual-auditory interactions; we have not tried visual-vestibular ones. The maps of macaque monkey cortex published by Van Essen show several discrete areas containing neurons that respond to more than one modality. We now know where these areas are — at least in the macaque monkey (Van Essen, D. In: Peters, A. and Jones E.G. Cerebral Cortex, Vol.3. Plenum Press, New York, N.Y., pp. 259-329, 1986). It seems likely that corresponding areas would exist in man. So, it would make sense to use the neuromagnetic brain recording technique in humans to search for intermodality interaction responses, because the neuromagnetic technique seems to have a higher spatial resolution than the evoked potential technique.

WEINBERG, CA: This is a beautiful technique, but how do you get 25,000 bins?

REGAN, CA: The best possible frequency resolution Δf Hz is approximately equal to $1/T$, where T is the recording duration. This follows from Heisenberg's Uncertainty Principle, and its relevance to signal analysis was first pointed out by Dennis Gabor. Thus, if you record a continuous sample of EEG 200 seconds in duration, and compute a frequency spectrum (e.g., power versus frequency), a resolution of $\Delta f = 1/200 = 0.005$ Hz is possible, giving 200 x 100 = 20,000 lines over a DC - 100 Hz bandwidth. The reason why you usually do not get this ultra-high frequency resolution is technical rather than theoretical — it is there for the taking. When conventional FFT is used to compute the spectrum, you obtain a spectrum from DC to some maximum frequency, fmax, and the number of lines depends on the size of the transform: a 1K transform gives about 400 lines and a 2K transform (i.e., 2048 samples) gives about 800 lines. Increasing the transform size soon becomes prohibitively expensive in spectral analyzers. The technique we use is called zoom-FFT. Let's say we have a 2K transform, giving 800 lines from DC to fmax, and we require about 25,000 lines over a DC to 100 Hz bandwidth. We analyze the signal in 3-Hz segments. First we set fmax at 3.0 Hz, and do an FFT giving 800 lines from DC - 3 Hz. Then we take the original signal and multiply it by 3.0 Hz, giving two sets of beat frequencies (sum and difference), and remove one set by filtering. This procedure converts the original 3.0 Hz to DC, so we can apply the FFT again. Then we re-label the frequencies, and thus have 800 lines from 3.0 - 6.0 Hz. And so on. Our version of this technique stores the original signal, and allows the off-line analysis to be carried out at very high speed. High "zoom" factors are available — we routinely use a factor of 32.

SQUID INSTRUMENTATION FOR NEUROMAGNETIC STUDY OF COMPLEX BRAIN ACTIVITY

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SUMMARY

The impressive results obtained during the last few years by applying the neuromagnetic method to the investigation of brain physiology and pathology have given an extraordinary impulse to the development of large multi-sensor systems, which should permit, in a relatively near future, to simultaneously detect the distribution of the magnetic field over a large area of the scalp and to achieve a real time functional localization of active cerebral sources. In this paper an outline of the main instrumental problems in the choice of an optimal sensor configuration - for large multichannel systems - is presented, with particular emphasis on the capability featured by different kinds of superconducting gradiometers to identify complex cerebral sources, and on the need for more sophisticated model sources.

INTRODUCTION

During the last few years exciting results have been obtained in the neuromagnetic investigation of spontaneous and evoked cerebral activity(1). A unique capability of the technique is the possibility of achieving a three-dimensional identification of active areas in the brain, namely a "functional localization". Therefore the method might turn into a powerful tool to study higher levels of brain functions, like those related to attention, memory, etc.

In order to achieve this goal large multichannel systems must be developed, to simultaneously measure the distribution of magnetic fields at numerous sites of the scalp. The few systems (four to seven adjacent sensors) based on SQUID technology so far operating in the world(1) can provide only a limited view of this distribution and, as a consequence, the measurements must be repeated several times at different scalp locations. This procedure - which is based on the hypothesis that cerebral responses are stationary - causes two drawbacks: 1) re-positioning errors can be introduced, and this strongly affects the localization reliability; 2) the measurement is prolonged for one hour or more, and a variability in the psychological conditions of the subject occurs. This variability might be acceptable as far as primary cortical areas are concerned, but proves to be a major constraint when studying higher levels of brain functions.

It is therefore commonly agreed that the new generation of neuromagnetic systems should be in the "class 100", i.e. consisting of a number of adjacent magnetic sensors of the order of 100, distributed onto a spherical surface in such a way to cover a scalp area of at least 150 cm^2. There are, however, different possible choices for the array of superconducting sensors to be used in the system. As a consequence of this choice, particular attention should be devoted to the capability of a specific array to detect biomagnetic sources. For example, gradiometers with planar geometry have a most interesting feature: an enhanced sensitivity with respect to higher spatial frequencies. This might prove to be a major advantage when facing the problem of distinguishing complex source configurations.

SENSOR CONFIGURATION

"Wound-wire" detection coils - magnetometers and/or gradiometers - have been so far widely used both in shielded and in unshielded environments. Alternatively, planar geometries, directly fabricated onto silicon chips, have been proposed by several groups (3-5). (see Fig.1). In this case the detection coil - independently of the specific configuration, i.e. magnetometer, first-order gradiometer, second-order etc. - is inserted in the SQUID itself. The efficiency of coupling between the detection coil and the SQUID, namely the flux transforming ratio (2) of the superconducting loop, is

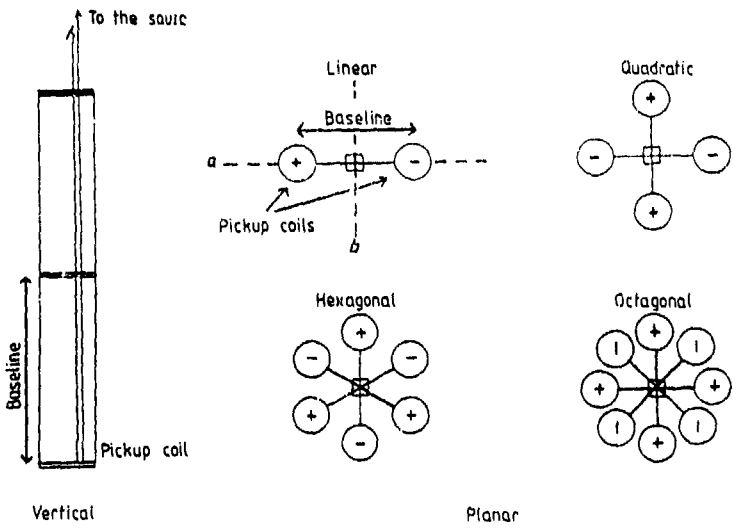

Figure 1. Schematic drawing of a "vertical" second-order gradiometer and of the four simplest geometries of planar gradiometers. The parameters used for the simulations reported in the text are as follows: vertical gradiometer, 1.5 cm coil diameter and 5 cm baseline; planar gradiometers, 0.5 cm coil diameter, 1.5 cm baseline. The square in the center of each planar gradiometer schematically represents the DC SQUID.

therefore maximum (unitary), differently from what happens with wound-wire coils, where coupling to the SQUID inductance unavoidably reduces the efficiency of the loop to a few percent. It has been also shown (2) that planar gradiometers feature additional advantages, like the absence of superconducting contacts and a higher feasibility to integration in large arrays. Conversely, the shape of the pattern detected in presence of a typical biomagnetic source, namely a current dipole, is generally more complicated with respect to that featured by arrays of "vertical" gradiometers, and this can be considered a partial drawback as far as a clinical use of the technique is concerned. Fig.2 shows a simulation of the spatial-temporal characteristics of the signals detected by an array of vertical (a) and of planar (b) (quadratic) gradiometers, respectively(6). To get these simulated tracings it was assumed that a dipolar source was located at a depth of 5 cm below the surface of a homogeneously conducting half space. The source intensity was assumed to be modulated accordingly with the typical morphology of a somatosensory evoked signal (median nerve stimulation, see insert of Fig.5). The simulated tracings represent signals actually detected by an array of 36 gradiometers, 6 by 6, spaced 2 cm from each other. The geometrical dimensions of the gradiometers are reported in the caption of Fig.1. It is worth noting that the scaling factor is different between (a) and (b): as pointed out in (6), the comparison between planar and vertical gradiometers is even more favoreable to the former if a realistic value for instrumental noise is taken into account. This turns to be an important advantage when facing the localization problem. On the other hand, as already mentioned, we have to pay the penalty of an increased complexity in the detected pattern, as clearly illustrated by the two iso-field maps in Fig.3.

Another advantaged provided by planar geometries is their higher capability to reject disturbing sources. It has been shown (2) that this effect can be orders of magnitude larger than that achievable with a corresponding array of vertical gradiometers. This property has obvious implications for what concerns the use of magnetic shieldings with large neuromagnetic systems.

COMPLEX SOURCES

There is, however, another point which is particularly significant for the purpose of the present article. It is common opinion that the simple dipolar model (7) can be used as a model source to account for neural activity only to a limited extent. More specifically, it is relatively infrequent that a cerebral event involves only a

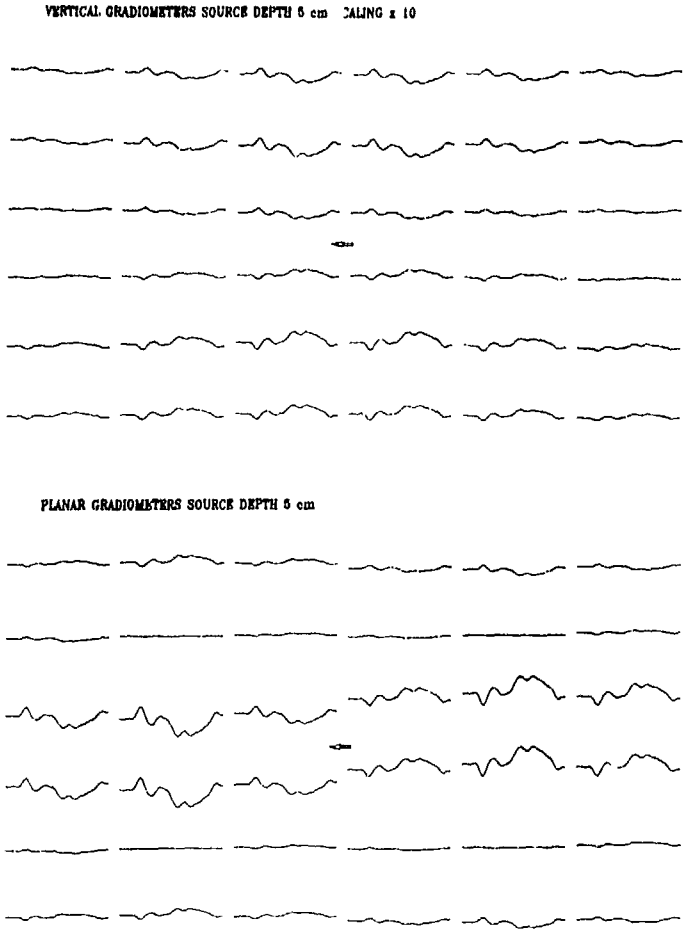

Figure 2. Simulated evoked signals from a current dipole, the intensity of which is made to vary with time according to an actually measured evoked field, as sensed by an array of 36 vertical (top) and of 36 planar (quadratic) gradiometers (bottom). Sources are located 5 cm below the center of each array. Note the different scaling factor.

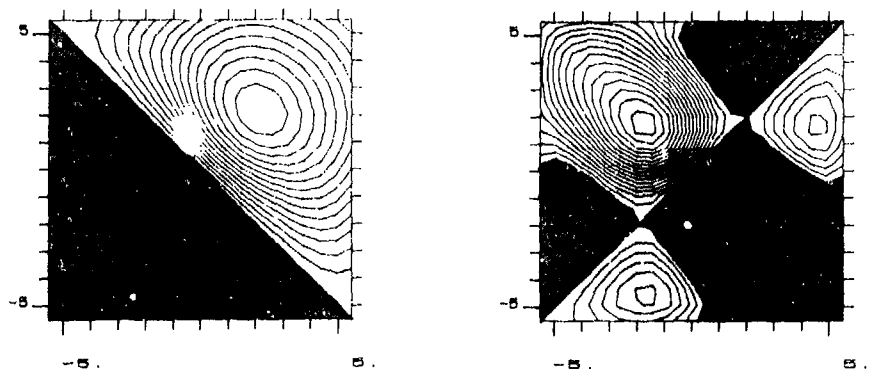

Figure 3. Simulated iso-field contour maps illustrating the field distribution from a current dipole (5 cm depth) as detected by an array of 36 vertical (left) and planar (quadratic, right) gradiometers respectively.

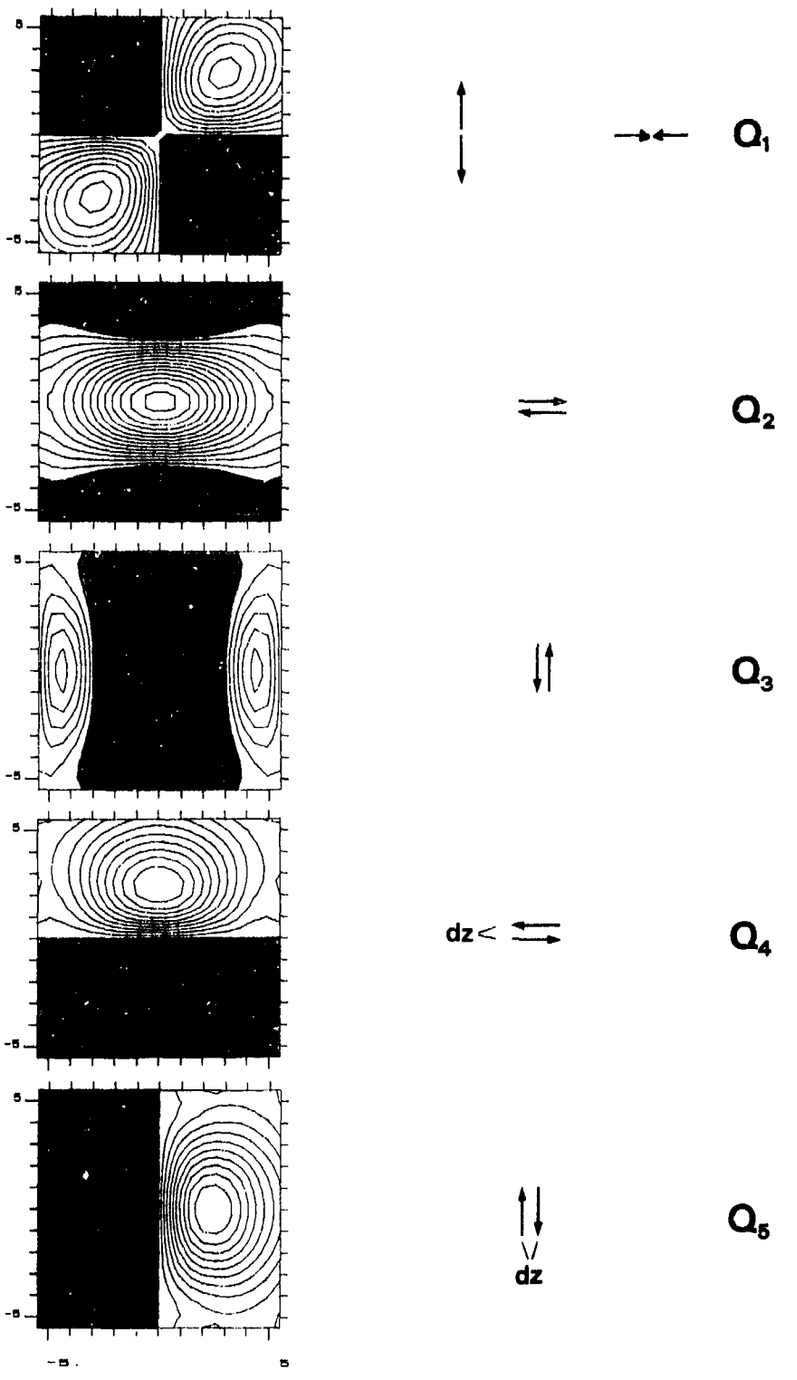

Figure 4. Simulated field patterns from the 5 components (depicted on the right) of a current quadrupole (5 cm depth) as sensed by an array of 36 vertical gradiometers (8).

concentrated population of neurons in a small portion of the cortex. This most likely happens for the early cortical components in the auditory and in the somatosensory modalities. But even in this relatively well-understood events - as we will see in the following - and certainly in all those functions which are event-related in some way, a simple dipolar model is oversimplifying and cannot be used for source localization. A detailed simulation (2) on the performances of arrays of vertical and planar gradiometers with respect to their respective capability to identify two dipolar sources showed the superiority of the second kind of geometry. This property may be related to the larger sensitivity featured by the planar devices with respect to higher spatial frequencies.

In general, multiple dipoles, more or less synchronously active, or more complex source configurations, involving quadrupolar components (8) should be considered for the analysis of experimental data. Fig.4a schematically illustrates the shape of different components of a quadrupolar source. We want to remark that all these components consist in combinations of two antiparallel dipoles. Fig.4b shows the the theoretical field patterns associated to each of these components (8,9). Although the physiological meaning associable to these configurations is certainly less intuitive than that of a simple dipolar source, it is however not unrealistic to have current circuits either in the cortex or in sub-cortical - cortical connections which can be accounted for by one, or by a combination of, quadrupolar component(s).

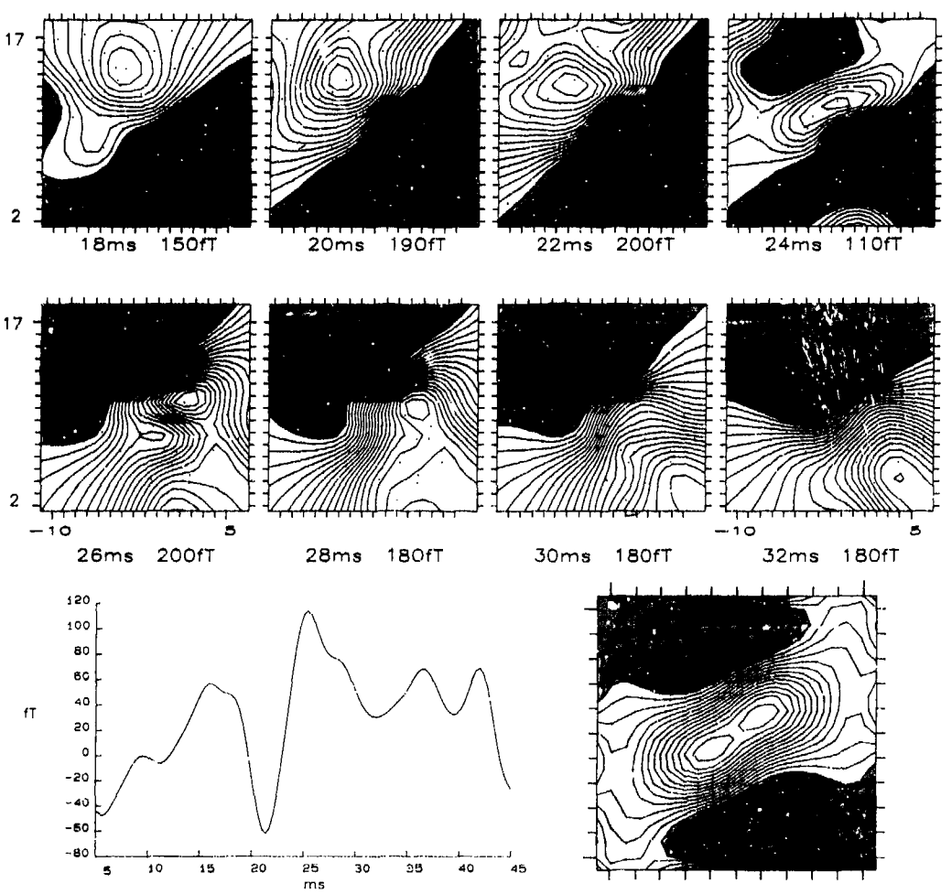

Figure 5. (top) Sequence of 8 iso-field contour maps illustrating the temporal evolution of the field distribution as measured after median nerve stimulation. Iso-field step, 5 fT. (bottom, left) Evoked field as measured at position (-5,13) of the grid. (right) Simulated iso-field map illustrating the field distribution from equally intense components Q_1 and Q_2 of a current quadrupole at 5 cm depth (8).

We want to remark that a motivation for this kind of theoretical analysis stems from the experimental observation of complex field patterns during cerebral evoked response. Evidence for this was observed, for instance, in the scalp distribution of magnetic fields generated in a CNV experiment (10). But even in the investigation of evoked fields originating in primary areas is not infrequent to observe clearcut spatial patterns strongly resembling those produced by a quadrupolar model source. Fig.5 shows a sequence of 8 iso-field maps illustrating the spatial-temporal evolution of the magnetic field evoked by stimulation of the left median nerve at the wrist, as measured over the contralateral somatosensory cortex. The reference frame is a coordinate system the origin of which is located at the intersection of the Nasion-Inion horizontal line with the ear-ear line through the vertex. The positions where the magnetic field was measured are identified by dots in each map. The time at which each map was calculated (reported below each map) is identifiable on the evoked magnetic field as measured in one of the two "maxima" (measuring site -5,13 on the grid) shown in the insert (bottom, left). The dipolar character evident in maps (1-3, 5-8) suggests a source progressively shallower from 1 to 3, and progressively deeper - and differently located - from 4 to 8. Nevertheless, the field pattern illustrated in map 4 strongly resembles the theoretical one generated by a simple combination (Q_1-Q_3) of quadrupolar components (bottom, right). We want to stress that this consideration is merely qualitative, but may provide a hint on the need for more sophisticated model analyses.

CONCLUSIONS

Although the development of large neuromagnetic systems is still at the beginning, it should be carefully considered that the choice of the geometry for the array of sensors has a fundamental importance. Indeed, as we have briefly reviewed, each choice has advantages and disadvantages. It is therefore not a simple task to establish the optimal configuration and, probably, different systems should be designed for different experimental requirements, including the use or not of shielded rooms, the need for studying complex brain activity, etc. What should be pointed out, however, is that, in spite of the mentioned difficulties, which are being or are going to be solved by more sophisticated studies, the neuromagnetic approach is going to provide a unique tool to investigate cerebral activity and to achieve a real time functional imaging.

ACKNOLEDGEMENTS

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DISCUSSION

OFFENLOCH, GE: In your presentation, you showed evoked magnetoencephalographic recordings of sensory afferents. We know from neurophysiology and neurology that these afferents project to specific thalamic nuclei, and they project sharply to the motor sensory cortex. Why do we see such large fields in your maps?

ROMANI, IT: In the first place, you should be aware that magnetic measurements are more sensitive to tangential current flows than to radially oriented currents. This is a fundamental point. In principle, if the head were a sphere we would never see radially oriented currents. Secondly, when we looked at the distribution of isofield maps, the first three or four had maxima which were much more widespread than those obtained later on. These are contributed by a deep brain source.

KAUFMAN, US: The question as I heard it was that, since we know from neurophysiology that activity of this type is very focal, why are the magnetic fields that we measure so widely distributed? If you have a short segment of current, then it is surrounded by a magnetic field which extends forever. It falls off inversely as the square of the distance, but it is very widespread. The field which appears above the surface of the head also has a pattern which is very widespread. By measuring the entire pattern, you get information about the focal source. In fact, the only way in which to image this source is to think of it as being analogous to a point source in optics -- an infinitesimal point of light from which you can measure a different pattern in the distribution of light in space. Similarly, you can treat a clump of many neurons, say 100,000, as seen from a distance of 3 cm as though it were a point source having a magnetic field that is spread throughout space. Although the field is widespread, the source is exactly as you described it; it is focal in this model.

LANDOLT, CA: Both Dr. Kaufman and Dr. Romani alluded to the possibility of designing a 100 to 120 sensor system for MEG recording. I presume that's a conceptual goal. In such a system, what would be the diameter of the sensors, and what is the anticipated brain volume from which you expect to record? Are you looking at a system that is the real-time equivalent of nuclear magnetic resonance imaging?

ROMANI, IT: The first answer is that the diameter of the coils that are currently used is about 1 to 1.5 cm. Secondly, these coils must be placed in an array having a particular spacing which is specific to the range of depth that you want to investigate. It is useless to reduce the diameter of the coils and put them closer together than a couple of centimeters. This would simply increase the spatial sampling rate without providing any significant improvement in the localization, if the source is deeper than 1 cm (which is the minimum depth that you can record from a source through the scalp). As you said, the large system that Dr. Kaufman and I discussed is conceptual, but it is certainly possible with present state-of-the-art technology. A 100-sensor system coupled to a powerful computer for on-line real-time imaging is a goal that can be achieved in the next 4-5 years.

KAUFMAN, US: I subscribe to everything Dr. Romani said except that I believe it will only be 3 years, because physically it is already being developed.

GEVINS, US: I subscribe to everything that Dr. Romani and Dr. Kaufman said, except that I think it will probably take 6 years. The reason for this is that the analysis of three-dimensional real-time imaging, whether the signals are magnetic or electric, or, preferably, both is very complicated. This is not a trivial problem because as more complex source configurations are required, better and better signal-to-noise ratios are needed. It will take a great deal of effort; it will not be solved overnight with a Cray computer. Additionally, all the issues that have to do with contaminants from eye movements, muscle potentials, etc. will also have to be dealt with in the MEG, as they have in the EEG. There are many issues that must be addressed besides physically building the system, so I am less certain of the time for completion, although I certainly think that it is possible.

Electric and Magnetic Brain Activity Related to Cognitive Performance

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Summary

I. Introduction and Overview

II. Research Background
A. Cognitive Performance and Brain Activity
B. Memory Storage Component in Evoked Potentials
C. Connotative Meaning
D. Syntactic Differences in Words and Linguistic Processing

III. Prospects for Electrical and Magnetic Recording

I. Introduction and Overview

Electrical potentials recorded from the scalp have been successfully used to study various brain processes. It has become possible to record magnetic fields under similar conditions (Cohen, 1968). Magnetic and potential fields produced by the nervous system have different properties that can be exploited for the study of brain activity related to information processing (e.g., Cohen and Cuffin, 1983; Romani and Leoni, 1985; Romani and Williamson, 1983; Romani, Williamson, and Kaufman, 1982a, 1982b; Williamson and Kaufman, 1981).

Electrophysiological and behavioral research has pointed to meaningful components and temporal events in Evoked Potentials that, in conjunction with behavioral measures, could elucidate targeted cognitive processes. This research has not only involved P300 and CNV components, but also has utilized other components that may be measured and related to cognitive performance, including short-term memory and linguistic processing. For example, research on the relations between connotative meaning of words and brain activity shows that the brain activity in different individuals is sufficiently similar for a common model to discriminate word classes significantly better than chance. Furthermore, these brain response discriminations among stimulus word classes survived variation in the subject's task.

Memory and memory organization are research areas that are fundamental to learning and cognitive processing. Failures to learn may be due to failures at the time of input to memory, during retention, or at the retrieval stage from memory. It has been difficult to disentangle what is occurring at each of these stages without interfering with the ongoing cognitive processes. Assessing memory with behavioral techniques can only be done at the retrieval stage, of course, but some clever experimental designs have been applied to uncover what is in memory at various stages. These have used behavioral measures of response timing, probe techniques, priming techniques, etc. In addition to these behavioral measures, it would be extremely helpful to have physiological indices of these fundamental processes in learning. We have developed some physiological indices that relate to storage in short-term memory and to semantic processing, and therefore, show great promise of aiding understanding of fundamental processing in learning.

Section II-A outlines the general nature of Evoked Potential (EP) recording of brain activity related to cognitive performance. It describes earlier experimental results and the early use of multivariate techniques to separate P300 and CNV. Section II-B explains how such an approach, using multivariate analysis techniques, has uncovered a brain activity component that is related to storing information in memory and how that Storage Component was subsequently used to predict recall in a cognitive experiment using a behavioral, probe technique. Section II-C concentrates on a body of work which has shown relations between connotative meaning of words and brain activity. This work suggests that the brain activity in different individuals is sufficiently similar for a common model to discriminate word classes significantly better than chance. Section II-D extends the research to syntactic performance that has shown a basic distinction between two syntactic classes of words, function words and content words. Electrical activity related to parsing performance in sentences that contain local structural ambiguities has also been studied. The results obtained make us optimistic about the utility of recorded brain activity in answering these and other questions about sentence comprehension, as well as other kinds of cognitive performance.

II. Research Background

A. Cognitive Performance and Brain Activity

One of the most direct methods of studying the neural bases for learning and memory in man is studying Evoked Potentials (EPs) and performance while the human subject is processing information. The neurophysiological evidence may not only set limits on the kinds of models that may be reasonably entertained and assist in differentiating between competing theories, but also may provide new indices of various cognitive processes. Evoked Potential research provides the opportunity to look within the black box between stimulus and behavioral response, because systematic brain activity can be recorded during this stimulus-response interval.

Several Evoked Potential components have been related to various information processing functions, some of which are the most specific cognitive EP components yet identified. For example, a component has been found that relates to memory storage of stimulus information (Chapman, McCrary, & Chapman, 1978).

Now there is an opportunity to study both electrical and magnetic brain activity of human subjects while they process cognitive information, with the research based on careful stimulus control, systematic task selection, sophisticated experimental design, and multivariate data analysis techniques.

In general this research is at the confluence of several scientific disciplines, including information processing, neurophysiology, low-temperature physics, experimental psychology, data analysis, and modeling. The Evoked Potential is the only response now available with adequate temporal resolution to study neurophysiological activity related to central processing of cognitive information in intact human beings. Behavioral studies of memory and cognitive processes have depended primarily on measures of performance, e.g., speed and accuracy. These measures are limited to the behavioral output of the cognitive processes which occur between the stimuli and the behavioral responses. The recording of brain activity occurring between the stimuli and the behavioral responses affords the opportunity of not only using another class of measures, but more important, using measures of events which may be specifically related to the cognitive processes. As Posner (1975) has pointed out for the study of attention, the field of information processing "will benefit from close ties between human performance studies and electrophysiological explorations." The development of neuromagnetic techniques is providing a new and powerful tool to aid in the study of memory and learning.

One of the EP components which has received a great deal of study is a late, positive wave which has become known as P300. P300 amplitudes are enhanced by: task-relevant stimuli (Chapman and Bragdon, 1964); an occasional stimulus change (e.g. Ritter Vaughan Costa, 1968); a signal for a simple or choice reaction (e.g., Wilkinson and Morlock, 1967); the detection of a threshold level stimulus (e.g., Hillyard, Squires, Bauer and Lindsay, 1971); a stimulus which confirms or refutes a prior guess (e.g., Sutton, Braren and Zubin, 1965); and a letter which completes a word or sentence (e.g., Shelburne, 1972; Friedman, Simson, Ritter and Rapin, 1975). The P300 seems to be independent of the physical characteristics of the target and non-target stimuli, so long as they are discriminable. Indeed, P300 can be triggered by a target cue which is the omission of a stimulus from a repetitive sequence (for review, Picton, Hillyard, and Galambos, 1976). Much of the data on the P300 component has been accumulated in three experimental paradigms: the guessing or prediction paradigm, the counting or "oddball" paradigm and the reaction time paradigm. The amplitude of P300 is an inverse function of the predictability of the stimulus when the subject's task is to guess the next stimulus in the sequence (e.g., Donchin et al., 1973; Sutton et al., 1965; Tueting et al., 1971). However, varying stimulus probability is not necessary for varying P300 amplitude (Chapman, 1966, 1969; Chapman and Bragdon, 1964). In the counting paradigm, a random sequence of two or more stimuli is presented and the subject is instructed to covertly count one of the stimuli. The general finding is that the P300 component is larger to the counted stimuli, especially when the counted stimuli are infrequent (Courchesne et al., 1975; Galambos, Benson, Smith, Schulman-Galambos, and Osier, 1975; Hillyard, Hink, Schwent and Picton, 1973; Mast and Watson, 1968; Picton et al., 1974; Picton and Hillyard, 1974; Squires, et al., 1975). When the same sequence of stimuli is presented under "ignore" or "alternate task" conditions, the P300 is small or absent. Thus, the stimulus probability is not a sufficient determinant of the P300. It appears that for P300, the stimuli must engage substantial cognitive processing, either directly required by the task or initiated by subject options.

In most of the paradigms finding P300 effects, the eliciting stimuli were relevant to the subject's task. Since Chapman and Bragdon's (1964) early demonstration, the evidence continues to support the hypothesis that task-relevance is an important condition for P300 elicitation (Chapman, 1965, 1966, 1969, 1973, 1974; Chapman, McCrary, Bragdon and Chapman, 1979; Donchin, 1968; Donchin and Cohen, 1967; Donchin and Smith, 1970; Smith et al., 1970; Donald and Goff, 1971; Eason, Harter, and White, 1969; Ford et al., 1973; Friedman, Simson, Ritter, and Rapin, 1975a; Sheatz and Chapman, 1969).

About the same time as the early reports about P300 (Chapman & Bragdon, 1964; Sutton et al., 1965), a Contingent Negative Variation (CNV) was reported (Walter et al., 1964) to occur in anticipation of a significant stimulus. A controversy then developed from the suggestion that late positive effects in EPs (e.g., P300) may be nothing more than

the turning off of a preceding CNV. In an experiment which manipulated both (a) stimulus relevance and (b) expectancy of stimulus relevance, both P300 and CNV were obtained by Principal Components Analysis of the data (Chapman, 1974). In that analysis the components were orthogonal and thus the independence of P300 and CNV was established. This conclusion is consistent with other analyses of the same question (Chapman, 1973; Donchin, Ritter, Tueting, Kutas and Heffley, 1974, pp. 71-72). Human cognitive experiments investigating the CNV have also used magnetic techniques (e.g., Fiumara, Campitelli, Romani, Leoni, Caporali, Zanasi, Cappiello, Fioriti, & Modena, 1985).

B. Memory Storage Component in Evoked Potentials

That sharper distinctions and greater specificity of the relationships between cognitive processes and EP components may be obtained is illustrated next (Chapman, McCrary, Bragdon, & Chapman, 1979) We applied multivariate analysis techniques to EP data obtained during controlled information processing tasks. Principal Components Analysis identified several EP components which were functionally related to various aspects of information processing, e.g. letter encoding, alphabetic comparison, expected stimulus relevance, and storage of information in short-term memory.

One of the components identified in the analysis (maximum near 250 msec.) was found to be specifically related to storage of stimulus information. Successful task performance in that experiment required the subject to store in his/her memory the information contained in the first relevant stimulus, which occurred randomly in either the first or second intra-trial position. We reasoned that irrelevant information as well may be stored when the first stimulus is presented since there is no previous short-term memory load at that time in the trial. In agreement with this analysis, the "storage" component scores were relatively high under the appropriate conditions. The pattern of scores for the EP "storage" component agreed with this information storage interpretation, whereas other EP components in the same experiment showed a different pattern. The "storage" component (Component 3) was not like P300 (Component 2) which had relatively high scores for all relevant stimuli, not just relevant stimuli in intra-trial positions 1 and 2. Nor was the "storage" component like CNV-resolution (Component 1) which related to expectancy of relevant stimuli. Nor was the "storage" component attributable to differences in physical stimulation, since both numbers and letters gave relatively high or low scores depending on whether or not they were being stored by the subject. Furthermore, the timing of the "storage" component is appropriate for information storage, namely near 250 msec., when the short-term visual storage fades (Sperling, 1960). This "storage" component may not have been detected in other EP experiments because the peak of this component tends to occur shortly after a prominent positive peak in EPs and special measurement techniques, such as Principal Components Analysis, more clearly reveal it. The "storage" component appears to be robust, having been found in strikingly similar form in additional experiments that use three different stimulus intensity levels spaced 1.0 log unit apart (Chapman et al., 1978). The coefficients of factorial similarity among four data sets ranged between 0.85 and 0.99.

It was important to check more directly the storage interpretation by a behavioral experiment specifically designed to assess storage in short-term memory under the same experimental conditions (Chapman et al., 1978). The behavioral experiment used a memory probe technique to test subjects' recall of individual stimuli for each of the conditions in the electrophysiological experiments. The pattern of correct recalls obtained from 52 subjects was strikingly similar to the pattern of "storage" component scores. CNV and P300 component measures were poor predictors of recall performances (Chapman et al., 1981). This is one of the few occasions that performance on a cognitive task was predicted first from electrophysiological data.

C. Connotative Meaning

Internal representation of meaning (specifically, connotative semantic processing) can be assessed by analysis of Evoked Potentials (Chapman, Bragdon, Chapman, and McCrary, 1977; Chapman, McCrary, Chapman, and Bragdon, 1978; Chapman, 1979; etc.). EPs were averaged to many visually presented word stimuli whose semantic meanings were specified along Osgood's semantic dimensions of Evaluation, Potency, and Activity (E, P, A) (Miron and Osgood, 1966; Osgood, 1952, 1964, 1971). Multivariate analyses classified the EPs to the six multidimensional semantic classes (E+, E-, P+, P-, A+, A-) with success rates more than twice chance expectation. The pattern of brain activity related to the six semantic classes was similar for (i) two sets of words, (ii) different subjects used to develop the analyses, and (iii) new subjects. The finding that the EP effects related to connotative meaning held for all of the subjects suggests that the physiological representation of meaning is similar in different individuals. This was not a result we were expecting, which made its appearance all the more refreshing.

In an extension of this research (Chapman, McCrary, Chapman, and Martin, 1980, we studied the effects of two kinds of experimental manipulation of semantic meaning: (1) the semantic class of the stimulus word used above, and (2) the dimension of the semantic scale (E, P, A) which the subject used to make semantic-differential judgments about the stimulus words. These variables were experimentally combined in that for each trial the subject used a designated semantic scale to judge a specified stimulus word. Would we be able to see in the brain response to a word, particular effects related to the meaning of the word and also other effects related to the judgment scale used by the subject?

Overall, the unidimensional analyses of word meanings (classifying EPs along one semantic dimension at a time) had an average apparent success of 94% and average

jackknifed cross-validation success of 87%. It is to be noted that this success rate was obtained across subjects; the same classification functions were used for all ten subjects. When the same classification functions were applied to the EP data obtained from a second word list, the overall success rate was 74%. These success rates are very similar to the corresponding rate obtained in our previous results when the subjects were merely repeating the words (compare 94% to 97%, 87% to 90%, 70% to 73% for the E, P, and A dimensions). Separate analyses identified word class and scale dimension effects in the EPs at better than chance levels and indicated that their effects do not interact. The evidence indicates that at least two kinds of semantic information are available in EPs: (1) processing of the semantic meaning in words, regardless of the semantic-differential scale being used by the subject, and (2) semantic-differential scale dimension being used by the subject, regardless of the semantic content of the words.

D. Syntactic Differences in Words and Linguistic Processing

Additional studies were directed toward evaluating EP sensitivity to syntactic differences in words. A basic distinction in the lexicon has been proposed between two syntactic classes of words, function words and content words. There is, in fact, some evidence that function and content words do result in different EPs (Kutas and Hillyard, 1983). Word length and normative frequency were, however, not controlled and both of these are confounded with word class.

Controlling for these variables Garnsey and Chapman (1985; Garnsey, 1985) measured reaction times (RTs) and evoked potentials (EPs) for function and content words during a lexical decision task. The RT data revealed no differences between function and content words. On the other hand, the EPs showed differences not only between word and nonword stimuli but, more important, were significantly different for function and content words. Thus, there is evidence that separable aspects of this important linguistic distinction can be detected in EP data that cannot be found in RT data.

Kutas and Hillyard (1980a,b) found a late negativity in the EP associated with words that completed a sentence in a semantically anomalous fashion.

Part of understanding a sentence is understanding the grammatical relationships among the words. The part of the comprehension process that assigns grammatical roles to words has also begun to be studied using Evoked Potential techniques (Garnsey, Tanenhaus, & Chapman, 1987). Sentences that contain local structural ambiguities provide a window into the comprehension process. Ambiguity like this is pervasive in language and is a problem the parser must deal with regularly. Discovering how the parser handles ambiguous sentences could tell us much about general principles that the parser uses.

Different parsing strategies make different predictions about what happens during the comprehension of a sentence; therefore, it is helpful to have a response measure that can monitor comprehension processes as they occur. Evoked Potentials (EPs) were used to look at filler-gap sentences because EPs can provide a profile across time while subjects read sentences presented one word at a time. Exploiting the finding that the N400 component of the EP is sensitive to a word's implausibility in context (Kutas & Hillyard, 1980a,b), the approach of Garnsey, Tanenhaus, and Chapman (1987) has been to measure EPs during structurally ambiguous sentences. Sentences were constructed so that if the ambiguity is resolved in one of the possible ways, an anomaly results, while there is no anomoly with the other possible resolution. Thus, the occurrence of N400 can be used as a diagnostic for showing which path is initially chosen. The results obtained make us optimistic about the utility of the EP in answering many questions about sentence comprehension.

III. Prospects for Electrical and Magnetic Recording

It has become possible to study spontaneous and evoked brain activity by neuromagnetic measurements and significant results have been achieved in the last few years. This new approach, in conjunction with the well established electrical one, holds great promise. The neuromagnetic method has proved to be particularly fruitful in the investigation of primary cortical areas, the investigation of event-related fields is now at a preliminary stage. Nevertheless, the first findings obtained in a few laboratories suggest that the magnetic technique is likely to become a powerful tool for the study of higher levels of brain functions. Indeed, the spatial-temporal expression of magnetic fields and electric potentials produced by the nervous system contains different information which can be exploited for the study of brain activity related to information processing.

A procedure for utilizing simultaneous magnetic and electrical recording has been developed which we call the Relative Covariance method. It has been successfully applied to two different problems: alpha EEG (Chapman, Ilmoniemi, Barbanera, and Romani, 1984; Romani & Leoni, 1985; Ilmoniemi, 1985) and epileptic EEG (Chapman, Romani, Barbanera, Leoni, Modena, Ricci, and Campitelli, 1983; Ricci, Leoni, Romani, Campitelli, Buonomo, and Modena, 1985).

For each magnetometer location, the ratio of the covariance of the magnetic and electric signals to the electric variance was calculated, producing a Relative Covariance map reflecting the magnetic field pattern. The Relative Covariance method is a measurement method that can be applied to the signals obtained by the recording instruments before the modeling and interpreting of the relationship between sources and field

distributions. It deals with the question of what to use as the measures to be interpreted. It would be advantageous to use measures which have greater stability and a tendency to measure fewer phenomena. The stability of the Relative Covariance method stems from (i) its integration over time, (ii) the fact that it is relative to another simultaneous measure, and (iii) its filtering out other phenomena. The tendency to measure fewer phenomena is achieved by its filtering action; the covariance operation may be viewed as passing the magnetic data through the EEG data acting as a filter. This Relative Covariance method may prove generally useful in studying and localizing bioelectrical sources such as spontaneous brain rhythms, epileptic activity, and EPs related to cognitive performance.

Electrophysiological and behavioral research has pointed to meaningful components and temporal relations in Evoked Potentials that, in conjunction with behavioral measures, could elucidate targeted cognitive processes. This research has not only involved P300 and CNV components, but also has utilized other components that may be measured and related to significant processes, including short-term memory and linguistic processing. Combined measurement of magnetic fields and electric potentials will lead to significant progress in the investigation of the described cerebral functionings. The advent of large multichannel magnetic systems is an important step in achieving this goal and increases the scope of possibilities.

Research on cognitive processes using evoked potentials has achieved interesting, challenging results concerned with short-term memory and with semantic processing. We anticipate that systematic investigation of these areas with the combined techniques of electrical and magnetic recording will provide a powerful approach to understanding significant aspects of cognitive processes and brain activity.

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DISCUSSION

GEVINS, US: My questions relate to the topographic maximum of the open versus closed class effect. In the experiment, you showed the factor which had the highest loading on the open versus closed class word distribution. Could you comment on why that factor had the most differentiation in C_z? Could you also comment on the lack of a strong effect on your posterior parietal electrode, and the effect on the prefrontal electrode?

CHAPMAN, US: These analyses are not completed yet, so I'm not very comfortable answering those questions. I can say that one of the differences between an open and closed class function is that they show up in brain damaged patients with differential effects, which suggests that they ought to be located in different regions in the brain.

NEUROMAGNETIC EVIDENCE OF PLACE MECHANISMS FOR FREQUENCY AND INTENSITY CODING IN THE HUMAN AUDITORY CORTEX

by
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SUMMARY

The influence of two decisive parameters of the acoustic stimulus - frequency and intensity - on the auditory evoked magnetic field in response to tone-burst stimulation was investigated in four normal-hearing subjects. The influence was quantified in terms of changes of the parameters of an equivalent current dipole (spatial coordinates, direction, and strength). The frequency dependence was investigated by varying the carrier frequency of the tone-burst between 250 and 4000 Hz in octave steps with the intensity kept constant at 60 dB HL, while the intensity dependence was investigated by varying the intensity of a 1000 Hz tone-burst between 30 and 80 dB HL in 10 dB steps. The parameters of an equivalent current dipole (ECD) were determined such that a maximum correspondence between observed and calculated field distribution (semi-infinite volume model) was obtained. The main results are as follows: The location of the ECD changes significantly as a function of test frequency and intensity. Especially the depth increases with the logarithm of test frequency which proves that also in humans the tonotopic organization of the cochlea is maintained in the auditory cortex. The decrease in depth of the ECD with increasing stimulus intensity supports the hypothesis that place mechanisms also play a role for intensity coding.

INTRODUCTION

The most intricate encoding of sound in the peripheral hearing organ is unique for all sensory systems. Even before the mechano-electric transduction takes place, the sound signal - conducted to the inner ear with equal group delay - undergoes a remarkable spatio-temporal dispersion: It gives rise to a travelling wave which assumes an amplitude maximum at a place more or less distant from the stapes, depending on frequency. High frequency components of the sound signal are represented at the beginning, lower ones at the end of the cochlear partition, and the scale of this "tonotopic" representation is a logarithmic one. By this way, frequency information is encoded as place information at the cochlear level. Closely related to this spatial dispersion is a temporal dispersion caused by the different travel time which increases exponentially with increasing distance from stapes. But not only frequency determines the representation of a sound signal along the cochlear partition; it is also distinctly influenced by the intensity of the sound signal in a higly non-linear manner: The excitation spreads with higher intensity, recruiting additional nerve fibres into the active population (1) which again is an expression of a place mechanism.

Hence it has been intriguing to investigate to what extent such place mechanisms can be traced throughout the central auditory pathways. Place mechanisms in frequency coding have been considered for more than a century. The idea of a tonotopic organization, i.e. the arrangement of structural elements of the auditory system (such as receptors or neurons) in space according to that frequency to which they respond best ("best" or "characteristic" frequency) was conceived long before physiological measurements could be done. It is as old as the renowned hearing theory of Hermann von Helmholtz (1862) according to which radial fibres of the basilar membrane in the cochlea form a set of resonators, like the strings of a piano. Though the resonance theory of von Helmholtz was later superseded by more sophisticated hearing theories, one principle remained unchallenged: the place principle - which is of cause not sufficient to explain all pitch sensations, e.g. that of complex tones. But physiological research - from G. von Békésy (2) to S.M. Khanna (3) - have safely established the basis for the tonotopy at the cochlear level: the mechanics of the cochlea. Microelectrode studies gave further evidence that the tonotopic organization is maintained in different nuclei and fibre tracts of the central auditory pathway (4), and this is even true for the primary auditory cortex as was established in several experimental animal species, e.g. for the monkey (5), the squirrel (6) and the cat (7).

Less attention has been paid to place mechanisms for intensity coding. Phillips et al. (8) recently detected cells in the AI cerebral cortex of the cat and the monkey displaying non-monotonic rate-vs.-intensity functions. The most effective stimulus intensity differed from one cell to the next, i.e. similar to the best frequency there exists a "best" intensity to which the cells respond best. Changing SPL results in a shift in the active neuronal population such that many neurons once maximally active become less so while others marginally active or unresponsive are brought to maximal

response (9), a finding which leads to the hypothesis of a place mechanism of intensity coding which has not been tested yet in either cat or monkey. However, evidence for an "amplitopic organization" has been obtained for the primary auditory cortex of the mustache (10).

This increasing interest in the structural and functional organization of auditory cortical projection areas was also induced by the development of cochlear implants to stimulate persisting auditory nerve fibres in totally deaf patients. It goes without saying that the primary interest was for the human auditory cortex in the hope to improve stimulation and encoding strategies for the artifical auditory stimulation. But investigations in humans failed. Celesia (11) who recorded auditory evoked responses from the exposed human cortex during neurosurgery, could not find significant differences between responses to tone-bursts of 600 and 1000 Hz.

Hence it was likely to tackle the problem indirectly by applying dipole localization methods (DLM). DLM are mathematical procedures which allow, under certain limiting assumptions, to localize a dipole in a body by approximating a calculated surface distribution of electric potentials or magnetic fields to the observed one. A basic prerequisite for the application of DLM to evoked neural activity is that a population of neural generators in the brain which are lying closely together and are, to a large extent, parallely oriented in space, is simultaneously brought to discharge. The single current dipoles representing the intracellular current flow in the dendrites of the individual neurons can then be regarded in terms of a so-called equivalent current dipole (ECD), which is the vectorial integral of all individual dipoles and is located in the "centre of gravity" of the excited neuronal population. We know from histological studies as well as from evoked potential studies that this prerequisite is given for most of the nuclei and fibre tracts of the central auditory pathway though we have to be aware of the fact that more than one population may be active at the same time. With respect to cortical evoked responses, sources of neural activity seem to be ensembles of dipolar current sources oriented parallel to each other and perpendicular to the cortical surface (12). If the activated cortical area happens to be located in a sulcus, than the case arises that the main ECD component is lying tangential to the surface of the skull.

As mentioned before, DLM can be based on measurements either of the scalp distribution of electric potentials or that of magnetic fields. There are several pros and cons associated with both methodologies. The electric potential distribution is brought about by volume-conducted extracellular currents whose propagation is considerably distorted by the anisotropic tissues from brain, skull and scalp. Its spatial resolution is poorer, and there exists the need for a reference electrode. On the other hand, only the tangential component of a current dipole gives rise to a magnetic field normal to the surface which is measurable outside the head (13). There are two major implications associated with this fact: The more radial the dipole is oriented or the closer the dipole is located to the centre of a sphere (which is a rough approximation of the head), the smaller is the field which can be measured outside the skull, i.e. deep sources are difficult or not to detect. Another shortcoming associated with these physical limitations of biomagnetic measurements is that expensive equipment (multichannel squid system, magnetically shielded room) is needed, at least for routine investigations.

Scherg and von Cramon (14) who employed dipole localization methods based on the scalp distribution of evoked potentials described the slow cortical auditory evoked potential in terms of tangential and radial "dipole source components". They did not consider the tonotopic organization, but one important finding is that the main dipole component is the tangential one which is, as mentioned above, a prerequisite for neuromagnetic measurements.

It was in 1978 when the transient auditory evoked magnetic field (AEF) elicited with brief clicks was first detected by Reite et al (15). Since then it has been shown in quite a few papers that biomagnetic measurements are indeed a highly appropriate tool for the investigation of cortical auditory evoked activity. Before addressing to special aspects of AEF it seems to be justified to begin with briefly summarizing the characteristic features of AEF. It was shown that

(1) the ECD is located in the parieto-temporal region and is oriented in superior-inferior direction, being almost perpendicular to the Sylvian fissure (e.g. 16, 17, 18, 19),
(2) the ECD is located approx. 14 mm posterior in the left hemisphere as compared to the right hemisphere (e.g. 20, 21),
(3) the strength of the magnetic field is generally stronger over the left hemisphere as compared to the right hemisphere (e.g. 20, 22),
(4) contralateral stimulation produces stronger fields than ipsilateral or binaural stimulation does (e.g. 20, 23, 24),
(5) the 100 ms component occurs approx. 9 ms earlier with contralateral stimulation as compared to ipsilateral stimulation (e.g. 17, 22, 23),
(6) the depth of the ECD generated by steady-state stimulation increases with the logarithm of test frequency (e.g. 25, 26), and
(7) statements (2) and (3) hold only for right-handed subjects while the reverse is true for left-handed subjects (27, 28).

Whereas the tonotopic organization of the human auditory cortex has been studied using the steady-state response (25) and the transient evoked response (18, 29, 30), the hypothesis whether there exists an amplitopic organization of the human auditory cortex

has not at all been tested so far. This gave rise to our study of both the tonotopic and the amplitopic organization of the human auditory cortex, based on tone-burst evoked cortical magnetic fields.

MATERIAL AND METHODS

Since the technique of stimulation, data collection and data processing is published elsewhere in great detail (22, 24, 31) it shall be repeated only in brief outlines. Subjects were four normal-hearing, paid volunteers two of whom were right-handed and two left-handed. To obtain maximum possible field amplitudes, the left hemisphere was investigated in right-handed subjects and vice versa, using contralateral stimulation with tone-bursts with a duration of 500 ms and rise/decay times of 15 ms. To study the frequency dependence, the carrier frequency of the tone-burst was varied between 250 and 4000 Hz in octave steps with the intensity kept constant at 60 dB HL, while the intensity dependence was studied with 1000 Hz tone-bursts whose intensity was varied between 30 and 80 dB HL in 10 db steps. Measurements were carried out in an electrically, but not magnetically shielded room. The radial field component of the evoked field was measured at 50-60 posititions over the scalp using a single-channel SQUID (BTI) equipped with a second-order gradiometer. Partial averages of the filtered waveforms or individual responses were stored in a Prime computer system. Off-line data processing consisted in compilation of data matrices for each sampling instant from corresponding samples recorded at each position. These matrices served to generate isocontour plots after interpolation and filtering as well as to calculate the ECD parameters including the goodness of fit, from which time functions were composed and plotted.

Fig. 1 shows a lateral view of the head with the sampling positions inserted: a rectangular grid (reference T3 and T4, resp.) with an intercept of 1.5 cm, indicating the area scanned. On top of the sampling positions an exemplary set of raw data is inserted from which the polarity reversal of the field distribution along the Sylvian fissure is evident.

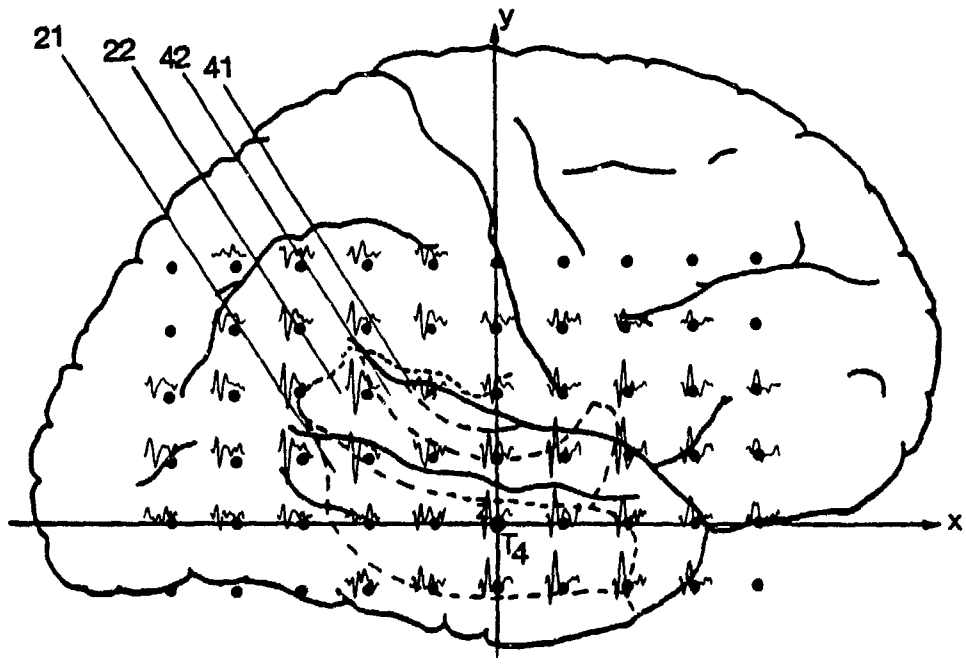

Fig. 1: Sampling matrix with its reference in T3, projected onto the contours of the supralateral surface of the left cerebral hemisphere with the acoustic area AI (Brodmann areas 41 and 42) and the secondary acoustic area AII (Brodmann areas 21 and 22). On top of the sampling positions an exemplary set of raw data is inserted.

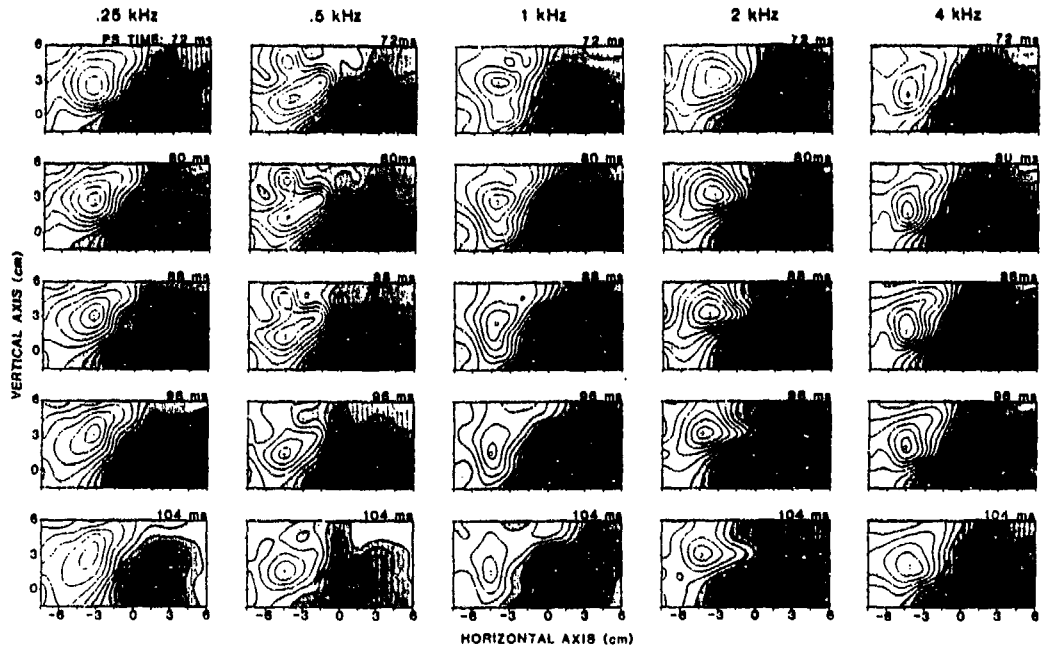

Fig. 2: Isofield contour maps computed for five consecutive instants around the 100m component, illustrating the dependence of the field distribution on the frequency of the test stimulus and the time elapsed since stimulus onset (inserted on top of each map). The field strength is encoded using a grey scale, the spacing between two adjacent isocontour lines being 40fT. Areas between isocontour lines are shaded according to field strength. The heavy lines designate zero field strength, darker areas outward going magnetic flux, brighter ones inward going flux. The cross indicates the origin of the coordinate system. The dark arrow represents the location and the angle of the equivalent current dipole in the tangential plane, its length being proportional to the dipole moment (length of the arrow head corresponds to 10 nAm).

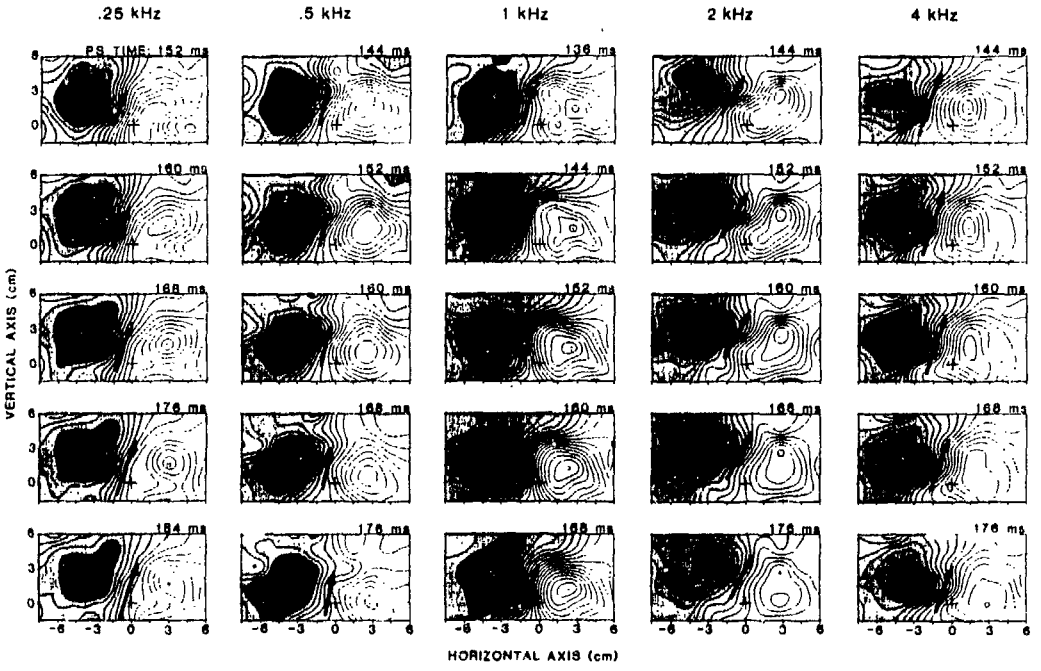

Fig. 3: Same as Fig. 2, but for the 160m component.

FREQUENCY DEPENDENCE

Figs. 2 and 3 show selected sets of isocontour maps, calculated for each test frequency investigated, for time instants every 4 ms around the two most prominent peaks whose latencies are approx. 100 and 160ms (they will be referred to as 100m and 160m). Each column was obtained with a different test frequency. Though the figures permit the inference that the field distribution changes with both time elapsed since stimulus onset and frequency of the stimulus they do not allow to quantify the effect of both variables.

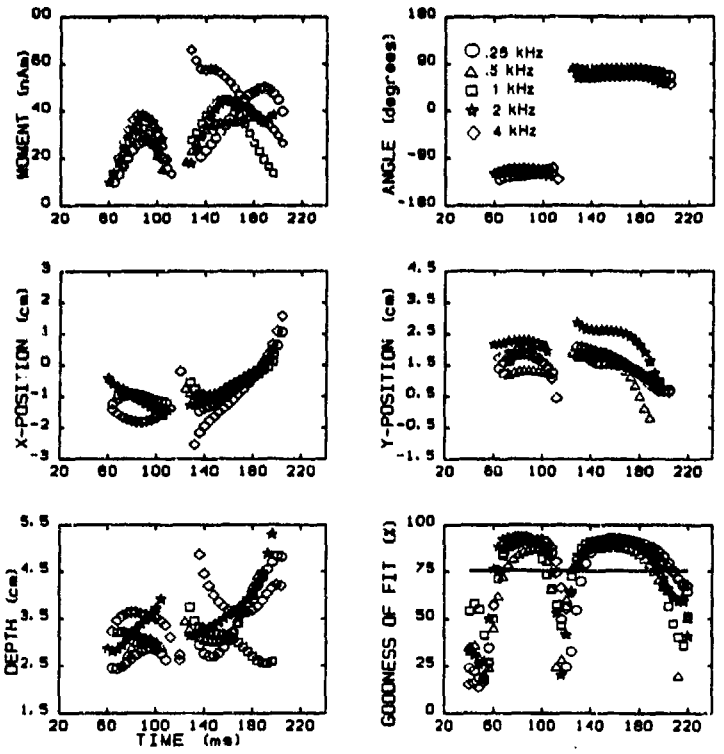

Fig. 4: Time dependence of the parameters of the equivalent current dipole and of the goodness of fit. Only those values are plotted which have a goodness of fit better than 75%.

Temporal aspects become evident from the time functions. A set of such functions, obtained from one representative subject for all frequencies investigated, is shown in Fig. 4. Different test frequencies can be distinguished by different symbols. Only those parameter values were plotted whose goodness of fit exceeds 75%. As to be expected, the goodness of fit is highest when the amplitude of the dipole moment is maximal. Except of the angle, there is an obviously different behaviour of the parameters of components 100 m and 160m. In the case of the 100m component, the position in the tangential plane, for most test frequencies also the depth, remains fairly constant around the maximum of the dipole moment. In the case of the 160m component, however, we find a certain systematic change with time of the position in the tangential plane while no systematic behaviour can be detected with respect to depth.

The influence of stimulus frequency becomes more obvious when the ECD parameters of specified response components are plotted as a function of frequency. This was done for components 100m and 160m (Figs. 5 and 6). Both components were determined in time by an extremum of the dipole moment in the time function. A general observation is that the data of the 100m component are more consistent than those of the later component 160m which exhibit a more pronounced interindividual variability. The dipole moment of the 100m component (Fig. 5) changes only gradually with frequency. The mean is virtually constant, independent of frequency, except of the lowest test frequency investigated where it is slightly diminished. The data of the dipole moment computed for the 160m component are less consistent, but again the mean does not show a significant frequency dependence. The functions obtained for the dipole angle (Fig. 5) do not show a systematic, monotonous frequency dependence, neither for the 100m nor for the 160m component. The individual variability would be basically similar for both components if there was not one case with a distinct smaller angle for the 160m component.

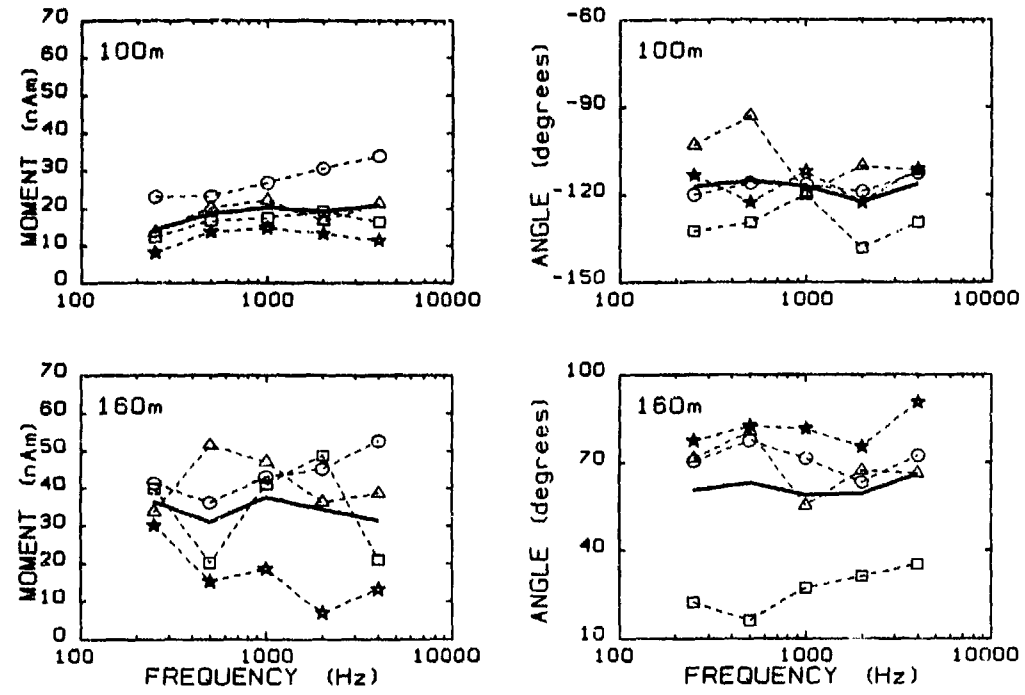

Fig. 5: Amplitude (left column) and angle (right column) of the moment of the equivalent current dipole as a function on test frequency, computed for component 100m (top) and 160m (bottom).

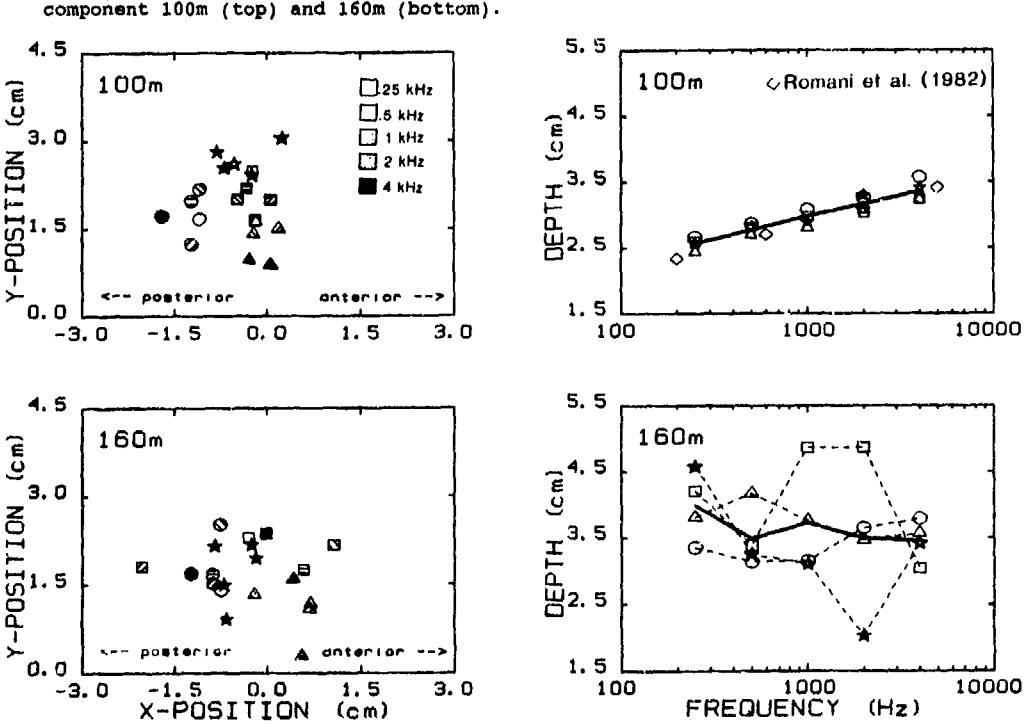

Fig. 6: Location of the equivalent current dipole in the tangential plane (left column), computed for component 100m (top) and 160m (bottom). Different symbols and different patterns are used to distinguish between different frequencies and subjects. The right column shows the dependence of the depth of the equivalent current dipole on test frequency, computed for component 100m (upper half) and component 160m (lower half).

Fig. 6 shows the projection of the dipole locations onto the tangential plane as well as the depth of the equivalent current dipole as a function of test frequency. For both components (100m and 160m) the x-y-coordinates form circumscribed clusters in each subject, though they scatter a little more for the 160m component. If the frequency is increased from 250 to 4000 Hz the mean x-position of the 100m component is shifted in posterior direction by approx. 6 mm while no significant shift was observed in superior-inferior direction. The values of the depth calculated for the 100m component are very consistent and show an obvious logarithmic dependence on test frequency. In contrast to that, the results computed for the 160m component do not show a similar behaviour. In the case of the 100m component, we found an almost pure logarithmic dependence on frequency and a negligible interindividual variability. The 160m component, however, exhibits a pronounced deviation from a logarithmic function as well as a distinct interindividual variability. A comparison between the coordinate pairs of the locations of the 100m and the 160m component reveals a non-significant difference for the x coordinate, but we found the y-coordinate of the 160m component to be located 0.3 cm inferior to (t-test for paired data yields $p<0.03$) and 0.6 cm deeper than ($p<0.01$) the 100m component.

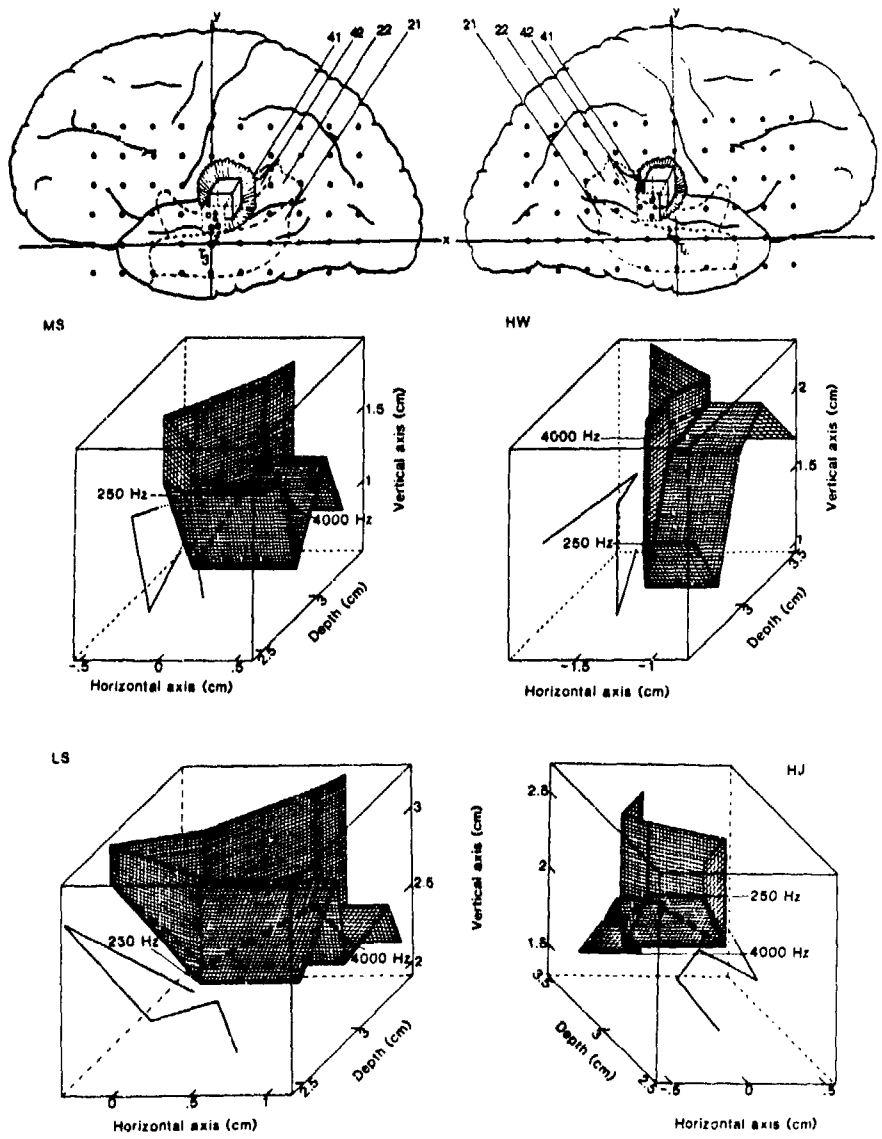

Fig. 7: Spatial arrangement of dipole locations in dependence on test frequency, drawn for all four subjects. For explanation, see text.

It would be desirable to have a three-dimensional image of how the dipole location moves in space with decreasing the test frequency. An attempt to mediate such an impression of the spatial arrangement was undertaken for component 100m in Fig. 7. The x- and y-coordinates estimated for the position of the equivalent current dipole are projected (see shaded window) onto the rough contours of the supralateral surface of the right hemisphere (left-handed subjects) or the left hemisphere (right-handed subjects), resp. Also inserted are the sampling positions with their reference (T4 in the right hemisphere and T3 in the left hemisphere, resp.) and the Brodmann areas 21, 22, 41 and 42. A cube lying underneath the shaded window in the tangential plane which contains the dipole locations for all test frequencies, is enlarged and perspectively drawn below the corresponding sketch of the brain. The projections of the dipole locations onto three orthogonal planes of the cube are indicated. In order to facilitate the visualization how the dipole locations are arranged in space, two cross-hatched planes that are perpendicular to the planes of the cube and intersecting with them along the dipole projections are drawn up to their intersection with each other. These intersections are marked with a heavy solid line (for the visible part) or a dashed line (for the hidden part). Most of the projections of the dipole locations onto the y-z planes (vertical axis/depth) of the cube exhibit, besides a distinct interindividual (and possible interhemispheric) variability, a more or less sigmoidal shape, whereas the projections onto the x-z plane (horizontal axis/depth) are v-shaped. The highest variability of the shapes are found for the projections onto the tangential plane.

INTENSITY DEPENDENCE

Similar to the corresponding figure representing the field distribution produced by different test frequencies, Fig. 8 mediates how the evoked magnetic field distribution changes with the intensity of the acoustic stimulus. Isocontour maps computed for both the 100m (left) and the 160m (right) component show how the location in the tangential plane and the strength of the ECD change with stimulus intensity. The vertical line is inserted to better visualize the different dipole locations.

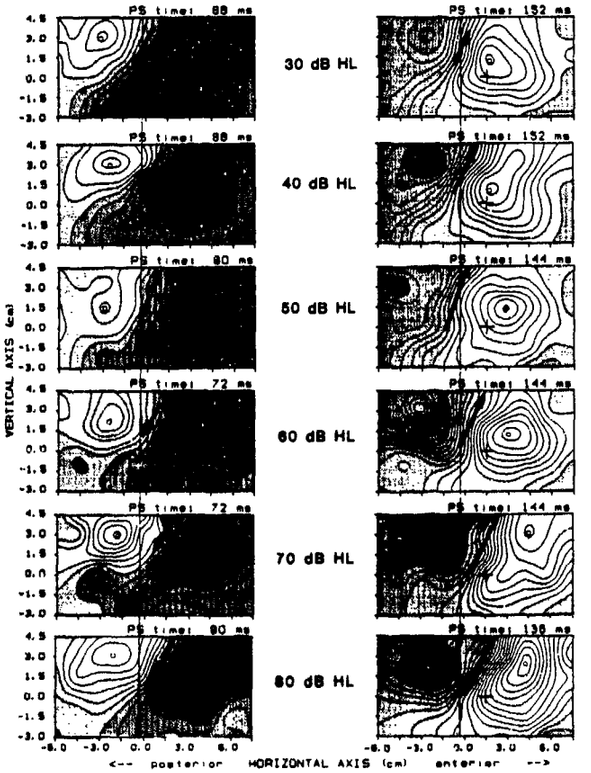

Fig. 8: Dependence of the magnetic field distribution on intensity. Maps computed for stimulus intensities of 30 to 80 dB HL are plotted for those instants (inserted on top of each map) when the moment of the equivalent current dipole assumes a maximum.

Time functions of the dipole parameter are shown in Fig. 9, exemplary for the stimulus intensity of 40 dB HL. Similar to Fig. 4, only those parameter values were plotted whose goodness of fit exceeds 75%. Noteworthy is that the values of all dipole parameters remain fairly constant around the maxima of both components.

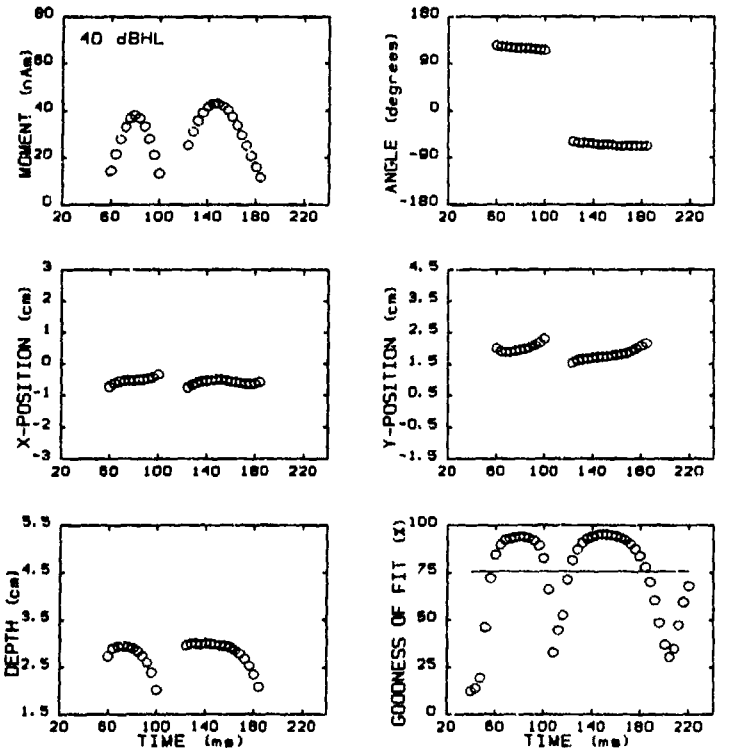

Fig. 9: Time dependence of the parameters of the equivalent current dipole and of the goodness of fit, computed for a stimulus intensity of 40 dB HL. Only those values are plotted which have a goodness of fit better than 75%.

More instructive are the next two figures (Figs. 10 and 11) which are composed similarly to those showing the frequency dependence: We generally found a systematic behaviour of all dipole parameters of the 100m component but not of all parameters of the 160m component. The dipole moment of both components (Fig. 10) increases with increasing stimulus intensity assuming a maximum at 50-60 dB HL, and then diminishes. The dipole angle (Fig. 10) of the 100m component also deviates from a monotonous course. The declination is maximal at 50 dB HL and diminishes both with increasing and decreasing stimulus intensity. There is again a slight increase of the declination at 30 dB HL. The dipole angle af the 160m component does not show a significant dependence on frequency. The depth (Fig. 11) of the 100m component decreases almost continuously with increasing stimulus intensity whereas the depth of the 160m component does not show any systematic change. The location of the equivalent current dipole in the tangential plane shows, for both components, an anterior displacement (8.4 mm for the 100m component and 7 mm for the 160m component) with increasing stimulus intensity, but again this behaviour is more obvious for the 100m component. No significant shift in the superior-inferior direction could be observed for both components when the stimulus intensity was increased from 30 to 80 dB HL.

DISCUSSION

The most intriguing one of these findings which has never been described so far and which is consistent in all subjects is certainly the influence of the stimulus intensity on the location of the equivalent current dipole. The higher the stimulus intensity, the more superficial is the cortical excitation. This variation goes in line with an anterior shift of the ECD location with increasing intensity. On the other hand, increasing stimulus frequency causes an increase in depth of the ECD location, along

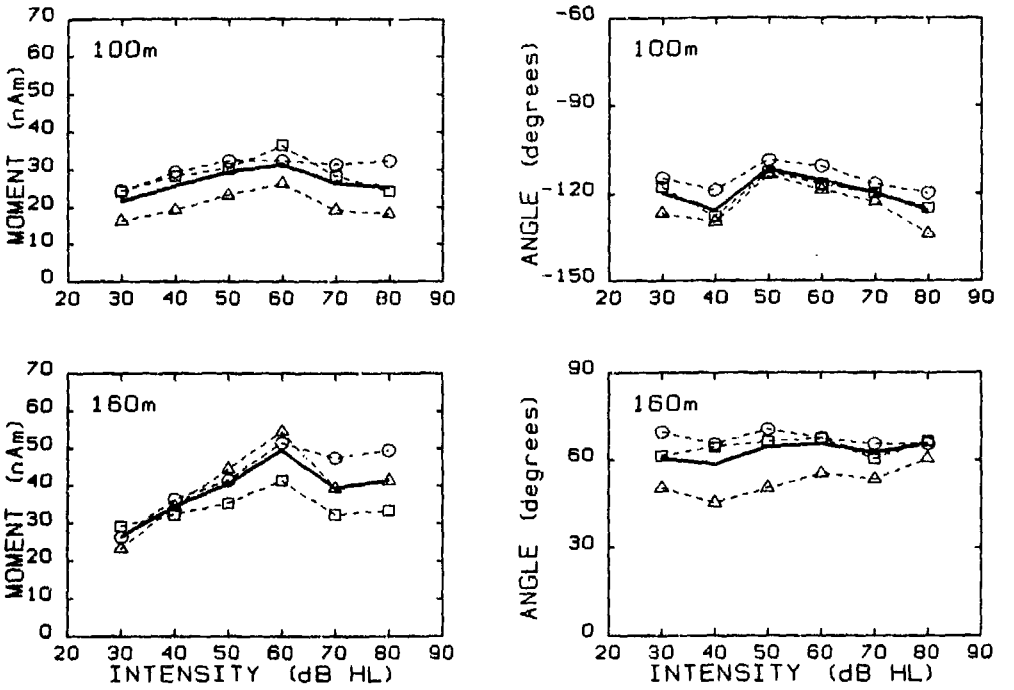

Fig. 10: Amplitude (left column) and angle (right column) of the moment of the equivalent current dipole as a function on stimulus intensity, computed for components 100m (top) and 160m (bottom). Different symbols are used to distinguish between different subjects.

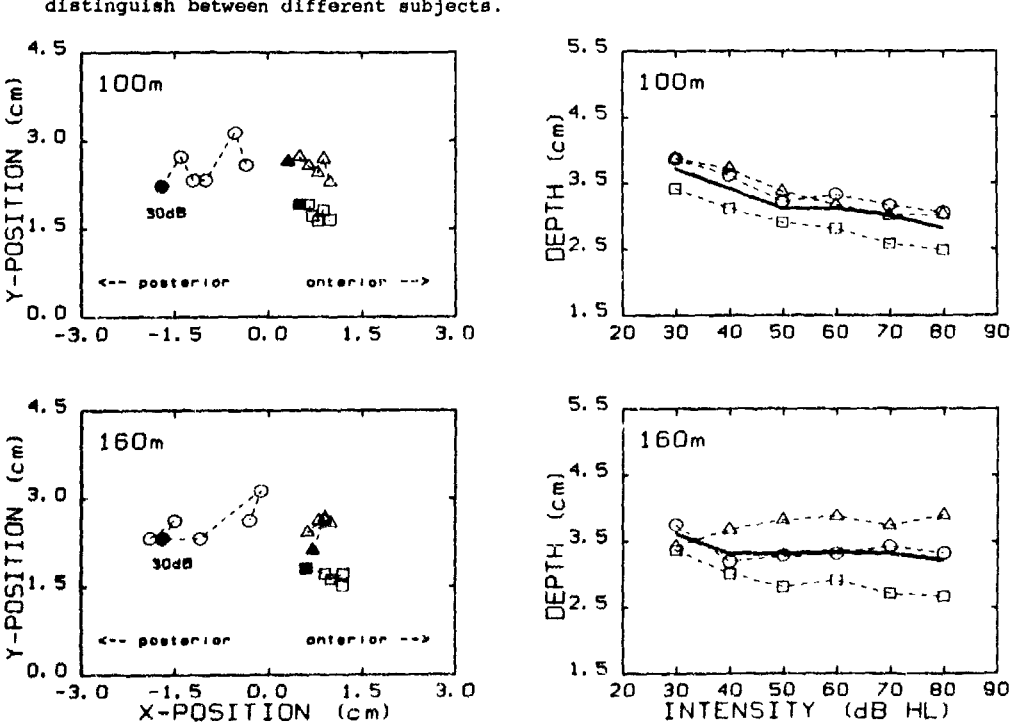

Fig. 11: Locations in the tangential plane (left column) and depth (right column) of the equivalent current dipole as a function on stimulus intensity, computed for components 100m (top) and 160m (bottom). Different symbols are used to distinguish between different subjects. The symbols corresponding to dipole locations computed for an intensity of 30 dB HL are filled.

with a posterior shift. This implies that - analogous to the thoroughly investigated tonotopic organization (cf. 25, 26) - there also exists an amplitopic organization of the auditory cortex as was hypothesized by Brugge and Reale (32). Comparing the shift of the ECD location in the x-z plane (horizontal position versus depth; the vertical position was neglected since no significant shift was observed between the highest and lowest intensity and frequency tested) with a variation of either frequency or intensity, our findings suggest that obviously both variables are represented at different places.

The calculated ECD locations correspond sufficiently well with the transverse temporal gyri or their immediate vicinity which was checked in concomitant anatomical investigations (26). By this way, neuromagnetic measurements have been helpful to decide upon two contradictory hypotheses, i.e. whether the scalp-recorded cortical evoked potentials originate from the specific primary cortical projection area rather than from a "non-specific" cortex which has been discussed for almost two decades. It is unequivocal now that evoked potentials (and their magnetic counterpart) do originate from specific cortical projection areas. Moreover, the neuromagnetic evidence of a tonotopic and amplitopic organization of the human auditory cortex has demonstrated the high significance of neuromagnetic measurements for physiological research.

ACKNOWLEDGEMENTS

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DISCUSSION

KAUFMAN, US: Do you think that the change in depth of the equivalent current dipole source with intensity could possibly be related to the well-known broadening of the tuning curves of single neurons with the intensity of stimuli with particular frequencies? As I recall, the tuning curves characteristically show a flattened peak as the intensity goes above a point where they saturate; and then they continue to broaden, shifting the center of gravity, if you will, of the mass of cells responding to the stimulus. That would probably cause the current dipole to shift.

HOKE, GE: Actually, the process works the other way around. The change in functional depth of the dipole should increase the intensity as it increases with frequency because the ordering of the excitation goes to a higher frequency.

THE INTERACTION OF THALAMO-CORTICAL SYSTEMS IN THE 40 Hz FOLLOWING RESPONSE

by

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Introduction

Galambos, Makeig and Talmachoff (1981) described what they called the 40 Hz response. This steady-state response was a sinusoidal EEG following response to repetitive auditory stimulation which was of maximal amplitude at rates between 35 to 45 Hz. Galambos suggested that the response was a superimposition of brain-stem responses (waves iv and v) and thalamic mid-latency responses. Assuming there is volume conduction of these responses, the widespread distribution of the 40 Hz response is consistent with the interpretation of the sources being primarily of thalamic or brainstem origin. Spydell, et al. (1985) measured the latencies of wave V of the auditory brain-stem response assuming they should be different in normals and patients with brain-stem lesions. He came to the conclusion that there were independent generators. He also observed that in a group of patients with unilateral temporal lobe lesions the 40 Hz response appeared unimpaired. He concluded from this that temporal lobe was not involved in the response. Weinberg, et al. (in press) reported a study in which both electrical and magnetic recordings were obtained from two healthy right-handed subjects with normal hearing. The auditory stimuli consisted of 55 db 1000 Hz sinusoidal tone bursts of 5 msec duration (non-ramped), presented binaurally at repetitition rates of 30 and 40 Hz. Electrical recordings were taken from a vertex electrode, magnetic recordings were obtained sequentially from a wide distribution. We suggested that a "source-system" was active during 40 Hz auditory stimulation which included bilateral temporal cortex. We suggested, as did Borda (1984), that when the brain is in a steady-state as the result of being driven by repetitive auditory stimulation it is likely that resonance within a limited portion of the auditory pathways could account for some of the enhancement at 40 Hz stimulus rates. This interpretation is supported by current studies regarding the organisation of the thalamocortical auditory system in the cat.

Further examination of the functional organisation of the auditory system may help elucidate mechanisms by which resonance effects may account for augmentation of the steady-state response. Anderson, Snyder and Merzenich (1980) have described the main ipsilateral and contralateral ascending pathways to auditory cortex, where there is crossing over of pathways at levels of the cochlear nucleus and inferior colliculus. It is known that there is efferent innervation of basilar membrane through medial geniculate nuclei, inferior colliculus and cochlear nucleus and there is good evidence for efferents from Al of auditory cortex to inferior colliculus, and efferents from inferior colliculus to medial geniculate nuclei. Ryugo and Weinberger (1976) argue that corticofugal mechanisms ordinarily support rhythmic discharges which may involve thalamus. They also describe another corticofugal mechanism which may include tonic inhibitory influences which reduce the level of bombardment from thalamus in the absence of changes in the acoustic environment. These effects appear to mediated via corticothalamic fibres which are known to synapse on the proximal dendrites and soma of interneurones in the ventral medial geniculate nucleus. They speculate that these synapes are in a position to "drive" Golgi type II cells, which in turn would inhibit the principal neurones. Although completely speculative it could be argued that the delays seen in early auditory brain stem responses in chronic alcoholic humans, reported by Porjesz and Begleiter (1975), may not have resulted from only increased transmission time in brain-stem, but may have been the result of increased driving of inhibitory Golgi cells. the effect of which would be seen at the colliculus. Furthermore, Orman and Humphrey (1981) report clear evidence of the influence of cortical arousal on cortico-geniculate activity through the route of cortex-colliculus-geniculate. This loop, Al - inferior colliculus - medial geniculates - Al is very likely involved in the 40 Hz response and could be the basis of a resonance resulting in an enhancement of a response to 40 Hz. If the convergence of primary auditory input and cyclic activity in a cortico-thalamo-cortical system resulted in increased number of fibres firing in Al this enhancement would be seen at cortex as well as in other parts of the system. Imig and Morel (1983) have reported evidence that corticothalamic and thalamocortical connections are reciprocally organised such that thalamic areas projecting to a cortical location receive a projection from the same location. Corticothalamic projections have the same anatomical patterns as thalamocortical projections with respect to their tonotopic organisation. Our data suggested that temporal cortex is involved but make no claim to that being the location of the enhanced amplitude seen in the EEG with 40 Hz stimulation. It is not unlikely that a resonance effect would be seen wherever the system is sampled. This interpretation is consistent with Romani, et al. (1982) who reported auditory MEG responses to single frequencies that were modulated at 32 Hz. Although Romani et al. discussed their data in the context of tonotopic organisation of the auditory cortex, rather than in relation to the 40 Hz response, their data complement our own in that the "source" is reported to be in temporal cortex. If our speculation about the source-system involved in repetitive

stimulation at frequencies approximating 40 Hz is correct the sources reported must have included corticofugal-cortical modulation.

The study reported here is an extension of our inital auditory experiments (Weinberg et al., in press) to include the study of 40 Hz vibration of glaborous skin receptors and examination of the interaction of simultaneous (in phase) auditory and tactile stimulation.

Methods

Conditions:

Three conditions of steady-state stimulation were examined: Tactile (T), Auditory (A) and simultaneous, in phase stimulation of Both auditory and tactile stimulation (B).

Stimuli:

Pressure vibration was applied to the right forefinger by means of a small plastic piston with an annulus-shaped tip, 4 mm in diameter. The piston and piston housing was 4 metres in length allowing an electromechanical vibrator to drive the piston without magnetic artifact. The vibrator was driven by a sine wave oscillator controlling amplitude and frequency. The vibratory stimulus was applied to the tip of the right forefinger held in place by a wooden form fitting device, and consisted of a maximum sinusoidal displacement of 1 mm. The force was sufficient to displace 50 g over this distance measured with a force-displacement transducer (Grass Model TC10C) and was experienced by the subject as a strong fluttering sensation at the finger tip. The auditory stimuli consisted of 55 db(HL) 1000 Hz sinusoidal tone bursts of 5 msec duration (non-ramped) presented binaurally at repetition rates of 30 and 40 Hz and monaurally at 40 Hz in the combined auditory-tactile condition. In order to eliminate magnetic artifacts the sound was conducted to the subjects through plastic tubing and earpieces from a small speaker fixed to the top of the dewar. The orientation of the speaker was fixed with respect to the gradiometer sensing coils so that no artifact was measured regardless of the position of the gradiometer. A steady-state paradigm was used for both tactile and auditory stimuli with a sampling rate of 1 point/sec and a time interval of 100 msec for each data record for 1000 repetitions. When auditory and tactile stimuli were presented simultaneously, onset time was adjusted such that maximal displacement of the piston coincided with the onset of the tone burst at the earpiece.

Subjects:

The data reported here are from three male subjects ranging in age between 21 and 35 years; one received only Condition A; one received only Condition T; and one received Conditions A, T and B.

MEG and EEG:

MEG data was collected with a 3rd order gradiometer in an automated gantry system. The subject's head shape was digitized and served as a model for automatically positioning the dewar over at least 40 preselected sites over both hemispheres. Coordinates of the positions and orientation of the sensing coil were recorded for use in dipole estimates. Configuration of the MEG system has been described elsewhere (Vrba et al., 1982). EEG was recorded from Cz referenced to linked mastoids with a bandpass of 10.6 to 70 Hz. EEG was recorded primarily for the purpose of ensuring that the 40 Hz EEG response was present but was not used in estimating sources.

Data Analysis:

For topographical analysis of the MEG data, Fourier analysis was used to compute the amplitude and phase of the 40 Hz component from the MEG average at each recording position. These values were then plotted as vectors in polar coordinates. Since a phase difference of 180 degrees is equivalent to a polarity reversal of the same signal, the average phase was calculated as that angle for which the root-mean square amplitude of all vectors projected onto that angle was maximal. The resulting amplitude values were used to produce isocontour maps of the field over the surface of the head. The interpolated values for these maps were calculated as the weighted sum of all recording positions within a specified search radius; the weight for each position being proportional to the reciprocal of its distance. For subject U. R. the topography of the phase vectors have also been plotted. A least-squares method for estimating one or two dipole fits to the data as described by Harrop et al. (1986) was used for approximating the location of equivalent current dipole sources. The method takes into account the number, size, spatial separation and orientation of the gradiometer coils. The least-squares method utilises multiple radii defined as the distance to each recording position from an origin near the centre of the head (computed as a point on a horizontal plane defined by nasion and preauricular points). Anatomically, this origin lies in the vicinity of the brainstem at the midline of the ventral surface of the upper pons.

Results

Auditory (A):

EEG: The vertex EEG response to 30 and 40 Hz shows a clear following response which is consistant with what would be expected from the literature of previous studies (Fig. 1). The electrical response is consistent throughout subjects for both unilateral and bilateral auditory stimulation; the response to 30 Hz is a triphasic waveform and of lower amplitude than the 40 Hz response which is sinusoidal in form and of approrimatly twice the amplitude as that of the 30 Hz response.

MEG: Isofield plots of the 40 Hz component of MEG responses indicate bilateral equivalent dipole sources in the vicinity of primary auditory cortex. For both binaural and monaural auditory stimulation bilateral dipolar fields are observed over the temporo-parietal regions. For monaural stimulation (subject U.R., Fig. 2) the fields are quite symmetrical; two-dipole fits of the data estimate sources 2.0 cm posterior, 4.5 cm lateral and 4.4 cm superior to the origin placing bilateral sources roughly in the vicinity of either primary auditory cortex in superior temporal gyrus (Fig. 3). The orientation of these dipoles are approximately vertical and directed toward midline indicating that such sources may comprise equivalent sources orientated vertically in the superior plane of the temporal lobe. The strength of the current dipole estimates for the responses reported here are in the range of 2 to 3 nanoampere-meters which corresponds to values previously reported for steady-state fields by Romani et al. (1982).

Tactile (T):

EEG: The vertex EEG from tactile stimuli for 40 Hz follows the stimulus but its amplitude and phase are highly sensitive to variations in the area and position of the forefinger stimulated and is generally lower in amplitude than the auditory response.

MEG: At maximum amplitude of the EEG response the MEG appears to be dipolar contralateral to stimulation. The fields may be complex; however if only contralateral data are used in dipole estimates, equivalent dipole fits which account for 80% of the variance of the observed fields can be achieved. The position for this dipole in subject R.G. was 3 cm posterior, 3 cm lateral (left hemisphere), and 8 cm above the origin placing the equivalent dipole source in the area of the finger locations of somatosensory cortex (postcentral gyrus). For subject U.R. a single dipole fit to all the data from both hemispheres also places a single equivalent dipole in the same area of contralateral somatosensory cortex, accounting for over 70% of the variance. Using only observed data from contralateral hemisphere again increases this fit to account for more than 80% of the variance (Fig. 3).

Combined Auditory and Tactile (B):

EEG: The EEG at the vertex shows a following response which is similar in waveform and period to tactile and auditory following responses, with an amplitude somewhat larger than that for auditory stimulation alone when the individual responses were in phase relative to each other (Fig. 1).

MEG: The observed MEG data is shown in Fig. 2. A complex distribution of fields appear to result in patterns of maxima and minima in both hemispheres. However, the arithmetic sum of the tactile and auditory fields is very close to the observed field. As can be seen maxima and minima have the same distribution over the head, as if the result of simultaneous stimulation is the sum of what would be expected from stimulation of each of the modalities separately. Two dipoles fit to this data account for 80% of the variance and result in a right hemisphere estimate being very close to that of the right hemisphere auditory estimate (slightly more lateral) but the left hemisphere dipole being placed quite lateral and above the temporal lobe (6 cm above the plane of the origin) -- possibly what would be expected if the left hemisphere fields were the result of the combined activity of the contralateral tactile dipole estimated near vertex, and the left hemisphere auditory dipole estimated in temporal lobe.

Discussion

The data presented here suggest that different systems are active in response to 40 Hz tactile vibration and auditory stimulation, although the EEG response at the vertex remains quite similar. The evidence which remains to be established is the response with homologous bilateral tactile stimulation. However, it is clear from both monaural and binaural stimulation that two auditory systems are active in either case; one in right hemisphere and one in left. The data from subject U.R. clearly indicated two bilaterally symmetric fields arising from sources in auditory cortex. Analysis of the fields resulting from tactile stimulation is consistant in both subjects and results in estimates of a sources for tactile vibration in the expected hand and finger locations of the sensory homunculus of the postcentral gyrus.

The data from U.R. which results from simultaneous stimulation of auditory and somesthetic modalities is instructive. Interestingly, the relative latencies of the auditory and tactile EEG following responses coincide with simultaneous stimulus onset (as described in Method) and these relative latencies could be shifted by changing the relative onset of either the auditory or tactile stimulus. Moreover, the electrical responses for the auditory condition (A) appear greater than for the tactile response alone, and slightly larger for auditory-tactile combined (condition B), suggesting the possible summing of responses from deep thalamic sources at the vertex when the stimuli

are in phase. However, the MEG data suggests a much more complex interaction of cortical sources. If only left hemisphere fields are considered the data can be seen to be a combination of the contralateral response to somesthetic stimulation and the left hemisphere response to auditory stimulation. The data from the right hemisphere of subject U.R. is similar to the right hemisphere data of subject T.R. Taken as a whole, the bilateral data from U.R. is what would be expected if the tactile and auditory stimulation were producing fields which summed on left side, and since tactile stimulation does not result in ipsilateral fields, only the auditory fields are seen in right hemisphere. This conclusion is supported by the result of summing the fields resulting from separate auditory and tactile stimulation; the sum is remarkably similar to the observed data for simultaneous stimulation in auditory and somatosensory modalities. The appropriate dipole analysis for the combined observed fields (auditory and somesthetic) would be a three dipole solution; such a configuration of sources may in fact account for the unusual fit for the left hemisphere dipole when trying to fit two dipoles to this data. Unfortunately software for the solution of three simultaneous dipoles is not currently available, but we are in the process of developing it.

If it is the case that the combined fields for dual modality stimulation are the sum of the fields for single modality stimulation it suggests that the 40 Hz response is confined to sensory systems related to the modality of stimulation; if there were an interaction of these modalities in the 40 Hz response the combined fields would undoubtedly not be a simple linear sum of of the two. The data suggests that the two modalities may be driven independently by 40 Hz stimulation and supports the interpretation that the response reflects a resonance in the sensory system stimulated.

Although source estimates of the observed fields assumed a single equivalent dipole, or two equivalent dipoles active simultaneously, and the fits for these dipoles account for a large percentage of the variance between predicted and observed fields, the observed fields are, nonetheless, clearly non-dipolar. The data for separate tactile and auditory stimulation suggest that several dipoles are simultaneous active. This interpretation is supported by the topography of phase angles shown in Fig. 4. If only a single dipole were active, all magnetic data would be in phase; there would be no topographical distribution. The topographical distribution of phase is relative to an arbitrarily defined temporal origin; it is not possible with steady-state stimulation to determine which parts of the brain are leading with respect to stimulation. However, the systematic change in phase from posterior to anterior locations is consistent with the interpretation that there is a thalamo-cortical system involved some parts of which when active result separately in dipolar fields that summate to produce the sinusoidal 40 Hz response normally observed. Although the estimated locations of equivalent dipole sources are consistent with the appropiate functional cortical sites, it does not mean that the source of the 40 Hz responses is entirely cortical. Clearly a thalamo-cortical system is involved, and the reason we estimate sources in cortex is that, being closest to the gradiometer, this signal is largest.

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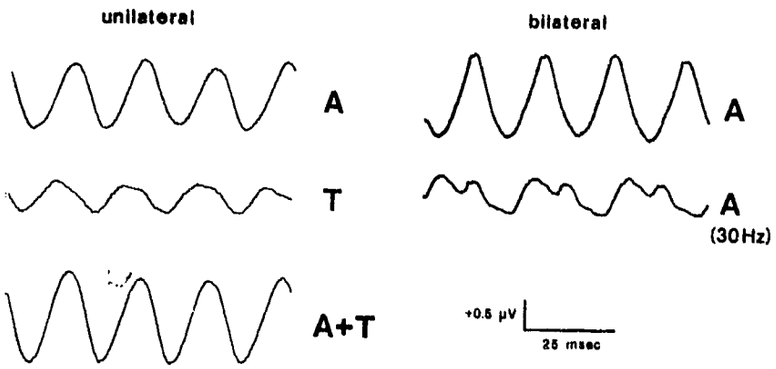

Figure 1. Average EEG responses to (A) bilateral sinusoidal tone bursts presented at rates of 30 and 40 Hz and unilateral tone bursts (right ear) at 40 Hz; (T) vibrotactile stimulation at 40 Hz (right index finger); and (A+T) combined (in phase) stimulation of right ear and right index finger at 40 Hz. Cz electrode referenced to linked mastoids.

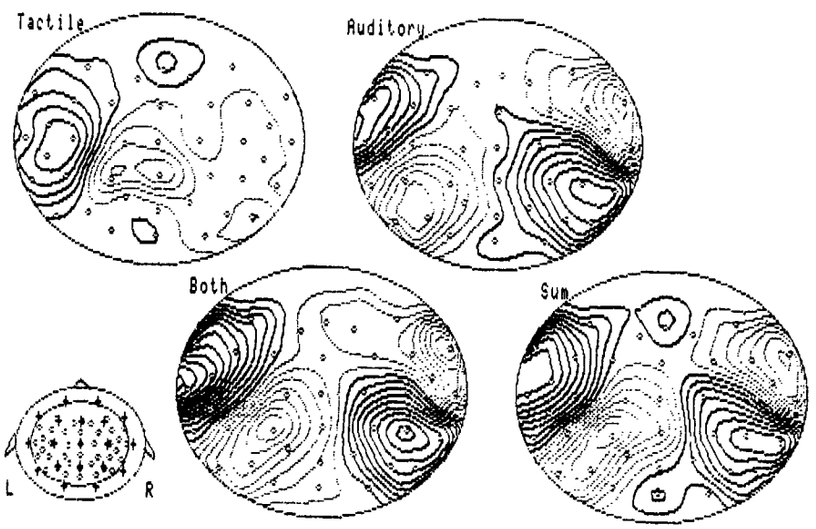

Figure 2. Isofield contour maps of the magnetic 40 Hz amplitude for three stimulus conditions and the sum of the tactile and auditory responses (subject U. R.). The maps are shown as equidistant projections of the head surface with vertex as the center and recording positions shown as small circles. The map border lies approximately at the level of T3/T4 -- indicated by the innermost circle on the inset diagram showing 10-20 system locations. Each contour level corresponds to 2.5 femtotesla and light and dark lines indicate fields of opposite direction.

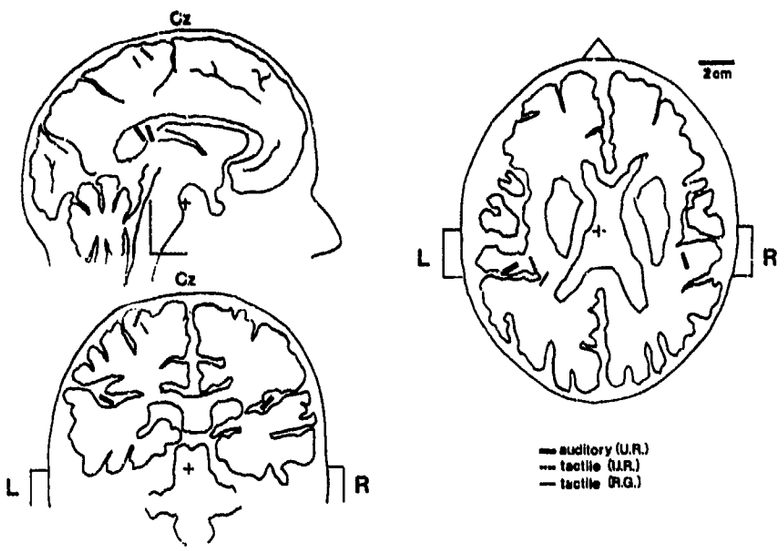

Figure 3. Three-dimensional representations of the location of equivalent dipoles source estimates fitted to the observed frequency components shown in Fig. 2, using a least-squares fitting routine. Two-dipole estimates were fitted for the auditory condition (dark bars) in homologous regions of superior temporal lobe, accounting for 86.2% of the variance in the observed values. Single dipoles were fitted to the tactile data for two subjects both in left postcentral gyrus and account for 70% (U.R.) and 81% (R.G.) of the variance. Drawings are taken from representative brain sections and a small cross indicates the relative position of the origin of the coordinate system used in dipole localization.

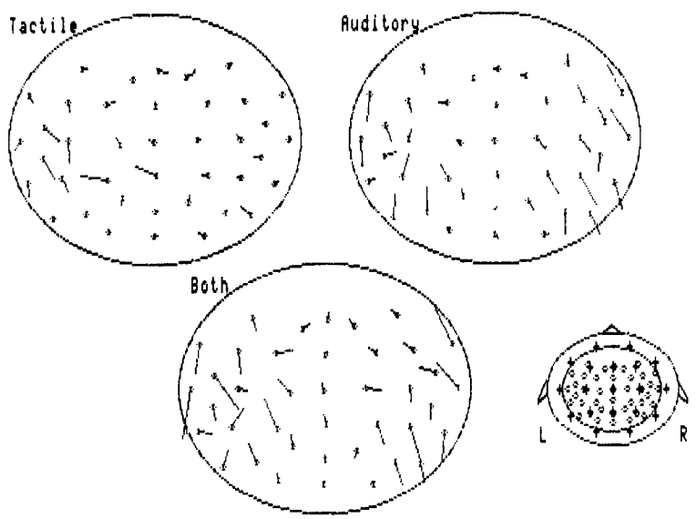

Figure 4. Phasor plots of the 40 Hz frequency components used to produce the isocontour maps and dipole estimates for 3 conditions in subject U. R.. Direction of lines indicate the relative phase of the 40 Hz component at each recording location. Length indicates the magnitude of the 40 Hz component, the largest magnitude (left-most position for condition Both) corresponding to approximately 36 fT.

A study of sources in the human brain associated with stereopsis.*

by

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Stereopsis is an important and interesting subject of study for many reasons. Clearly, the brain codes, and stores, complex information about the relative positions of objects in space; how this is accomplished is not only important for an understanding of stereopsis but could also be instructive for the analysis of other processing systems in the brain. For example, disparate visual input is simultaneous input and, from what is known about stereopsis, that processing appears to occur in parallel. Local stereopsis is the point-by-point comparison of the images on the two retinae and the calculation of the associated disparity for every feature on the visual image. Global stereopsis is the integration of all the coded, local disparities into an overall perception of a three dimensional scene.

Twenty years ago Barlow, et al. (1967) and Nikara, et al. (1968) showed that different cells in the retina are maximally excited by relative distance, i.e., by stimuli behind or in front of the plane. Many subsequent studies have shown that these "disparity neurones" are not uniformly distributed amongst cortical areas. For example, some cells which appear to be tuned to fine disparities are most common in striate cortex, whereas, others tuned to coarser disparity are more prevalent in prestriate cortex, and those responding to changes in disparity caused by moving stimuli are found in the superior temporal sulcus (for review see Bishop, 1983). Fine stereopsis is a specific pattern matching of local features of the two retinal images; it usually functions only within 1 to 2 degrees in the central visual field. Coarse stereopsis functions within a much wider range of retinal disparities, primarily in peripheral visual fields. Subjects may have qualitative perceptions of depth but may not be able to fix their absolute positions in space (for example, subjects with double vision, diplopia, may have coarse stereopsis).

Many studies have attempted to tease-out the various brain systems responsible for stereopsis through systematic lesions of visual and non-visual cortex. For example, it has been shown that global stereopsis of random-dot stereograms (RDSs) is more significantly impaired by damage to right, than to left hemisphere (Benton, et al., 1970). However, when age, IQ and lesions size are matched, the effects of penetrating wounds on stereopsis does not suggest hemisphere differences (Lawler, 1981). Several authors have raised the question of whether hemispheric differences after brain damage could not be simply a reflection of greater right hemisphere involvement in pattern recognition of stereoptic images. Whether these effects are influenced by impairments in vergence is not known, however it is known that global stereopsis can occur in the presence of diplopia.

Cowey (Cowey & Porter, 1979; Cowey, 1979; 1985) has pointed out that the organisation of visual input, in which medial hemiretinae project contralaterally and lateral hemiretinae project ipsilaterally, results in those binocular cells concerned with mid-line targets receiving part of their input via the corpus callosum. This route for mid-line stereopsis was established by Mitchell and Blakemore (1970) who studied stereopsis after corpus callosum and anterior commisures had been surgically divided. Cowey (1985) demonstrated that damaging macular representation in striate cortex leads to very high stereoacuity thresholds, however, when RDSs were used well above the threshold stereoacuity, stereopsis could be impaired by damage well outside the primary or secondary visual areas, even though there was only minimal impairment with large inferotemporal lesions. Although it is clear that striate and non-striate cortex is involved in stereopsis (Poggio and Fischer, 1977), it is also true that binocular visual information is first combined in the cortex and not in the lateral geniculates where afferents from each eye area segregated into separate layers which do not interconnect (Hubel and Wiesel, 1961).

The idea that local stereopsis is a separate process from depth perception is also supported by studies of the responses to random-dot correlograms, visual stimuli for which the left and right patterns are alternately either identical or uncorrelated. Such stimulation is an effective cue for local, but not global, stereopsis and produces an electrical evoked response (Lehmann, Skrandies, and Lindenmaier, 1978). For the human infant, an evoked potential is detectable at 3 months of age for correlograms (Braddick et al., 1980), but not until 4.5 months for stereograms (Petrig et al., 1981). Furthermore, adults have been found to generate normal evoked potentials to correlograms presented at up to twice the limiting frequency for stereograms (Julesz, 1960; Julesz et al., 1980). Assuming that two different processes are involved in the response to dynamic random-dot stereograms,

it seems reasonable, at least in hindsight, to expect magnetic fields to be observed from at least two distinct sources.

One advantage for investigations of stereopsis using dynamic RDS's is that the disparity can be changed instantaneously without introducing monocular cues due to image shift or stroboscopic motion. The first electrophysiological studies of cortical binocularity using dynamic RDSs (DRDSs) reported the averaged evoked potential recorded from the human scalp (Mol & Caberg, 1977; Lehmann & Juless, 1978). As was also shown by more recent research, the waveform of the evoked potential normally features a single negative component, peaking at 150 to 350 ms after the onset of disparity in the dynamic RDS (Herpers, Caberg & Mol, 1981; Neill et al., 1982). Topographically, this potential is distributed widely over much of the posterior scalp, with a maximum amplitude for most subjects occurring somewhat paradoxically at the left posterior temporal area (Neill, 1984). Interpretation of this distribution is problematic due to the inherently poor spatial accuracy of source localisation based on scalp-recorded evoked potentials due to the effects of varying resistivities of tissues in the head (Nunez, 1981).

A preliminary investigation, conducted in our laboratory, of the magnetic fields evoked by DRDSs has been previously published (Weinberg et al., 1985). Briefly summarized, the results of this study were that the evoked magnetic field showed two components that were temporally and spatially distinct. The early component, maximum at 160 to 180 ms after onset of stimulus disparity, indicated a vertically-orientated source located in the occipital area. The later component, seen at 220 to 300 ms, showed outward-going magnetic flux maximal at the right temporal-parietal area. One explanation for these results is that the two magnetic components were related to two successive stages of visual processing, notably fusion of the two images and subsequent depth perception.

The idea that there are at least two separate processes involved in stereopsis has been suggested as the result of other research which has utilized for visual stimuli dynamic random-dot correlograms (DRDCs), for which the left and right patterns are either identical, or uncorrelated. These stimuli are effective in producing an electrical evoked potential which is similar to that evoked by dynamic RDS's (Lehmann, Skrandies, & Lindenmaier, 1978). If there are two separate neural generators, one active during the process of fusion and another associated with depth perception, it might be the case that electrical potential recordings show only one component because of a summation effect due to volume conduction. Regardless of whether there are one or two processes involved, the evidence clearly points to the fact that, although stereopsis depends on visual stimuli, more than striate and prestriate visual systems are involved. This may be why an individual's capability for stereopsis appears to be particularly sensitive to all of the factors which influence attention and memory (Ross and Hogben, 1974); indicating that the neurophysiological processing required cannot be relegated to a pre-perceptual mode. For example, in a study of binocular depth perception in a hostile environment, Kobrick (1969) investigated errors in distance judgement as a function of low ambient temperature and wind exposure. Both factors were found to increase errors in depth discrimination for objects viewed at a distance. Another example concerns the effects of sleep deprivation. Horne (1978) reported as one of the effects of sleep deprivation the impairment of binocular convergence, particularly for night vision, although stereopsis per se was not tested. Paul (1965) did measure the degree of stereopsis with a graded series of stereoscopic stimuli and found that stereoacuity decreased after 38 hours of sleep deprivation. In another study of the effects of drugs on visual function subjects were not sleep deprived, but were given triprolidine (Actifed) which is reported to cause drowsiness when taken as a relief for sinus congestion (Luria et al., 1979). Normal doses of this drug were found to have no effect on stereopsis, however.

The Experimental Programme

The purpose of the initial stage of the research was to confirm with MEG the evidence for multiple stages of processing binocular information, establish what these stages are, and estimate location of generators. Initial experiments are designed to compare the magnetic fields evoked by dynamic RDSs and dynamic RDCs in the same subjects to see if the DRDC evoked field is similar to the early component of the response to the DRDS. Previous publications give details of the first studies, and recording of the stereoscopic evoked field in this laboratory (Neill and Fenelon, 1981; Weinberg et al., 1985).

The continuation of these experiments is concerned with the later component of the evoked field and the nature and location of the estimated sources. We are also interested in the presence of edges, and whether changes in disparity are as effective as disparity onset versus offset. Since it is known that the direction of disparity (e.g. whether a square appears in front of, or behind, the surround) significantly affects the response (Neill, 1984), the method being designed will attempt to eliminate this effect through the use of a "reversing disparity checkerboard" for which alternate squares appear closer. This stimulus would have about the same feature size as the usual square stimulus if only four squares made up the checkerboard. Along with the physiological recordings, psychophysical measures are being adapted for use with the same stimuli to accurately measure the sensitivity

of subjects for small disparities in DRDSs by measuring disparity thresholds. What is reported below are the initial results from an attempt to use anaglyphs in the study of sources associated with stereopsis.

Experimental Methods

The anaglyph technique was used to present random-dot stereograms recorded on 16 mm movie film. Each frame was originally generated on a microcomputer bit-mapped graphics display with a resolution of 640 by 225 pixels. A total of thirty-two different frames were generated, 16 of which consisted of identical patterns of red and green dots which were displaced laterally by 12 pixels. The remaining 16 frames were similar except that in addition a central square area in both the red and green patterns was displaced in the opposite direction by 12 pixels and the 24 pixel-wide area of overlap was shifted to the other side of the square to cover the gap created. These two sets of frames, when viewed with red and green filters over the correct eyes, appeared, respectively, as random dots in a single plane of depth located behind the projection screen, or else in the same depth plane with a central square area located closer to the observer. Frames were back-projected onto a translucent screen at approximately 1 m distance from the observer and the total stimulus display subtended a visual angle of approximately 20 degrees, while the interocular disparity of the central square was 1 degree. In addition, a small square fixation point was present in the centre of the display in the plane of the screen; the background was behind the plane of the screen equal to 1/2 degree of disparity and the stimulus (square) was in front of the screen by the same amount (Fig. 1).

For each trial seventeen consecutive frames consisting of the single depth plane and five frames with the disparate central square were presented. Each frame was randomly selected from the appropriate set with the restriction that the same frame was never repeated. Five to seven different selections of 22 frames were made into film loops for projection at 24 frames per second, producing an inter-trial-interval of 915 msec.

Acquisition of MEG and EEG data by computer was triggered by the film frame preceding the onset of the disparate stimulus and 256 points were digitised at 3 msec per point. At each MEG recording position, three averages of 80 trials each were collected on-line and later averaged together. Artifacts, which were mainly eye blinks in the EEG and magnetic noise in the MEG due to motor vehicles passing nearby the laboratory, were automatically rejected when the recorded data amplitude exceeded a preset threshold. EEG was recorded from a midline occipital (Oz) electrode referenced to a midline frontal (Fz) location. Low-pass filters were set at 30 Hz; time constant was 0.3 sec.

MEG recordings were done with a SQUID 3rd order gradiometer (CTF Systems, Inc.; Vrba et al. 1982) which has a 38 mm sensing coil and 55 mm inter-coil separation. Positioning of the gradiometer was done with a computerised gantry system (Vrba et al. 1985) which moved the bottom of the dewar close to the subject's scalp after the position of the head was localised with a three-dimensional digitiser. Manual control was then used to make fine adjustments to ensure that the dewar was normal to the head and as close as possible but not actually touching the scalp. Recordings over left and right temporal areas were performed with the subject lying on the opposite side and an optical system was used to rotate the visual stimulus. For occipital recordings the subject looked down through a hole in the head support and viewed the visual stimulus reflected in a mirror. An origin was defined as a position near the centre of the head computed as a point on a horizontal plane defined by nasion and preauricular points where a line projecting from nasion to inion intersects that plane and a vertical plane defined by a line from vertex perpendicular to the horizontal plane. MEG and EEG were recorded from three subjects. One subject was used for the extensive mapping study.

Data Analysis and Source Localisation Methods

After the MEG has been recorded from a sufficient number of positions and the evoked magnetic field obtained by averaging the artifact-free data, topographical maps were made for selected time intervals. An extension of a least-squares fitting program previously reported was used, in which the accuracy of source localisation of current dipoles implanted in a human skull, containing an electrically-conductive medium could be localised with an average error of 3.5 mm. (Weinberg et al., 1986). This extension allows two independent sources to be estimated from one set of recorded data (Harrop et al., 1986). In this method the values are computed by employing the Biot-Savart formula to determine the magnetic field at an arbitrary point arising from a current dipole at a fixed point. Account is taken of the nonuniformity of flux distributed across the faces of the gradiometer coils, and the actual direction of the gradiometer (which need not be normal to the head). The calculations due not require a spherical model; furthermore it is not assumed that radial components of dipoles will have non-detectable fields. These calculations ignore volume currents, the contribution of which may be non-negligible. However, for dipoles located near the cortex these methods appear to be as accurate as those which assume a spherical model and have the advantage of being able to describe any orientation of a theoretical equivalent dipole by taking into account the non-normal

component of the dipole field. We believe this method to be as valid as those which assume sphericity of non-spherical heads. This technique was applied to the estimation of multiple sources simultaneously active during the intervals of interest.

Results and Discussion

The results reported here are the data from one subject (P.B.) in which we have completed the analysis. Figure 2 shows the isocontour magnetic field maps for the intervals centered at 283, and 346 ms. The cursor positions show these intervals in relation to the EEG response averaged from the vertex. Examination of the maps makes it clear that the fields are not dipolar in nature, that there are bilateral responses, and that the right hemisphere activity could better be described as resulting from two equivalent dipoles.

The least-squares estimates of source locations for the early response, fitting two right hemisphere dipoles and one left hemisphere dipole, are shown in Fig. 3. The right hemisphere fits of two dipoles shown in Fig. 3 accounted for 74% of the variance of the recorded MEG after 1300 iterations. The single dipole fit shown for the left hemisphere accounted for 50% of the data after 400 iterations. For the later component, the two dipole right hemisphere fits for this response accounted for 59% of the variance after 1400 iterations and the single dipole in the left hemisphere fit 37% of the variance.

The locations shown in Fig. 3 are estimates with respect to the origin described above. The origin was located on an anatomical atlas and the positions of the dipoles were related to the anatomical locations shown which were similar for both the early and late components. In the right hemisphere the anterior dipole is estimated to be in the Inferior Frontal Gyrus, possibly in areas 8 or 9 of Broadman's map. The right hemisphere posterior dipole location is estimated as Broadman's area 19, a prestriate visual association area near the border of parietal and temporal lobes. The left hemisphere dipole was located in the posterior mid-temporal to superior temporal lobe described by Broadman as area 22.

Fig. 4 shows the pattern of covariances which were in the upper 95th percentile. The early component (left panel) shows a pattern which is confined to striate and prestriate areas, in which polarities of covariance in right hemisphere are generally opposite that in left hemisphere, although there are asymmetries. The pattern of covariances for the later component (right panel) shows a much more widespread distribution of related activity in which the right and left hemispheres are generally of different polarity. There is a high covariance between striate and non-striate on right side possibly suggesting the involvement of right hemisphere in the processing of input to striate. These covariance patterns suggest, as does the dipole analysis, that multiple dipole sources are involved and that they have a specific temporal relationship to each other. The distribution of those sources is different and more widespread for the later component of the electrical evoked potential.

The results reported in this study are preliminary, although suggestive. The next stage of this experiment is to study the ways in which environmental factors such as fatigue (Angus and Heslegrave, 1985) influence brain function associated with the registration and processing of dynamic RDSs.

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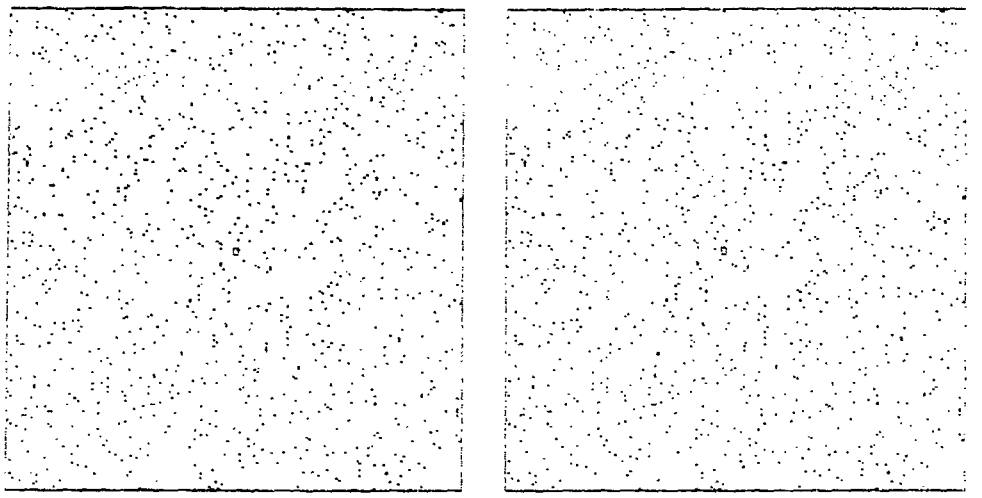

Fig. 1. One frame of the random-dot stereogram. For reproduction in black and white the red and green images which were superimposed on the screen at the central fixation point have here been printed at the left and right. When viewed with the left and right eyes, respectively, a central square appears closer to the observer.

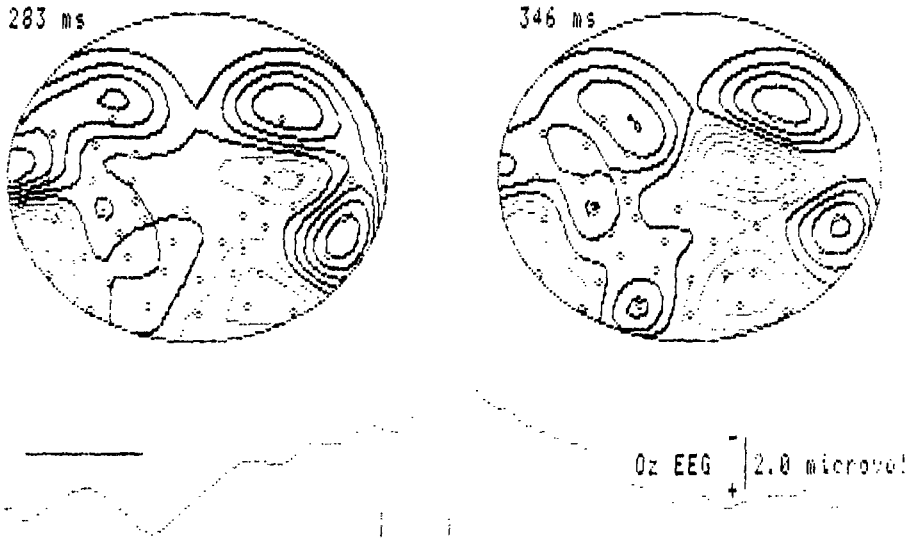

Fig. 2. MEG maps for two 21 ms time intervals centered at the time points indicated. The head is represented in equidistant projection with the vertex at center and the nose at the top. Recording positions are shown as small circles. Each contour line represents approximately 10 femtotesla; thicker lines indicate emergent flux. Grand average Oz EEG shown at bottom was recorded over a 766 ms epoch. Horizontal bar indicates stimulus duration.

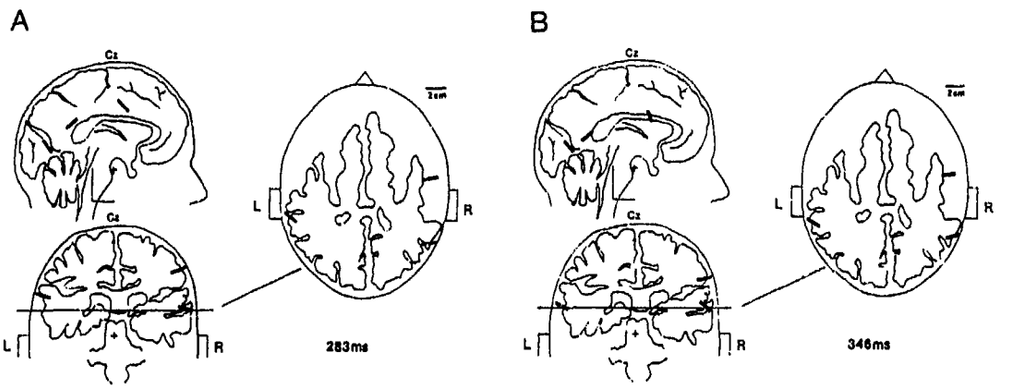

Fig. 3. (A and B) Sagittal, horizontal, and coronal sections of the head showing the locations of the three equivalent dipoles for the two time intervals investigated.

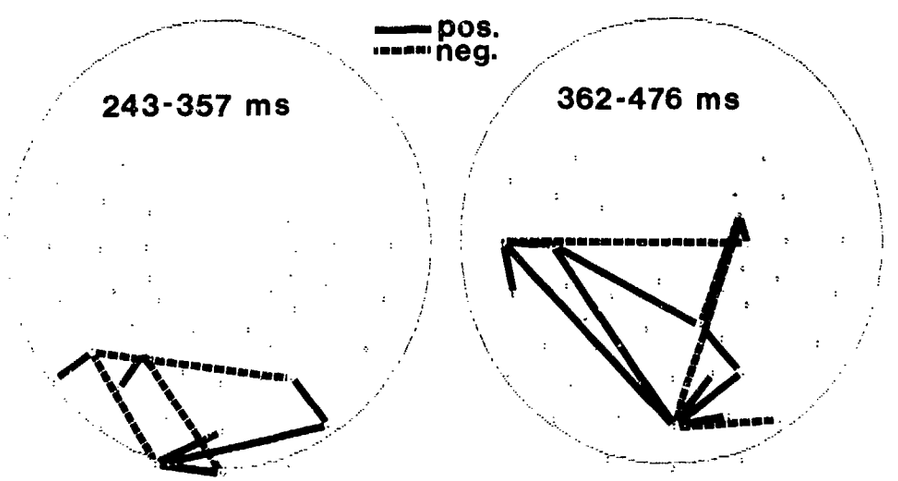

Fig. 4. Equidistant projections of the head with lines connecting those positions for which the recorded MEG showed the highest covariances over the time intervals indicated.

DISCUSSION

KAUFMAN, US: We know from the results of Carmon and Bechtoldt (Neuropsychologia 7: 29-39, 1969) that stroke victims with right temporal lobe damage are unable to report stereoscopic depth but those with left temporal lobe damage can do so. In your work with this problem, have you considered that the results may be due not to the perception of stereoscopic depth but, rather, to the presence of a disparity stimulus to disjunctive or convergent eye movements? Also, is there an experimental control to test the fact that locally there is no correlation in the disparate region when you present stimuli of that type?

WEINBERG, CA: We tried to measure eye movements to vergence in the EEG and were not able to see anything.

KAUFMAN, US: May I make a suggestion? The disparities that you are using for stereopsis are probably Panum-area types that would be on the order of about 8 minutes of arc, which you could not possibly detect using electro-oculographic recording. This is one of the problems with convergence. However, the vertical disparity would produce no depth, and since there are few disjunctive vertical eye movements, the control condition might be right to test for correlation.

WEINBERG, CA: We haven't done the studies on correlation that we intend to do. Some of these responses may be the results of correlation rather than stereopsis. Neil did this effectively in his thesis (reference in text); in fact, we used his random dot stereogram system originally but we did not do the correlograms. It is something that we still need to do.

JOHN, US: I would like to compliment you on the consistent and analytical way you approach these questions. I know that the steps are difficult, but I wonder if one shouldn't use the double-labelled 2-deoxyglucose method to look at the distribution of neuronal activity in some of these situations. This should be done with C14-labelled glucose or F18-labelled glucose in positron emission tomography (PET) in man. If one looks with "moving" microelectrodes in the conscious animal during information processing what one finds is a pervasive engagement in responding to stimulation in many regions in the brain. It seems to me that someone should make MEG measurements at the same time as surface measurements of the electrical activity on the scalp are made, evoked or EEG, while probes are entering the brain into regions where these dipoles are apparently located. The distribution of activity around the dipole could be measured and its gradient drawn. Serial sections could be taken afterwards to determine from the 2-deoxyglucose uptake exactly where the activity was located. I do not understand why these direct correlations between metabolism, single cell activity, slow potentials, and these distributions as inferred at a distance have not been made. Maybe you could explain it?

WEINBERG, CA: Some work is being done to obtain estimates on source metabolism using MEG and PET, but this is a difficult process because it is necessary to rotate the co-ordinate system that you are using in these two modalities.

KAUFMAN, US: Yoshio Okada at New York University is doing work using slices of turtle cerebellum and utilizing the techniques developed over the years by Nicholson and Llinas and others. He is able to work very carefully stimulating specific fiber tracts, plotting the associated field in a shielded environment, and is locating current dipoles inside the neurons.

WEINBERG, CA: I agree that Dr. Okada's work will provide much needed insight into the way sources are estimated from current flow or "sheets" of neurons. However, I think Dr. John is asking for something additional to that. He wants to actually produce a dipole estimate for some somatosensory, auditory or other stimulus in an intact "breathing" brain which is processing information, and then put an electrode through that part of the brain to see if there are any reversals. If there are no reversals, then we are in trouble.

JOHN, US: There are a number of published papers by Ramos, Morgades, and John, in one order or another in which chronically implanted multiple microelectrodes were used to probe long distances in the brain in naive and trained animals in which we were looking for poststimulus histograms, evoked potentials, and gradients that would give some indication of whether or not there were sinks and sources. We found none.

WEINBERG, CA: People have been doing this for some time and have been finding reversals; certainly in the temporal lobe. However, these are not associated with the dipoles which are estimated as a result of sensory stimulation. I think that this needs to be done.

BERRY, US: How might these techniques actually be used to predict performance in various kinds of tasks? Would you look for changes in the location of dipoles or changes in the strength or what?

WEINBERG, CA: The stereopsis study, for example, is being supported by DCIEM. One of the ideas behind this project is to see if you can observe the character of these sources and their changes under conditions of stress. You should be able to predict when stereopsis falls apart, for different conditions of stress, without having to bring individuals to those states of stress. Secondly, you might be able to identify those people who have more capabilities for maintaining stereopsis under different kinds of stress.

EVENT-RELATED BRAIN POTENTIALS AS INDICES OF MENTAL WORKLOAD AND ATTENTIONAL ALLOCATION

by

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Over the past decade considerable strides have been made in explicating the antecedant conditions necessary for the elicitation, and the modulation of the amplitude and latency, of a number of components of the event-related brain potential (ERP). We focus in this report on the P300. Much work in our laboratories and elsewhere has begun to elucidate the functional significance of the P300 (Desmedt, 1980; Donchin, 1981; Pritchard, 1981; Sutton and Ruchkin, 1984). These data contribute to the analysis of cognitive function and are therefore of theoretical interest. However, in this paper we will dwell mostly on the degree to which these psychophysiological measures contribute to issues in two real-world domains; communication devices for the motor imparied and the assessment of mental workload of aircraft pilots. Although these two domains may appear to be quite heterogenous they both require relatively rapid communication of information, a problem for which components of the ERP may prove useful. It is important to note that techniques are available in both of these domains that address the communication problem. Thus, if the ERPs are to prove truely useful in this endeavour they must be shown to provide information that complements the information already obtained from these other techniques.

One characteristic of the P300 component of the ERP that makes it a candidate measure of cognitive processes of interest in these domains is its sensitivity to the task relevance of a stimulus or response. Numerous studies have demonstrated that a P300 is elicited only if a subject actively processes or attends to a stimulus. Ignored stimuli do not elicit a P300 (Donchin and Cohen, 1967; Duncan-Johnson and Donchin, 1977). In the context of the assessment of pilot workload, it would be of interest to know whether the P300 would reflect the graded decrement in processing that is characteristic of gradual increases in workload level (Donchin, Kramer and Wickens, 1986; Kramer, 1987). Thus, within this domain it is not enough that the amplitude of the P300 discriminates processed from unprocessed events, but magnitude of processing must also be reflected in the P300. In contrast, the construction of a "mental prothesis" for the motor imparied requires only that the P300 reflects which item in an array of items is being actively processed. However, it is important that such a commun cation device does not require the user to fixate the item to be communicated.

Experiment I - Assesment of Pilot Workload

The program of research that we have conducted to address issues of mental workload is particularly consistent with a resource theory framework (Freidman and Polson, 1981; Navon and Gopher; 1979; Wickens, 1980; 1984). Within this framework the performance decrements observed in multi-task paradigms are attributed to the depletion of one or more of a set of finite resources. Thus, if two difficult memory tasks are timeshared it is assumed that one of the tasks will require a majority of the resources, leaving an insufficient supply for the performance of the other task. Within this context, mental workload can be described as the cost of performing one task in terms of a reduction in the capacity to perform additional tasks given that the two tasks overlap in their resource demands. Although this theory provides a good account of the results in both laboratory and operational environments, the hypothetical resources must be inferred from performance measures.

In research performed in a number of laboratories, it has been found that the amplitude of the P300 component mimics the resource tradeoffs presumed to underlie dual task decrements (Defayolle, Dinand and Gentil, 1971; Horst, Munson and Ruchkin, 1984; Isreal, Chesney, Wickens and Donchin, 1980; Kramer, Wickens and Donchin, 1983, 1985; Lindholm, Cheatham, Koriath and Longridge, 1984; Natani and Gomer, 1981; Strayer and Kramer, 1986; Wickens, Kramer, Vanasse, Heffley and Donchin, 1983). The general paradigm employed in these studies requires subjects to perform two tasks concurrently. One task is designated as primary and the other task as secondary. Subjects are instructed to maximize their performance on the primary task and devote any additional resources to the performance of the secondary task.

Primary tasks have included system monitoring, decision making, and manual control. Secondary tasks have required subjects to discriminate between tones of different frequencies or lights of different intensities. In general, the response demands of the secondary probe tasks have been minimal, requiring subjects either to covertly count the total number of one type of event or respond to an occasional target probe.

ERPs are elicited by events in either one or both of the tasks. Increases in the perceptual/cognitive difficulty of the primary task result in a decrease in the amplitude of the P300s elicited by the secondary task. Conversely, P300s elicited by discrete events embedded within the primary task increase in amplitude with increases in primary task difficulty. Furthermore, changes in response related demands of a task have no influence on the P300 (Isreal et al., 1980).

The reciprocal relationship between P300s elicited by primary and secondary task stimuli is consistent with the resource tradeoffs presumed to underlie dual-task performance decrements (Kahneman, 1973; Navon and Gopher, 1979; Sanders, 1979; Wickens, 1980). That is, resource models predict that as the difficulty of one task is increased, additional resources are re-allocated to that task in order to maintain performance, thereby depleting the supply of resources that could have been used in the processing of other tasks. Thus, the P300 appears to provide a measure of resource tradeoffs that can only be inferred from more traditional performance measures. Furthermore, P300s elicited by secondary task events are selectively sensitive to the perceptual/cognitive demands imposed upon the operator. This selective sensitivity may be especially useful in decomposing the changing processing requirements of complex tasks (Kramer et al., 1983).

One might ask why ERPs should be used to monitor changes in resource demands given that several technically simpler approaches to the assessment of mental workload have already been proposed. Although numerous performance-based measures of mental workload exist, they suffer from several drawbacks. First, some of the measurement techniques require subjects to perform a secondary task which frequently interferes with the performance of the task of interest (Knowles, 1963; Rolfe, 1971; Wickens, 1979). This is clearly unacceptable in an operational environment in which the safety of the operator must be assured. Even in the laboratory setting it is difficult to determine which of the two tasks generated an observed performance decrement since the performance on the two tasks is easily confounded. Second, performance-based measures of mental workload provide an output measure of the operator's information processing activities (e.g. RT, accuracy). Thus, at best, performance measures provide only an indirect index of cognitive function. Third, performance measures do not always correlate highly with the actual workload of the tasks (Brown, 1978; Dornic, 1980; Ogden, Levine, and Eisner, 1979). It has been shown in a number of situations that subjects may compensate for increased workload by expending additional effort. However, this effort is not always reflected in performance measures (Vicente, Thornton and Moray, 1987). Fourth, although subjective measures are relatively easy to collect and possess high face validity they do not reflect the moment to moment variations in workload that are indexed by physiological measures.

The goal of the present experiment was to augment the conclusions drawn from the studies cited above by demonstrating that the dual-task ERP paradigm could be employed in a complex real-world situation to provide information concerning mental workload and residual capacity. Student pilots performed a series of dual-task flight missions. In each case, the primary task consisted of performing a specified flight scenario under Instrument Flight Rule (IFR) conditions. The difficulty of the primary task was varied in two ways. "Between mission" difficulty was manipulated by varying the direction and speed of wind conditions, the severity of turbulence, and the probability of a subsystem failure during a critical portion of the mission. A second way that difficulty was manipulated might be labeled "within mission" difficulty. In this case we capitialized on the different levels of processing demand inherent in the flight task (i.e. straight and level vs. approach to landing).

The secondary task consisted of a concurrently performed go/no-go auditory discrimination task in which subjects pressed a button in response to the presentation of one of two tones. ERPs associated with the secondary task tones, overt performance measures from the flight task and discrimination task, and subjective indices of task difficulty were examined to assess the extent to which the manipulations of primary task difficulty modulated the mental workload associated with the flight task.

Method

Subjects Seven student pilots enrolled in Aviation 210 at the University of Illinois' Willard Airport participated in the study. The student pilots possessed a private pilots license and had a basic familiarity with IFR flight skills. All of the pilots were between the ages of 20 and 26 and had normal hearing and normal or corrected to normal vision.

Simulator and Stimulus Generation Equipment The ILLIMAC flight system used in the experiment consisted of a fixed based flight simulator that was designed around the INTEL 8086 digital microprocessor. In the present study the simulator was configured to mimic the flight characteristics of the BEECHCRAFT Sport 180, a single engine aircraft with fixed gear and a fixed propeller. The ILLIMAC flight panel contained the instrumentation and navigational radios required for instrument flight conditions. Flight performance measures were digitized at the rate of 30 Hz and transferred via a RS232 link to a DEC PDP 11/73 computer. Performance measures included deviations from assigned heading, altitude, airspeed and glideslope.

The auditory stimuli employed for the secondary task were produced by an audio-generator and binaurally presented to the pilots through headphones. ERPs, flight performance data, and secondary task RTs were recorded on magnetic tape for off-line analysis.

Procedure An IFR flight plan, roundtrip from Champaign. Illinois to Octoe intersection, formed the framework within which the processing demands imposed upon the student pilots were investigated (see Champaign approach plate AL-709, ILS Runway 32 for additional details). The flight included a takeoff, straight and level segment, three holding patterns, and an instrument landing system (ILS) approach to landing. Each pilot flew a total of four 45 minute missions in the flight simulator. In the first session, the students flew the course twice. These flights served to familiarize the subjects with the IFR flight plan and the dynamics of the simulator. Both of the missions were flown under the easy flight conditions (no wind, turburlence or subsystem failures). Since the flights were considered practice, the performance data will not be dealt with in the present report.

In the second session, subjects again flew the flight path twice. However, in this session one of the two flights included 30 mph winds from 270 degrees, moderate turbulence, and a partial suction failure in the heading indicator during approach to landing. The presentation order of the easy and difficult flights was counterbalanced across subjects. A Certified Flight Instructor (CFI) was present during each flight to instruct the subjects on the flight scenarios and to evaluate their performance. Upon completion of each of the two flights, subjects were asked to rate the difficulty of the flight as a whole, as well as each of the individual flight segments. Each of the flight missions lasted approximately 45 min. Subjects recieved a 15 min rest break between flights.

In addition to the flight task subjects performed another task both separately and concurrently with the flight. The task required the student pilots to monitor a Bernoulli sequence of auditory stimuli presented binaurally through headphones. Two different tone frequencies (1000 hz and 1500 Hz) were used. One of the tones was designated as the target and was presented on 30% of the trials. Subjects responded to targets by depressing a switch located on the left side of the control yoke. Both speed and accuracy were emphasized in the instructions. Non-targets, which were presented 70% of the time, did not require a response. Tones were 50 msec (including a 10 msec rise/fall time, 65 dB) in duration, and were presented every 1.4 to 1.7 secs.

ERP Recording System Electroencephalographic (EEG) activity was recorded from three midline sites (Fz, Cz, and Pz according to the International 10/20 system: Jasper, 1958) and referred to linked mastoids. Beckman Biopotential Ag-AgCl electrodes filled with Grass electrode paste were attached to all scalp sites as well as to a forehead ground. In addition, identical electrodes were placed above and below the subject's right eye to evaluate Electrooculographic (EOG) activity in the vertical plane. All electrode impedances were maintained below 10 kohms.

The EEG and EOG channels were amplified by Grass model 12A5 amplifiers with a 10 second time constant and an upper half amplitude of 35 Hz, 3 dB/octave rolloff. The recording epoch for all channels was 1300 msec beginning 100 msec prior to the presentation of secondary task tones. The data channels were digitized every 5 msec and were digitally filtered off-line (-3 dB at 6.27 Hz; 0 dB at 14.29 Hz) prior to further analysis. Artifactual contributions to the EEG from EOG activity were evaluated and eliminated off-line by submitting the data to an eye movement correction procedure (Gratton, Coles, and Donchin, 1983).

Results

Flight performance and probe discrimination data The flight performance data were collected to assess the validity of the difficulty manipulations, both within and across missions. Two measures of flight performance, heading and altitude deviation, were recorded in all flight segments in both easy and difficult missions. These indices were submitted to a two-way repeated measures analysis of variance. One additional measure, deviation from the glideslope, was recorded in both the easy and difficult scenarios in the final flight segment. Table 1 presents the mean values of the flight performance measures for both easy and difficult flights.

All three of the flight performance measures indicated that our between mission experimental manipulations successfully influenced the difficulty of the flight task. When the student pilots were required to fly the 45 min mission with high winds, moderate turbulence, and a subsystem failure during approach to landing their deviations from command altitude increased ($F(1,6)=6.6$, $p<.05$), their ability to accurately track the glideslope decreased ($F(1,6)=8.0$, $p<.05$), and their deviations from assigned headings increased ($F(1,6)=9.1$, $p<.05$) relative to the mission with no wind, turbulence, or subsystem failures. Flight performance was also influenced by mission segment irrespective of between mission difficulty (see table 2). Subjects were more accurate at maintaining their assigned headings during straight and level flight and holding patterns than they were during takeoff and landing. ($F(3,18)=4.3$, $p<.05$). However, students performance on the altitude measure did not differ as a function of flight segment. Thus, flight performance measures most strongly discriminated between easy and difficult flights, while inter-segment differences were found for only a

subset of the performance measures.

Performance measures for the ERP eliciting probe task are presented in Table 1 for the between mission comparison and in Table 2 for the comparison across flight segments. Subjects were uniformly accurate across missions and flight segments with response accuracy ranging from 89 to 93 percent. Neither RTs nor accuracies differed as a function of flight segments or missions ($p>.05$). Thus, any differences among the ERPs elicited in different flight conditions cannot be attributed to the subjects' failure to perform the probe task in the more difficult flight missions or segments.

TABLE 1

Mean simulator performance, probe discrimination reaction time and accuracy, and subjective workload ratings for easy and difficult flights (standard deviations are in parentheses).

MEASURES	FLIGHT MISSIONS	
	EASY FLIGHT	DIFFICULT FLIGHT
Heading deviation (degrees)	1.86 (.67)	3.08 (.90)
Altitude deviation (feet)	40.3 (17.8)	70.9 (37.8)
Subjective workload ratings	115.2 (12.7)	137.8 (21.6)
Probe reaction time (msec)	580.0 (139.5)	604.0 (119.3)
Probe accuracy (percent correct)	92.4 (6.0)	89.0 (7.2)
Glideslope deviation (degrees)	.35 (.21)	.74 (.38)

TABLE 2

Mean simulator performance, probe discrimination reaction time and accuracy, and subjective workload ratings for the four flight segments (standard deviations are in parentheses).

MEASURES	FLIGHT SEGMENTS			
	Takeoff	Straight and Level	Holding Patterns	Landing
Heading deviation (degrees)	2.89 (1.03)	1.87 (1.06)	1.92 (.81)	3.19 (1.44)
Altitude deviation (feet)	53.6 (32.2)	60.1 (12.5)	41.9 (11.2)	67.4 (58.6)
Subjective workload ratings	128.6 (18.5)	117.2 (10.1)	128.4 (13.1)	133.0 (21.7)
Probe reaction time (msec)	604.0 (101)	564.0 (135)	584.0 (127)	617.0 (146)
Probe accuracy (percent correct)	89.4 (7.3)	93.1 (6.0)	92.2 (6.4)	89.6 (6.4)

Subjective Workload Ratings Table 1 presents the subjective workload ratings for the between mission comparisons while Table 2 displays the ratings for each of the flight segments. Each of the flight segments in the easy and difficult flights were rated relative to a straight and level segment that was flown prior to the experimental flights. Subjects made their ratings subsequent to each mission and were permitted to assign any numerical value to their estimates of subjective workload. The ratings were normalized prior to statistical analysis.

Subjects rated the flight mission with high winds, moderate turbulence, and a partial suction failure in the heading indicator during ILS approach as having a significantly higher workload than the flight without wind, turbulence or subsystem failures ($F(1,6)=18.7$, $p<.01$). Subjective ratings also discriminated among flight segments ($F(1,6)=6.0$, $p<.01$). The subjects' estimated the takeoff, holding pattern and landing segments to be equally difficult, while straight and level flight was estimated to be easier than the other three segments ($F(1,6)=9.8$, $p<.01$).

A comparison of the flight performance measures and the subjective workload ratings suggest that, for the most part, the pilots' subjective estimates corresponded well with their performance on the flight task. Both the performance measures and the subjective ratings discriminated between easy and difficult missions. Flight segments were also differentiated by subjective and objective measures.

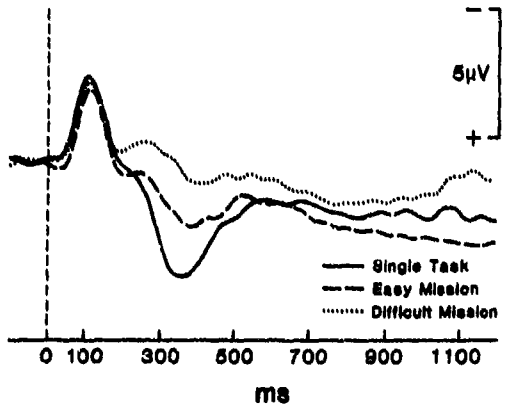

Figure 1. Parietal grand average ERPs overplotted for the tone discrimination task alone and both of the flight missions.

Event Related Potentials Figure 1 presents the ERPs recorded at Pz overplotted for the three conditions. Although a number of components can be discerned by visual inspection of the waveforms we will concentrate on the large positive deflection occurring at approximately 350 msec post-stimulus. This component increases in amplitude from the frontal to the parietal recording site and appears to discriminate among levels of task difficulty. In a single task condition the amplitude of this component was influenced by both stimulus probability and task relevance. Based on these criteria the component can be identified as the P300 (Donchin, Ritter and McCallum, 1978; Kramer, 1985; Sutton and Ruchkin, 1984).

The single trial ERPs were corrected for eye movement artifacts and then averaged within experimental conditions. The amplitude and latency of the P300's were obtained from single trials. Peak latencies and amplitudes were defined as the largest positive deflection within a 300 to 600 msec window relative to the pre-stimulus baseline. Two separate analyses were performed on the P300 data. In the between mission analysis, P300 measures were submitted to three way repeated measures analyses of variance (2 single/dual tasks x 2 probe types x 3 electrodes). Three factors were also entered into the within flight analyses of variance (4 flight segments x 2 probe types x 3 electrodes).

One of the major questions in the present study was the extent to which P300 amplitude would discriminate among levels of workload imposed upon the student pilots by the flight tasks. The main effect of flight mission indicated that P300 amplitude was sensitive to the task demands of the different missions ($F(2,12)=4.7$, $p<.05$). Post-hoc comparisons further indicated that P300s elicited by the tones in the discrimination task were largest in the single task conditions, of intermediate amplitude when the students were flying with no wind, turbulence, or subsystem failures, and smallest with high winds, turbulence and a heading indicator failure (for all comparisons $p<.05$). This systematic decrease in the amplitude of the P300s elicited by the tone discrimination task alone and combined with the flight missions mimics the resource tradeoffs presumed to underlie multi-task performance.

A main effect of flight mission was also found for the P300 latency variable ($F(3,18)=11.3$, $p<.01$). Post-hoc comparisons indicated that this effect could be attributed to the significant difference between single and dual-tasks ($p<.05$). However, latencies did not differ between the two flight missions. This finding suggests that the difference in P300 amplitude between the two flight missions cannot be accounted for by increased latency variability in the difficult flight. Given that single task P300 latencies are often shorter than dual-task latencies, we feel that we can safely conclude that the P300 component successfully discriminated between single and dual-tasks as well as between the two versions of the flight task.

Our second analysis compares ERP components elicited during the four flight segments. It was predicted that the P300s elicited by the tones in the more difficult flight segments would be smaller than those recorded during the easier flight segments, reflecting increased processing demands in the more difficult conditions. Although the within mission comparisons yielded weaker effects for the performance and subjective measures than the between mission analysis, an ordering of the flight segments could be ascertained. The straight and level flight segment and the holding pattern were flown with smaller heading deviations than the takeoff and landing components of the missions. The student pilots also rated the straight and level segment to be subjectively easier than the other three segments. Although the ordering of the P300 amplitudes was consistent with these measures (the mean amplitudes of the segments were 209, 525, 508 and 283, respectively) the main effect for flight segment did not attain statistical significance ($p>.05$). However, a small but significant correlation was obtained

between the amplitude of the P300 and the deviation from command heading (R = -.27), indicating that the amplitude of P300 decreased with increases in heading deviation. The latency of P300 did not differ across flight segments.

Discussion

The results of the present experiment provide preliminary support for the assertion that components of the ERP can provide sensitive and reliable measures of the task demands imposed upon operators of complex, real-world systems. The P300 varied in a systematic manner in response to the demands of different versions of the flight task. Relative to conditions in which the tone discrimination task was performed alone, the amplitude of the P300 decreased when the student pilots performed the easy version of the flight task. Further decreases in P300 amplitude were observed when the difficulty of the flight task was increased through the manipulation of wind speed, turbulence, and the probability of subsystem failures. Although the within mission effects were not as dramatic as the between mission comparisons, a small but significant correlation between P300 amplitude and heading deviation was obtained across flight segments.

The sensitivity of the P300 to the processing demands of the different flight missions is noteworthy for several reasons. First, the changes in the amplitude of the P300 as a function of task demands mimics the modulation of resources presumed to underlie variations in operator performance. Resource models predict that as task demands increase additional resources will be allocated to the high priority task thereby withdrawing resources from tasks of lesser importance (Navon and Gopher, 1979; Wickens, 1980). The amplitude of the P300s elicited by the secondary probe task decreased with increases in the difficulty of the flight task. Other studies have found that P300s elicited by primary task events increase in amplitude with increases in task demands (Kramer et al., 1985). Thus, it appears that the P300 provides a measure of the hypothetical resources that can only be inferred from more traditional measurement techniques.

A second point concerns the use of the secondary task procedure in the assessment of mental workload. The resource demands of a primary task are usually inferred from decrements in secondary task performance (Ogden et al., 1979). However, a particular difficulty of the secondary task methodology is the intrusion of the secondary task into primary task performance, thereby complicating the interpretation of the performance decrements. In the present study, our secondary probe task required a relatively simple discrimination and an occassional overt response. In fact, secondary task performance did not discriminate among levels of primary task difficulty. Secondary task reaction time and accuracy was uniformly high in all conditions. On the other hand, the P300 elicited by the probe stimuli did discriminate among the demands of the flight task. Thus, the ERP eliciting probe task provides a sensitive metric of resource demands without intruding upon the performance of the task of interest, a clear advantage in operational settings. However, this is not to imply that even a relatively nonintrusive secondary task is an ideal workload assessment procedure in complex, real-world systems. Clearly, a more acceptable solution would be the elicitation of ERP components by primary task events, thereby negating the requirement for any type of secondary task. Such a procedure has been successfully employed in the laboratory and we are currently exploring its efficacy in operational settings (Kramer et al., 1981; Sirevaag et al., 1984).

A third point concerns the nature of the metric. Although ERP components certainly qualify as physiological measures, they are somewhat unique in that they are selectively sensitive to a subset of processing demands. Autonomically mediated measures such as heart rate variability, respiration, blood pressure, and skin conductance are influenced by ambient environmental conditions, anxiety and physical exertion in addition to mental workload (Williges and Wierwille, 1979). Therefore, these measures are sensitive to workload in general but are not diagnostic in the sense of identifying the source of the processing demands. The P300 is sensitive to information processing demands, and more specifically it is influenced by perceptual/cognitive demands but not motor processes. Thus, unlike other physiological measures, ERP components are quite diagnostic.

Experiment II - Proposal for a Mental Prothesis

This program of research has focused on the development of a system that provides a means for an individual to communicate using ERPs. The development effort capitalizes on the sensitivity of the P300 component to the task relevance of a stimulus or response. Thus, if an individual selectively processes a single item embedded in a matrix of items the attended item will elicit a P300. P300's will not be elicited by the unattended items. We propose that the sensitivity of the P300 to this category distinction can be exploited to communicate information that an individual wishes to convey. It is important to emphasize that neither speech nor any other motor system is necessary for this communication process.

The system works in the following manner: a 6-by-6 matrix containing the letters of the alphabet and a few single-word commands is displayed on a CRT (see Figure 2). In the test of the system, the subjects task was to communicate a word by sequentially attending to a set of letters in the matrix. The computer flashes rows and columns of the matrix and detects the flashes that evoke ERPs characterized by a P300. Since flashes of the attended letters would be both rare and task relevant they were expected to generate larger P300's than unattended letters.

The present study represents a preliminary assessment of the efficacy of this ERP based communication system. The major goal of the experiment was to examine the parameters of the system that were expected to have an impact on the communication process. The parameters investigated include: the type of detection algorithm, the number of trials, and the rate of intensification of elements in the matrix that are required to achieve a specified level of accuracy and rate of communication.

CRT Display Used in the Mental Prosthesis

MESSAGE

BRAIN

Choose one letter or command

A	G	M	S	Y	*
B	H	N	T	Z	*
C	I	O	U	*	TALK
D	J	P	V	FLN	SPAC
E	K	Q	W	*	BKSP
F	L	R	X	SPL	QUIT

Figure 2. CRT display used in the mental prothesis. The rows and columns of the matrix were flashed alternately. The letters selected by the subject were displayed at the top of the screen.

Method

Subjects Four healthy subjects, 3 females and one male, whose ages ranged from 20 to 36 years, participated in the study.

Procedure Subjects were presented with a 6-by-6 matrix whose cells contained the letters of the alphabet as well as several one-word commands for controlling the system. The matrices were displayed on a computer-controlled CRT. In each "trial," the 6 rows of the matrix, or the 6 columns, were each intensified for a period of 100 msec. The rows were selected for intensification in a random order, and then the columns were similarly intensified.

The subjects task was to select each of the letters in the word "BRAIN" in turn, and silently count the flashes of the row or column containing the letter until the system displayed the letter it had selected. For purposes of the off-line analysis of the operating characteristics of the system the rows and columns were flashed approximately 30 times for each of the letters. After the letters spelling the word "BRAIN" had been displayed, the subject selected the "TALK" command, and the word was spoken by a Votrax speech synthesizer. A real-time discriminant function was used to detect differences between the attended and unattended letters.

In order to collect sufficient data to analyze the operating characteristics of the system the subjects spelled the word 10 times. Half of the blocks were run with a 125 msec delay between the onset of the intensification of a given row or column and the onset of the intensification of the next row or column to be flashed and half with a 500 msec inter-stimulus interval (ISI).

ERP Recording The EEG was recorded from Ag-AgCl Beckman Biopotential electrodes placed at Pz and referred to linked mastoids. EOG was recorded from electrodes placed above and below the right eye. Ground electrodes were positioned on the forehead. Electrode impedance did not exceed 5 kohm. The signals were amplified by Grass model 12 amplifiers. Low and high-pass filters had half-amplitude frequencies of 35 and 0.01 Hz respectively. The data were digitized at a rate of 50 Hz. The ERP and EOG data were digitized continuously from 20 msec prior to the first flash until the end of each letter trial (30 flashes of the rows and columns). Eye movement artifacts were removed by the Eye Movement Correction Program (Gratton et al, 1983).

Data Analysis In analyzing the data, we sought to determine how many trials were required to detect the letter on which the subject was focusing at different levels of accuracy, for each of 4 different detection methods. For the purpose of analysis, each trial was divided into 6 data windows or subtrials, each consisting of the data for 600 msec after onset of the flash of a row or column. Since the ISI was less than 600 msec, the subtrials contained overlapping data. For each of these subtrials we computed a score that measured the magnitude of the P300 in the epoch following the presentation of the row or the column.

Four different algorithms were used to compute the scores: (a) stepwise linear discriminant analysis (SWDA), (b) peak picking, (c) area, and (d) covariance. We will briefly describe each of these algorithms. For more details, see Donchin and Heffley (1975) and Coles, Gratton, Kramer, and Miller (1986).

A. Stepwise discriminant analysis. SWDA is a classification procedure. In the present case, the procedure computes a score that reflects the "distance" between each epoch and the mean of a group of trials known to include a P300 as well as the distance from the mean of a group that does not include a P300. This measurement is performed by applying a discriminant function to the epoch's data. That function is developed on the basis of a "training set" of trials whose group membership is known. We used as a training set the data collected while the subject was focusing on the first 2 letters ("B" and "R"). The remaining data became the "analysis set." We used the training set data to compute discriminant weights that distinguished between the attended and unattended subtrials. These weights were applied to individual subtrials in the analysis set and summed across trials in order to identify the attended cell of the matrix.

B. Peak picking. The amplitude of P300 was defined as the difference between the most negative point prior to the P300 window (defined as the time range within which the average attended waveform in the training set was positive) and the most positive point in the P300 window.

C. Area. The "area" of P300 was defined as the sum of the data points in the P300 window.

D. Covariance. A P300 template was computed as the average of the attended subtrials in the training set. P300 scores in the analysis set were derived by computing the covariance of each subtrial with this template.

Row and column scores were summed to compute a unique score for each cell in each pair of trials (one trial in which rows were flashed and one trial in which columns were flashed). For example, the score for "B," which is located in the first column and the second row was the sum of the score for the first column and the score for the second row. The scores computed for each letter were summed across trials to determine which cell was identified as the cell selected by the subject. On each test there were one correct response and 35 possible errors. The test was considered a "hit" if the algorithm yielded the largest total score, summed across trials, for the letter on which the subject was focusing.

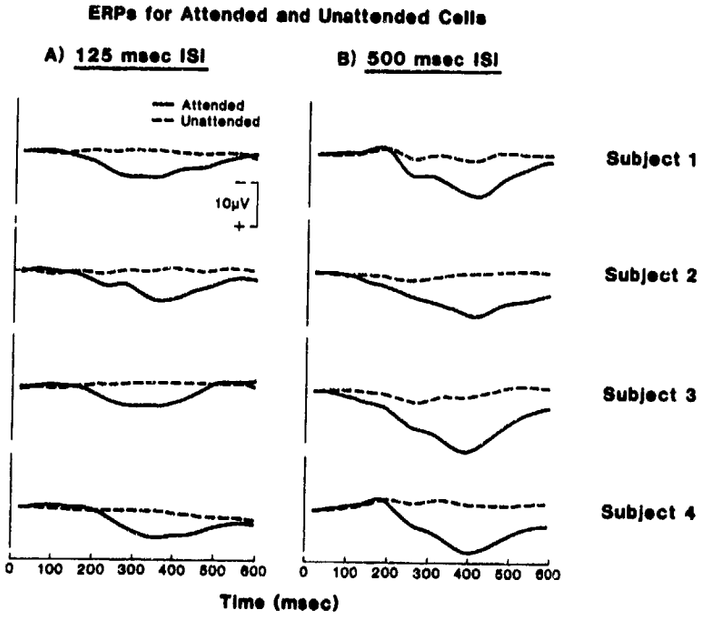

Figure 3. Average waveforms for attended and unattended letters for each of the subjects and both ISI's.

Results

The principal question we addressed in this study was the speed and accuracy with which the ERP based mental prothesis could communicate single letters. Figure 3 shows that when the attended and unattended letters were separately averaged there was a clear difference in the P300's elicited by the two conditions. However, if the technique required the presentation of 30 trials for correct detection it would be quite limited, the rate of information transmission would be one character per 37.4 seconds, even when data windows are overlapped by shortening the ISI to 125 msec. The P300, however, can be detected with a smaller number of trials (Squires and Donchin, 1976). We examined, therefore, the accuracy of detection as a function of the number of trials at each ISI for each of the 4 detection algorithms. Detection accuracy was estimated by means of a bootstrap technique (Efron, 1979).

We randomly chose 1000 sets of 2 trials, 1000 sets of 4 trials, and so on up to 1000 sets of 40 trials from the data set. The sampling was with replacement. We applied the 4 signal-detection algorithms, computed scores for each of the 36 stimuli, and determined how many times out of 1000 that the stimulus the subject was attending had the highest score with each algorithm. This provided an estimate of the percent of correct identifications of the chosen stimulus out of the 36 presented, as a function of the number of trials considered in the analysis. By multiplying by the inter-trial interval, we obtained an estimate of the accuracy as a function of time.

As can be seen in Figure 4, there are considerable individual differences in the subjects' ability to use the system, as well as in the relative effectiveness of the different detection algorithms. Moreover, different algorithms were more effective for different subjects. All of the subjects, however, were able to achieve a high level of accuracy in communicating their choices to the system at a speed of several seconds per choice.

Table 3 presents speed and accuracy figures for the fastest algorithm for each subject at each ISI. When the subjects' optimal ISI and signal-detection algorithm were used, the mean time required to achieve 80% accuracy was 9.0 seconds. For 95% accuracy, the mean time required was 15.3 seconds. A choice of one out of 36 contains 5.2 bits of information, so the speed at 95% accuracy was 0.34 bits per second, or 20.4 bits per minute. By using the "BKSP" (backspace) command (see Figure 2) with the same speed and accuracy, a subject could correct errors and achieve over 99.9% accuracy with a speed of 0.30 bits per second, or 18.3 bits per minute.

SPEED/ACCURACY: FASTEST ALGORITHMS

	A) 80% Accuracy				B) 95% Accuracy			
ISI (msec)	125		500		125		500	
Subj. #	Time (sec)	Algo.	Time	Algorithm	Time	Algorithm	Time	Algorithm
1	12.2	Area	12.0**	Peak	19.0**	SWDA/Area	22.0	Peak
2	11.4**	Peak	11.7	Peak	19.1**	Peak	20.7	Peak
3	9.8	Peak	6.2**	Area	17.8	Peak	11.5**	Area
4	8.7	Peak	8.1**	Peak	14.1	Peak	11.6**	Peak
Mean		11.4		9.9		18.4		17.9
Mean time to 80% accuracy, fastest ISI and Algorithm for each subject				9.0	Mean time to 95% accuracy, fastest ISI and Algorithm for each subject			15.3

Peak picking proved to be the most efficient algorithm. When considering the 4 subjects, 2 ISIs, and 2 accuracy criteria peak picking yielded the fastest times to reach the accuracy criterion in 12 cases out of 16. Area was the fastest in 3 cases. SWDA and area measures were tied in one case.

Discussion

This study addressed two distinct questions. First, we sought to determine if the P300 could be employed as a binary switch by means of which the subject can toggle a choice. This question is clearly answered in the affirmative. Indeed, the specific arrangement we used to present choices to the subject can amplify the choosing power of the switch as a series of binary choices allows for the reliable identification of a choice among 36 distinct objects. In principle, this method can be used in a manner that would allow for a choice among more items, as the number of rows and columns can be increased. However, such an increase would entail a cost in that the total number of flashes required for each choice would be increased. The optimal size of the matrix remains a matter for further investigation.

The utility of the communication channel based on the P300 depends, as do all communication channels, on the signal-to-noise ratio. It is evident that the P300 on which this channel is based is buried in the "polyneural roar of the EEG," to use Ross Adey's felicitous phrase. The detection and measurement of the P300, as is true for other ERP components, requires signal averaging. Thus, it was conceivable that while the P300 can, in principle, serve as a switch, its

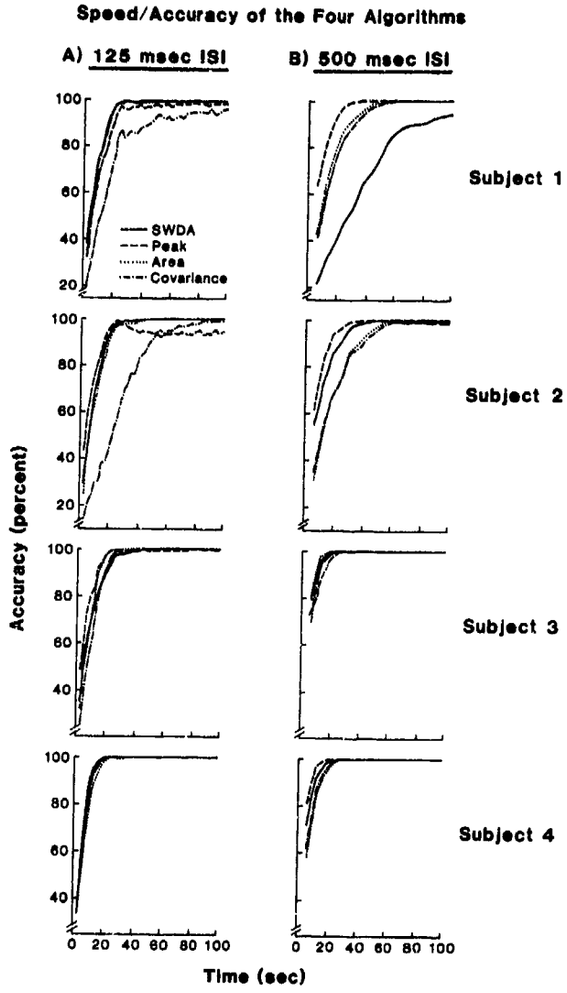

Figure 4. Plots of the accuracy of identification of attended letters for each of the subjects, algorithms and ISI's.

reliability under the signal-to-noise conditions which it presents would have been quite impractical for actual use. Our second goal in this study was to examine the operating characteristics of the communication channel.

The conclusions are quite clear. The channel can operate reasonably well at the speed of 20.4 bits per minute. A character, chosen from among 36 items, can be detected with 95% accuracy within 15 seconds. The ISI proves to be an important variable. There seems to be a relatively fixed relationship between the number of trials required for detection at a given level and the interval between stimuli. At the values we chose, there seems to be a constant level of signal-to-noise reduction that is required. This can be achieved by increasing the interval between stimuli from 125 to 500 msec, allowing for a better definition of the P300. Alternately, the signal-to-noise reduction can be achieved by an increase in the number of trials. The speed of the communication remains constant under these two variations.

This general conclusion is tempered by considerable variability across subjects. Different detection methods varied in their effectiveness when applied to the data of the different subjects. The differences in effectiveness are due to an interaction between the nature of the procedures and the specific attributes of the subject's data. It is useful to consider the differences among the detection algorithms.

Covariance computes, essentially, how similar the individual ERPs are to a template consisting of the average waveform for the attended cell in the training set. All time points are included, and each point is weighted according to the mean amplitude of that point in the training set.

SWDA involves much more extensive computations on the training set data than covariance, but it is in general more efficient because it gives greater weight to time points that were more effective in distinguishing between attended and unattended cells in the training set.

The primary weakness of both SWDA and covariance is sensitivity to latency variability. If an ERP component, such as P300, appears in a given trial with much longer or shorter latency than the modal latency in the training set, then the discriminant weights (or, similarly, the weights in the covariance algorithm) will not be applied to the points that best characterize the P300, and accuracy will be lost. Latency jitter during the training set, also, will add noise to the system and result in less effective weights.

Peak picking, on the other hand, is highly insensitive to latency variability. The P300 peak can be located anywhere in a relatively wide time window. However, all of the information contained in the other points is lost by this procedure.

Area, like covariance, considers all of the points in a broad range, but it is a purely additive, rather than a multiplicative procedure, and does not use a training set. Therefore it misses some information contained in a consistent, distinctive ERP shape and time course, but also avoids some of the noise introduced into SWDA and covariance by variability in the time course and shape of ERPs. It takes advantage of information contained in a broad, flat ERP that is lost in the peak picking algorithm, but by the same token is influenced by noise at points at a distance from the peak.

Because of these differences, different algorithms are more effective in different cases. For a subject whose P300s have a distinct peak with considerable latency variability, peak picking is likely to be the most efficient algorithm. For a subject whose ERPs have any distinctive shape and little latency variability, SWDA is likely to be the most efficient. For a subject whose P300s tend to be broad and flat, without much of a peak and with considerable latency variability, area is likely to be the most efficient. These differences notwithstanding, the general conclusion is sustained by the data. It is quite possible to use the P300 as an effective binary switch, and the communication channel can be organized so that the choices can be communicated using a relatively small number of trials.

Although the speed of the mental prothesis is rather slow relative to other modes of communication such as typing or speech, there are several techniques that might be used to increase the rate of transmission. For instance, the value of the channel may be further enhanced if the procedure is used as a method for choosing from a menu of commands rather than as a method for spelling words. The elements in the matrix may well be words rather than letters. Each of these choices may in turn call for another menu. In such a paradigm the rate of communication would be enormously amplified, even though the domain of the communication would be constricted.

Furthermore, the communication speed we have assessed in this study examined the channel without any attempt to benefit from a number of obvious procedures for accelerating the communication. As a computing device must be a part of the system, it is relatively trivial to incorporate in the channel the known constraints of the language. With each letter presented the number of actual options is reduced, as combinations of characters appear with quite uneven probabilities in English. The system may be allowed to "guess" so that, for example, having detected a "TH" pair it can be relatively sure the following character would be an E, an A, or an I.

It may also be possible to enhance the speed of the system by incorporating additional components of the ERP. If, for example, we were to present the rows and columns in a regular sequence, one would expect to see a CNV develop as the time for the appearance of the correct column, or row, neared. The relative effectiveness of a random presentation utilizing the P300 solely and a presentation that capitalized on both a CNV and the P300 is a matter for further research.

Conclusions

The procedures we describe in this paper and the data we adduce serve to illustrate the feasibility, and the limitations, of the "biocybernetic" concept. The term "biocybernetics" has been used to describe an attempt sponsored during the 1970's by DARPA to develop a "biocybernetic" channel. That channel was to enhance the communication between people and machines by adding channels of communication that employed psychophysiological means. Several approaches were proposed (see Gomer, Beidman, and Levine, 1979). There were several attempts to use the ERP as a switch. Vidal and his associates have, for example, used the differences between the responses to different checkerboards which flashed on

different parts of the screen to create an EEG-driven joystick that controlled the movements of a displayed "mouse" (Hickman and Vidal, 1976).

The mental prothesis described in the present article provides further support for the usefulness of ERPs as alternate communications channels. Evidence has also been provided which supports our arguement that the amplitude of the P300 can be used as an index of the demands imposed upon an operator of a complex system. Although both studies reported here were sucessful within their restrictive domains, they provide, at best, preliminary evidence of the efficacy of ERPs in real-world tasks. Further research is necessary to discover the limitations of the ERP procedures and to examine how ERPs might be used in conjunction with other measures to enhance the communication process.

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DISCUSSION

GEVINS, US: Regarding the ERP traces in your study, where subjects were trying to covertly generate the word "brain", what were the bandpass filter characteristics of the eye-movement channels?

KRAMER, US: The method that we used to deal with eye movements in that particular study was the EMCP procedure (Gratton,G., Coles, M.G.H., and Donchin,E. Electroenceph. clin. Neurophysiol. 55:468-484, 1983). We did not reject trials in which eye movements occurred; but, instead, filtered the eye movements with that particular regression-based procedure.

GEVINS, US: The question has to do with the fixation of the eyes at the moment of the delivery of the stimulus. This work reminds me very much of the paradigm that was first done to institute the era of biocybernetics by Jacques Vidal at UCLA, in which he used stepwise discriminant analysis on single-trial data to try to move a "mouse" on a screen through a cursor. It turned out that the measurements that he was picking up were actually exquisitely sensitive to very small shifts — a fraction of a degree — in the fixation of gaze. Therefore, although the mouse was moving across the screen seemingly as a result of the generated brain potentials; in fact, it was actively responding to signals that were related to these very small shifts in the fixation of gaze. In order to establish that fixation is actually at the centre of the screen, it would be necessary to record fixation independently with a measurement of direct eye position such as an infrared detector or with DC-coupled electrodes. (Any AC coupling on the eye-movement channel; i.e., any time constant would not allow fixation of gaze precisely at the centre of the screen.) In this way, you will be able to establish that the signals you are picking up do reflect covert mental activity. This is an important point, because DARPA in instituting the era of biocybernetics in the 1970's, set out to use brain wave measurements as indices of covert mental activity. In other words, they felt it was possible to tell the difference between two words — let's say between the words "rhinoceros" and "hippopotamus" — just by virtue of differences in the brain wave measurements. In a sense, your work returns us to that era.

KRAMER, US: For this particular experiment, we used Grass amplifiers and the bandpass was from DC to 60 Hz, so we didn't have this particular problem. I have done other work using an infrared eye tracker (down to DC in terms of bandwidth) for EOG recording and found it lacking in terms of precision for tracking microsaccades. I've also done other work with an eye tracker, having much better resolution than the infrared detector, that detects a difference between the sclera and the iris. We have used the method in some workload experiments in which we were able to have subjects maintain fixation and not worry about eye movements. (This is the Stanford Research Institute eye tracker that measures the distance between the first and third Purkinje images. The system is claimed to have a precision within 10 minutes of arc.)

KAUFMAN, US: Almost any method that is being used in evoked potential research today is designed to pick up the electrical artifacts of the moving eye. The EOG, no matter how good it is, has a precision only of about one-half degree. One-half degree is a substantial portion of the fovea centralis, which occupies most of the visual cortex (because of the cortical magnification factor). Consequently, an eye movement of a few minutes of arc will result in an extraordinary excursion of activity in the visual cortex by centimetres. Now, the brain waves, which are changing ostensibly because of some condition in the exogenous components, may really be changing because of a change in location of the activity of the brain as brought about by a shift in fixation. That shift would not be detected unless you use a contact lens method, or a search-coil method on the sclera of the eye. Without a precise location of the source of activity in the brain, you won't even know that there is a problem. Dr. Gaillard has discussed the negatively-different wave variations in exogenous and endogenous components that are a function of the imposed conditions. As he indicated, you can present identical stimuli and give different instructions and get different results. These very different results, in part, could be due to changes that are secondarily related to the task. For example, let's consider the case of the orientation reflex as construed from the work of E.N. Sokolov (Perception and the Conditioned Reflex, Pergamon Press, 1960). In discussing the orientation reflex, he referred to changes in brain blood volume, eye tremors, and an extraordinary widening of the pupillary aperture resulting in a difference in the light level stimulating the eyes. All of these events are task dependent and could mediate changes in the brain activity that is being recorded, and which is quite independent of the effect of instruction alone. Therefore, there is a need for a substantial amount of research in which one looks, under carefully controlled conditions, at the effects of very small eye movements, fixation changes, pupillary diameter changes, and the stimulus properties that are often forgotten in doing cognitive studies, in order to see whether the distribution of brain activity is related to these secondary factors rather than to those that are endogenous.

FOWLER, CA: Why did you use an auditory secondary task rather than a visual task for your mental workload experiment? What would you predict for a visual task with respect to the resource model that you used?

KRAMER, US: To begin with, the resource model was developed by Christopher Wickens at the University of Illinois. We have used both auditory and visual tasks and found essentially the same effect. Dr. Wickens is currently revising his model so that modality will no longer be an important distinction within the structural energetical space, regardless of whether the task employed is ERP-based or performance-based.

FOWLER, CA: Did you get any interference with reaction time when you did this task in the visual mode?

KRAMER, US: The oddball task is fairly simple, in this particular case, and it doesn't seem to interfere much, whether it is auditory or visual.

THE EFFECTS OF HYPOXIA ON P300 AND REACTION TIME

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SUMMARY

This experiment investigated the effects of three levels of arterial oxyhemoglobin saturation (SaO_2 of 75%, 70% and 65%) on reaction time (RT) and P300 latency and amplitude. Ten subjects responded to visually presented male or female names in an oddball paradigm with accuracy controlled at a high level. Hypoxia increased both RT and P300 latency in a dose-related manner and these variables were strongly correlated. Hypoxia did not influence P300 amplitude. The increase in P300 latency is interpreted as further evidence that hypoxia slows stimulus evaluation processes and that, under the right circumstances, P300 could be used to index the effects of hypoxia on performance.

1. INTRODUCTION

Reaction time (RT) is the traditional measure for assessing the timing of cognitive stages of information processing but it is an end product and therefore includes the time to evaluate a stimulus, choose a response and organize it [1]. It has recently been proposed that RT could be supplemented by P300 as a means for distinguishing between stages of processing [2,3]. P300 is a positive going, endogenous, event related brain potential (ERP), occurring within the period 300 to 600 ms after the stimulus. The latency of P300 is related to RT under circumstances which suggest that P300 indexes stimulus evaluation time rather than the time to select and execute a response [4,5,6,7,8]. The amplitude of P300 is also sensitive to certain aspects of cognitive processing [9].

It is known that hypoxia slows RT and it has been proposed that brightness discrimination plays a role in this slowing but not the stimulus-response choice stage [10,11]. Various aspects of vision are sensitive to hypoxia [12] which interacts with stimulus brightness [13] and peripherally located visual stimuli [14,15] to slow RT. Furthermore, it has been demonstrated that a critical factor limiting performance on a complex machine-tool task under hypoxia was the unreliability of visual feedback compared to either tactile or auditory feedback [16].

This line of evidence raises the possibility that P300 may be sensitive to hypoxia. The purpose of the present experiment was to measure the effects of hypoxia on P300 latency and amplitude concurrently with RT to determine whether a dose-response relationship exists between any of these variables. The oddball paradigm was used and P300 was measured on a single trial basis with accuracy maintained at a high level in order to maximize the relationship between RT and P300 latency [4].

2. METHOD

Subjects

Ten normal or corrected-vision right-handed volunteers between the ages of 21 and 28 years were paid for their participation in the experiment. They were medically examined and signed an informed consent document.

Administration of Breathing Mixtures

Hypoxia was induced by the inhalation of gas mixtures from four high-pressure bottles that varied in O_2 content from 8.0% to 13.0% O_2, with the balance nitrogen. Air from another cylinder was breathed as a control. Valves (Matheson, Model 9-580) reduced the pressure from the cylinders to 5.2 x 10^5 N . m^{-2}, and each mixture was then fed into a common valve (Industrial Projects, Model 8N5-T8L). This allowed for the manual selection of any one of the five mixtures to a demand regulator (ARO Model MD-1) that reduced the pressure to ambient level. The breathing mixture was then transmitted to an oronasal mask (Canadian Forces, Model A13A) via flexible corrugated tubing. This arrangement allowed any desired level of arterial oxyhemoglobin saturation (SaO_2) to be maintained by monitoring it and switching between breathing mixtures as necessary during the experiment. SaO_2 was measured with an ear oximeter (Hewlett Packard, Model 47201A) and continuously recorded on a strip-chart recorder (Perkin-Elmer, Model 023).

Stimulus Presentation

The stimuli were pairs of five letter male and female given names. The names in each pair were presented singly a total of 150 times in random order so that the probability of occurrence was 80% for the male name (high probability) and 20% for the female name (low probability). Seven different pairs were used, two for practice and five for the experiment proper. Each name was displayed in upper-case letters on a computer screen (Commodore, Model SP9000) for 1300 ms with an inter-stimulus interval of 700 ms. The visual angle subtended was 2.2°. Intensity was fixed at a value judged to be comfortable and easily discriminable by pilot subjects. The screen was viewed from a comfortable reclining chair and the task was to indicate whether a male or female name was displayed by pushing either a left- or right-hand button (Microswitch, Model PK 85022) mounted on each armrest. RT was defined as the latency between stimulus onset and button depression.

Recording

Electroencephalographic (EEG) activity was recorded inside a Faraday cage at Fz, Cz and Pz electrode sites of the 10-20 international system. The electro-oculogram (EOG) was recorded horizontally and vertically by electrodes affixed to the outer canthi of both eyes and supra- and sub-orbitally to the dominant eye, respectively. All electrodes were Ag-AgCl with an impedance of 5 K Ω or less, and were referenced to linked earlobes. The subjects were grounded with an electrode on the forehead. Gould pre-amplifiers (Model, 11-5407-58) and amplifiers (Model, 13-4615-58) were used with a bandpass of 0.05 - 30 Hz (-3 dB, 6 dB/octave rolloff). The EEG was digitized every 5 ms for a 1500 ms epoch with a 100 ms prestimulus baseline and stored by a PDP 11/04 computer, which also controlled stimulus presentation and collected the RTs. A pen recorder (Gould, Model 2400S) was used to monitor both the EEG and EOG. P300 trials which contained EOG signals exceeding 45 μV in amplitude were discarded. The system was calibrated with a 2 Hz sine wave from a function generator (Wavetech, Model 30) over the range 0 - 50 μ V.

Quantification of P300

The single-trial waveforms from Fz, Cz and Pz were filtered using a fourth-order zero-phase Butterworth digital filter with an upper cut-off frequency of 4 Hz. The latency and amplitude of P300 were determined using the Woody filter technique with a search window extending from 250 ms to 650 ms [17]. This technique was validated by hand scoring filtered waveforms from Cz according to the criteria specified for P300 by Warren and Wideman [18] and it was confirmed that these data were virtually identical to those obtained with the Woody procedure.

Design and Procedure

A repeated measures design was used in which air was presented as a control both before and after three low-oxygen mixtures adjusted to produce SaO_2 levels of 75%, 70% and 65%. These values are equivalent to altitudes of approximately 11,500 feet, 12,500 feet and 13,250 feet, respectively (see Reference 19 for details on how these altitudes are calculated). For each subject, a different pair of names was used in every condition. The order of presentation of the five pairs of names was randomized and the order of administration of the three hypoxic mixtures was partially counterbalanced by presenting six subjects with the mixtures in a fully counterbalanced order and the remaining four subjects with four of the possible six mixture orders. The assignment of high and low probability names to left- or right-hand responses was fully counterbalanced between subjects.

Prior to the experiment, the subjects were trained on the task while breathing both air and a low-oxygen mixture corresponding to an SaO_2 level of 65%. They were judged to be trained when: 1) obvious movement artifacts disappeared from the EEG, 2) eye blinks and eye movements were minimized during the collection of EEG data, 3) responding was stable and as fast as possible while maintaining an error rate of between 0.67% and 2% (an error constituted pressing the wrong button) and 4) breathing could be maintained at a natural and regular rate under hypoxia.

In the experiment, the subjects were tested individually in a single session which lasted approximately 80 min. The oronasal mask was donned and eye movements were calibrated with respect to the centre of the stimulus display. Then the five conditions were performed in succession with a 15 min waiting period between each one to stabilize the SaO_2 level. If the error rate was not maintained between 0.67% and 2%, the data were discarded and the run repeated immediately. This was a rare occurrence.

3. RESULTS

SaO_2 was calculated for each subject by averaging the readings from the pen recorder at 10 s intervals (Table 1). The RT error rate was very low and was comparable across conditions (Table 1). This low rate prevented any meaningful assessment of error RTs which are therefore not considered further. The percentage of trials eliminated due to all causes was also comparable across conditions (Table 1). The vast majority of the rejections were due to eye movements.

An average EEG waveform was calculated for each subject. The superimposed waveforms are illustrated in Figure 1 for the first air control and the SaO_2 level of 65%. For both conditions at Cz and Pz, the low probability P300 is clearly identifiable but the high probability P300 is much smaller or virtually absent in most cases. At Fz, P300 is attenuated but still identifiable.

TABLE 1

Arterial oxyhemoglobin saturation (SaO_2), reaction time (RT) error rate and trials eliminated due to eye movements and other causes. Values are means based on 150 trials.

PARAMETERS	BREATHING CONDITIONS				
		Hypoxia Levels			
	Air 1	1	2	3	Air 2
SaO_2 (%)	97 ± 0.2*	75 ± 0.3	70 ± 0.3	65 ± 0.3	97 ± 0.1
RT error rate (%)	0.7	0.9	1.2	1.6	1.2
Trials eliminated (%)	25	26	27	26	21

* SEM

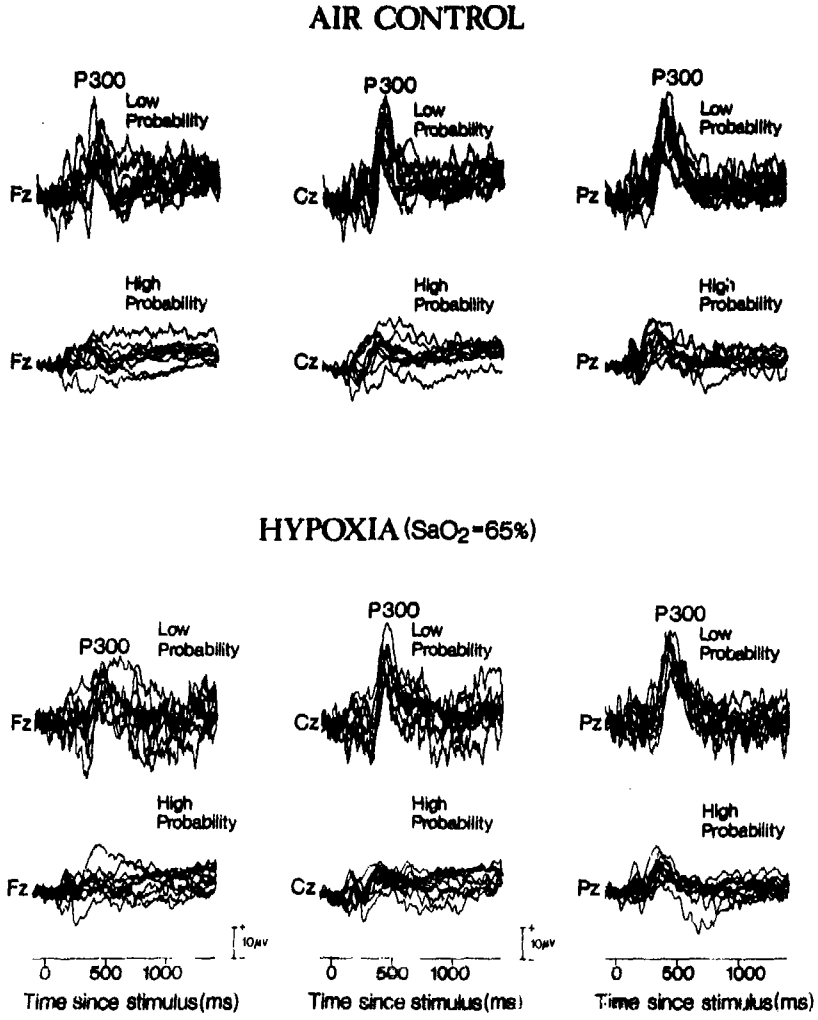

FIGURE 1. Averaged event-related potentials for the first air control and 65% arterial oxyhemoglobin saturation (SaO_2) as a function of stimulus probability and electrode site. The waveforms from each of the ten subjects are superimposed to show variance across individuals.

The effects of hypoxia on RT and on single-trial P300 latency and amplitude are summarized in Figure 2. A two-way repeated measures analysis of variance on the RT data in Figure 2A revealed that probability level ($F(1,9) = 60.19$, $p = 0.0001$), breathing mixture ($F(4,36) = 15.66$, $p = 0.0001$) and the probability level X breathing mixture interaction ($F(4,36) = 3.76$, $p = 0.02$) were all significant. These results indicate that RT was faster to the high probability stimuli and increased as a function of SaO_2 level in a manner which was dependent on probability level. In particular, RT increased from Air 1 to 75% SaO_2 for low probability stimuli (Duncan's test, $p = 0.05$) but not for high probability stimuli, while the reverse was true from 70% to 65% SaO_2 (high probability, $p = 0.01$; low probability, NS). Finally, RT decreased from Air 1 to Air 2 for high probability stimuli ($p = 0.01$) but not for low probability stimuli.

Figure 2B shows that P300 latency also increased as a function of SaO_2 level but preceded low probability RT by approximately 20 ms. An analysis of variance on these data revealed that breathing mixture ($F(4,36) = 33.26$, $p = 0.0001$) and the electrode site X breathing mixture interaction ($F(8,72) = 2.22$, $p = 0.04$) were significant. This interaction is accounted for by the longer latency at Fz than at either of the other two sites for 65% SaO_2 ($p = 0.01$) and also by the absence of a significant increase in latency at Pz from 70% to 65% SaO_2 when compared with the other two sites (Cz, $p = 0.05$; Fz, $p = 0.01$).

An analysis of variance on the P300 amplitude data in Figure 2C revealed that electrode site ($F(2,18) = 16.57$, $p = 0.0001$) was significant but no other effect. These results indicate that amplitude at Fz was 6 - 8 μ V less than at either Cz or Pz but was not influenced by SaO_2 level.

Within-conditions and between-conditions Pearson product-moment correlations for RT, P300 latency and P300 amplitude are presented in Table 2. The pattern for the within-conditions correlations indicates that virtually no relationship exists between either RT and P300 amplitude or P300 amplitude and P300 latency. On the other hand, RT and P300 latency are substantially related at Cz and Pz with some attenuation at Fz. The between-conditions correlations show a pattern similar to that described above for the within-conditions correlations. While RT and P300 amplitude, and P300 amplitude and P300 latency show little or no relationship, there is a substantial correlation between RT and P300 latency at Cz and Pz with some attenuation at Fz.

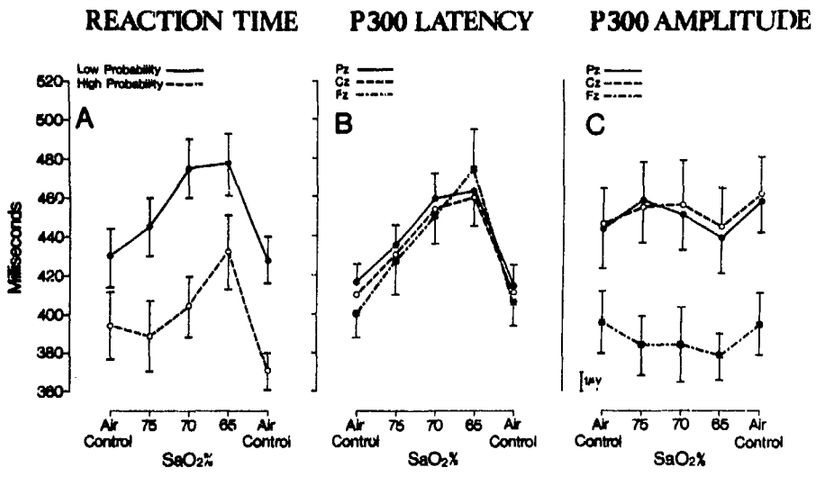

FIGURE 2. A - Mean reaction time as a function of arterial oxyhemoglobin saturation (SaO_2) level and stimulus probability.

B - Mean P300 latency to the low probability stimulus as a function of SaO_2 level and electrode site.

C - Mean P300 amplitude to the low probability stimulus as a function of SaO_2 level and electrode site.

Bars represent SEM.

TABLE 2

Within-conditions and between-conditions correlations (r) for reaction time (RT), P300 latency and P300 amplitude. Values are means based on the individual single-trial correlations for each subject (N = 10).

WITHIN CONDITIONS

	BREATHING CONDITIONS				
		Hypoxia Levels			
ELECTRODE	Air 1	1	2	3	Air 2
SITE	Arterial Oxyhemoglobin Saturation (%)				
	97	75	70	65	97
	RT and P300 Amplitude				
Fz	.01	-.17	.07	-.04	.08
Cz	-.08	-.23	-.03	.00	-.07
Pz	-.15	-.20	-.17	-.03	.07
	P300 Amplitude and P300 Latency				
Fz	-.02	.05	-.02	.06	-.04
Cz	.01	-.09	.09	.17	-.07
Pz	.00	-.04	-.05	-.04	.03
	RT and P300 Latency				
Fz	.52	.55	.42	.23	.42
Cz	.61	.63	.56	.54	.71
Pz	.59	.70	.60	.56	.65

BETWEEN CONDITIONS

	Electrode Site		
	Fz	Cz	Pz
RT and P300 Amplitude	-.07	-.07	-.08
P300 Amplitude and P300 Latency	.04	.03	-.01
RT and P300 Latency	.41	.61	.67

4. DISCUSSION

In this experiment, the within-conditions correlations for RT and P300 latency were substantial while those for RT and P300 amplitude were negligible. These results are consistent with previous findings where high accuracy was emphasized with a familiar name discrimination oddball paradigm [4,6,20]. Under these circumstances, P300 latency usually precedes RT by approximately 40 - 90 ms [6] but in the present experiment the difference amounted to only 10 - 20 ms. In a previous experiment with nitrous oxide conducted in our laboratory using the same paradigm and instructions, a difference of 70 ms was obtained [21]. The reason for the smaller difference in the present instance is unclear.

As expected, hypoxia slowed RT in a dose-related manner. Of particular significance is that hypoxia also slowed P300 in a dose-related manner at all three electrode sites. Furthermore, the slowing of RT and P300 was closely related. This is demonstrated by their substantial between-conditions single-trial correlations. On the other hand, there is no clear evidence from this experiment that hypoxia influenced the amplitude of P300.

An obvious explanation for the link between P300 latency and RT found in this experiment is that hypoxia slows some aspect of the stimulus evaluation process. Hypoxia affects a variety of visual processes [12] and it has been argued that a disruption of brightness discrimination contributes to the slowing of RT [11,13]. Since P300 latency is thought to index stimulus evaluation processes [4,5,6,7,8], it follows that P300 should be sensitive to hypoxia. At present, this hypothesis is speculative but it is open to investigation using the additive factors model which has applicability to studies involving both RT and P300 latency [3]. The foregoing issue is not only of theoretical concern but is relevent to the practical question of whether or not P300 latency could be used as an index of hypoxic performance deficits on complex tasks associated with flying.

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DISCUSSION

GEVINS, US: Did you look at the effects of hypoxia on the frequency of the alpha activity and the amount of energy in the theta and delta bands? I would think that these measures would be extremely sensitive to changes in the blood levels of O_2 and CO_2; perhaps, more so than the evoked potential components.

FOWLER, CA: We didn't do that because these measures cannot be related to reaction time, and our principle interest was to find a correlation with reaction time.

JOHN, US: I'd like to return to the point raised by Dr. Gevins. It requires the use of the EEG spectrum, sampled over a brief time period to compute the mean and standard deviation of the extracted spectral features, which is then Z-transformed and compared against subsequent EEG spectral epochs. Now, you find in cardiopulmonary bypass patients, in whom the mean arterial pressure is maintained constant, and where the temperature is 27°C — approximately one unit of Q_{10} below the normal body temperature — that as little as a 10% decrease in blood flow (which would be equivalent to a 10% decrement in the available oxygen) causes a clear increase in the content of theta as a percentage of total activity. Given that the decrease in temperature has dropped reaction time or demand by 50%, this suggests that a decrease or change in blood flow as little as 5 to 6%, or a change in hypoxia would be reflected in the EEG spectrum. It seems to me that, if your goal is to look at reaction time as a function of change in state, that there are some very elegant and precise relationships between blood flow, oxygen, and the EEG spectrum that are not being explored. I wonder why such relatively exotic and non-continuous indices as the latency of P300 are given priority as against basic indicators of state.

FOWLER, CA: I think that you may be saying that I have some interfering variables in this experiment. I'm interested in P300 because it is supposed to measure cognitive aspects of performance. It is quite possible that there are other variables that are also important. However, I cannot see that any EEG measures, at present, can be related to performance in any meaningful way. Therefore, I used P300, because it seemed that there was a very clear-cut relationship there. You may be right, but the problem is how can I use your particular measures and relate them to performance?

JOHN, US: In my paper, I discussed the "Mahalanobis distance" across the percentage of theta for the whole brain as a function of Global Deterioration Scale in our aging subjects. It is quite clear that as memory function deteriorates the excess of theta activity in the brain increases. It is also quite clear that the first sign of diminished blood volume at constant pressure is a change from alpha to theta, and a drop in the dominant frequency. It seems to me that in regard to your question on how to relate EEG to reaction time, that you do the following protocol. Take reaction time at full blood flow — stipulate the mean arterial pressure and oxygen content of blood available to the brain as 100% — and scale changes in reaction time as you scale changes in theta. It seems to me that that is where you should start to correlate brain state to reaction time.

OFFENLOCH, GE: We see EEG changes due to a fall in oxygen partial pressure or to cerebral circulation, and yet you found no correlation with amplitude. I find it strange that the amplitude of P300 is unaffected by such an enormous change in oxygen partial pressure.

FOWLER, CA: This is the first experiment that we have done on hypoxia with P300, so I cannot explain why the amplitude didn't change. Our subjects were hypoxic for about 50 minutes. It took about 20 minutes to stabilize them and about 30 minutes to take our measurements.

KRAMER, US: Do you have any speculations about the decrease in correlation between P300 latency and reaction time as a function of the changes in oxygen content? It seems that there would be correlation decreases as oxygen available to the individual decreases.

FOWLER, CA: It's a very small effect and I am inclined to think that it is related to subject variability. It is very difficult for the subjects to pay attention to the centre of the screen and ignore all subjective sensations of hypoxia. They have a headache, they are not feeling well, and it takes a long time to train these subjects to perform well. If you try this experiment with an untrained subject, you will get very poor correlation. I'm inclined to think that if I continued training the subjects beyond their current level, that the correlations would not decrease.

PORCU, IT: Do you think that P300 latency could be used as an electrophysiological measure for evaluating early variations in the mental status associated with aging? That is, is the anoxic hypoxic brain a good model for studying the aging brain with your technique?

FOWLER, CA: If you are talking about the fact that in the aging brain you get memory deficits in terms of performance, you also get this with hypoxia. I've also studied nitrous oxide, an anesthetic gas, and I get the same sort of latency shifts in P300 as I do with hypoxia. You also get it with alcohol. So it may be the case that stressors that affect memory allow you to generalize to aging performance effects where you get the same sort of thing.

USING ERPS TO STUDY HUMAN INFORMATION PROCESSING

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SUMMARY

The ERP technique may provide an inobtrusive measure of the processing of psychological information during task performance. Some investigators regard ERPs even as a direct manifestation of the ongoing psychological processes. Before such a strong claim can be made several methodological problems have still to be solved. The present paper discusses the definition and identification of the various components in the ERP, the separation of exogenous and endogenous components, and the different ways in which inferences can be made about psychological processes on the basis of ERP measures. Another methodological problem which hampers the establishment of the psychological significance of ERP components, is the low comparability of ERP measures across paradigms.

1. INTRODUCTION

Event-related brain potentials (ERPs) have been used to evaluate the psychological processes going on during the performance of a task. The ERPs are obtained by averaging the EEG time locked to the events of the task (e.g., stimuli or responses). In the early seventies researchers concentrated upon the effects of psychological factors on the amplitude and latency of the peaks of the 'evoked potential'. Later it became evident that psychological processes could also produce waves which were not strictly related to the peaks of the 'evoked potential'. It is important to make a clear distinction between waves, peaks, shifts in the ERP on the one hand and ERP components on the other hand. A 'component' is assumed to originate from one neurophysiological generator, whereas 'waves' are dependent measures used to describe the peaks and troughs in the ERP waveform. A particular ERP wave or peak may consist of several components. In this context it is also important to make a distinction between endogenous and exogenous components (Donchin, Ritter & McCallum, 1978; Gaillard & Ritter, 1983). Exogenous components are evoked by events outside the central nervous system and their variance is primarily determined by the physical characteristics of the stimulus. Endogenous components are not directly affected by the physical parameters of the stimulus and the variance of their amplitudes and latencies is primarily determined by the psychological processes invoked by stimulus events and the instructions assigned to them. Depending on the task requirements, endogenous components may vary over a considerable time range.

The ERP technique can only be used for the assessment of cognitive functioning, workload, etc., when the psychological significance of the ERP components is known. In this paper some methodological considerations are presented around the issue of the determination of the psychological significance of endogenous components. It is discussed how ERP components may be identified and how endogenous components can be separated from exogenous components. Discussions on the psychological significance of ERP components have been obfuscated by misunderstandings between investigators on the level at which ERP are assumed to be measured; an ERP parameter can be regarded as a direct manifestation of the ongoing psychological processes or as an 'arousal' response, which only indirectly reflects the information processing in the task.

It is argued that it is difficult to compare ERP results obtained in different paradigms. These comparisons are important, however, because ERP components may be very prominent in one task and nearly absent in another one. To determine the psychological significance of a component, it is essential to know which characteristics of the task are decisive in producing the component. Therefore, a taxonomy of tasks is proposed to delineate the essential differences between the paradigms most often used in ERP research.

2. THE DEFINITION OF ENDOGENOUS COMPONENTS

The large and still increasing number of endogenous components has raised the question of how to define a component and which criteria should be used to decide whether two ERP waves represent the same component. Sutton & Ruchkin (1984) list the following criteria to define a component: (1) latency, (2) polarity, (3) sequence, (4) scalp distribution, (5) relation to physical parameters of the stimuli, (6) relation to behavior, and (7) relation to population and state of the organism variables. In contrast to exogenous components, endogenous components may vary over a considerable time range depending on the requirements of the task. For example, the processing negativity, originally regarded as an enhanced N1 component (latency 100 ms), is now reported to have peak latencies up to 200-300 ms (Näätänen, 1982). Also the classical late positive wave was called P300 because it was thought that its latency would vary around 300 ms. Now several studies have reported similar waves with latencies up to one second (e.g., Mulder, 1986). When one accepts that endogenous components may vary over a considerable time range, they can no longer be defined as occurring strictly in a certain time period and latency can no longer be used as a criterion.

Polarity appears to be the most straightforward criterion. It allows, however, for only two categories. Sequence is mostly used implicitly; for example, it is generally assumed that N2 will occur before P3. It has been demonstrated (Näätänen & Gaillard, 1983), however, that N2 and P3 are determined by different psychological processes; therefore N2 may be delayed, whereas the P3 component remains unaffected. The debate as to whether or not the N400 (Hillyard & Kutas, 1983) and the N2 are the same component is a good example of the problems which may arise when components are defined in terms of latency and sequence. The criteria based on their relation to physical parameters, to population vari-

ables or to the state of the organism either have a direct effect on exogenous components or affect the way in which the stimuli are processed. In the latter case, they will result in a change in behavior. The criteria of Sutton & Ruchkin (1984) can be rearranged into three categories: A. A definition in terms of dependent variables, such as latency, polarity, sequence and scalp distribution; B. A definition in terms of psychological (or behavioral) variables; C. A definition in terms of the state of the organism or the physical characteristics of the stimulus. For endogenous components a definition in in terms of dependent variables is rather difficult, given the large variability in latency and morphology. Since endogenous components are, by definition, not affected by the stimulus or state variables, endogenous components should be defined in terms of the psychological processes which determine their occurrence. In contrast, exogenous variables are defined in terms of the physical characteristics of the stimulus and state or personality variables which modulate the response to the stimulus.

In addition, ERP components can also be defined in terms of their neurophysiological generators. Ideally experimental results should converge. That is, endogenous components which have been associated with a particular psychological process should also have a similar scalp distribution. To establish the psychological significance of an endogenous component two approaches can be followed, which may be developed conjunctively: the neurophysiological approach attempts to discover the neurophysiological mechanism generating the component and the information processing concentrates on the psychological processes producing the component.

3. THE NEUROPHYSIOLOGICAL APPROACH

In this approach, the morphology of the wave and its distribution on the scalp are the critical factors in deciding whether or not two ERP waves represent the same component. If two waves have the same scalp distribution, they are assumed to be generated by the same neurophysiological mechanism. This way of reasoning is based on the assumption that, what we call a "component", is in fact generated by one underlying neurophysiological structure only. Given the complexity of the brain, this assumption appears to be debatable. Even within the same study and within the same paradigm the scalp distribution of the 'same' component (e.g., N2) may vary considerably from one condition to another. If one would rigorously apply the criterion that a different distribution always implies a different component, one would end up having as many components as there are experimental conditions. It seems more plausible, therefore, to assume that a particular component is generated by a stable cluster of neurophysiological mechanisms. The cluster always consists of the same mechanisms, but their relative contributions to the component may change across conditions. This may result in small shifts in the scalp distribution. A similar view is taken by Vaughan et al. (1983) who argue that the locus of the neurophysiological mechanism associated with a particular type of psychological processing is likely to change, as a function of the nature and modality of the task. Although this will result in small changes in scalp distribution, there is no need to regard the different waves as representing different components. By the introduction of the conception of a 'generic' component, Vaughan et al. retain the definition of a specific component, in that its generator source produces a stable topographic distribution. In both views ERP waves showing minor differences in topography and morphology can still be regarded as belonging to the same family of waves representing a particular component. Given the large number of components relative to the small number of studies and investigators, it is advisable to adopt stricter criteria for the establishment of "new" components; at the moment there is the tendency among investigators to call each wave or deflection a new component, even if only minimal differences in distribution are observed. Research should concentrate on the reliability and validity of the existing components. Only in this way the psychological significance of ERP components can be established.

4. THE INFORMATION-PROCESSING APPROACH

It is also possible to define an endogenous component in terms of the psychological factors which determine its occurrence. In this approach, the amplitude and latency are investigated as a function of task variables, which are known to be related to a certain psychological process (for example, on the basis of reaction time (RT) studies). The psychological process reflected in the component can then be inferred from the pattern of the effects of the task variables. This approach is similar to the additive-factor method used to identify stages of processing (Sternberg, 1969).

As in RT research, we are not so much interested in the ERP as an absolute measure but in the relative changes in latency and amplitude as a function of task variables. These changes may be associated with the processes assumed to be involved in the manipulation of these variables. As with the measurement of RT, there are factors, such as conduction time, which are assumed to be constant for all conditions and do not play a role when conditions are compared. In ERP research it has always been a major concern to ascertain that the exogenous components do not change between experimental conditions. This can be established by keeping the physical characteristics of the task constant. Even then, comparisons between conditions may be difficult because the summation of exogenous and endogenous components results in complex waveforms. One way to solve this problem is to subtract ERP waveforms from each other, sample by sample.

5. DIFFERENCE WAVEFORMS

To facilitate the demonstration of experimental effects on the endogenous components, ERP waveforms obtained in different experimental conditions are subtracted from each other. Under the assumption that the exogenous components are the same in the two conditions, the difference waveform will consist of the endogenous components only. Subtractions can be done, in at least three ways: (1) Within blocks: The ERPs subtracted are obtained in conditions within the same block of trials (e.g., frequent vs. infrequent, attended vs. unattended stimuli), (2) Between blocks: The ERPs subtracted are obtained in different blocks of trials, (3) Control: It is also possible to make subtractions with ERPs obtained in separate control conditions; Such a condition might be one in which subjects are presented with the same stimuli, but are given another task to ensure that they do not pay attention to the stimuli. Comparisons with control conditions have been criticised on the grounds that the psychological and physiological state of the subject may differ considerably between experimental and control conditions. Of course this criticism

does not apply to within-block subtractions and is less likely to be substantial for between-block subtractions because of the close similarity of the conditions compared. The general state of the subject in control conditions may be assessed by recording of other physiological variables, such as background EEG or heart rate. The general state in the control condition can also be controlled by giving the subject a task, which is as demanding as the experimental task. For example, a task similar to the experimental task could be given, but in a different modality. NÄÄTÄNEN (1985) reported that when ERPs are recorded to auditory stimuli which are to be ignored, it makes little difference whether they are obtained while subjects are reading or performing a video game.

Control conditions have several advantages (1) The use of the same type of control condition (e.g., reading) in different studies facilitates the comparison of difference waveforms across studies (i.e., across paradigms, laboratories, and investigators). (2) The ERPs recorded in control conditions appear to be the best estimate of the exogenous components prevailing in a particular stimulus configuration. This assumes that (a) endogenous components are hardly present in the control ERPs and (b) exogenous components do not change between control and experimental conditions. A disadvantage of both within- and between-block subtractions is that the extent to which endogenous components are still present in the reference condition is not known. A reference condition is devised in such a way that the demands on the psychological process investigated are absent or minimal. However, it is hard to determine to what extent the endogenous component is still present in the reference condition. This implies that in the difference waveforms not only the exogenous, but also a part of the endogenous components may be removed. Even if the endogenous component in the reference condition is small, the amplitude in the difference waveforms is reduced, which may seriously distort the interpretation of the results. For example, in a dichotic-listening task at least some processing negativity may be present in the ERPs to the stimuli presented at the unattended ear (NÄÄTÄNEN, 1982). This is important because the ERP technique provides the unique possibility to examine to what extent subjects are processing stimuli which are supposed to be ignored. When the amplitude in the difference waveform is reduced it is not known whether this is caused by a reduction of the component to attended stimuli or by an increase in the component to the unattended stimuli. It seems therefore worthwhile to make subtractions, within the same modality both between experimental conditions, and between experimental and control conditions.

6. FROM ERP MEASURES TO PSYCHOLOGICAL PROCESSES

The ERP technique may provide an inobtrusive measure of the neurophysiological mechanisms involved in information processing during task performance. Some investigators even regard ERP components as a direct reflection of the ongoing psychological processes. Most physiological variables have only an indirect relationship to psychological processes. Heart rate, for example, may reflect the processing of task information, because the task demands influence the central nervous system, which in turn affects the cardiovascular system. Thus, heart rate parameters (e.g., frequency, variability or blood pressure) are direct measures (manifestations) of the cardiovascular system, but may also be regarded as indirect measures of the central nervous system. For most psychophysiological variables intervening concepts, such as arousal, activation or effort, are used to relate physiological measures to psychological processes. The argumentation mostly runs as follows: the information processing required in the task is so demanding that more effort has to be invested in the task and therefore heart rate increases. Thus, most theoretical frameworks in psychophysiology involve both energetical mechanisms (e.g., effort) inferred from physiological data (heart rate parameters) and cognitive processes postulated on behavioral data (e.g., RT).

As is outlined in Table I the unique position of the ERP technique is that ERP measures are related to both cognitive processes and to energetical mechanisms. When ERP parameters are regarded as providing results on the same level as behavioral data, ERP components can be investigated by using paradigms, methods and theoretical constructs borrowed from cognitive psychology. Fruitful examples from this information-processing approach (see above) are the studies on stage analysis, selective attention and memory load. ERP parameters may even be used to evaluate existing cognitive models or to construct new models together with behavioral data. It has also been debated whether ERP parameters should be regarded as a manifestation or as a marker of a psychological process. In the first case an ERP component is regarded as a direct reflection of the ongoing psychological process, whereas in the latter case it is a reflection of collateral processes, which run parallel to the information processing itself. For example, the subject may keep track of the sequential and probability structure of the stimulus series; and P3 may be regarded as a reflection of this 'context' updating. When ERP measures are regarded as reflecting energetical mechanisms, they bear only an indirect relationship to psychological processes. The energetical mechanisms indexed by the ERP measures should be related to cognitive models based on behavioral data.

ERP components may also be regarded as reflecting the state or functioning of cortical structures, such as the hippocampus. In this neurophysiological approach (see above) the topographical data obtained with scalp electrodes is compared with 'depth' electrodes and data obtained with animal models. Discussions on the psychological significance of ERP components have been obscured because it was not made clear at what level ERPs are assumed to be measured on. Even within one study the same ERP components are sometimes regarded as reflecting both psychological processes and energetical mechanisms.

Table I. ERP parameters may be regarded as (1) Behavioral data, such as RT, on which cognitive models are based, (2) Psychophysiological data, such as heart rate, reflecting energetical mechanisms (e.g., effort), and as (3) Neurophysiological data indexing cortical mechanisms or structures (e.g., hippocampus), which are compared to data collected with 'depth' electrodes or animal models.

DATA	MODELS
Behavioral	Cognitive
Psychophysiological	Energetical
Neurophysiological	Cortical

For example, the amplitude of the N2 component may be larger with an easy discrimination, because of the larger arousal value; it may also be argued that the amplitude is larger, because more processing is needed with the more difficult discrimination. It should be realized that ERP components, such as N2 and P3, are most prominent to task-relevant, but rare, stimuli. This suggests an arousal response and can be interpreted in terms of an orientation response theory. However, even then the component can be used as a marker for the timing of a psychological process (i.e., the discrimination of the stimulus).

7. COMPARISONS ACROSS PARADIGMS

One important factor which hampers progress in evaluating the psychological significance of endogenous components is that they are usually obtained in quite different paradigms. Even when the same task is used, there may be considerable differences in the manipulation of task variables, the procedures (instructions, training, etc.), and the stimulus (modality, presentation rate, etc.) and response characteristics (responding, counting, etc.). Moreover, most investigators tend to concentrate on one or two components obtained in one particular paradigm. Thus, comparisons between ERP waves or components most often involve comparisons between paradigms and between investigators. This makes it extremely difficult to review the literature in the area and to decide whether a particular wave obtained by one investigator is in fact the same component as the one obtained by another investigator in a somewhat different paradigm. Comparisons between paradigms are necessary to establish the psychological significance of endogenous components and to examine their generalizability, reliability, and validity. This is also an important issue in human performance research, where the question may be raised as to what extent differences between models of information processing are caused by the particular paradigms used; or whether an information-processing model based on a particular paradigm can be generalized to other task configurations or to task performance in real-life situations. Thus, comparisons between paradigms should be made within one study using the same subjects and experimental procedures. Whenever possible the same type of stimuli and responses should be used, and the probability and the time structure should also be the same.

Gaillard and Verduin (1985) clearly showed that it is indeed hazardous to make comparisons between experiments, even when they are carried out in one laboratory with the same stimuli and procedures. Endogenous components obtained in an odd ball and a memory comparison task were compared within the same study and with results obtained previously in separate studies. Some of the differences between the tasks obtained in the separate experiments were replicated, but others were not. In the latter case the differences may have been originated by 'small' changes in task variables, such as interstimulus interval, or they may have been due to random variations (e.g., caused by different subject differences). A direct comparison within one experiment, using the same subjects, stimuli, procedures, etc., demonstrates more clearly similarities and differences in the latencies and amplitudes of the endogenous components. On the basis of this direct comparison, experimental findings obtained in studies using only one task may be better understood and evaluated.

8. A TAXONOMY OF TASKS

Since a generally accepted taxonomy of tasks is not available it is very difficult to specify the characteristics of the tasks commonly used in ERP research. To establish the psychological significance of endogenous components it is important to know which task characteristics determine the occurrence of a particular component. One way of doing this, is by examining within one task which task variables influence onset, latency and amplitude of a component. However, comparisons across paradigms are necessary, because it is impossible to devise a task in which each component occurs. Since investigators regularly make comparisons between tasks, either explicitly or implicitly, it is important to have a taxonomy of tasks. Although comparisons between paradigms are difficult (see above), much stronger statements can be made due to the large differences between tasks in their potential to elicit particular ERP components. The taxonomy proposed here is especially devised for classifying tasks used in ERP research and it is based on the three tasks most often used: the odd ball (OB), selective attention (SA) and the memory-comparison task (MC). The OB task involves the discrimination between two stimuli, of which one (the odd stimulus) is infrequent. In the SA task series of stimuli are presented in two 'channels' (e.g., two ears) and the subject is asked to detect occasional targets in one channel. In the MC task subjects search for stimuli designated as targets from among several nontargets. The most important aspect of any taxonomy is the choice of dimensions in terms of which the tasks are to be described and categorized.

First, task variables are considered which can be manipulated within each task and therefore cannot be used for a classification of tasks. These are the parameters, that determine the stimulus configuration, such as (1) modality, (2) interstimulus interval, and (3) probability of the stimuli, or the way of responding (4) response mode (RT, delayed response, counting) and (5) choice versus selective response: a response is required to each stimulus or to a selection of the stimuli. None of these variables does capture the essential differences between the tasks.

Now the task variables are discussed which appear to be sufficient and necessary to delineate the three types of tasks (OB-, SA-, and MC-tasks) most often used.

(1) One- vs. two-choice: In one-choice tasks there are only two stimulus categories, of which one is mostly infrequent and the stimuli in this category are designated as targets. In a two-choice task there are four stimulus categories, which are separated along two dimensions (e.g., pitch and location). The subject is requested to make a conjunction, i.e., to search for the stimuli in one category (e.g., high tones in the left ear). It is of course also possible to use a three-choice task, involving three stimulus dimensions, for example duration, pitch, and location (see also Hillyard & Kutas, 1983).

(2) Homo- vs. heterogenous background: In most OB and SA tasks there is only one stimulus per stimulus category (OB: high/low tone; SA: high/low tone in each ear). In MC tasks, however, there are always several nontargets. A stimulus background is called heterogenous when the nontarget category consists of more than one stimulus, and the background is homogenous, when there is only one nontarget stimulus. The MC task is still a one-choice task because the nontarget stimuli differ from each other and from the target stimuli along the same dimension.

(3) Number of targets: Another important factor is the number of targets the subject is searching for. In most OB and SA tasks there is only one stimulus in the target stimulus category, but in SA tasks there can be more than one stimulus in this category. Again it is assumed that the targets differ on the same dimension from each other as from the nontargets; if not, then it is a two-choice task. For example, when

a subject has to search for two high pitch tones among several lower pitched tones, this will be called a one-choice task; when the subject has to search for two high pitch tones among several lower pitched tones in one ear only it will be called a two-choice task, involving two targets and a heterogenous stimulus background.
(4) Stimulus complexity: This factory refers to the type of dimension and may range from a salient physical parameters, such as pitch, to cognitive variables, such as male/female names. The following type of dimensions may be distinguished: (a) Simple physical dimension (location, pitch, color, etc.), (b) Complex physical dimension (pictures, sounds, etc.), (c) Phonetic dimension (letters, digits, symbols), (d) Semantic dimension (words).
(5) Discrimination difficulty: Although this factor can be investigated in any task it is discussed here because it fundamentally changes the nature of the task (compare for example an RT task with a signal detection task) and because it is closely related to the previous factor. Depending on the complexity of the stimuli, discrimination difficulty may have a quite different character and therefore will affect information processing in a different way, which in turn will have its effects on the characteristics of the endogenous components. The factors 'complexity' and 'difficulty' are often confounded under the assumption that discriminations on a lower level of stimulus complexity are necessarily easier or precede discriminations that are more cognitive. However, the discrimination between 1000 Hz and 1010 Hz may be more difficult than a discrimination between letters and digits. Thus discrimination difficulty may be varied on each of the dimensions mentioned under (4).

The tasks can now be characterized in terms of the above factors. An OB task is a one-choice task, involving a frequent and an infrequent stimulus. In this task all sorts of stimuli have been used, varying from tones to words. In a SA task two-choices have to be made on two, often simple physical, dimensions. The discrimination along the most salient dimension is assumed to be made first. A SA task may be regarded as a two-choice task with an OB task within each 'channel'. A MC task is a one-choice task, involving one or more targets and a heterogenous stimulus background. Targets are stimuli belonging to a designated set of items, which is held in memory. Most MC tasks use letters or digits as stimuli, but it is also possible to use speech sounds or tones differing in pitch. Semantic categorization tasks can be seen as MC tasks in which the targets are words belonging to a particular semantic category (e.g., animals; nonwords). Tasks using complex stimuli, such as letters or words, will be regarded as one-choice tasks, because the differences between the stimuli (for example, between targets and nontargets) are along the same psychological dimension, although the stimuli may differ along several physical dimensions from each other. There is one task situation which is between OB and MC task, i.e., a one-choice task with one target but with several nontargets. It is also possible to combine a MC and a SA task; for example, when the subject has to select a particular syllable among several syllables only in one ear, ignoring syllables presented to the other ear.

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DISCUSSION

WEINBERG, CA: Have you any new thoughts regarding the amplitude of the evoked response as an index of information processing? For example, if you "load" information into a P300 component or the stimulus that produces it, you obtain a decreased amplitude which results presumably from an increase in information processing. On the other hand, I've usually considered that increases in the amplitude of N100 are associated with increased information processing.

GAILLARD, NE: I have no definite answers, but I do have some thoughts. I think that it is very important to make a distinction as to whether an ERP measurement like P300 or N200 refers to an energetical process or to an information process. For example, N200 is associated with arousal, an energetical process. Critics say that they expect a large N200 amplitude with such easy discrimination, because you also find it with GSR and heart rate. Critics also expect a large amplitude with difficult discriminations because there is more information processing. This is seldom specified before doing the experiments; therefore, afterwards, the data can easily be interpreted in either way. In the review of Fitzgerald and Picton (Biol. Psychol. 17:241-276, 1983), where they discuss the N200 component, it's fairly clear that they have a mixed model of arousal and information processing, and that they do not want to make a decision either way. I think that similar arguments can be applied to interpreting P300. In general, latency measures are used to indicate information processing, and amplitude indexes energetical processing.

COGNITIVE TASK DEMANDS AS REFLECTED IN PHYSIOLOGICAL MEASURES

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SUMMARY

Three experiments will be described in which cognitive demands were manipulated. The task was a modified Sternberg paradigm comprised of three task stimuli: the cue, providing information about the memory set, the memory set itself, and a test stimulus, a member of the memory set on half the trials. Among variables investigated were set size and nature of the stimulus material. Physiological measures included EEG Event-Related Potentials to the three stimuli ("Task-ERPs"), ERPs to "probe" stimuli ("Probe-ERPs"), flashes irrelevant to performance. Three measures derived from the eye blink and one heart rate measure were used.

Results demonstrated ERP changes related to task difficulty. Some involved the ERP to the memory stimulus and some, the probe ERP. Heart rate changes, some related to expectancy, others to task demands, were also obtained. Blink probability, duration and timing, all reflected stimulus expectancy and difficulty.

These results suggest that work load, as well as attention, can be evaluated using physiological measures.

That cognitive activity should be reflected in altered patterns of brain activity, is a working hypothesis adopted by all workers in this field. Specific documentation in support of that assumption has been somewhat more elusive, but as other speakers in this meeting have demonstrated, progress is being made. The approach that our laboratory has taken in evaluating physiological indices of cognitive activity differs from that taken by others in two major ways. Although measures of brain activity should play a "central" role in our understanding of cognitive processes, we believe that other physiological measures may be equally important reflectors of perceptual, cognitive, and affective processes. Accordingly, we have selected the eye blink and heart rate as additional measures, along with EEG measures, to be used in decoding the intricacies of human cognition.

Why have we selected the eye blink and heart rate rather than electrodermal, peripheral vascular changes, muscle potentials, or other physiological indices? The selection is based, in part, on prior research from our laboratory on the eye blink, and, in part, derives from the research of the Laceys, relating heart rate changes to aspects of information intake and rejection. A reason for limiting ourselves to these three measures is that we still like to monitor all data as they are being acquired (one of the mottos of the State of Missouri, where we work, is "Seeing Is Believing," a motto I have taken dearly to heart), and our polygraph limited us to a maximum of seven channels including stimulus artifacts. Another, more practical reason for this limitation is that the likelihood of a channel of data collection going "bad" increases, it seems, at least as the square of the number of channels of data being recorded.

The second way in which our research differs from much of the material reported in this symposium and in the published literature, deals with the procedures used to elicit event-related potentials (ERPs). As others, we are interested in changes in the ERPs elicited by task-relevant stimuli as variables, such as difficulty and nature of task requirements, are manipulated. We are equally interested, however, in changes in the ERPs in response to what are called "probe" stimuli (1). These stimuli do not demand an overt or covert response by the participant; that is, they are irrelevant to the assigned task. In this sense, the probe stimuli used in our studies are less intrusive than those used by others.

Our probe stimulus procedure differs from that of others in one further, and important, way. In other laboratories, the probes are often presented at random points during primary task performance, and responses to these temporally random events are pooled; thus, the time dimension is lost in the analysis. Assuming that information processing follows a reasonably consistent pattern, sequential or otherwise, then introducing probe stimuli at specific points, and evaluating the ERPs separately for each of these points, should give us some clues about the time course of processing. For example, a probe presented when the subject is committing information to memory might

elicit a different ERP pattern than one presented when he is rehearsing or anticipating information. Accordingly, we present such probes at specific times during primary task performance and average the ERPs separately for each time point. Our guiding hypothesis (or hunch) is that, to the extent to which cerebral space, so to speak, is allocated to the processing of the primary information, this "space" is not available for dealing with irrelevant information, the probe stimuli in this case. Thus, the ERP to the irrelevant information should reflect this increase in the demands of the primary task.

I will briefly review the results of three studies that have, in part, dealt with all of the above issues. The experimental paradigm used is a variant of the Sternberg varied set memory task: one commits to memory a set of items (most commonly, letters) and some time later, a TEST stimulus is presented. The decision must be made as to whether the TEST stimulus is, or is not, a member of the memorized set, and a discriminative response must be made. Our variant of this task, as displayed in Figure 1, presents the participant with a CUE stimulus, which provides information about the nature of an upcoming memory set. After a fixed interval, the MEMORY set is presented. This is followed again after the same interval, by the TEST stimulus. The TEST stimulus may, or may not, be a member of the memory set. The first, or CUE stimulus, thus, alerts the subject about WHAT to expect and WHEN to expect it. The WHAT depends on the study: In one study it identifies both the number of items in the memory set and the nature of the stimulus material, that is, letters or "random shapes." The WHEN defines the interstimulus interval. One would expect that "attentional resources" will be mobilized so that attention would be greatest at the point immediately preceding memory set presentation, and that more such resources would be mobilized for a difficult (large) memory set than a small one. During the MEMORY interval, one first has to perceive the stimulus material (presented for a short period of time), commit the information to memory, and retain the information for the duration of the memory period. Again, anticipation plays a role, since the TEST stimulus occurs after a fixed delay following the memory stimulus. Response to the TEST stimulus, again, involves perceiving it (it is always a single item), comparing it to the items committed to memory, making an appropriate response, and then waiting for the next CUE stimulus, which occurs a fixed time after presentation of the TEST stimulus.

In the initial study, all task stimuli were presented for 700 msec. Three different set sizes were used: 1, 3, or 5 letters. The interstimulus interval, the period between the offset of one stimulus and the onset of the next, was 5 sec for all three intervals in a trial, that is, between CUE offset and MEMORY set onset, between MEMORY set offset and TEST onset, and between TEST stimulus offset and the onset of the next CUE. On each of two days, subjects were given a brief set of practice trials, followed by two 30-minute periods of task performance consisting of 225 trials. Thus, there were 450 trials in all. On 90% of the trials, a probe stimulus (a dim, four-foot candle, diffuse light), 100 msec in duration, was presented at one of three positions following the MEMORY period. The three positions were: early, in the middle, or late in the interstimulus periods.

Event-related potentials evoked by task stimuli have been investigated in two studies which differed quite radically, with respect to the nature of stimuli used and in placement of electrodes. In the first study, all stimuli were letters in set sizes of 1, 3, and 5, and the electrodes were located at Pz and Fz. In the second study, stimuli were letters (in 2- or 6-item sets) or Japanese Katakana characters (in 1- or 2-item sets) and electrodes were located at bilaterally symmetrical sites over parietal and temporal areas. We will, in general, restrict our comments to results that were concordant across these two studies.

In both studies, set size had significant effects on P3 amplitude to both the memory set and the test stimulus. P3 to the memory set <u>increased</u> in amplitude as a function of set size, while the same component <u>decreased</u> in amplitude as a function of set size for the <u>TEST</u> stimulus. The decrease in P3 as a function of set size, had been previously demonstrated by Gomer, Spicuzza, and O'Donnell (2) as well as others. This decrease in P3 amplitude has generally been attributed to setsize-related increases in equivocation or subjective uncertainty. Squires, et al. (3,4) have demonstrated reductions in P3 amplitude in association with increased uncertainty more directly.

Our interpretation of the increase in P3 amplitude to the memory set, is that it reflects a graded mobilization of processing resources in direct proportion to the number of items which must be encoded from the memory set, i.e., P3 amplitude increases as a positive function of the amount of information provided by the eliciting stimulus. This view is also consistent with the reported positive relationship between stimulus novelty and P3 amplitude (5). Another possibility, though remote, is that the greater P3 amplitude to the more complex stimulus may be attributable solely to the larger area of stimulation associated with five than with fewer letters. If this were the case, we would expect that earlier exogenous components would more likely be affected by this manipulation than P3.

What about differential ERPs to probe stimuli as a function of task difficulty? The findings from our first study, in which we utilized set sizes of 1, 3, and 5 letters, will be reviewed here. Probe stimuli, you will recall, were introduced at three points in the CUE and MEMORY periods. Differential effects, attributable to set size, were found only for the probe late in the CUE period, i.e., in anticipation of the memory set, and for the first probe following memory set presentation. The amplitude of P1-N1 was positively related to set size for the late probe position in the CUE interval, while the amplitude of N1-P2 was negatively related to set size at the early probe position following the memory set. This effect was

seen principally for lead placement Pz. The positive relationship of set size and P1-N1 amplitude, immediately preceding the presentation of material to be committed to memory, suggests that this early ERP component might index the mobilization of a selective attentional system.

The use of the term, "selective," given the use of letter symbols here, is based upon the finding that this component alone increased in amplitude as a function of set size. Our expectation, derived from the "cerebral space" notion, had been that if attentional resources specific to letter processing had been invoked, then less in the way of resources would have been available to process the visual probe stimuli, which would result in a reduction in probe ERP amplitude. The increases in P1-N1 as a function of set size, however, suggests to us the mobilization of attentional resources less specific than those restricted to letter processing. How general this attentional system is cannot be determined at this time. Since the probe stimulus here was visual, we hypothesize that the mobilization extends to the entire visual system. The failure of an auditory probe to produce a similar augmentation would tent to support such an interpretation. However, until such an experiment has been successfully conducted, we feel more comfortable using the broader descriptor--"selective attentional system."

As we will see later, it is only the ERP to stimuli presented at this probe location, which mirrors such a process. Neither the HR nor the blink variable allowed for the identification of such selective attentional processes.

How do we account for the probe set size effect found early in the MEMORY interval (within 1-2 seconds after memory set presentation)? The effect here is a reduction in amplitude of the Ni-P1 component as set size increases. This result is in line with a limited capacity model and our speculation that as processing resources are allocated to the memory task, they are not available for processing the irrelevant information.

As we will see below, these results are, in a sense, corroborated by both HR and blink data. Why is the ERP set size effect limited to the early interval in the MEMORY period? A number of suggestions come to mind. If retention of the memory set involves rehearsal of the letters, then, with the larger set, the subject may still be in the first "repetition" of the letter set, when the early probe stimulis is presented, while, for smaller letter sets, he may be at other points in the processing chain. If the response to the probe ERP is affected by the processing of the primary information, then the alteration in this component would only be seen when this stimulis is time locked to such processing.

How might Task and Probe ERPs be used in flight simulation as well as in flight, to evaluate aspects of "work load"?

1. We have demonstrated that the ERP to primary task stimuli (presentation of CUE, MEMORY set, TEST stimuli) demonstrates attenuation or enhancement of selected components.

   Could we distinguish between ERPs associated with looking at a particular instrument display when that look is a simple periodic check, and when it is a critical check (such as in checking heading during flight or checking heading as waypoint is approached)?

2. We have demonstrated that ERPs to probe stimuli are affected by difficulty level of the primary task.

   Can the response to such probe stimuli be used to assess "spare channel capacity," and work load demands of the primary task?

Let us turn briefly to the heart rate and eye blink data, collected under these same experimental conditions. Heart rate (HR) and blink analyses are presented from a study in which the interval between stimulus presentation (6 and 10 seconds) and two levels of task difficulty (2 or 6 letters) were manipulated. Figure 2 depicts the results for the HR analysis. It will be remembered that the Laceys' prediction would have cardiac deceleration associated with the readiness to take in environmental information, while cardiac acceleration is associated with the shutting out of environmental inputs and the internal manipulation of information. Our data clearly demonstrate that in anticipation of the MEMORY set, as well as the TEST stimulus, there is significant cardiac deceleration. This deceleration, however, is independent of expected "load," i.e., the expectation of a large memory set produces the same level of deceleration as a small set. (This result replicates an earlier study which utilized set size of 1, 3, and 5 letters. Here, too, no set size effect was noted for the decelerative response).

During all three time periods, the HR pattern is one of initial acceleration followed by deceleration. The absolute amount of acceleration is greatest following the execution of the discriminative response, and also appears to be affected by the interstumulus interval. The accelerative effect is greater for the 10 second, than the 6 second, period for both the CUE and TEST stimulus periods. During the MEMORY period, the cardiac accelerative effect discriminates between the two load conditions, with earlier and steeper acceleration obtained for the two- as compared to the six-letter condition.

We can conclude that the deceleration seen in anticipation of any event (MEMORY, TEST, or CUE stimulus) is not affected by task demands, but most likely reflects a general attentional process. The accelerative component which follows stimulus presentation is affected by the nature of the task demand, with higher task demands associated with

slower cardiac acceleration. Whether this effect is attributable to differences in rehearsal processes, or a direct reflection of task difficulty, cannot be determined from the present set of results. It is also clear that the accelerative component is affected by the duration of the interstimulus interval, with greater acceleration during the CUE and TEST period for the longer ISI. The cardiac system, as far as its response to perceptual and cognitive demands are concerned, is rather sluggish. One might also go so far as to suggest that accelerative and decelerative components are triggered by different CNS mechanisms. Thus, the smaller cardiac acceleration seen following presentation of the CUE and TEST stimuli for the six second ISI condition, may be a function of decelerative components coming into play earlier for this, as compared to the 10 second, ISI interval.

Our results certainly suggest that we can learn much about attentive and information processing attributes from studying moment-to-moment changes in HR; that the Laceys are correct about their interpretation of the cardiac decelerative response, but that the accelerative response is subject to a wider range of variables than "shutting out environmental input" and "interval processing." How such "internal processing" is accomplished may be reflected in aspects of the accelerative response.

Our procedures for evaluating the eye blink are a bit more complex than simply counting blinks. Counting blinks, over a 30 second or one minute period, is inadequate for evaluating the moment-to-moment changes in perceptual/cognitive processes that occur during the performance of the Sternberg memory task. Rather than looking at averages over a relatively long time period, we have perferred to look at the likelihood of blink occurrence during successive one-second periods of task performance. Thus, in Figure 3 we depict the proportion of trials on which a blink occurred in any one-second period in the trial. It is expressed in blinks per minute, a measure which can readily be converted to the likelihood of a blink occurring during each second, by dividing the observed rate by 60. Thus, a blink rate of 30 indicates that the likelihood of a blink occurring during that second is 0.5, or, in other words, that blinks occurred in this second on half the trials.

What do our results demonstrate? Like the cardiac response, the anticipation of any significant event, be it the MEMORY set, the TEST stimulus, or the CUE stimulus, leads to a decrease in blink likelihood, as the event approaches. Unlike the cardiac response, which we described as sluggish because of differences in deceleration between the 6 and 10 second ISI, the blink response is more responsive. The level of blinking at the end of the 6 second period is comparable to that seen for trials on which the ISI was 10 seconds. Like the cardiac response, the reduction in blink likelihood is not affected by task demands, a two item list producing as much of a decrease as a six item list. The major effect of task demand occurs with the presentation of the memory set, where, with the small set size, the likelihood is great that a blink will occur during the second of stimulus presentation, while the larger set size does not produce such an effect until the second after the stimulus set is terminated. Figure 4 depicts this effect somewhat differently. What we have done here is to measure the latency of occurrence of the first blink following presentation of the CUE, MEMORY, and TEST stimuli. Blink latency to the CUE stimulus, the numeral "2" or "6," does not reflect set size. The blink is initiated approximately 800 msec following stimulus onset, that is, 100 msec after stimulus offset. Similarly, for the test stimulus, which is one of 18 letters, blink latency does not discriminate set size. Although blink latency is somewhat longer for the TEST letters than the CUE numbers, these differences were not statistically reliable. It is only when we deal with the memory set, where either two or six letters are presented, that we get a set size effect with significantly longer blink latencies to the larger stimulus set. Latency for thesmall set is approximately 865 msec, 165 msec after stimulus offset. This falls into the first one-second window. Blink latency for the larger set was 1030 msec which puts theblink well into the second one-second window. We would like to suggest that the viewer inhibits blinking until he has "stored" the memory set in some short-term memory register. That storage process transcends stimulus duration for the larger set size.

Returning to Figure 3, we can further note that the time course of blink likelihood during the memory period discriminates the 2 and 6 item memory sets nicely. Blink likelihood for seconds 3, 4, and 5, is consistently greater for the larger memory set. Again, we suspect that the difference in rehearsal processes for the 6 vs. 2 items, produces this differential effect. Although we cannot definitely demonstrate it, we suspect that, to the extent that subjects use a vocal or subvocal rehearsal strategy, the frequency with which the two item letter set is so rehearsed, is considerably smaller than is true of the rehearsal of the larger letter set. With respect to the interstimulus interval, this again appears to play no role. Thus, as we have demonstrated in other contexts (6) the likelihood and timing of blinks can provide us with data on aspects of information processing.

In addition to differences in likelihood of blink occurrence as a function of stimulus expectancy, we find that the quality of the blink is also affected by such expectancy. These results are depicted in Figure 5. Blink closure duration is defined as the time interval between the blink entering and leaving a window defined by half the amplitude of lid closure. It is readily apparent from this figure that blinks occurring immediately preceding informative stimuli, are of consistently shorter closure duration than those which occur earlier. Again, neither set size nor ISI has an appreciable effect. We suspect that the "cognitive apparatus," located somewhere between our ears, makes these decisions quite automatically, and with considerable precision.

We have attempted, in the short time allocated, to review the impact of attentional, perceptual information storage, information retention, and comparator functions on aspects of brain, heart, and eyelid functioning.

The three physiological measures provide complementary information. Aspects of HR and blinking provide information about attentional processes not available from ERP analysis alone. With respect to unique attributes of each analytic procedure, our ERP analyses demonstrate that late components, such as P3, are differentially affected by manipulating information storage and retrieval requirements. Increasing storage demands leads to an increase in P3 amplitude, while increasing information retrieval demands leads to a decrease in this component. Probe ERPs, as used in these studies, are also instructive in tracking information storage and expectancy variables. The components affected are so-called "exogenous," or early components, and demonstrate that information processing is not a simple bottoms-up process, but is affected by higher level processes.

Heart rate deceleration appears, as suggested by the Laceys, to be associated with the expectation of taking in information. It is not affected, somewhat surprisingly, by WHAT is being expected. Cardiac acceleration is affected by a wider range of information processing considerations than suggested by these researchers. Task difficulty, with respect to information storage, differentially affects the cardiac acceleratory response, with lower processing requirements leading to earlier and steeper cardiac acceleration than more difficult tasks.

In addition to demonstrating attentional attributes, blink rate also discriminates between easy and difficult information storage requirements, with blink inhibition during the early stages of information processing as a major finding.

How can these findings be applied in the "real world?" We have applied them, and continue to do so with more than modest success, in flight simulation environments (7) and, as will be demonstrated by Skelly, Purvis, and Wilson later this afternoon, in fighter pilots performing during airborne missions.

We've come a long way, but still have a long way to go!

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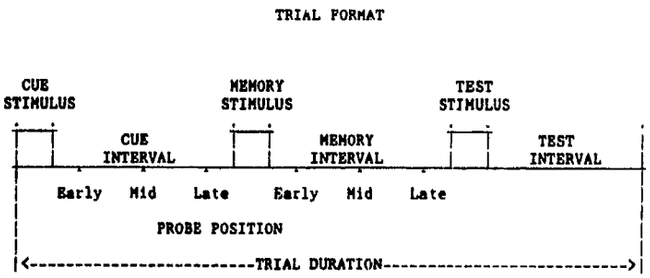

Figure 1 - Jeneralized trial format.

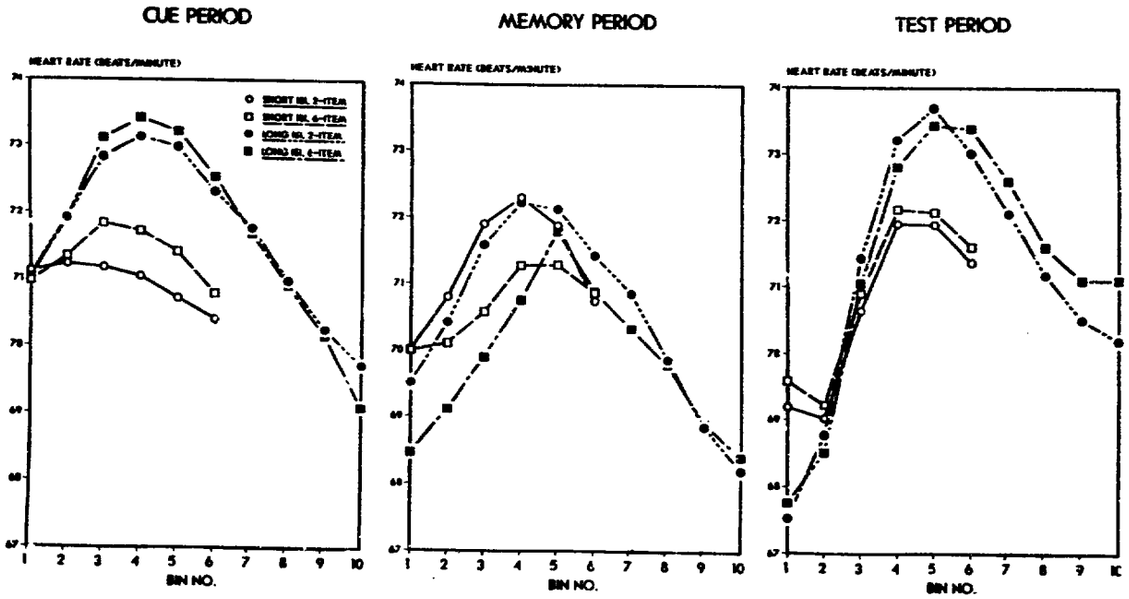

Figure 2 - Heart rate (bom) across the CUE, MEMORY, and TEST periods as a function of interstimulus inte-val and set size. Task stimuli are presented within the first bin.

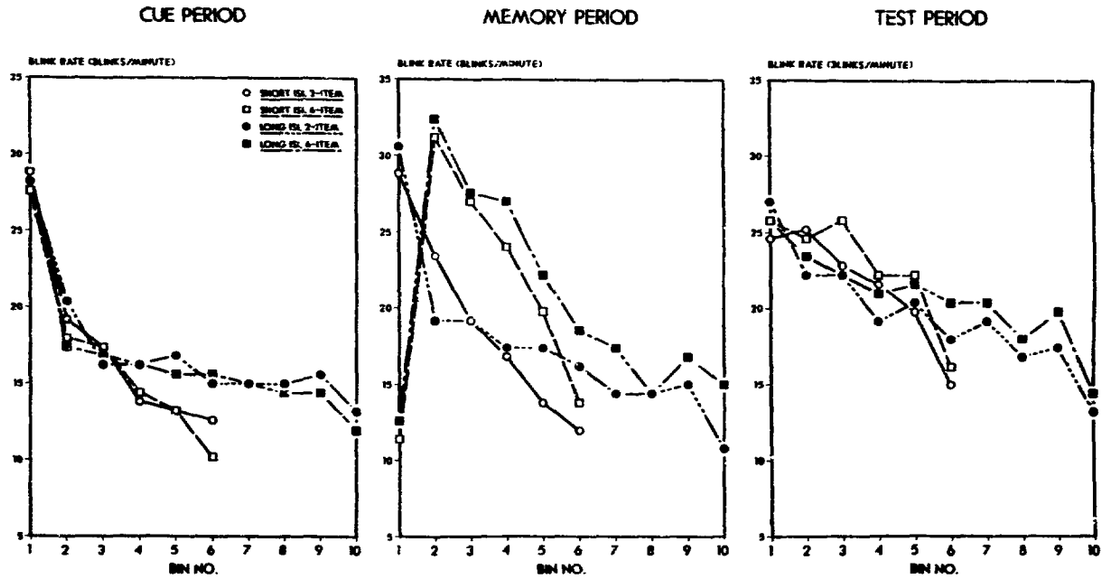

Figure 3 - Blink rate (bpm) across the CUE, MEMORY, and TEST periods as a function of interstimulus interval and set size. Measure is derived for a given bin by summing blinks in that bin over all trials and dividing by the number of minutes accumulated in that bin over all trials.

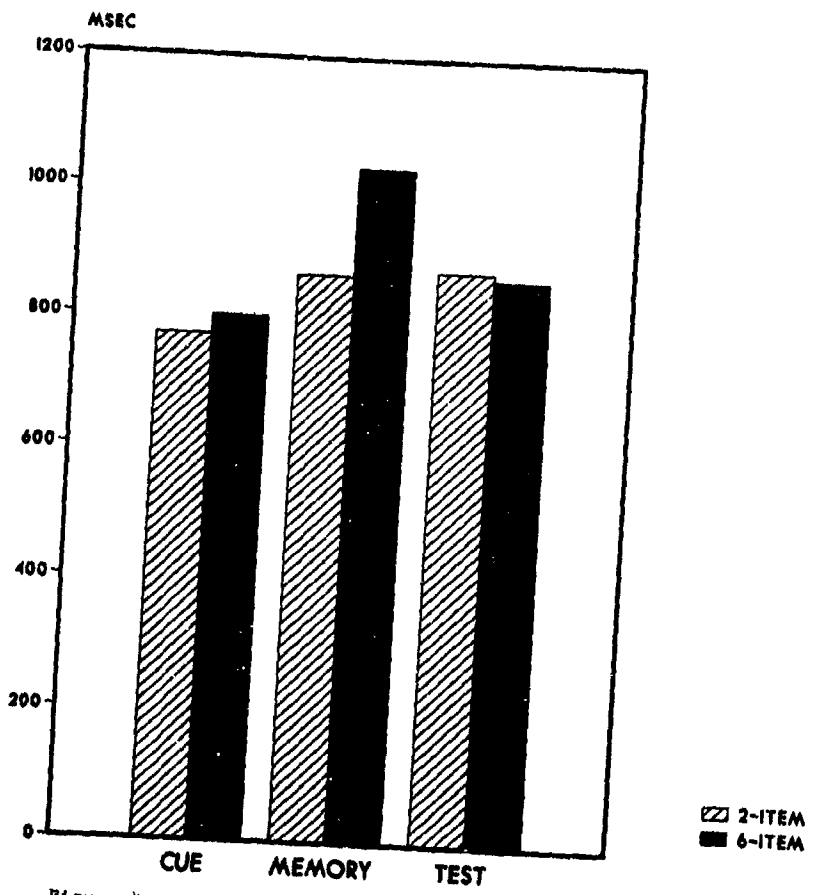

Figure 4 - Mean latency of the first blink following CUE, MEMORY, and TEST stimulus onset, as a function of set size.

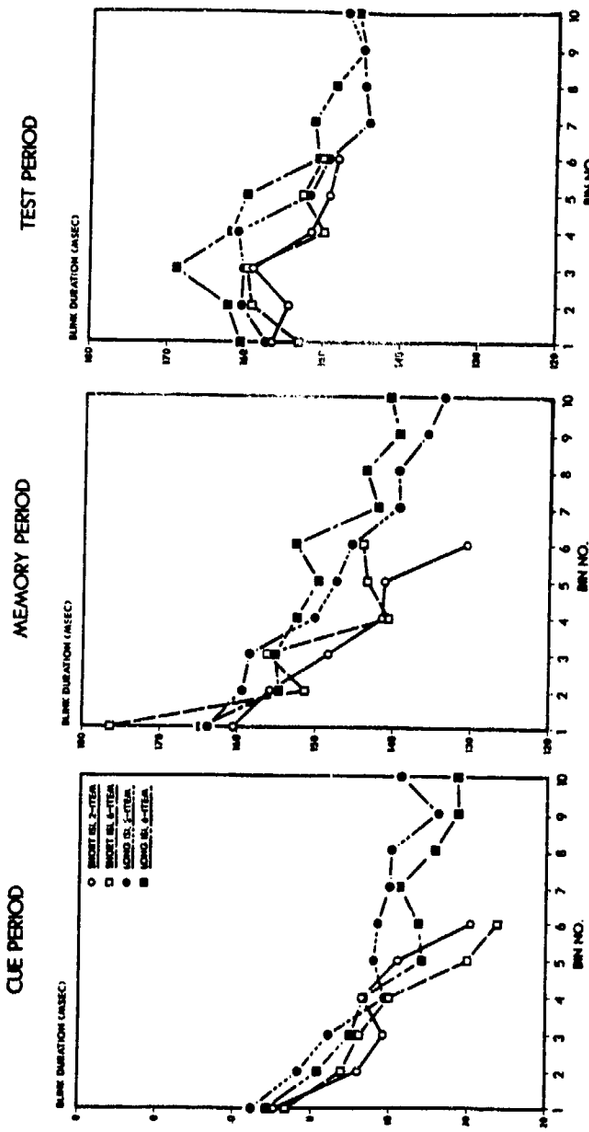

Figure 5 - Blink duration across the CUE, MEMORY, and TEST periods as a function of interstimulus interval and set size. Duration is defined as the interval between a point at which half the amplitude of the closing lid is achieved to a point at which the same level is reached in the opening phase.

DISCUSSION

WILSON (re paper by STERN ET AL.), US: We have done similar experiments to those of Dr. Stern. I would like to reinforce his statement that the probe does not need to be presented during the time at which active processing takes place. We performed a study in which the probes were randomly interspersed with discrete-task stimuli, and we found no effect. Then we did another condition, in which we linked the presentation of the probe to the presentation of a discrete-primary-task stimuli, and, indeed, found very similar results to Dr. Stern's.

KRAMER, US: I have trouble making the analogy between an irrelevant probe technique and a secondary task technique as described in John Stern's paper. The analogy seems to be that if someone isn't performing the primary task then any residual resources will be allocated to the probe task. That is not the way that it is traditionally done. For example, in Michael Posner's work, all of the probes are relevant ones that require some response -- usually a simple reaction time response; sometimes a choice reaction time response. The problem I have with irrelevent probes is that we have no idea what subjects do with such probes, or if, in fact, different subjects do the same or different things with the probes. Whether or not subjects process these probes is completely up to them. We have no behavioural anchors, as Posner had in his probe technique, against which to check our assumptions about what is happening. So, I have great difficulty interpreting any ERPs elicited by those probes because there is no behavioural anchor and I don't know what the subjects are doing.

WILSON (re paper by STERN ET AL.), US: You are right, but I see it as an advantage that it is not a secondary task. In other words, you are not requiring subjects to react to one more task than you want them to do. We find, with both electrical and magnetic recordings, in all of our subjects, a nice decrement in response to the probe as we increase the difficulty of the workload of the primary task. It correlates well with reaction time, subjective measures and so forth. So we are using it as a probe even though we are uncertain how subjects are processing it.

KRAMER, US: Finding a decrement in the amplitude of the P300 as elicited by the probe is nice, but it is still the case that smaller P300 amplitudes could be due to very different strategies in different subjects. We would never know, because there is no reaction time to that probe. It is irrelevant; it is not to be responded to. So I'm not quite sure how you relate it back to subjects, strategies or any other factors that might be relevant.

CAN CNV AMPLITUDE PREDICT ABILITY TO ACCOMPLISH A DEMANDING TASK?

by

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SUMMARY

Increased CNV amplitude has been related to attention, effort and quick response to stimuli, while decreased CNV amplitude has been related to distraction, delayed reaction time and disorder of mental or emotional functioning.1 These observations suggest that CNV amplitude measured in the laboratory might be a useful predictor of an indivudual's ability to accomplish a demanding sensori-motor task under operational conditions. One such task is the operation of a surface-to-air missile known as "Blowpipe". Firing this weapon requires rapid accurate processing of information from the target, and precise, varying responses to that information, under stressful conditions. It also requires strength and a postural response to the missile's discharge which is cued by auditory stimuli emanating from the weapon. Thus the firing operation is not unlike a CNV-generating situation.

The "Blowpipe" training program afforded an opportunity to test the usefulness of CNV measurement for predicting operational performance as assessed during the firing of real missiles on a testing range. It was hypothesized that low laboratory CNV amplitude would predict unsuccessful "Blowpipe" firing and vice versa.

CNV amplitude was measured in 75 soldiers engaged in training as missile operators. Sixty-nine subjects completed the qualifying course and fired real missiles. Those who showed poor firing performance had CNV amplitudes at the extremes of the range. Selection strategies are discussed.

METHOD

Sixty five trainees attended the laboratory prior to starting their missile training program. Ten more attended subsequently. S's were seated in a large, quiet, darkened room kept at a comfortable temperature. Eyes were closed and still. The CNV paradigm consisted of a warning click delivered at approximately 70 dB through earphones, followed one second later by a train of light flashes at 16 fps from a stroboscope 25 cms in front of the subject's face. S's were instructed to terminate the sequence of flashes as quickly as possible by pressing a button. The intertrial interval varied irregularly between 5 and 15 seconds.

EEG was recorded from Ag/Ag Cl electrodes located at F_{PZ}, C_Z and P_Z. Linked ear lobes served as reference. C_Z was compensated for eye movements as described by Mc Callum and Walter (1968). The skin was slightly abraded under each electrode to give resistance of < 1K Ω . The EEG was recorded with a 10-second time constant on analog tape. CNVs were averaged offline in sets of 24 using a PDP 12 computer. Artefact contaminated trials were rejected at this stage.

An electronic weapon simulator was used in training. Performance at the end of the initial phase of training determined whether the trainee qualified to fire real missiles. Sixty-two qualified first time and seven more did so after further training. On the missile firing range performance was assessed by an instructor standing beside the trainee as he fired. Rating was made on a ten point scale taking into account such factors as accuracy and degree of control. The instructor had no knowledge of the CNV data. Six trainees failed to fire for a variety of reasons and will not be considered further.

RESULTS

CNV amplitude was based on a mean value for the 200 ms preceding the imperative stimulus (S_2) averaged over the 24 trials of the acquisition phase. Average CNV amplitude for the total group of 69 trainees who qualified was -23.8 μv. The distribution of CNV amplitudes was approximately normal.

The subgroup of 6 trainees who failed to qualify initially on the simulator (ie excluding one case of failure due to illness) showed significantly lower CNV amplitudes ($t = 2.7$, $df = 66$, $p < .01$) and lower performance scores in the live firing situation than the main group of 62 who qualified first time as shown in Table 1.

TABLE 1

		CNV Amplitude		Firing Accuracy Score	
	Number	Mean	SD	Mean	SD
Initial Non-qualifiers	6	15.5	7.7	5.5	2.6
Initial qualifiers	62	24.5	8.2	7.2	1.7

Figure 1 shows a monotonic relationship between CNV amplitude and firing performance for the six initial non-qualifiers and the relationship for the whole group of trainees, including the six initial non-qualifiers. Poorer performers tend to have either a high or low CNV amplitudes.

DISCUSSION

The mean CNV amplitude of the main group of 62 subjects was higher than most previous studies (see Tecce, 1972). Reasons for this are not obvious as the experimental paradigm used was a "standard" CNV one, employed on many previous occasions. The subjects differed from other normal groups only in that they were soldiers, above average in physical fitness with a high level of enthusiasm in the laboratory situation.

The lower CNV amplitudes of the sub-group who failed to qualify initially on the simulator and the relationship of these to firing performance were consistent with the initial hypothesis, although the finding that some individuals with very large CNVs also performed poorly was contrary to prediction. The relationship between CNV amplitude and performance appears to be complex. Whether it is best expressed by an inverted U curve remains to be substantiated by further experimentation.

Although rejection of soldiers with CNV's at the extremes of the range might eliminate most of the worst performers, (at the expense of twice as many adequate ones), a more economical strategy might be to reject those who failed to qualify quickly on the simulator.

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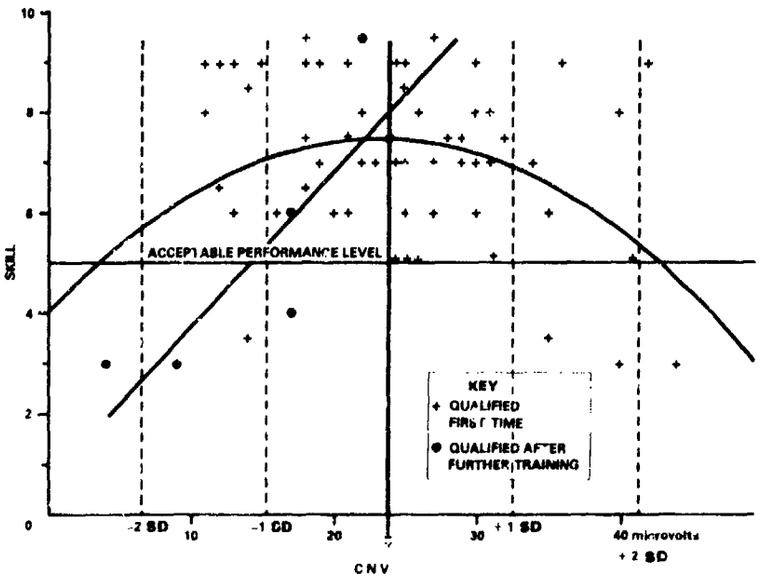

Figure 1: RELATIONSHIP BETWEEN CNV AMPLITUDES AND FIRING PERFORMANCE IN QUICK AND SLOW LEARNERS

THE EFFECT OF ENDOGENOUS ALPHA ON HEMISPHERIC ASYMMETRIES AND THE RELATIONSHIP OF FRONTAL THETA TO SUSTAINED ATTENTION

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SUMMARY

Data are presented which suggests that degree of hemispheric alpha asymmetry (for tasks hypothesized to induce such asymmetries) is related to resting eyes closed endogenous alpha activity. Also, it is demonstrated that frontal theta activity varies with difficulty level of an addition task. Both results share a common emphasis on electrophysiological individual differences.

EEG recordings from 54 right-handed subjects (P3,P4,F3,F4 referenced to linked ears) performing 5 cognitive tasks were collected and quantified using period analysis. The subjects were rank ordered on the basis of their hemispherically averaged (P3+P4/2) alpha activity during an Eyes Closed (lights off) baseline condition. Subjects comprising the top, middle and lower thirds of this ranking were ascribed the status of HIGH, MIDDLE or LOW alpha generators. A similar procedure was performed for frontal theta to distinguish theta generators. Before the experiment the tasks were ordered a priori for their hypothesized hemispheric involvement. The tasks, ordered from right to left hemisphere involvement, were: 1) FOCUSING, 2) STRUCTURED FOCUSING, 3) COUNTING ARTICLES, 4) COUNTING NOUNS, and 5) CONTINUOUS ADDITION. The addition contained trials with varying levels of difficulty. All tasks were performed with eyes closed and lights off.

Utilizing a L-R/L+R asymmetry index the results indicate that HIGH and MIDDLE alpha generators displayed the hypothesized asymmetry relationship (ie. increasing right hemisphere alpha activity for the a priori ordered tasks) whereas the LOW alpha generators did not. This implies that low alpha generating subjects may negatively affect EEG laterality studies. Results from the addition task indicate that hemispherically averaged (F3+F4/2) theta activity varies curvelinearly as a function of increasing task difficulty (ie. theta increases and then decreases as difficulty increases). Subjects displaying higher performance scores on the addition task also demonstrate higher frontal theta values, suggesting theta is associated with sustained focused attention or higher order cognitive processes (or both).

INTRODUCTION

This study addresses two research issues. The first investigates the effect, on EEG, of tasks chosen to differentially engage the cerebral hemispheres. The second concentrates on an hypothesized relationship between frontal theta activity and sustained focused attention. Both issues share a common emphasis on electrophysiological individual differences. Not to be confused with the psychophysiology of individual differences (see 9), this study demonstrates the need to pay greater attention to electrophysiological differences among individuals, and the degree to which these differences influence results in EEG research.

Hemispheric Asymmetries:

The theoretical basis for laterality research has its origin in research from a number of disciplines: anatomical studies (e.g., 16, 39), commissurotomy, hemispherectomy and lesion studies (e.g., 14, 27, 40, 41) and behavioural studies (e.g., 3, 42). Efforts to investigate laterality using EEG, however, has yielded many inconsistent and conflicting results. For example, when measuring EEG laterality during task performance some studies have found that females are more lateralized than males (e.g., 4, 7, 21, 31), others that males are more lateralized than females (e.g., 2, 35, 36, 44), and still other have found no sex differences at all (e.g., 12, 20, 22, 30). The issue of whether

EEG is sensitive and robust enough to reflect asymmetrical cognitive processes is highlighted by well a known controversy. In 1979, Gevins and his colleagues published a series of papers asserting that EEG hemispheric asymmetries during cognitive tasks (specifically chosen to induce such asymmetries) were due to efferent activity, stimulus characteristics and performance related factors, rather than to cognitive differences among the tasks (17, 18, 19). Their results challenged a cognitive interpretation of hemispheric EEG asymmetry supported by the research of Galin, Ornstein and their colleagues (6, 10, 11, 12, 13, 33, 34). Among the many factors used to explain the conflict include: electrode montage, type of quantification procedure, statistics, methodology and task type. One factor which has not been addressed, however, is the effect due to electrophysiological individual differences.

The present study was prompted by the results of a pilot study in which the authors found that if the subjects were divided (post hoc) into high and low alpha generators, high alpha generators showed the hypothesized asymmetries during task performance whereas low alpha generators did not. The groups did not differ on task performance scores, nor did they differ demographically. It was also demonstrated that tasks could be ordered a priori with respect to the amount of asymmetry each task was expected to produce. However, because the pilot study suffered from too few subjects (N=13) and too many tasks (seven), an attempt to replicate these important findings seemed necessary.

Theta Activity and Attention:

In an excellent review of theta and psychological phenomena, Schacter (39) isolated two "grossly different" psychological processes associated with theta activity: 1) active and efficient information processing during problem solving due to the selective and intensive components of attention (e.g., 1, 6, 24), and 2) apparently the opposite, theta associated with sleep onset (hypnogogic) and low level of pre-stimulus alertness (e.g., 26, 32). The latter is a common phenomenon and is used as a criterion to define stage 1 sleep (37). The former is less well established but frontal midline theta has received attention from researchers in Japan. Ishihara and Yoshii (24) reported frontal midline theta activity during continuous arithmetic addition and performance on an intelligence test. In a straightforward and convincing study, Mizuki, Tanaka, Isozaki, Nishijima and Inanaga (29) demonstrated that 19 out of 30 subjects exhibited prominent frontal midline theta activity during continuous arithmetic addition. Mizuki, Takii, Nishijima and Inanaga (28) demonstrated a relationship between theta and focused attention in a memory task. The results from these studies along with Schacter's review suggest that theta activity, especially at frontal sites, is associated with sustained focused attention.

The present experiment manipulated difficulty level among trials of a continuous addition task to investigate the relationship between frontal theta activity and sustained focused attention. It was hypothesized that as difficulty level increases theta would increase due to the heightened attentional demands of the task. As the task becomes too difficult, and thus focused attention lapses, theta should decrease (overall, an inverted U shaped function). Prompted by the alpha results of our pilot study (mentioned above), the possibility that endogenous levels of theta could influence the results was also investigated.

METHOD

Subjects:

Seventy subjects were tested; however, due to equipment malfunction, the data for 16 subjects were omitted. Of the remaining 54 subjects, 21 were males with a mean age of 22.8 yrs, and 33 were females with a mean age of 23.6 yrs. The subjects were either paid volunteers or introductory psychology students given course credit for participation. All subjects were functionally and familially right-handed, as determined by questionnaire. One subject's data were deleted from the study because she fell asleep during the FOCUSING task.

Apparatus:

Four electrodes, P3, P4, F3 and F4 referenced to linked ears, were secured using Grass EC2 electrode paste and headbands. Bipolar EOG and ground were secured using tape. The EEG and EOG were amplified using Grass EEG pre-amplifiers (Model P511J) with 60 Hz notch filters, and was simultaneously recorded on a Beckman type Rm dynograph and an 8 track Vetter Model A FM tape recorder running at 3 3/4 ips with flutter compensator. A real time clock activated by the experimenter while the subjects performed the tasks generated

an electrical signal lasting 10 seconds. These signals were recorded on the 8 track tape and demarcated single or successive 10 second EEG 'epochs'. Electrophysiological data reduction was performed using a dual channel band pass filter (A.P. Circuit Corp. 24 db/octave rolloff for each channel) and a DEC LSI 11/23 micro-computer with A/D converters, real time clock and mass storage (floppy and hard discs). The EEG amplifiers and the dual channel filter were counterbalanced across hemispheres for the frontal and parietal sites. All stimuli for the experiment were pre-recorded on audio tape.

Tasks

The FOCUSING and COUNTING ARTICLES tasks were chosen because they exhibited the largest alpha asymmetries in the pilot study. A second version of each task was created to induce greater left hemisphere activation.

FOCUSING, a meditative type task, was designed to require very little verbal-analytic-serial processing. It was intended to elicit a spatial-holistic experience. The structure of the task, in comparison to the counting tasks, contained fewer well defined task objectives and did not include requirements for serially placed responses. While minimally changing the spatial-holistic characteristics of the task, the second version of the FOCUSING task (i.e. STRUCTURED FOCUSING) included serially placed responses as well as a greater number of well defined task objectives. It was expected that the added structure would engender greater left hemisphere activation (relative to the FOCUSING task).

The COUNTING ARTICLES task involved counting the number of 'a's and 'the's in aurally presented text. During the pilot study it was suspected that the subjects may have adopted an auditory matching strategy for word detection instead of cognitive recognition. To control for this a second version of the task (i.e. COUNTING PROPER NOUNS) was included requiring the detection of proper nouns. A semantic evaluation is needed to identify proper nouns; simple auditory matching cannot be used. It was expected that the added verbal component would require greater left hemisphere activation (relative to the COUNTING ARTICLES task).

Although two versions of the ADDITION task were used, both versions were identical. The two versions simplified counterbalancing task presentations across subjects.

A more detailed description of the tasks follow. Note the order of the tasks reflect the (a priori) hypothesized right to left hemisphere influence of the tasks.

FOCUSING: Recorded instructions were given which attempted to elicit a self-directed internal focusing of attention designed to heighten bodily awareness (the instructions for this task were derived from Gendlin (15). Part of the instructions asked the subject to create a 'handle', a word or image, reflecting the present state of their internal bodily feelings (see appendix A for a transcript of the instructions). EEG was recorded in five 45 sec blocks (a total of 3.75 min) between which instructions were given to increase subject motivation and elucidation of the experience. At the end of the task the subject was asked to report their 'handle' and give a brief summary of their experience of the task.

STRUCTURED FOCUSING: Recorded instructions were given which attempted to elicit an internal focusing of attention to specific body parts. For each of the five 45 sec blocks the subject was requested to mentally focus on a particular (predetermined) part of the body. At the end of each 45 sec block the subject was asked to rate on a scale from 1 to 5 where 1 is 'not successful' and 5 is 'very successful' his ability to focus on that body part. As with the FOCUSING task a total of 3.75 min of EEG was recorded during five 45 sec blocks. Although similar to the FOCUSING task from a visual, spatial and holistic perspective, this task was designed to incorporate a sequentially ordered and less ambiguous set of instructions requesting temporally spaced responses (see appendix A).

COUNTING ARTICLES: A task similar to that described by Moore (30) was used in which a pre-recorded 2 minute nonfiction, simple, historical passage was played over the speaker. The subject was instructed to mentally count the total number of 'a's and 'the's (taken together) uttered in the passage. This was repeated for a second 2 min passage. EEG was recorded during both 2 min passages.

COUNTING PROPER NOUNS: Also using pre-recorded nonfiction, simple, historical passages, the subject was instructed to mentally count to total number of proper nouns uttered in the passage. The task was simplified by

instructing the subject to treat proper nouns such as 'Jacques Cartier' or 'United States of America' as 1 instead of 2 or 3 respectively. As in the COUNTING ARTICLES task EEG was recorded during both 2 min passages. It was anticipated that recognizing and counting proper nouns would require more verbal-analytic cognitive processing than COUNTING ARTICLES where an aural pattern matching strategy could be used.

ADDITION: The subject, with eyes closed was asked to mentally add numbers presented aurally for 10 sec. Eight numbers were presented per trial, 1 number every 1.24 sec, for a total of 24 trials. For each trial, difficulty level was manipulated by controlling the magnitude of the numbers to be added. For each trial, numbers from one of six difficulty levels were presented. They are:

EASY	Level 1:	1, 2
	Level 2:	2, 3, 4, 5, 6
	Level 3:	4, 5, 6, 7, 8
	Level 4:	6, 7, 8, 9, 12
	Level 5:	8, 9, 12, 13, 14
DIFFICULT	Level 6:	12, 13, 14, 15, 16

Each trial involved a random presentation (with replacement) of the set of numbers at a single difficulty level. Presentation order of the trials with respect to difficulty level was pseudo-random; that is, level of difficulty was chosen randomly (without replacement) within blocks of 6 trials. Hence, with 24 trials each of the 6 difficulty levels was presented 4 times. At the end of each trial the subject was asked for the following information:

1. the total
2. a subjective estimate of confidence concerning the correctness of their total, on a scale from 1 to 6 where 1 is 'very sure' and 6 is 'not sure'
3. a subjective estimate of the level of difficulty, on a scale from 1 to 6 where 1 is 'easy' and 6 is 'difficult'.

EEG was recorded only during the 10 second period for each trial the subject was counting, not during the subject's response.

Procedure:

Each subject was seated in an electrically shielded anechoic chamber with his head positioned in a chin-rest/head-restraint device to reduce involuntary head movements. Instructions and tasks were presented through a speaker situated 1 meter in front of the subject. Four EEG baselines were recorded before the tasks: 5 ten second epochs each for resting with eyes open lights on, eyes open lights off, eyes closed lights on and eyes closed lights off. During the experiment all tasks were performed in darkness, with the eyes closed.

The tasks were presented in counterbalanced order with the provision that no task's two versions were presented successively. The experimental session lasted approximately 40 minutes.

EEG Analysis:

Before the recorded EEG was computer quantified, the signal was bandpass filtered. EEG from the parietal leads were bandpass filtered from .5 to 60 Hz and the frontal leads from 4 to 60 Hz (to reduce the effect of eye movements). The event signal recorded on the FM tape by the experimenters during the experiment demarcated 10 sec epochs for EEG period analysis. From the polygraph tracings, any 10 second epoch of EEG which showed clear movement artifact was deleted from further analysis. The filtered EEG was A/D converted at 1000 samples per sec. Period analysis was performed on the digitized data producing 3 measures for each of 5 EEG bandwidths (delta .5-4 Hz, theta 4-8 Hz, alpha 8-12 Hz, sigma 12-16 Hz and beta 16-60 Hz). The 3 measures are: 1) zero-cross, 2) first-derivative, and 3) power. Briefly, a zero-cross analysis checks for a change in the sign of the voltage passing through zero. A measurement of the elapsed time between two zero-crossing events yields an estimate of the wave's frequency. First-derivative analysis checks for negative inflections in the EEG voltage; that is, a change from a decreasing voltage to an increasing one. The time between two such events provides an estimate of faster frequencies superimposed on the main waveform. A 7 uV threshold criteria was adopted for the first-derivative measure in order to eliminate very low amplitude high frequency activity which is often a consequence of equipment noise. The power measure is calculated by cumulatively adding the absolute voltage values between zero-cross events. For a more complete description of this period analysis see

Hoffmann et al. (23). Finally, for each frequency bandwidth and period analysis measure, an asymmetry index was calculated --- (Left-Right/Left+Right) x 100.

RESULTS

Less than 1% of the EEG was deleted due to artifact.

Alpha zero-cross values (i.e. percent alpha) at the parietal sites of each hemisphere during the eyes closed (dark) baseline condition were summed and averaged producing a mean parietal alpha measure for each subject. The subjects were rank ordered from highest to lowest on this measure and were divided evenly into high, middle and low alpha generators, 18 subjects per group. The subject who was deleted from the experiment for falling asleep was a high alpha generator, hence that group contained 17 subjects. When alpha power was used create the groups, all but 4 subjects were in the same groups and these subjects were borderline between low and middle, and middle and high. Table 1 displays the distribution of sex and mean age for each alpha group. A similar post hoc procedure was used with theta zero-cross values to produce high, middle and low theta generators (see table 2). The two factors (i.e., alpha and theta generators) were treated independently for hypothesis testing because the same subjects made up both conditions. Table 3 illustrates the distribution of subjects on both factors. Notice that similar high, middle or low groups in each factor share few subjects. Separate ANOVAs were performed on the ages of the alpha and theta groups. There was no significant difference among the mean ages for the alpha groups. A significant difference was found, however, among the theta groups ($F=3.92$, $df=2,50$, $p<.026$). High theta generators were younger than low theta generators.

The average alpha zero-cross values for Eyes Closed baseline (dark), Focusing (both versions), Counting (both versions) and Addition (all levels) are shown in figure 1. Using repeated measures ANOVA with tests for trends (i.e. orthogonal polynomial contrasts) there is a significant decreasing linear trend in alpha from the baseline condition to the Addition task ($F=47.95$, $df=1,50$, $p<.0000$). There was also a significant interaction between task and alpha generators ($F=5.06$, $df=6,150$, $p<.0001$) showing the expected pattern: low alpha generators show no decreasing trends, middle alpha generators show a marked decreasing trend and high alpha generators show a prominent decreasing trend.

A 3 between (alpha groups) by 2 within (Focusing vs Counting) by 2 within (version 1 and version 2) mixed design ANOVA was performed on the alpha asymmetry index (zero-cross) at the parietal location. A main effect for task ($F=13.46$, $df=1,50$, $p<.0006$) and more importantly a significant interaction between type of task and type of alpha generator ($F=3.83$, $df=2,50$, $p<.028$) was found. The interaction is shown in figure 2 and supports the hypothesis that Focusing and Counting show relative hemispheric differences in alpha production only for alpha generators. To test whether the tasks were correctly ordered a priori for their presumed ability to induce left of right hemisphere activation a 3 between (alpha groups) by 4 within (FOCUSING, STRUCTURED FOCUSING, COUNTING ARTICLES, COUNTING PROPER NOUNS) ANOVA was performed with tests for polynomial trends. There was a significant linear interaction between alpha generators and the tasks ($F=7.48$, $df=2,50$, $p<.0014$) for the alpha zero-cross asymmetry index. A similar interaction was found with alpha power ($F=3,25$, $df=2,50$, $p<.047$). The interactions are shown in figure 3 and 4. This effect is specific to the parietal site; similar analyses performed at the frontal site showed no significant results. Separate trend analyses for each alpha group on the same tasks showed a significant linear trend for high alpha generators ($F=8.78$, $df=1,16$, $p<.0092$), a significant linear trend for middle alpha generators ($F=11.76$, $df=1,17$, $p<.0032$) and non-significant trends for low alpha generators. There were no significant trends or interactions for the other EEG frequencies.

There were no significant main effects or interactions with alpha generators for the alpha power or alpha zero-cross asymmetry indices over the 6 difficulty levels in the ADDITION task, either at the parietal or frontal positions. To compare the amount of asymmetry induced by the Addition task (with respect to Focusing and Counting), a mean alpha zero-cross asymmetry index was calculated for each subject (collapsed across difficulty levels). The results are shown in figure 5. The Addition task produces an alpha asymmetry value more similar to Counting than to Focusing, as expected. However, there was no significant interaction between task and alpha groups, only a (linear) main effect for the tasks ($F=24.1$, $df=1,50$, $p<.0000$). As can be seen from figure 5 the inconsistent (compared to Focusing and Counting) asymmetry result in the Addition task for low alpha generators essentially eliminated any interaction. Within the Addition task asymmetrical alpha activity did not vary as a function of difficulty level for any of the alpha groups.

		SEX	AGE
ALPHA GENERATORS	HIGH	MALES = 8 FEMALES = 9	23.2 yrs
	MIDDLE	MALES = 7 FEMALES = 11	22.7 yrs.
	LOW	MALES = 6 FEMALES = 12	23.9 yrs.

TABLE 1. Distribution of sex and mean age across the alpha groups.

		SEX	AGE
THETA GENERATORS	HIGH	MALES = 8 FEMALES = 9	20.53 yrs.
	MIDDLE	MALES = 7 FEMALES = 11	22.72 yrs.
	LOW	MALES = 7 FEMALES = 11	26.39 yrs.

TABLE 2. Distribution of sex and mean age across the theta groups.

		THETA GENERATORS		
		HIGH	MIDDLE	LOW
ALPHA GENERATORS	HIGH	2	7	8
	MIDDLE	9	2	7
	LOW	6	9	3

TABLE 3. Distribution of subjects on both factors.

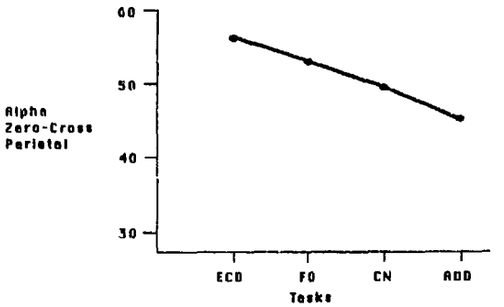

Figure 1: Hemispherically averaged alpha zero-cross for all subjects.
ECD = Eyes Closed Dark; FO = Focusing (mean of both versions);
CN = Counting (mean of both versions); ADD = Addition (mean of all levels).

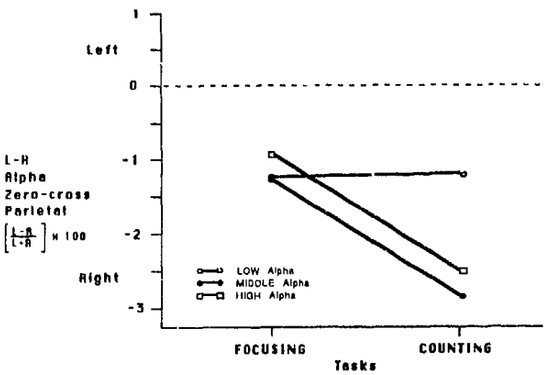

Figure 2: Alpha asymmetry index (zero-cross parietal) for means of both versions of the Focusing and Counting tasks for each type of alpha generator.

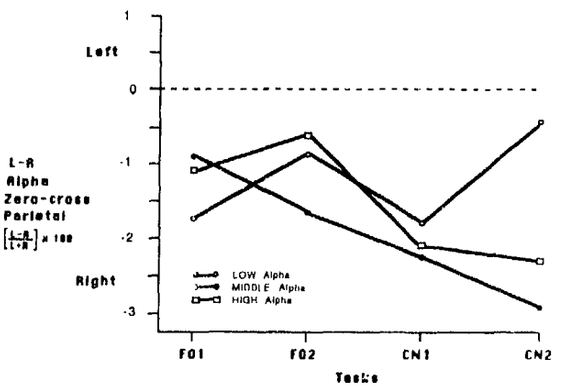

Figure 3: Alpha asymmetry index (zero-cross parietal) for the hemispherically ordered tasks for each type of alpha generator.
FO1 = Focusing; FO2 = Structured Focusing;
CN1 = Counting Articles; CN2 = Counting Proper Nouns

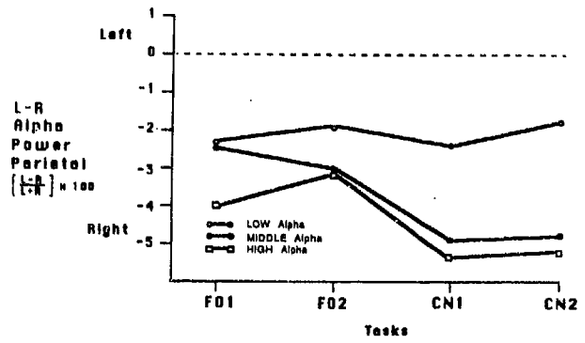

Figure 4: Alpha asymmetry index (power parietal) for the hemispherically ordered tasks for each type of alpha generator.
FO1 = Focusing; FO2 = Structured Focusing;
CN1 = Counting Articles; CN2 = Counting Proper Nouns

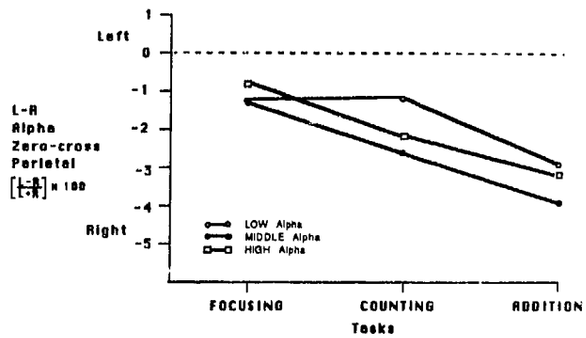

Figure 5: Alpha asymmetry index (zero-cross parietal) for the means of both versions of the Focusing and Counting tasks and the mean of all levels of the Addition task for each type of alpha generator.

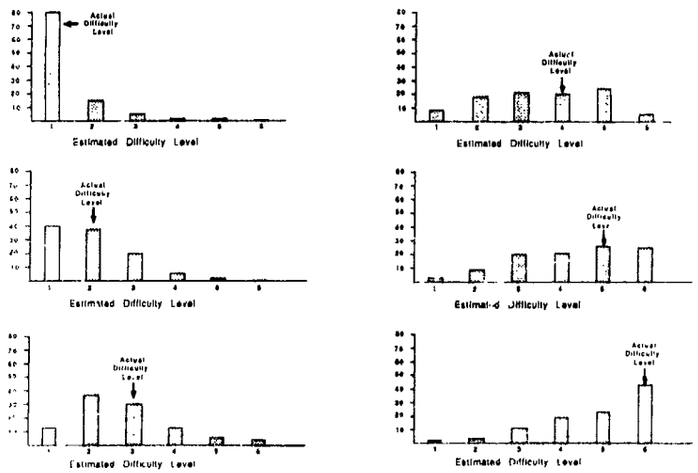

Figure 6: Percent frequency histograms of subjective difficulty with actual difficulty level for the Addition task

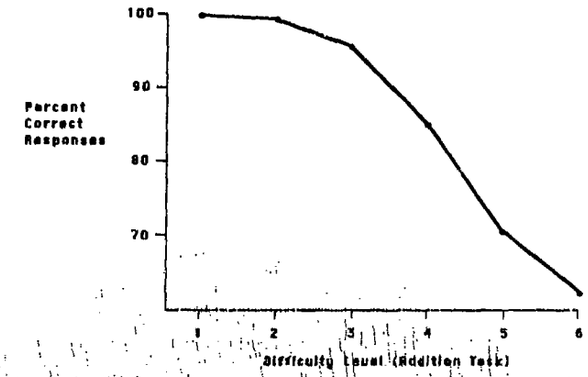

Figure 7: Percent correct responses (subject answer/correct answer) x 100 for each difficulty level of the Addition task.

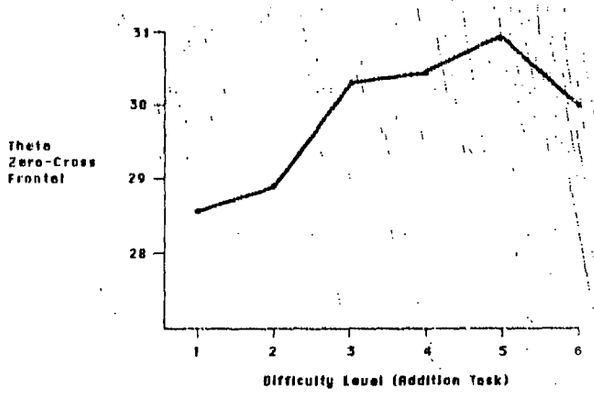

Figure 8: Hemispherically averaged theta zero-cross frontal for each difficulty level the Addition task.

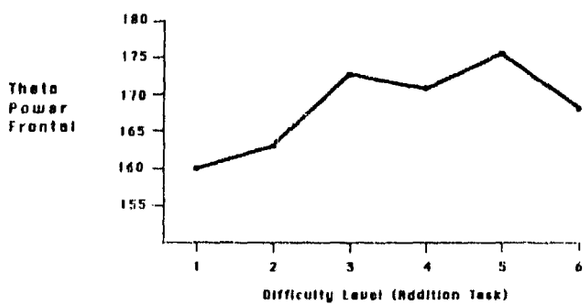

Figure 9: Hemispherically averaged theta power frontal for each difficulty level of the Addition task.

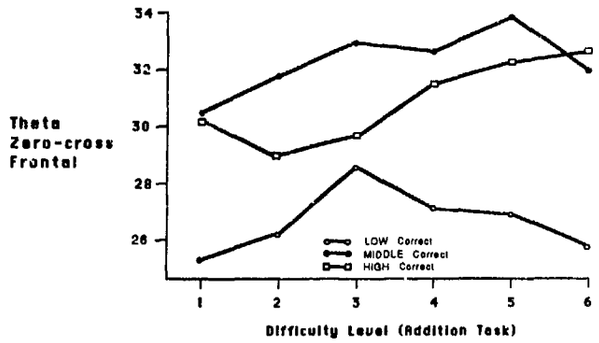

Figure 10: Hemispherically averaged theta (zero-cross frontal) for the three percent correct groups at each difficulty level of the Addition task.

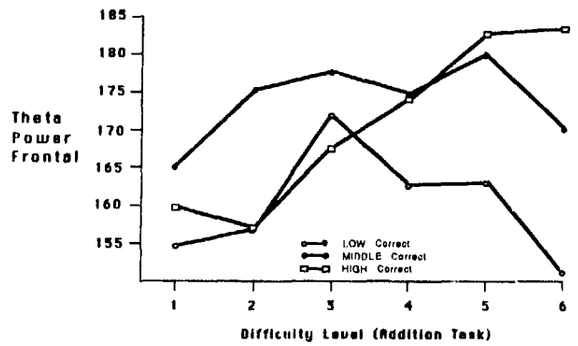

Figure 11: Hemispherically averaged theta (power frontal) for the three percent correct groups at each difficulty level of the Addition task.

Two analyses evaluated whether the ADDITION task indeed varied with difficulty level. First, the subjective responses of difficulty level for each trial with respect to the actual difficulty level were graphed and are shown in figure 6. It demonstrates that as actual difficulty level increased the subjects' estimate of difficulty also increased, with a correlation of r=.755. Second, the subjects' addition answers for each trial were divided by the correct answer and multiplied by 100 to produce a percent-correct estimate for each level of difficulty. As can be seen in figure 7 there is a clear decreasing trend from the easiest level to the most difficult (significant with F=73.34, df=1,50, p <.0000), demonstrating that as difficulty increased the subjects' percent correct scores decreased.

To test whether theta is related to difficulty level by an inverted U shaped function, theta zero-cross and theta power were averaged across hemispheres for each subject at each level of the Addition task. In figures 8 and 9 the results for each measure are plotted. There were significant linear main effects for difficulty level; that is, as difficulty increased theta increased. More importantly, however, there were also quadratic main effects both for theta zero-cross (F=4.57, df=1,50, p <.037) and theta power (F=4.96, df=1,50, p <.031). There were no significant differences among alpha or theta generators.

Although figures 8 and 9 are not inverted U shaped, they are curved. The results may have been influenced by individual differences in abilities to perform the Addition task. The subjects were rank ordered on the basis of their overall performance scores (i.e., percent-correct measure). The top, middle and bottom thirds were divided into 3 groups: high-correct, middle-correct and low-correct performers. ANOVAs (3 groups x 6 levels of difficulty) yielded a significant linear interaction for theta power (F=3.55, df=2,50, p <.036) and a significant quadratic interaction for theta zero-cross (F=4.18, df=2,50, p <.021). High and middle-correct performers maintain a higher level of theta activity than do low-correct performers (see figures 10 and 11).

These theta results were specific to the frontal site. Also, no hemispheric differences were detected.

DISCUSSION

It is well known that individuals differ with respect to the amount of alpha activity they produce. However, the effect of this individual difference has not been investigated in asymmetry research. Low alpha generators did not exhibit EEG asymmetries for tasks designed to induce such asymmetries whereas middle and high alpha generator did. The results suggest that past conflicts in the literature concerning EEG and asymmetry may be due partly to individual differences in EEG. For instance, studies demonstrating hemispheric asymmetries may have had subjects who were predominantly alpha generators. Ornstein, Herron, Johnstone and Swencionis (34) chose subjects on their ability to display alpha asymmetry during a screening session. Subjects displaying "negligible or reversed specialization (p.399)" were excluded. It is likely that subjects passing this test were high alpha generators. On the other hand, studies finding no hemispheric EEG differences may have had a sample of low alpha generators. Our pilot study, mentioned earlier, yielded non-significant asymmetry results when the data from both high and low alpha generators were taken together (N=13). When the two groups were separated a significant interaction was obtained.

It may be argued that the observed asymmetries were due to task difficulty and not hemispheric processing. Indeed figure 1 shows decreasing levels of alpha activity across the tasks, a result often seen for tasks of increasing difficulty (e.g., 45). But in the addition task, a task specifically designed to vary difficulty, asymmetries in alpha activity were not observed, even among middle or high alpha generators. It could also be argued that the focusing and counting tasks contained different stimulus characteristics: specifically, silence during focusing, and verbally presented text during counting. However, it is difficult to imagine a mechanism by which the physical presence or absence of an auditory signal could induce left hemisphere activation without also assuming asymmetrical cognitive processing. Even Jutai's (25) theory that the attentional demands of the right hemisphere may dominate the left during "...interoception, sustained attention, and early (primarily feature extraction and identification) stages of information processing" (p.224), would predict greater activation (i.e., less alpha) in the right hemisphere during the presence of a stimulus. Also the a priori ordering of the four tasks (i.e. both versions of Focusing and Counting) did produce a linear relative change in hemispheric alpha activity. That is, adding more 'left hemisphere' qualities to both tasks did produce an effect.

The most important result for this part of the study is that hemispheric shifts in alpha occur in high and middle alpha subjects only. As such, it suggests that the organization of brain activity and its relation to cognition could vary greatly in the population. Such variation could be related to characteristics such as preferred cognitive strategy, personality variables, cognitive skills, etc. Recently De Pascalis and Silveri (5) demonstrated that (alpha) biofeedback regulation of hemispheric asymmetry could augment the amount of alpha asymmetry observed during cognitive processing. This implies that hemispheric asymmetries can to some extent be learned. Furthermore, Townsend, Lubin and Naitoh (43) have found that by sinusoidally modulating light at the alpha frequency, EEG alpha can be augmented and stabilized. They suggested that this method may phase-lock scalp recorded alpha by influencing subcortical alpha generators. Using this technique, it may be possible for low alpha generators to produce larger amounts of alpha. It would then be interesting to determine if these individuals exhibit the asymmetries high and middle generators show. The issue is important because it would help determine whether low alpha generators are, or are not, lateralized.

The behavioural and subjective results from the ADDITION task demonstrate that level of difficulty was successfully manipulated in this study. Concomitant changes in theta activity as a function of increasing difficulty level suggests a relationship between theta and attention. An overall inverted U shaped relation was not observed due to individual differences during task performance. Subjects receiving higher performance scores produce more theta activity when task difficulty increases. Low performance subjects exhibit a peak in theta production at medium levels of difficulty and then show a decline with greater difficulty. It is assumed that theta varied in these individuals due to variable attention requirements, but this interpretation is not conclusive. The difficulty continuum in the addition task confounded attention with cognitive processing. However, indirect evidence supporting an 'attention' explanation is the significant difference in ages among the theta groups (determined during baseline). Assuming that younger and more naive university subjects experience greater anxiety or excitement at the beginning of an experiment they may, as a result, exercise greater attention during the baseline condition. Older, experienced subjects may relax more and therefore produce less theta. This effect was limited to the baseline condition. During task performance no differences among (baseline determined) theta generators were observed, suggesting that theta reflects relatively immediate processes.

Mizuki et al. (29) did not observe frontal midline theta activity in any of their subjects during baseline conditions. Also they found no performance differences between subjects exhibiting theta during the task and subjects not generating theta. Their results however, are likely due to the visual EEG scoring technique they used, which ignored important background theta activity.

In summary, endogenous levels of alpha activity effects the likelihood of detecting hemispheric asymmetries during the performance of tasks presumed to induce such asymmetries. From a methodological perspective this may account for some of the conflicting results in the literature. Differences in frontal theta activity seem to reflect immediate changes in attention, although more research is necessary to conclusively determine whether attention alone or cognitive processing (which includes attention) is the primary correlate.

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APPENDIX A

FOCUSING Task Instructions

1. If the instructions for this task seem vague, don't worry about it. From time to time I'll give you further instructions. There will be periods when I won't be saying anything and you'll be carrying out the instructions. Alright... When you are ready just sense into your body and ask yourself, "How am I inside right now?" and don't answer. Make a space for whatever comes up. Listen to your body. Don't put words on it... Just put all your attention on what is going on inside your body and see how it is.

>>> 45 seconds of silence <<<

2. Perhaps you are listening to several parts of your body. Choose the main one and go with it. Focus all your attention on that one feeling or sensation. You don't do anything except let it come up and be with it.

>>> 45 seconds of silence <<<

3. If this sensation changes or moves, let it do that. Whatever it does, follow the feeling and pay attention to it.

>>> 45 seconds of silence <<<

4. Now take what is fresh or new in the feel of it now, and as you feel it, try to find a word or two, or a picture which captures what your present feeling is all about. The word or picture is a handle on your experience and doesn't have to make sense to anyone but you.

>>> 45 seconds of silence <<<

5. Now match the handle to the feeling and see if the work or picture is just right in capturing your feelings. Change the image to match the feeling till they are a good fit.

>>> 45 seconds of silence <<<

STRUCTURED FOCUSING Instructions

1. For this task you'll be asked to direct your attention inward, to specific parts of your body. At each step I will direct you to which body part you should attend. There will beperiods when I won't be saying anything and you'll be carrying out the instructions. At the end of these periods I'll ask how successful you were in attending to that body part. Try not to let your mind wander. Try to 'experience' that body part. Remember, the purpose of this task is to focus on specific parts of your body and then tell me how successful you were, after I ask you. Alright... Relax and keep your eyes closed. Take a few deep breaths... When you are ready, just sense into your body and locate both your ankles. Focus all of your attention on your ankles. Ask yourself "How do they feel?" but don't answer. Just sense them.

>>> 45 seconds of silence <<<

2. On a scale from 1 to 5 where 1 is 'not successful' and 5 is 'very successful', rate your ability to focus on your ankles. (SUBJECT'S RESPONSE)... Now focus all of your attention on both your knees... Locate one feeling or sensation in them and go with it.

>>> 45 seconds of silence <<<

3. On a scale from 1 to 5 where 1 is 'not successful' and 5 is very successful, rate your ability to focus on your knees. (SUBJECT'S RESPONSE)... Now go from your knees to your stomach. Again locate one feeling or sensation. If this sensation changes or moves, let it do that. Whatever it does, follow the feeling and pay attention to your stomach.

>>> 45 seconds of silence <<<

4. On a scale from 1 to 5 where 1 is 'not successful' and 5 is very

successful, rate your ability to focus on your stomach. (SUBJECT'S REPONSE)... Now, focus your attention on your heart. Take what is fresh or new in the way your heart feels now, and focus on it.

>>> 45 seconds of silence <<<

5 On a scale from 1 to 5 where 1 is 'not successful' and 5 is very successful, rate your ability to focus on your heart. (SUBJECT'S RESPONSE)... From your heart, switch your attention to the inside of your head. Try to visualize and feel the inside of your head.

>>> 45 seconds of silence <<<

6. On a scale from 1 to 5 where 1 is 'not successful' and 5 is very successful, rate your ability to focus on your heart. (SUBJECT'S RESPONSE).

PSYCHOPHYSIOLOGICAL MEASURES OF DROWSINESS AS ESTIMATORS OF MENTAL FATIGUE AND PERFORMANCE DEGRADATION DURING SLEEP DEPRIVATION

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SUMMARY

This paper describes a methodology developed to measure 'drowsiness' electrophysiologically as an index of chronic fatigue experienced during periods of sleep loss.

Nine volunteers performed a continuous cognitive workload schedule with 15 min breaks occurring every 2 hrs throughout a 64 hr sleep deprivation experiment. To measure fatigue a 4 min eyes closed relaxation period was embedded once every hour within a battery of cognitive tasks. The subjects were instructed to relax with their eyes closed but remain awake and alert. At the end of this 4 min period, a bell sounded which cued the subjects to open their eyes and indicate their subjective level of drowsiness. EEG signals collected during these periods were both visually scored and computer quantified. Two raters visually scored the signals for: (1) time of first stage 1 sleep onset, (2) number of stage 1 sleep onsets, (3) shortest and longest time in stage 1 and (4) total amount of stage 1 sleep (or deeper). Period analysis was performed on the digitized data and a drowsiness scale was developed by subtracting the amount of theta and delta from alpha while controlling for individual differences by dividing the result by alpha minus theta minus delta activity present during baselines. Also, 'autoFFTs' were calculated providing 3-dimensional representations of the temporal and spectral EEG characteristics of abbreviated sleep onsets.

The results indicate that for individual subjects drowsiness onset latencies, performance, subjective scales and the drowsiness index are all intercorrelated. Also, autoFFTs provide striking visual examples of abbreviated sleep onset. It is suggested that these EEG techniques, as well as the methodology of embedding eyes closed relaxation periods, yield sensitive measures for detecting differential levels of drowsiness during sleep deprivation.

INTRODUCTION

Demands for around-the-clock operations often necessitate humans to perform tasks requiring complex cognitive skills and decision making abilities while experiencing sleep loss (e.g., monitoring nuclear power plants, coordinating naval ship operations, medical residents gathering and interpreting diagnostic information). However, when individuals remain awake for extended periods their reported levels of fatigue and sleepiness increase and their performance degrades (e.g., 12, 17, 19). These subjective and objective effects of sleep loss appear to be attributable to chronic fatigue, which is manifested as a condition of physical and cognitive enervation. Although other factors such as boredom, motivation or task specific factors may influence mood and performance, it is this chronic fatigue which appears to be the primary effect of sleep loss.

One method to optimize task performance during sleep loss is to individually monitor fatigue level and make adjustments when criterion values are exceeded. For instance, adjustments could be made either to individuals (e.g., intervene with rest, sleep or drugs) or to their work environment (e.g., alter the stimulus or response characteristics of the task) or both. At present, however, there is no satisfactory way to measure chronic fatigue objectively. Efforts to measure fatigue have generally been limited to self-report scales. To be useful both in applied and research settings fatigue measurements must be objective, non-intrusive, easily quantified, and minimally compromise the working environment. They should have face validity and be correlated with changes both in subjective estimates of fatigue and objective measures of performance (i.e. concurrent validity).

One potential objective measure of fatigue is the Multiple Sleep Latency Test (MSLT) (5). The MSLT is based on the simple and direct assumption that

"...those individuals who are sleepy will fall asleep more quickly than those who are not" (11, p.S108). Procedurally, the MSLT requires subjects to lay down in a dark, quiet room, close their eyes, and attempt to fall asleep. The basic unit of measurement is the latency to reach stage 1 sleep (as defined by 20) with a maximum allowable latency of 20 minutes. If the subject enters stage 1 sleep he is awakened and the latency is recorded.

The MSLT has enjoyed both clinical and experimental popularity (11) but in its present form, the MSLT is unsuitable for monitoring fatigue during periods of continuous cognitive performance. For work environments and experiments involving high work/rest schedules, such as the 7:1 (105 min work to 15 min rest) schedules found in studies of sustained work and sleep loss (2, 13), the MSLT can exceed the usual rest interval and reduce the work/rest schedule by more than fifty percent. Akerstedt and Gillberg (1) echoed similar concerns for their field studies on shift-workers when they shortened the MSLT to 10 min because "...we wanted a setting similar to that of our field studies where 10 min had to be used to avoid production losses" (p.221).

In contrast to the MSLT which defines sleepiness as the propensity (latency) to fall asleep, Gavins, Zeitlin, Ancoli and Yeager (9) have attempted to automatically measure the act of falling asleep itself. They developed a computerized drowsiness detector to identify and reject EEG signals contaminated by drowsiness. Their algorithm detected increases in the ratios of delta to alpha and theta to alpha after controlling for awake, alert baseline EEG. The results were consistent with raters' visual scoring of sleep onset. However, consistent with the purpose of their research, the algorithm provided only decisions for whether drowsiness was present or absent. It was not used as a quantitative measure of varying drowsiness.

The present study develops and evaluates a drowsiness metric (as a measure of fatigue) appropriate for sustained, high intensity, work environments. Features common both to the MSLT and the work of Gevins et al. (9) have been incorporated. Unlike the MSLT, where subjects try to fall asleep, a methodology was developed where subjects were instructed to relax, close their eyes and rest for four minutes while sitting at their work stations. This strategy permits close monitoring of the natural and uncontrollable effects of chronic fatigue and allows a quiet and relatively artifact free period of EEG acquisition.

The 4 min eyes closed relaxation procedure was embedded once every hour within a battery of cognitive tasks during a 64 hour continuous work experiment. Although instructed to remain awake during these relaxation periods, it was anticipated that subjects would experience increasing levels of drowsiness as sleep loss became more severe. By visually scoring the EEG for (1) the latency to stage 1 sleep onset, (2) number of stage 1 sleep onsets, and (3) shortest, longest and total time in stage 1 sleep or deeper, a modified Multiple Sleep Latency Test is achieved. The EEG signals were also digitized and analyzed to obtain a drowsiness index. The metric proposed in this study subtracts the amount of theta and delta from alpha while controlling for individual differences (such as the amount of endogenous alpha) by dividing the result by alpha minus theta minus delta activity present during baselines. The drowsiness index was based on previous findings showing that the transition from waking to stage 1 sleep is characterized by a reduction of alpha activity, and an increase in theta and delta activity (e.g., 9, 18, 20).

In the present experiment the drowsiness index provides a single estimate of fatigue for the entire 4 minute relaxation period which is then correlated with performance and mood. To investigate transient variations in drowsiness within a single 4 minute period a novel 'autoFFT' measure was used. The procedure is similar to an autocorrelation or an autoregression, and yields a 3-dimensional representation of the temporal and spectral EEG characteristics of abbreviated sleep onsets.

METHOD

Subjects:

For each of 16 male Canadian Forces volunteers EEG activity was recorded continuously for over 80 hrs. Seven subjects had incomplete data due to intermittent equipment malfunction (5 subjects) or excessive artifact in the EEG channels (2 subjects). The mean age of the remaining 9 subjects was 30.1 yrs.

Apparatus:

Subjects worked independently in 3 X 4 m experimental rooms each equipped with a DEC VT100 video display terminal, table, chair and desk lamp. All cognitive tasks, including the 4 min eyes closed instructions, were generated and controlled by a DEC PDP-11/44 computer and were displayed on the subjects' video terminals; when responses were required the subjects keyed their answers

into the terminals.

Closed-circuit televisions were used to visually monitor the subjects, and slave monitors displayed the information on each subject's terminal to the experimenter. By monitoring both the subjects and their responses experimenters were able to determine when the subjects fell asleep. Except for the 4 min relaxation period, if subjects fell asleep they were immediately awakened by the experimenter.

Continuous electrophysiology was recorded for each subject on an eight channel Oxford Medilog 9000 ambulatory cassette recorder. During waking portions of the experimental protocol the following channels were recorded: 3 EEGs (C3-O1, C4-A2, Fz-A1), an ECG, a bipolar EOG, respiration and actigraphy. To visually score the EEG, each 4 min relaxation period was copied from cassette tape to paper using the Oxford Medilog 9000 Replay/Display System connected to a Beckman Accutrance 2000 polygraph. For computer quantification the Oxford Medilog 9000 Replay/Display System replayed the signals through Khron-Hite analog filters to a VAX 785 computer with A/D converters and mass storage devices.

Procedure:

Subjects received the same experimental protocol in groups of four, and worked independently of each other. They arrived at 1000h on Monday and remained until 1500h on Friday. All time cues were removed and interpersonal communication with the laboratory staff was kept to a minimum. On Monday all subjects were briefed on the experimental protocol and given extensive training and practice on the battery of cognitive tasks used in the experiment. Training continued until 2000h, after which the subjects relaxed, watched a movie, had their electrodes applied and retired for 8 hours of baseline sleep at 2200h. They were awakened at 0600h Tuesday morning and began the experiment immediately. On Thursday morning at 0400h they were given a 2 hr nap, after which they immediately continued the experiment, until 2000h on Thursday night. Then they relaxed and went to bed at 2200h for 8 hours of recovery sleep. At 0600h on Friday they were awakened and worked until 1500h, at which time the experiment ended.

Throughout the sleep deprivation period the subjects were required to perform a work schedule consisting of 1 hr and 45 min of continuous cognitive work followed by 15 min of rest. During these rest breaks, the subjects consumed food, used toilet facilities, watched movies, conversed and had all electrode connections checked by the experimenters. In each work session two 15 minute periods (one immediately after their break and the other 1 hour into the work session) were devoted to self-report scales and a battery of short cognitive tasks which included the 4 min relaxation period. Therefore, estimates of subjective and objective fatigue as well as performance were gathered once every hour. Although numerous other tasks were performed during the work session only the results from these 15 minute test batteries will be presented.

Tasks:

Four min eyes closed relaxation period. On their video display terminal the subjects were instructed to relax in their chairs with their eyes closed. At the end of 4 minutes the terminal bell sounded and the subjects were ask to answer the following question.

"On the following scale, please type the number from 1 to 7 which best describes how you felt while your eye were closed.

1 - I was alert and wide awake.

2 - I was alert, somewhat relaxed but not at my peak.

3 - I was very relaxed and even a bit drowsy.

4 - I was very drowsy and almost fell asleep.

5 - I was extremely drowsy and I think I might have fallen asleep briefly.

6 - I fell asleep a number of times and it was difficult to stay awake for even short periods.

7 - I fell asleep and stayed asleep until the task was over and I had to be awaken by the 'beep' from the terminal or by the experimenter.

TYPE YOUR ANSWER HERE AND HIT RETURN / _____ "

Self-report scales. The subjects completed three self-report scales. The first was the U.S. Air Force School of Aerospace Medicine Subjective Fatigue Checklist (10) in which the subjects were sequentially presented with 10 statements, such as "very lively" and "petered out" and rated themselves as "better then", "same as", or "worse than" each of these statements. Total scores on this scale covered a 20-point range, with lower scores indicating greater subjective feelings of fatigue.

The second self-report scale was the Stanford Sleepiness Scale (14).

The third was the U.S. Naval Health Research Center's Mood Scale (16). The subjects were sequentially presented with mood-related descriptions (e.g., active, tense, considerate, happy), and then rated themselves on a 4-point scale, from "not at all" to "extremely", relative to each description. Nineteen positive and 10 negative mood descriptions were presented so that separate positive and negative mood scores could be calculated. The positive mood score covered a 57-point range; higher scores indicated a more positive mood. The negative mood score covered a 30-point range; higher scores indicated a more negative mood.

Complex iterative subtraction. Subjects were presented with a randomly chosen three-digit number between 500-999 on the screen (e.g. 674) and were asked to subtract 9 from the presented number, then 8 from the obtained difference, 7 from the next difference, 6 from the next difference, and 5 from the next difference, and then to repeat the sequence of subtrahends for the duration of the task (adapted from Cook, Cohen & Orne (7)). The original three-digit answer was removed from the screen immediately after the third digit was entered by the subject. This forced subjects to remember each difference, as well as a varying single-digit subtrahend. There were two trials each lasting 60 sec and terminated by a 'beep'.

Logical reasoning. This task involves understanding sentences of varying syntactic complexity (4). Sixteen sentences, such as "A is preceded by B", were presented individually on the subject's terminal followed by either the letter pair "AB" or "BA". The subjects were required to indicate whether or not each sentence was a true description of the pair of letters by pressing a key marked "T" (true) or "F" (false). The 32 possible sentences and letter pairs were presented in random order without replacement.

Visual Scoring of the EEG:

The EEG channel from the C3-O1 electrode site was visually scored for each subject for each 4 min relaxation period. The EEG signals were copied to a paper polygraph running at 10 mm/sec, with time constant of 0.1 and calibrated at 50 uV/cm. From the beginning of each relaxation period stage 1 sleep onsets were scored using the criteria of Rechtschaffen and Kales (20) with the following modifications. Two visual scorers independently scanned the C3-O1 EEG channel from the beginning of the trial until there was a 10 sec period during which no alpha activity was produced (or severe alpha attenuation in the case of high alpha generators) accompanied by an increase of theta and/or delta activity. The latency to the onset of this 10 sec period from the beginning of the trial was recorded as the time for the first onset of stage 1. If no segment of the EEG signal indicated a sleep onset then a maximum latency score of 240 sec (i.e. 4 minutes) was recorded. If movement artifacts or alpha bursts lasting at least 2 seconds were observed, this was taken as indication of arousal from sleep and a further 10 seconds of no alpha was needed to score another sleep onset. All times were recorded to the nearest second.

The following dependent variables were measured: (1) the latency of stage 1 sleep onset, (2) the number of stage 1 sleep onsets, and (3) the shortest, longest and total time spent in stage 1 sleep or deeper.

Computer Quantification

Prior to the experiment, the clocks on the cassette recorders were synchronized to the clock on the PDP 11/44 (which controlled and presented all task throughout the experiment). Every second the recorder encodes the time of day with the incoming signals, which allows retrieval of the electrophysiology associated with any task in the experiment. Each subject produced 5 cassette tapes during the experiment with approximately 16 hrs of electrophysiology on each tape. Since manually locating the desired section of tape for each trial of each task was difficult and labor intensive, the entire tape was digitized. With knowledge of the times at which the 4 min relaxation periods were given, the appropriate sections of the digitized signal were extracted and analysed.

Analysing the data in this manner, however, introduces a problem if the real-time clock of the A/D converters is used to sample the signal. During tape playback, any variances in tape speed would introduce large compounding errors for locating the correct segment of digitized data belonging to a particular

relaxation period. Instead, a 128 Hz square wave signal generated and recorded on the tapes by the Oxford recording system (to synchronize multiplexing of the 8 data channels) is used to activate a Schmitt trigger on the A/D converters. Since both the negative and positive inflections of the 128 Hz signal activate the trigger, a 256 Hz sampling rate is produced. The 128 Hz signal varies isomorphically with tape playback speed and generates digitized data temporally equivalent to the original signal. In fact, testing revealed that after 18 hours of digitization a difference of only .5 sec is detected between actual tape time and the time estimated from the sampling frequency.

All tapes were played back and digitized at 20 times real time. In all cases the bandpassed (.5-40 Hz) C3-O1 EEG channel was analysed using the following two techniques.

Period Analysis: Period analysis was performed on twenty-four 10 sec epochs during each 4 min relaxation period for each subject. This period analysis (cf. 15) produced 3 measures for 5 EEG bandwidths (delta .5-4 Hz, theta 4-8 Hz, alpha 8-12 Hz, sigma 12-16 Hz and beta 16-40 Hz). They are measures of zero-cross, power, and first-derivative. Briefly, a zero-cross analysis checks for a change in the sign of the voltage passing through zero. A measurement of the elapsed time between two zero-crossing events yields an estimate of the wave's frequency. Power is calculated by cumulatively adding the absolute voltage values between zero-cross events. The first-derivative checks for negative inflections in the EEG voltage and the time between such events provides an estimate of faster frequencies superimposed on the main waveform. However, since faster frequencies are not considered in this paper first-derivative measures are not reported.

For each 4 min eyes closed relaxation period mean values were obtained for each bandwidth across the twenty-four 10 sec epochs. The drowsiness index was calculated for both the zero-cross and power measures as follows:

$$(A-T-D)/(Ab-Tb-Db)$$

where A, T and D are mean alpha, theta and delta power or zero-cross and Ab, Tb and Db are mean baseline alpha, theta and delta power or zero-cross. Baseline values were calculated by averaging the EEG for each bandwidth for the first four relaxation periods in the experiment when the subjects were fresh and produced maximal alpha. It can be seen from the equation that subjects who are very low alpha generators may yield negative denominators and produce a different scale. For these instances (i.e., negative denominators) a corrected equation is used:

$$(A-T-D)/(Ab-Tb-Db) \times -1 + 2$$

The values from the resulting drowsiness scale for both alpha and non-alpha generators will vary from approximately 1 to a larger minus number, depending upon the depth of slow wave sleep.

AutoFFTs: It was anticipated that sleep deprivation would precipitate sleep during the 4 min eyes closed relaxation period. This provided the opportunity to investigate the spectral characteristics of abbreviated sleep onsets using Fast Fourier Transforms. However, traditional techniques appear to be unsuitable for detecting abbreviated sleep onsets. For instance, if repeated spectral estimates with a window length of 20 sec are used, only 12 successive FFTs would be produced providing only a crude measure for tracking sleep onset. A shorter epoch length (e.g., 2 sec) would yield 120 successive FFTs but would not produce smooth transitions among frequencies across spectra. Also, FTs on short epochs need windowing techniques to reduce the effect of abrupt onsets and endings in the digitized data.

To overcome these difficulties a new autoFFT technique was used which involved performing multiple FFTs with a window of 20 sec and a lag of 2 sec. For a particular 4 min segment of EEG from a relaxation period, the first 20 sec was Fast Fourier Transformed (i.e., from time 0 sec to time 20 sec). Next, a 20 sec FFT was performed from time 2 sec to time 22 sec. This procedure was repeated over the 4 min period resulting in 111 frequency spectra which were plotted 3 dimensionally. The plots provided a smooth visual representation of abbreviated sleep onset in the frequency domain through time.

RESULTS

Throughout the experiment all subjects received the same number of trials of all tasks and performed them at approximately the same time (i.e., roughly within 5-10 min of each other). Except for the autoFFT results, the data for all figures are collapsed across subjects and plotted in time.

Visual EEG scoring of sleep onset

Figure 1 illustrates the mean latencies to stage 1 sleep for all subjects across the experiment during the 4 min eyes closed relaxation period. The narrow vertical bar represents a 2 hr nap sleep period. Notice that a high frequency oscillation is apparent in the figure. This oscillation is due to the difference between those trials performed immediately after a 15 min break and those 1 hour into a work session. Figure 2 is the same data plotted for each condition ('AFTER BREAK' and '1 HR INTO SESSION'). All further graphs are similarly plotted. Additionally, since there were high intercorrelations among the EEG defined drowsiness variables (i.e., latency to stage 1, number of stage 1 onsets, shortest, longest and total time asleep), only the data from 'latency to stage 1 sleep' and 'total time asleep' will be presented.

Figures 2 and 3 illustrate the changes in sleep onset latencies and total sleep time during the 4 min eyes closed relaxation trials throughout the experiment. After 18-20 hrs of sleep deprivation (i.e. 2400h and 0200h Wednesday morning) a marked decline in sleep latencies and increase in sleep time is observed. Some recovery occurs between 32-38 hours of sleep deprivation (1400h and 2000h Wednesday), followed by further increases in sleepiness at 39-45 hours (early Thursday morning). After the nap some recovery is noticeable, and, although not shown in the figures, after 8 hrs of recovery sleep levels have returned to those observed during the start of the experiment. Figures 4 and 5 show very similar trends in performance, and Figures 6-8 exhibit these same trends for subjective assessments of sleepiness, fatigue and drowsiness. These data suggest that sleep-latency and total-sleep-time measured during the 4 min eyes closed relaxation period covary with performance and self-report scales. In order to quantify this covariation among the dependent variables, multiple correlations were performed between stage 1 sleep onset latencies and: (1) performance on the Subtraction & Logical Reasoning tasks; (2) scores on the Stanford sleepiness scale, Fatigue scale, Positive mood & Negative mood scales; and (3) scores on the Drowsiness scale. Multiple correlations for each subject are listed in Table 2. With the exception of the multiple correlation between sleep latency and task performance for subject #4, all multiple correlations are significant. Also, repeated measures ANOVAs show that impairment due to sleep loss increased significantly over the course of the experiment and most measures show reliable differences between trials occurring 'after breaks' and trials occurring '1 Hr into a work session' (see table 1).

Period Analysis

Figures 9, 10 and 11 illustrate the changes in alpha, theta and delta zero-cross activity as a result of sleep deprivation during the 4 min eyes closed relaxation periods. With increasing sleep loss alpha decreases and theta and delta increase, reflecting greater amounts of drowsiness and sleep during the relaxation period (power values show similar trends). The drowsiness index based on zero-cross and power values show very similar trends (see figures 12 and 13).

Both the zero-cross and power derived drowsiness indices yield significant trials effects, and significant differences between trials occurring after a break and trials 1 hr into a work session (see table 1). The similarity between the drowsiness index and performance is evident in figures 14 and 15 which show the drowsiness index plotted with Subtraction and Logical Reasoning respectively. More importantly, multiple correlations between the drowsiness index and performance and self-report scales were significant (see table 3). Subjects 4 and 9 demonstrate lower multiple correlations because a greater amount of noise is present in their EEG. This noise can be ignored during visual scoring of sleep latencies but is difficult to remove during computer quantification. Nevertheless, the generally strong relationship between the drowsiness index and both performance and subjective mood estimates is encouraging.

To determine whether or not the magnitude of the correlations among subjects was due to the amount of endogenous alpha they produced, the subjects were rank ordered both on the bases of endogenous alpha produced during baseline and the magnitude of their multiple correlations. The correlation between the two rank orders was not significant ($r=.45$, $df=7$, $p < .224$).

Auto FFTs

The results of the autoFFT are illustrated by the data from a single subject exhibiting an average amount of alpha during baseline. Figure 16 illustrates the temporal frequency spectrum of subject #1 during a 4 min relaxation period occurring 5 hours into the experiment. The subject is fresh, alert and exhibits a large peak in the alpha frequency throughout the entire 4 min. After 25 hours of sleep deprivation the same subject fell asleep (as determined by visual sleep stage scoring) 30 seconds into the relaxation period (see figure 17). Notice the dramatic reduction of alpha activity with a concomitant increase in slow wave activity. Figure 18 demonstrates the subject

TABLE 1: Results from repeated measures ANOVAs for each task and EEG indicators of fatigue.

	Main effect for differences between trials occurring "after breaks" and trials "1Hr into session". (df=1,8)		Main effect for differences among trials across the experiment. (df=22,224)	
	F	p<	F	p<
Performance				
Subtraction Task	10.30	.012	5.50	.001
Logical Reasoning Task	19.85	.002	6.62	.001
Subjective Estimates				
Stanford Sleepiness Scale	13.95	.006	6.80	.001
Fatigue Scale	8.05	.022	5.01	.001
Negative Mood Scale	5.04	.055	6.15	.001
Positive Mood Scale	4.87	.058	5.30	.001
Drowsiness Scale	22.52	.002	6.27	.001
Visual EEG Scoring				
Latency to Stage 1	59.98	.001	8.64	.001
Total Time Asleep	54.61	.001	8.72	.001
EEG Period Analysis				
Drowsiness Index (Zero-Cross)	15.23	.005	5.19	.001
Drowsiness Index (Power)	9.32	.016	4.24	.001

TABLE 2: Multiple correlations (R) for each subject between Stage 1 sleep onset and: (1) performance on the Subtraction and Logical Reasoning tasks; (2) Stanford Sleepiness scale, Fatigue scale, Positive and Negative Mood scales; (3) Subjective Drowsiness.

Subjects	Sleep Latency & Task Performance (R)	Sleep Latency & Subjective Scales (R)	Sleep Latency & Subjective Drowsiness (R)
S1	.559	.758	.727
S2	.574	.764	.791
S3	.713	.706	.785
S4	.142*	.524	.593
S5	.656	.682	.830
S6	.770	.785	.759
S7	.632	.484	.516
S8	.462	.723	.704
S9	.510	.445	.466

* p>.01.

TABLE 3: Multiple corrrelations (R) for each subject between Drowsiness Index and: (1) performance on the Subtraction and Logical Reasoning tasks; (2) Stanford Sleepiness scale, Fatigue scale, Positive and Negative Mood scales; (3) Subjective Drowsiness.

Subjects	Drowsiness Index & Task Performance		Drowsiness Index & Subjective Scales		Drowsiness Index & Subjective Drowsiness	
	Zero-cross (R)	Power (R)	Zero-cross (R)	Power (R)	Zero-cross (R)	Power (R)
S1	.632	.646	.810	.809	.788	.787
S2	.594	.591	.789	.783	.790	.762
S3	.691	.696	.743	.743	.727	.723
S4	.158*	.136*	.518	.391*	.139*	.047*
S5	.686	.657	.546	.534	.629	.611
S6	.762	.766	.711	.724	.785	.759
S7	.599	.596	.523	.520	.567	.580
S8	.580	.531	.679	.641	.826	.652
S9	.340*	.352*	.561	.544	.271*	.189*

* p>.01.

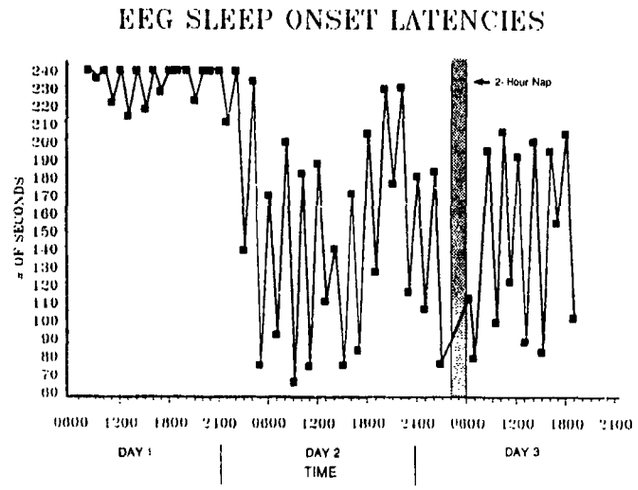


Figure 1: Mean stage 1 sleep latencies during the 4 min eyes closed relaxation period given hourly throughout a 64 hr sleep deprivation experiment. (Gray band signifies a 2 hr nap)

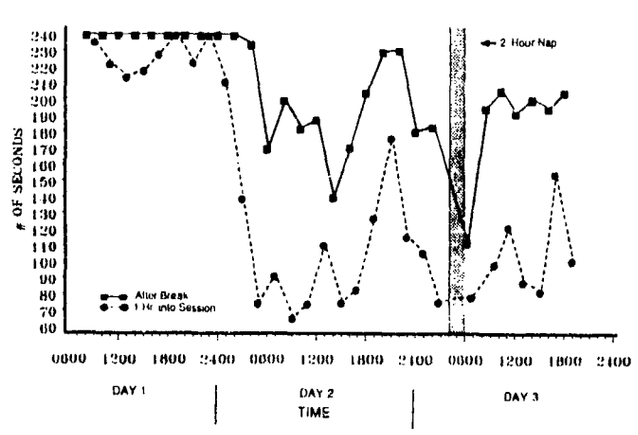


Figure 2: Same data as in figure 1 except the results are divided into trials occurring after a 15 min break and trials occurring 1 hr into a 2 hr work session.

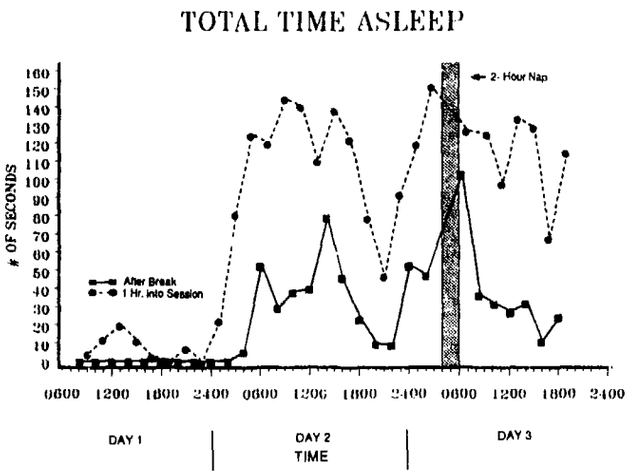


Figure 3: Mean total time spent in stage 1 sleep (or deeper) during the 4 min eyes closed relaxation periods.

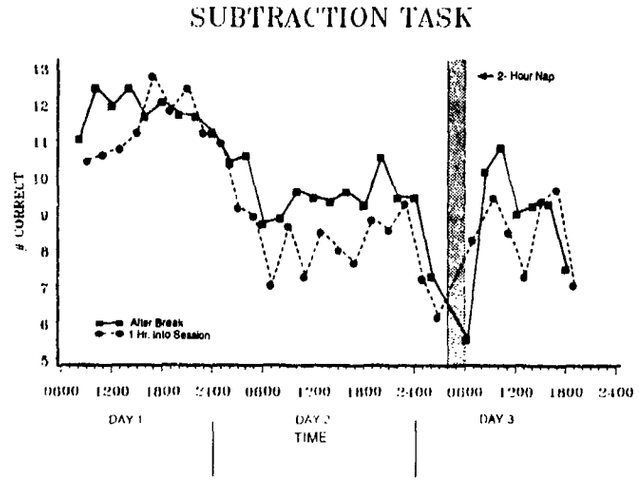


Figure 4: Mean number of correct responses per min in the Subtraction Task.

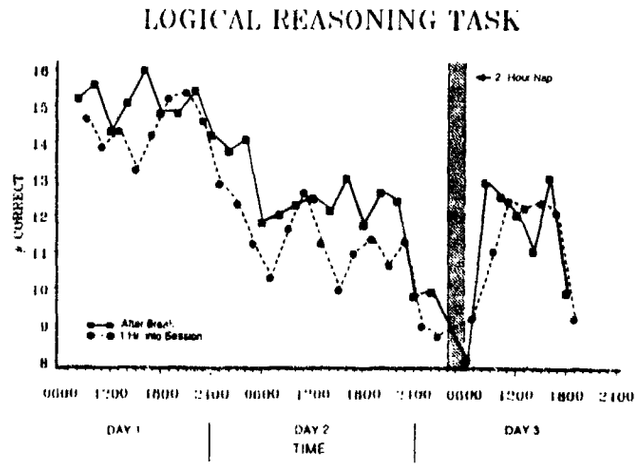


Figure 5: Mean number of correct responses per min in the Logical Reasoning Task.

Figure 6: Mean scores on the Stanford Sleepiness Scale; larger values represent greater subjective sleepiness.

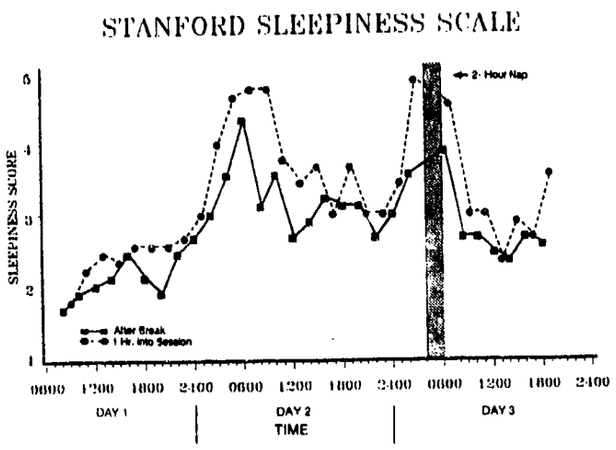


Figure 7: Mean fatigue scores on the Fatigue Scale; larger values represent less subjective fatigue.

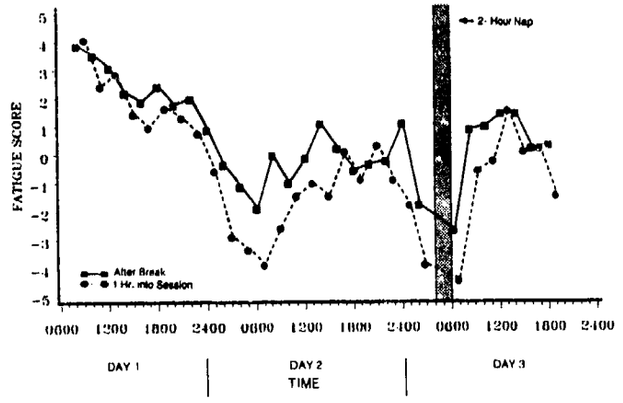
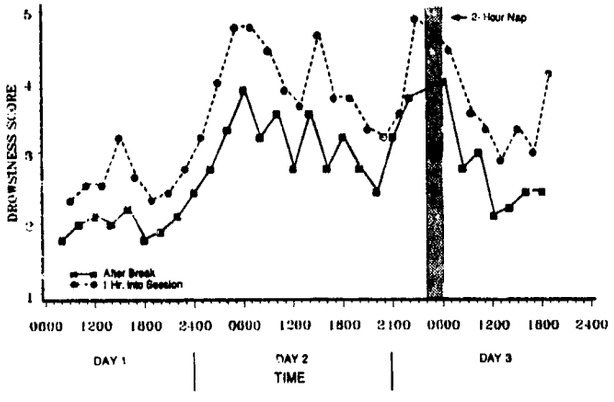


Figure 8: Mean drowsiness scores on the Drowsiness Scale; larger values represent greater drowsiness.



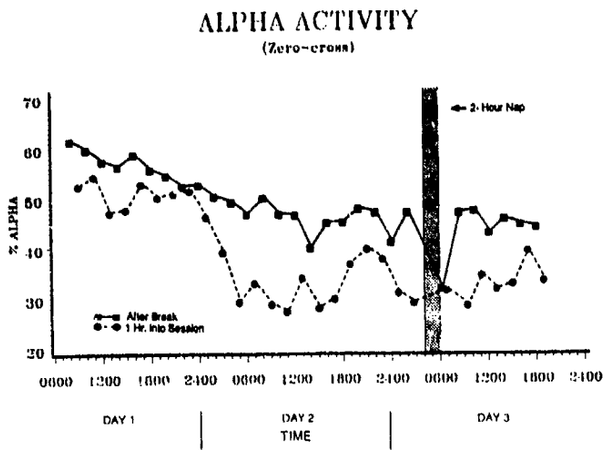


Figure 9: Mean percent alpha activity (zero-cross).

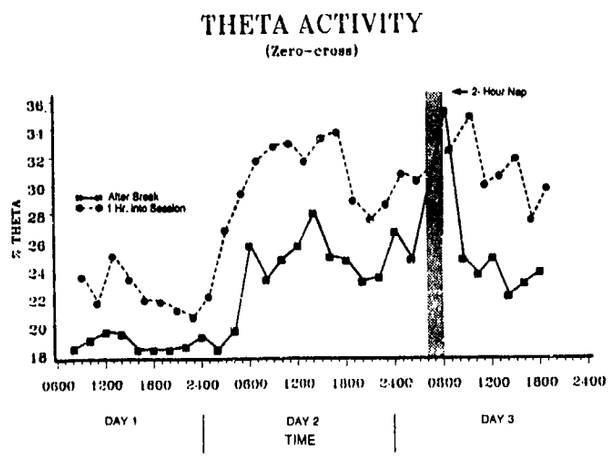


Figure 10: Mean percent theta activity (zero-cross).

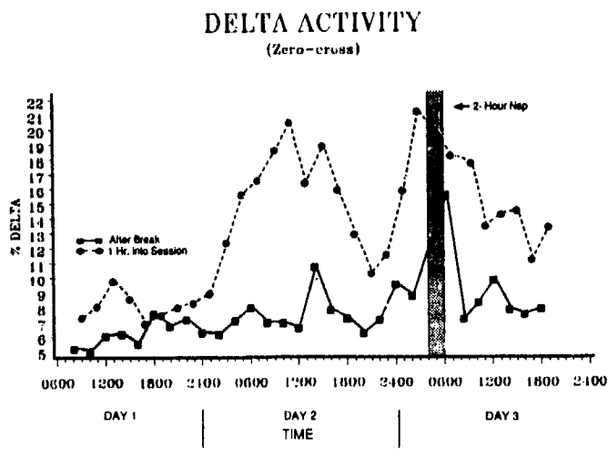


Figure 11: Mean percent delta activity (zero-cross).

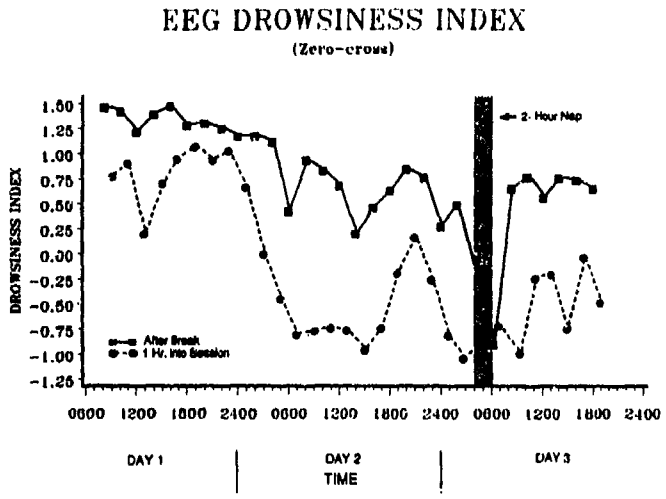


Figure 12: Mean drowsiness scores on the (zero-cross derived) EEG Drowsiness Index during the 4 min eyes closed relaxation periods; see text for a description of the algorithm.

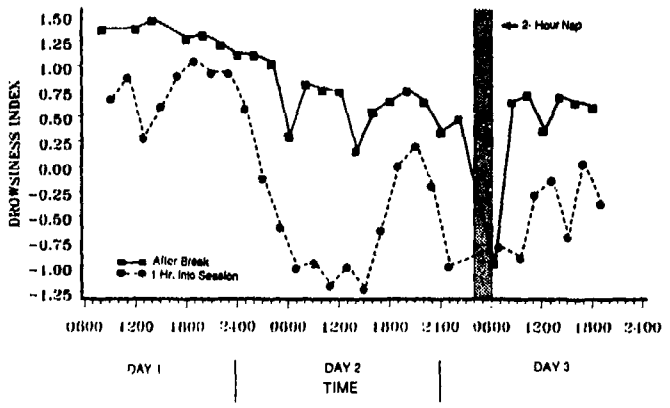


Figure 13: Mean drowsiness scores on the (power derived) EEG Drowsiness Index.

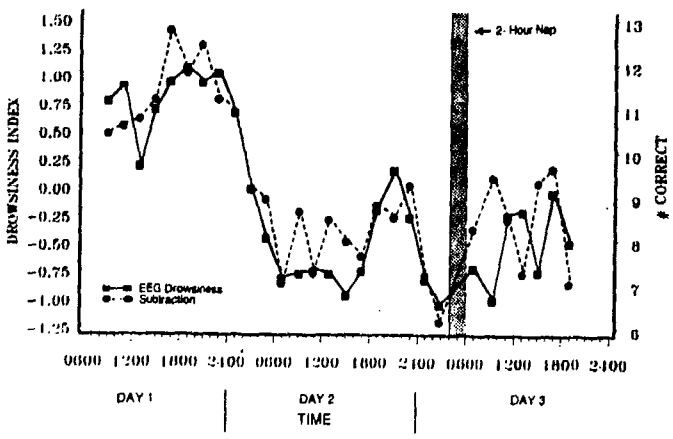


Figure 14: Mean drowsiness scores on the (zero-cross derived) EEG Drowsiness Index plotted with the mean number of correct responses per min of the Subtraction Task for trials occurring 1 hr into the work session.

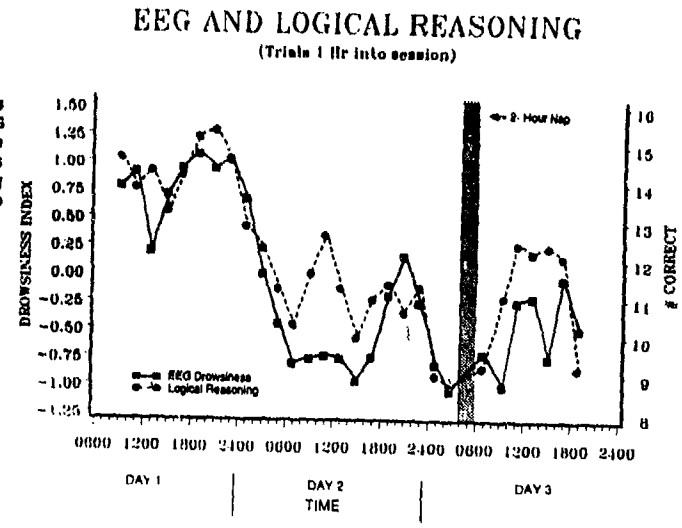


Figure 15: Mean drowsiness scores on the (zero-cross derived) EEG Drowsiness Index plotted with the mean number of correct responses per min of the Logical Reasoning Task for trials occurring 1 hr into the work session.

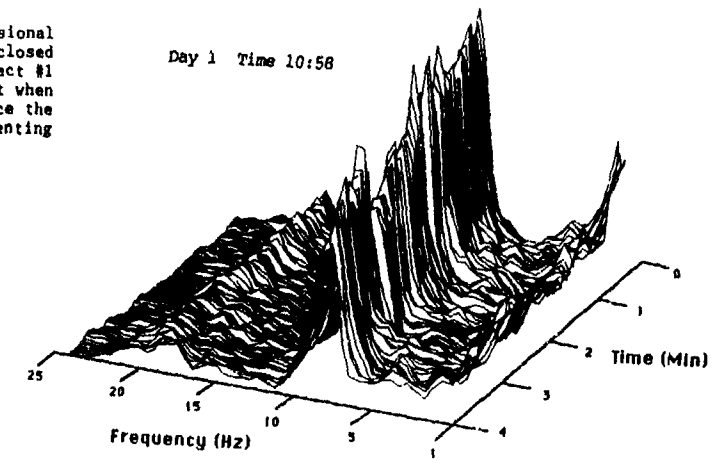


Figure 16: Three dimensional autoFFT of a 4 min eyes closed relaxation period from subject #1 taken early in the experiment when he is fresh and awake; notice the unbroken 10 Hz ridge representing sustained alpha activity.

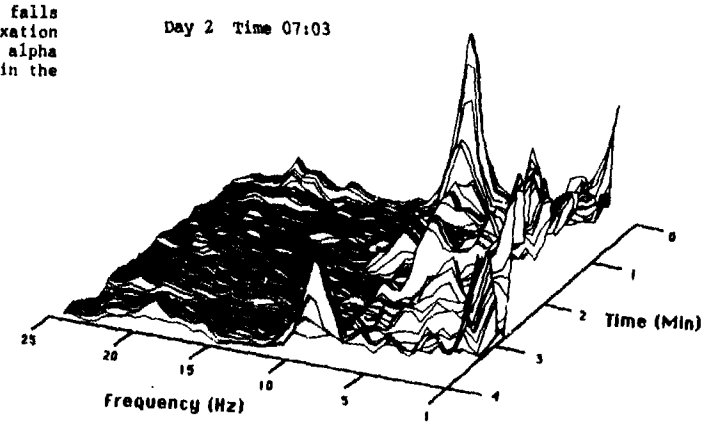


Figure 17: Three dimensional autoFFT from subject #1 who falls asleep 30 sec into the relaxation period; notice the declining alpha peak and increasing power in the slower frequencies.

Figure 18: Three dimensional autoFFT from subject #1 who falls asleep 3 times during the 4 min relaxation period; notice the 4 alpha peaks when he is awake and 3 alpha valleys when asleep; also notice declining height of the alpha peaks.

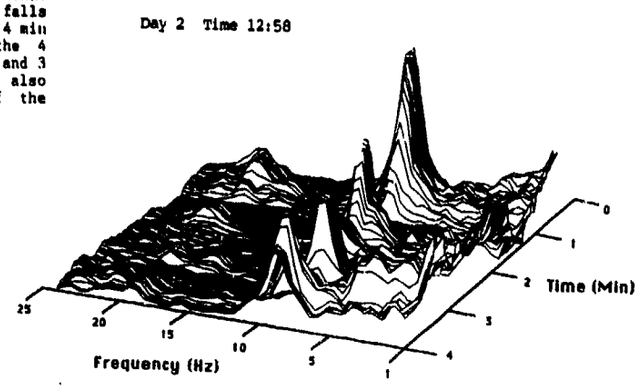


Figure 19: Three dimensional autoFFT from subject #1 who does not fall asleep despite 39 hrs of sleep deprivation; notice, however, the attenuated alpha ridge as compared to figure 16.

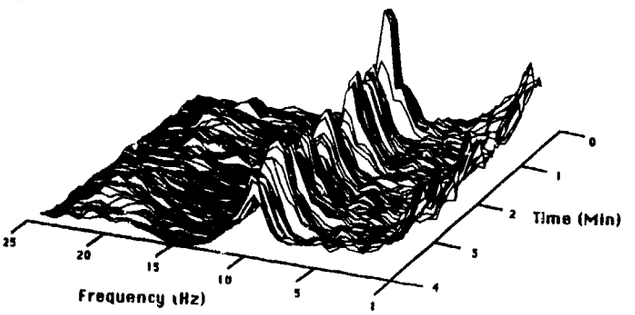
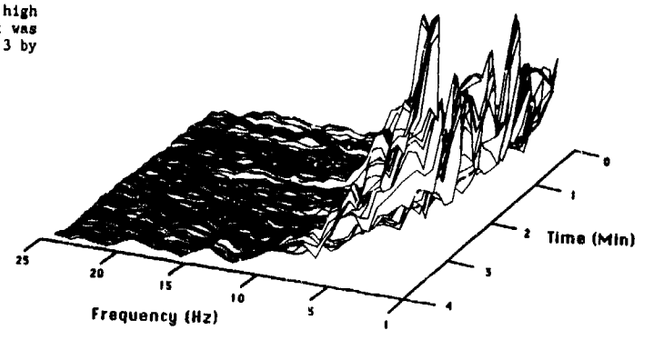


Figure 20: Three dimensional autoFFT from subject #1 who falls asleep 7 sec into the relaxation period and remains asleep until the 4 min are up; notice the very high theta and delta values (subject was in late stage 2 or early stage 3 by the end of the period).



falling asleep 3 times during the 4 min period (after 31 hrs of sleep deprivation). Four distinct alpha peaks can be seen signifying the subject is awake, and three distinct valleys are evident when he was scored asleep. In the next figure (figure 15), although the subject has undergone 39 hrs of sleep loss he did not fall asleep during this trial. However, the magnitude of the alpha ridge is very attenuated compared to figure 16. Finally, figure 20 illustrates the subject falling asleep 7 sec into the relaxation period and remaining asleep for the entire 4 min. The very high, slow frequency power values are consistent with visual scoring which indicated the subject was in late stage 2 or early stage 3 sleep by the end of the period.

DISCUSSION

The performance and subjective results in this study are consistent with earlier sleep deprivation studies emphasizing continuous cognitive workloads (2, 13). The addition of the 4 min eyes closed relaxation period embedded within the hourly battery of cognitive tasks and self-report scales allowed an opportunity to measure chronic fatigue. Visual scoring of the EEG during these periods provided an objective measure of sleep propensity, similar to the MSLT. Computer analysed EEG (specifically, the drowsiness index) provides a fast, automatic and equally sensitive metric of "physiological sleep tendency" (e.g., 6). Both measures were correlated with each subject's task performance and subjective mood states. Furthermore, the high correlations between subjective estimates of drowsiness during the relaxation period and the EEG derived measures provide additional validity for these EEG measures. It should be emphasized that we did not attempt to find direct EEG correlates of cognition during task performance (a common but controversial practice, cf. 8) in this study. Rather we used the robust differences between waking and sleeping EEG to support our contention that performance decline during sleep deprivation is mediated by pervasive chronic fatigue. The consistency of the results are a reflection of this strategy. As well, it appears that autoFFTs are useful both for providing striking visual examples of sleep onset, and also good examples of fatigue without sleep onset. For instance, figure 14 illustrates a result consistent with the findings of Armington and Mitnick (1) that alpha activity decreases in awake subjects during sleep deprivation.

The long term goal of this research is to provide, on an individual basis, estimates of performance degradation from electrophysiological indices. Most of the research in sleep deprivation has emphasized the effects of sleep loss on groups of subjects. Extending these results to individual subjects is equally important. Although rest breaks seem to have a short-lasting positive influence on performance and objective measures of drowsiness during sustained operations, it is expected that interventions tailored to the individual will offer greater potential of relief from chronic fatigue. For example, real-time intervention studies are now being planned in which subjects are given naps at times dictated by their performance and their scores on the drowsiness index. In this way, for each individual, chronic fatigue can be reduced by letting the subject's changing state control the administration of prophylactic or recuperative strategies.

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NEUROPHYSIOLOGICAL PATTERNS OF OPERATIONAL FATIGUE: PRELIMINARY RESULTS

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SUMMARY

Impaired behavior consequent to prolonged mental work is commonly attributed to the effects of fatigue on higher cognitive functions rather than to changes in rote perceptuomotor or motor functions. A deeper understanding of these effects awaits better knowledge of the underlying neurophysiological mechanisms. Here we make a modest contribution toward this end with a study of event-related, spatiotemporal neuroelectric patterns of five U.S. Air Force test pilots performing a high-load visuomotor monitoring task while alert, becoming fatigued, and fully fatigued. The preliminary results suggest that although neural systems responsible for primary visual stimulus processing remain relatively unaffected, cortical associative areas implicated in task-specific response inhibition are affected even during early stages of fatigue. With further research, it may be possible to design on-line devices for predicting "transient cognitive lapses" and performance decrements resulting from operational fatigue.

INTRODUCTION

It is well known that higher cognitive functions are more affected by fatigue due to prolonged, difficult mental work, than are rote perceptuomotor or motor functions. Although psychological theories have attempted to explain these changes, numerous reports of tragic accidents caused by fatigued pilots and operators of other complex equipment clearly demonstrate the need for a better understanding of these phenomena. Here we make a modest contribution toward this end with a study of event-related, spatiotemporal neuroelectric patterns associated visual stimulus processing and response inhibition: five U.S. Air Force test pilots performed a high-load visuomotor memory task while alert, becoming fatigued, and fully fatigued.

The study emerged from the collaboration of researchers from several institutions: (1) The USAF School of Aerospace Medicine, San Antonio (James Miller); (2) Systems Technology Inc., Hawthorne, California (Henry Jex and James Smith); (3) Washington University, St. Louis (John Stern); and (4) The EEG Systems Laboratory. A paradigm was developed that included several cognitive and perceptuomotor tasks requiring varying degrees of attention, working memory, and skill. Thirty-three or 51 scalp EEG, two eye-movement, and several other physiological channels of data were recorded from each of five U.S. Air Force test pilots as they performed the task battery. Preliminary analysis of the event-related covariance (ERC) data suggests that, although neural systems responsible for primary visual stimulus processing remain relatively unaffected, cortical associative areas implicated in task-specific response inhibition are already affected during the incipient stages of fatigue.

METHODS

Requirements

The present experiment took into account certain criteria that must be met in order to isolate the effects of operational fatigue on performance, and so that results will have a modicum of construct and face validity for real-life situations, such as piloting an aircraft. These criteria included: 1) tasks that are taxing in an alert state, yet manageable in a fatigued state; 2) tasks meeting constraints imposed by neurophysiological recordings and analysis, including minimal eye- and head-movements, and isolation of stimulus, response, and cognitive variables [1-4]; 3) experimental paradigms controlled for initial task learning and automatization of performance; and 4) recording sessions that extend from well-practiced, alert performance to fatigued and decremented performance due to extended time-on-task.

Experimental Protocol

The experiment was divided into four recording sessions, conducted over the course of four days. Recordings were 6-8 hours long per session. Pilots learned and performed the task battery during Session 1, until their performance was stable. The alert, well-practiced pilots performed the tasks for about six hours during Session 2. The recording of data for Session 3 ("Fatigue") began in the evening following Session 2 and continued until subjects did not wish to continue, or usable EEG data could no longer be recorded because of excessive eye movements or head nodding and drooping. Session 4 was recorded after a rest day in order to measure practice and automatization effects.

Recordings were made in an acoustically dampened, air-conditioned chamber. Room temperature, lighting, and seating position were adjusted as necessary.

Task Battery

The total task battery consisted of five tasks: (1) Visuomotor Memory Task, null memory condition; (2) Visuomotor Monitoring Task, memory load condition (called VMMT in this paper); (3) Auditory Monitoring Memory (AUM) Task; (4) Sub-critical Tracking; and (5) Critical Tracking [5,6]. Since the analysis reported here will focus exclusively on the difficult VMMT, it will be described in detail. Results for the other tasks will be described elsewhere.

Visuomotor Memory Task (VMMT): The VMMT was designed to allow for precise control of stimulus parameters, motor activity including eye movements, and cognitive processes. This was done by combining a numeric judgment task used previously [7,8] with a memory element based on the "delayed digit cancelling task." Each trial consisted of a warning symbol (disappearance of the letter X from the screen), a single-digit numeric stimulus 1 sec later, a finger-pressure response, and a 2-digit numeric feedback presented 1 sec after completion of the response. Subjects responded on each trial with a flexion of their right index finger, on an isometric finger pressure transducer, with a pressure proportional to the stimulus number presented two trials back. In order to add a recognition element and to avoid overly short response times, a random 20% of the trials were response-inhibition catch trials. On these trials, the current stimulus number matched the 2-back stimulus number and subjects were required to withhold their response.

Stimuli consisted of single-digit numbers (325 msec duration) presented on a Videographics-II amber CRT monitor 70 cm from the subject. Stimuli subtended a visual angle under 1.5 degrees, with an illumination of 0.5 log fL against a background of -1.5 log fL. The 2-digit feedback number indicated the exact force applied with a precision of 0.1 units. The feedback number was underlined if the response was a "win." A "win" response was based on an adaptive error tolerance, computed as the geometric average of the error (distance from the required response pressure) on the previous five trials [7]. This adaptive error tolerance served to equalize subjective task difficulty across the session and to indicate the current performance trend. After each 50-trial block, summary performance statistics were presented to the subject on the video screen. With an inter-trial interval of 1.8 sec, trials averaged about six seconds in length. The time between the presentation of a stimulus number and the response to that number was about 12 seconds. This pace was fast enough to allow well-practiced subjects to maintain the numbers in working memory without overt rehearsal [9].

This paper will focus on the post-stimulus interval of the response-inhibition catch trials.

Physiological and Anatomical Recording Methods

Fifty-one EEG channels, referenced to A2, were recorded for three subjects with a custom nylon mesh cap. Recordings of the first two subjects were made with a reduced 33-channel montage. Vertical and horizontal eye movements were also recorded, as were the responding flexor digitori muscle potentials, A1, EKG and respiration. All signals were amplified by a 64-channel Bioelectric Systems Model AS-64P with .016 to 50 Hz

passband, monitored on three 8-channel and two 16-channel polygraphs, and digitized to 11 bits at 128 Hz.

Before and after a recording session, the position of each electrode was measured using a 3-D digitizer. A general ellipsoid surface was fitted to the set of digitized positions, thus defining the outside shape of the head. For the three subjects with 51-channel recordings, full sets of 3-axis Magnetic Resonance Image (MRI) brain scans were made at 1-cm intervals over the whole volume of the head. After scaling, translation and registration with the EEG electrode positions, the MRIs allowed correlation of electrode positions and major cortical landmarks [10,11].

Reduction of Volume Conduction Blurring of EEGs

An optimal least-squares estimate of the Laplacian operator was applied to compensate for the blurring of brain potentials due to their transmission through the skull and scalp [11,12]. Electrodes at the periphery of the montage were excluded because, without taking into account the exact geometry of the montage, additional peripheral electrodes would have been needed to represent the signals of the original peripheral electrodes adequately. This left 18 remaining non-peripheral electrodes common to all five subjects. It should be noted that although Laplacian-transformed potentials are proportional to current density, the waveforms will be referred to as event-related potentials (ERPs) in keeping with common usage.

Formation of Data Sets

Polygraph records were edited off-line by two independent raters to eliminate trials with evidence of eye movement, muscle or instrumental artifacts. Trials in which response pressures were not unimodal or in which reaction time exceeded 1500 msec were discarded. The first two trials of each block, and no-move catch-trials in which the subject responded, were also eliminated.

In order to form properly controlled data sets for each neurophysiological hypothesis, the total set of artifact-free trials from each subject was submitted to an interactive program that displayed the means, t-tests and histogram distributions of about 50 behavioral and physiological variables [13]. Variables included stimulus parameters, response onset time, finger pressure, velocity, acceleration and duration, response error and adaptive error tolerance. Physiological indices included integrated energy in eye movement and muscle potential channels.

To divide trials into "alertness conditions," that is, "Alert," "Incipient Fatigue" and "Full Fatigue," behavioral variables (including adaptive error tolerance, response error, reaction time, number of time-outs on response trials, and number of responses on catch trials) were graphed across trials for each session. The "Alert" data set consisted of trials from Session 2 with optimal performance as evidenced by: 1) low adaptive error tolerance; 2) zero time-outs on response trials; and 3) zero false responses on response-inhibition catch trials. Trials from early portions of Session 3 with little or no performance decrement formed the "Incipient Fatigue" data set. Trials occurring later in Session 3 formed the "Full Fatigue" data set.

Averaged ERPs

Averaged event-related potentials (ERPs) were time-locked to the stimulus. Effects of fatigue on the amplitude of grand-average (over subjects) ERP components will be summarized here; a more detailed analysis will be presented elsewhere. "Subtraction ERPs" were formed by subtracting Incipient Fatigue from Alert ERPs, and Full Fatigue from Incipient Fatigue ERPs.

Event-Related Covariances (ERCs)

Spatiotemporal neurophysiological patterns were quantified by measuring the event-related covariance (similarity of amplitude-weighted waveshape and between-channel timing) between traces from all combinations of pairs of electrodes [8,14,15,16]. This type of analysis was developed to extract spatiotemporal patterns characterizing the rapidly changing, distributed processing networks of the brain during goal-directed behaviors [7,8,10,11,13-18].

ERCs were measured across brief intervals of bandpass-filtered, five-subject-averaged ERPs for each alertness condition; changes from Alert to Incipient and from Incipient to Full Fatigue conditions were assessed by computing ERCs on the appropriate subtraction ERPs. Intervals were positioned with respect to ERP peaks elicited by the stimulus. Interval width was 187 msec and a "theta-band" filter (4 to 7 Hz) was used. ERCs between each of the 153 combinations of 18 non-peripheral Laplacian channels were computed.

ERC features were the maximum absolute value of the timeseries crosscovariance function formed when the covariance function was computed to 8 lags (+/-62 msec) for the theta-band intervals. The delay specified for each covarying electrode pair is the lag time of the maximum absolute value of the crosscovariance function. The significance of the ERC magnitude was determined by reference to the standard deviation of an ERC "noise" distribution obtained from the set of alert trials. Multiple comparisons were accounted for using a Duncan procedure. For clarity, the top third of all significant ERCs in each interval were then graphed on 3-D perspective models of

the head, or on sagittal or horizontal views of the MRI scans.

RESULTS

Behavioral

In the original data sets, performance declined significantly over the three conditions (F=12.5, df=2,12, p<.001). Scheffe post-hoc tests revealed that performance did not decline significantly from the Alert (1.17 unit departure from target number) to the Incipient (1.51), but did decline significantly from Incipient to Full Fatigue (2.08) (F=12.28, df=2,12, p< 0.001). The number of false responses during no-response catch trials, as well as the number of time-outs on response trials, were also compared across alertness conditions. A significant effect was revealed for the number of false responses (F=17.5, df=2,12, p<0.0002). Scheffe post-hoc tests revealed that the number of false responses increased between Alert and Full Fatigue conditions (F=15.96, df=2,12, p<0.0004), and between Incipient Fatigue and Full Fatigue conditions (F=9.42, df=2,12, p<0.003). Although the number of time-outs tended to increase with increasing fatigue for all subjects, the effect was not significant. In order to test for effects of fatigue, unconfounded by these trends of declining performance, we selected trials with optimal performance from each condition to form the final data sets (see above).

Neurophysiological

There were too few trials in the no-response trial set to see the N1 peak against the noise. In the response trial set, the N125 grand-average ERP peak was highly localized to the midline parietal site due to the Laplacian transformation. Its amplitude declined slightly (.18 to .17 -uV/cm2) from the Alert to Incipient Fatigue conditions, and then increased slightly in the Full Fatigue condition (.19 -uV/cm2). The P380 was observed in five channels in the no-response trial set (bilateral and midline anterior central, midline frontal and central sites). Its amplitude significantly decreased across alertness conditions (F=7.3, df=2,12, p<.01). Scheffe post-hoc tests revealed that the amplitude of P380 was significantly smaller in the Full Fatigue average than in the Alert average (F=7.3, df=2,12, p<.01). The decrease in P380 amplitude from the Alert to the Incipient Fatigue condition did not reach statistical significance (Figure 1).

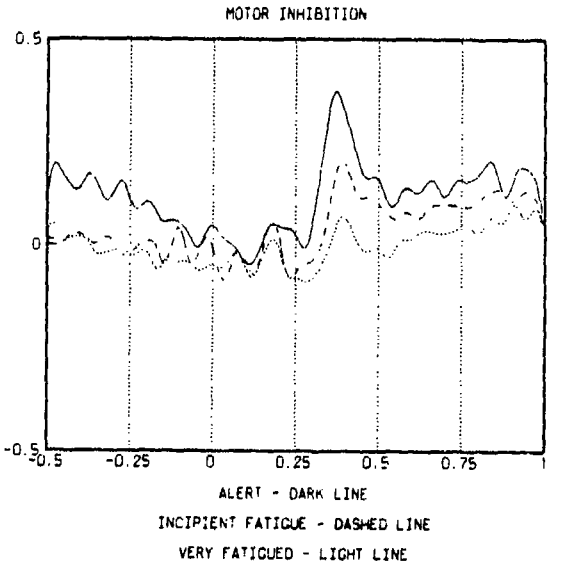

Figure 1. Stimulus-locked, 5-subject Laplacian Derivation waveforms from the midline anterior central (aCz) electrode site for the Alert (dark line), Incipient Fatigue (dashed line) and Full Fatigue (light line) conditions. The amplitude of the P380 declined significantly from Alert to Full Fatigue. Exiting current up.

For the interval spanning the stimulus-locked N125 peak, none of the ERCs that were computed from the Alert-minus-Incipient-Fatigue subtraction ERPs were significant for either the response or no-response trial sets. There also were no significant ERCs from the Incipient-minus-Full-Fatigue subtraction ERPs in the no-response trial set. For the response trial set, there was only one significant ERC, between the left and right posterior parietal sites.

Paralleling the decrease in amplitude of the P380 peak in the no-response trial set, the change between alertness conditions was indicated by the pattern of significant ERCs from the Alert-minus-Incipient-Fatigue subtraction ERPs. Significant ERCs were observed between the midline anterior central, right anterior parietal and right posterior parietal sites (not shown). No significant ERCs were found for Incipient-minus-Full-Fatigue catch-trial ERPs (not shown). The ERC pattern of the Alert condition involved extensive bilateral and midline sites (Figure 2, left), the Incipient Fatigue pattern involved bilateral and midline anterior central and midline central sites (Figure 2, right), and in the Full Fatigue condition, there was a single ERC between the midline anterior central and midline central electrodes (not shown).

Figure 2. View of the top third of significant between-channel stimulus-evoked event-related covariance (ERC) patterns spanning the P380 (281-468 msec) for the Alert (left) and Incipient Fatigue (right) conditions. The width of a line indicates the significance of the covariance between two electrodes; the color of the line indicates the time delay (lag time of maximum covariance). Arrows points away from the leading channel towards the lagging channel. The color scale at the left, representing wave amplitude, covers the range from minimal to maximal values of the two maps.

ERCs in the Alert no-response trials in the interval centered 380 msec post-stimulus involved the midline frontal, bilateral and midline anterior central, left and midline central, bilateral anterior parietal, bilateral and midline parietal, and bilateral posterior parietal electrodes. ERCs in the Incipient Fatigue condition only involved the bilateral and midline anterior central and midline central electrodes.

DISCUSSION

We have reported preliminary results of a study that used state-of-the-art technology to document neurophysiological activity associated with different aspects of perceptuomotor and cognitive function in five U.S. Air Force test pilots during three stages of alertness: Alert, Incipient Fatigue and Full Fatigue. Over one billion bytes of data were collected. We have summarized the results high-load visuomotor memory task (VMMT) for the different alertness conditions, and have discussed the results of event-related covariance (ERC) analysis of event-related potentials (ERPs) obtained by subtracting the grand-average 3-subject ERPs from the different alertness states for the stimulus-registered event. A detailed report of these data will be made elsewhere, as well as analyses of the pre-stimulus-, response- and feedback-registered events of the VMMT, relatively accurate and inaccurate performance trials, Follow-Up Rested Session, and the Auditory Monitoring and Critical and Subcritical Tracking Tasks.

These first results are quite exciting in suggesting how fatigue may selectively affect areas of the brain implicated in higher cognitive functions. The N125 ERP peak and corresponding ERC pattern during the first 200 msec of the visual stimulus

processing were relatively unaffected. By contrast, the later response-inhibition ERC patterns, from about 280 to 470 msec post-stimulus (and to some extent the P380 peak amplitude), clearly showed neurophysiological changes consequent to incipient fatigue. Consistent with results of a previous study in our laboratory of visuomotor performance [16], the midline anterior central focus of the P380 catch-trial ERC patterns may reflect changes in neural systems responsible for motor inhibition. This electrode overlies supplementary motor and premotor cortices involved in the highest level of control of voluntary movements [19,20].

The highly specific temporal (ERP peaks) and spatial (ERC patterns) changes associated with time-on-task suggest that the patterns are due to localized changes in areas of association cortex, and not to anatomically diffuse changes associated with decreased overall arousal. We are currently conducting an analysis in which the data sets are balanced between Alert, Incipient and Full Fatigue conditions for level of accuracy; by partialing out the accuracy effect, we will be able to confirm that the ERP changes and ERC patterns are due to prolonged time-on-task and not to variability in performance accuracy over the many hours of task performance.

We must also emphasize that while the ERC patterns reported here suggest fatigue-related degradation of functional coordination between immediately underlying cortical regions, the actual neural sources of the ERC patterns are, in fact, not yet known. Determining the distributed source network suggested by the scalp ERC patterns is the major focus of our current technical efforts.

The present results, analyses of the remaining data, and source localization studies will all elucidate the differential effects of incipient fatigue on areas of the brain implicated in higher cognitive functions. When these analyses are completed, it may be possible to specify studies leading to the design of on-line devices for predicting "transient cognitive lapses" and performance decrements resulting from operational fatigue.

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DISCUSSION

ABRAHAM, UK: Can you tell me what method you used to establish the baseline for your CNVs? If I understood you correctly, there were a series of events going on one after the other. Is that correct?

GEVINS, US: Each trial took about 6 seconds and there was an intertrial interval. The CNV measure that we used was the integrated energy of the CNV, and the comparisons were between conditions. That is, the area under the curve was compared between conditions. The CNV measurement was not referred to a baseline as such.

ABRAHAM, UK: Over what time interval was the integrated area determined?

GEVINS, US: The window width of the covariance was used for this purpose, which involved the last 400 ms before the stimulus was delivered.

ABRAHAM, UK: This is important, because it seems to me that the trials showed considerable post-imperative negativity, which might have been carried over into your baseline.

GEVINS, US: Yes, there is a continuous shift throughout the trial, and it's probably one of the more interesting phenomena that occurs. I think that the slow potentials which Dr. McCallum showed are very important for looking at changes in state and performance. I think the time is opportune to focus attention again on these types of potentials, as they seem to have been somewhat ignored over the past fifteen years or so.

McCALLUM, UK: These slow potentials indicate what is at the focus of consciousness. If you overlearn skills and they become automated, then a different system is involved and you do not see slow potential changes. Dr. Gevins, you show very nicely in your incipient fatigue condition, how the focal conscious conditions are disappearing. You can continue performing the same tasks at the same level and performance lasts, but you are clearly in a different central state. You must be careful, however, because this focal state is not lost only through fatigue, and you will see the drop in CNV or slow potential at other times. You only have to divert your attention elsewhere from the task; e.g., what you will be having for supper, to see that these slow potential changes will drop. So before you use them operationally, you must be sure of what is causing these slow potentials to drop.

KRAMER, US: I have an observation on the recognition running memory task that you used. That's the task in which you attempt to match the number that has come up on the screen with a finger force response that is proportional to the number that appeared two trials back. An additional complexity was that, in 20% of the trials, subjects withheld their response if the number appearing on the screen matched the one two trials previously. I can see at least three reasons why subjects could make errors in conducting these trials. One reason could be that they did not, in fact, maintain the items in memory; so it may be a memory loading problem. Another reason could be that they might have forgotten the mapping between stimulus and response; i.e., the proportional push on the button. The third reason could be that they did not execute the response correctly; i.e., they didn't push the correct amount of force although their original intention was correct. I think in this particular task, it's fairly difficult to figure out why errors occurred when they did; and, therefore, how to go about localizing the effects of errors.

GEVINS, US: Those are good points. What I presented was only the results pertaining to the constant level of performance. I didn't describe the results from the really bad performances. I selected trials from alert, and incipient and full fatigue subjects that did not differ in performance accuracy. The results that I presented were not influenced by the level of performance. There are other aspects of the tasks that affect the quality of performance which I will publish separately. I will say that the stimuli were organized so the numbers on successive trials always differed by more than 3, and, for trained subjects, the error of response was always less than 10 units. So there may be sets of trials in which there is a reasonably strong inference that the sets of errors are due to errors of memory rather than errors of response execution. One could also see that as time progressed, and the pilots became fatigued, the number of response inhibitions went down. That clearly reflected a degradation in ability to maintain the image of two numbers in their minds; in other words, memory was clearly degrading. The number of times that they didn't respond when they should have responded also went down.

GAILLARD, NE: I have some difficulty in interpreting your results. If you want to dichotomize, you should indicate somehow that memory processes are affected, but not automatic processing. In your preparatory interval, you are confounding the preparation for the next motor response and the activities of the memory which are contingent on the stimulus that had just been delivered. Problems will arise when you compare match/mismatch, same/difference, or target/non-target features; e.g., a P300 may be a misdiagnosed motor-related positivity. Would you have the same type of results; e.g., when no motor response is involved but the same memory processing is involved? For example, you could ask the subject just to count the stimulus or not to give a fast response, but to give a relaxed delayed response. The data show that these measures are sensitive to sleep deprivation and fatigue, but it is also possible that the intervening variable represents the effort which the subject puts into the task.

GEVINS, US: I used these terms to describe what is happening during the pre-stimulus period, which includes preparation, maintenance of working memory, and attention. Likewise, the terms that are used for motor inhibition can be called reaction to novelty, motor inhibition, and maintenance and updating of the memory. So that relates to the terms that I used. Another point is that neither the stimulus-related processing nor the motor responses changed as a function of incipient fatigue. What did change, however, were those intervals in those brain components that are associated with higher-order cognitive processes. The important thing is that this was a very difficult task, requiring a tremendous amount of concentration and maintenance of the working memory, and that the processes were interfered with during the early stages of fatigue well before they showed up in behaviour. Another point is that when we subtracted the preparation response from the inhibition response, what remained was a left frontal-right parietal pattern. We had the same pattern when we subtracted the feedback response from the preparation response. From that, I infer that this pattern relates to attention and maintenance of the working memory as opposed to the

preparation and motor-inhibition of the response and the response updating.

LANDOLT, CA: My question relates to the operational use of the small biocybernetic unit that you want to place on the back of the pilot's head. How do you see it working -- as some sort of a jury-selection system that makes a decision on the basis of a variety of maladaptive responses to signals that it picks up? Secondly, given the premise that pilots are highly individualistic and that they are "macho" types, how do you forsee them putting up with that kind of unit on the back of their heads? Do you not think that they will try to defeat its intended purpose; in particular, if the function of the unit is to take over command of the aircraft under certain flight conditions?

GEVINS, US: I think the unit would be useful in training, but I would not like to see it in the cockpit. I can see its use in a simulator where the pilot would be "punished" if he loses his attention. It would make simulation and training more demanding; e.g., it would allow the training of an aspect of attention that is very often neglected; viz., the immediate return to a threat when the mind has been "wandering". But putting it into a cockpit and taking control away from the pilot; well, that's a different matter. It's the difference between playing a game and fighting a battle; it relates to the degree of accuracy required, and how foolproof the system should be. I can't see these measures going into the biocybernetic control of the aircraft; that's another level of development. If it were to work well in a simulation, then the proposal could be made to take it to the next level, but that's quite a ways away.

LANDOLT, CA: What does the unit measure?

GEVINS, US: It measures complex patterns of brain electrical and, hopefully, magnetic activity. It will respond to very complex patterns of the interactions of these measurements, that vary exclusively within a fraction of a second to changes in intentional deployment.

DUSHENKO, US: This is just a brief comment for Dr. Landolt. We're approaching the problems that Dr. Gevins spoke of from a somewhat different perspective, as we are looking at the neurophysiological background state. We found that once the pilots were confident that we were not about to ground them as a result of the measurements, and that we had no intention of letting the device take over command of the aircraft, then they were very cooperative, even to the extent of letting us put the rather-invasive device on their heads.

PIGEAU, CA: I would like to make a comment about your data where you showed the slope of the error rate as increasing. The point is that these slopes in error rate were increasing at around the same time that the curve of the circadian rhythm was decreasing. If the experiment had started 6 hours earlier, then that slope might have been lesser because it would have happened before the circadian curve started its descent. We have noticed from work in our laboratory that fatigue is a function both of time on task and the circadian cycle.

FIGHTER PILOT PERFORMANCE DURING AIRBORNE AND SIMULATOR MISSIONS: PHYSIOLOGICAL COMPARISONS

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SUMMARY

The growing importance of simulators for training, research, and certification focuses attention on how little we know about whether the behavioral outcomes obtained in a simulator really represent the operational situation. The research reported in this paper addresses this issue, and proposes the use of physiological measures to examine the correspondence between pilot responses during actual missions and comparable simulated missions.

Physiological measures of electrical brain activity, heart rate, and eye movements were taken while pilots flew tactical training missions in both the A-7 aircraft and simulator. These measures did discriminate between: (a) flight position (wing vs. lead), (b) actual and simulated flight, (c) type of mission event (e.g., takeoff, maneuvers, weapons delivery, etc.), and (d) individual pilots.

INTRODUCTION

The Human Engineering Division of the Armstrong Aerospace Medical Research Laboratory (AAMRL) has been conducting real-time design simulations in support of the Strategic Air Command since 1969. Our data have been collected in high fidelity simulators using line crewmembers. We have always been proud of the measurement precision we have been able to achieve in these environments. However, until recently we have not had technology available to measure a crewmember's physiological responses in an airborne environment that preserved safety of flight and that permitted unobtrusive reliable recording. This technology is now available and AAMRL has initiated a unique research program designed to establish systematic methods to identify and quantify differences in behavioral and physiological performance between simulator and aircraft environments.

We believe our objective is an important one in view of the increasing use of simulators for: training; engineering research; and licensing and certification. Knowledge of HOW and WHERE simulator fidelity affects crew performance is necessary before these simulator applications can be efficient and cost-effective. Hennessy and Deutsch (1) have stated that a primary reason for lack of knowledge in this area is the traditional belief that physical correspondence to the aircraft is the principal requirement for simulators, regardless of their intended applications. What is missing in the traditional approach, is understanding the behavioral requirements that are necessary to produce the same behavioral outcomes in a simulator as occur in the operational situation.

A consequence of over-reliance on physical fidelity without a concomitant attendance to behavioral requirements, is data credibility. Since we do not know with any certainty how well obtained behavioral outcomes in a simulator represent the operational situation, we are also unable to objectively refute such comments as: "He wouldn't fly that way in the real aircraft!" Thus, performance data obtained during simulator missions will have limited credibility until we are able to answer fundamental questions of: WHERE during simulated and actual missions is there most likely to be behavioral correspondence (or divergence) to the flying tasks? WHAT are the mission factors that contribute to either similarities or differences in the crewmember's response? HOW much of a difference is a meaningful difference when there is a lack of behavioral correspondence between simulated and actual mission events? However, a basic obstacle to answering these questions is that before we can determine behavioral correspondence, we must first be able to measure performance on a near real-time basis. At present this capability is limited, especially in operational situations. Our approach to this problem is to measure performance in terms of the crewmembers' physiological responses to the workload imposed during both airborne and simulator missions. In this way, we will be able to measure the physiological correspondence between actual and simulated missions on a near real-time basis.

The use of physiological techniques have several advantages over traditional behavioral and subjective measures taken during flight. For example, physiological measures are nonintrusive and continuous and do not require the introduction of artificial stimuli into the cockpit. Researchers (2), (3), (4) have shown that these techniques can be used successfully in operational environments. Their data show that during high fidelity simulated wartime missions, changes in workload variability across a mission are reflected in measures of electrical brain activity, eye movements, and heart rate activity. These changes can be directly related to crewmember flight responsibility, cumulative fatigue, and cognitive demands associated with different types of mission events, (e.g., weapons delivery, threat evasion, terrain avoidance, and takeoff/landing). Further, since these measures are recorded continuously, any unforeseen situation arising during flight can be evaluated in terms of the subsequent physiological changes of the crewmember. Thus, we believe that physiological measures can provide important information about: (a) how well the physiological performance outcomes in the simulator represent the operational situation; (b) the degree of physiological correspondence between simulated and actual mission events; (c) individual differences in response to the same mission events; and (d) what behavioral requirements will be necessary to improve the efficiency and cost-effectiveness of simulators.

METHODOLOGY

For our first study we chose to work with single seat fighter aircraft investigating a typical training mission. The choice of the tactical environment has the advantage of reducing the experimental complexity as compared to the strategic environment. For example, the tactical mission is shorter (1 1/2 hours compared to a minimum 5 1/2 hour strategic mission), one pilot versus multi-crew positions, and last but not least, a simulator training mission comparable to the actual training mission.

Experimental Design

We used a complete within subject design in order to make comparisons across actual and simulated missions. In addition to the aircraft and simulator comparisons, we were interested in how flight responsibility might affect the pilot's physiological responses. For this comparison, all pilots flew the same mission twice in the aircraft: once in the formation lead position and once in the wing position. We hypothesized that since the flight leader is responsible for success of the entire mission, his workload should be greater than the wing position. For example, the leader's responsibilities include: (a) mission planning and conducting mission brief and debrief; (b) navigation and tactics; and (c) establishing all altitude and route changes to insure the mission progress. With these differences in flight responsibility, we would expect changes in cognitive load to be reflected in the pilot's physiological responses.

And finally, we wanted to identify significant mission areas where there was physiological correspondence (or divergence) between the actual missions and the simulated one. We planned to examine how the pilot's physiological profile during the simulated mission related to his lead and wing flights in the aircraft. In this way we hoped to ascertain WHERE physiological profiles corresponded, and HOW differences were manifested when there was lack of correspondence. Thus, in addition to the two actual missions, all pilots flew a simulated mission of comparable length and complexity.

Measurement Techniques

Our physiological measurement techniques were selected from the AAMRL Neurophysiological Test Battery (NWTB). We chose to measure changes in heart rate activity (ECG), electrical brain activity (EEG), and eye movements (EOG). These measures were chosen on the basis of reliability, unobtrusiveness, and pilot comfort during our equipment test flights. The following is a brief description of each measure.

Eye Movements (EOG). This procedure is relatively easy to implement and eye movement parameters of blink frequency and duration are sensitive to individual differences in attentional demands and fatigue effects (5). The eye movement signal is relatively insensitive to operational "noise" produced by electrical equipment and G stress.

Heart Rate (ECG). This technique is useful for measuring workload variability across different mission segments. The technique is also sensitive to changes in task difficulty, thus making it useful for looking at both general and specific workload effects. The procedure is relatively easy to implement.

Electrical Brain Activity (EEG). These techniques are useful for measuring overall fatigue effects and changes in attentional states. This signal is sensitive to the stress of high G environments.

Data Recording Equipment

A compact ambulatory physiological tape recorder, Del Mar Avionics Model 5509 recording system, was used to collect data and time markers accurate to a second. The recording system was worn in the left leg pocket of the pilot's G suit and allowed complete freedom of movement. The unit measures 6.6 inches wide by 3.75 inches in depth by 1.75 inches in height with a weight of 1 lb. - 14 oz. The system is capable of 24-hour continuous recording of eight channels of physiological data along with an event marker channel. It is important to note that with this recording system, the physiological signals are recorded as analog signals rather than digitized during recording.

Recording Procedures

ECG, EOG, and EEG were recorded from eight Air National Guard A-7 pilots. To enhance conductance, skin and scalp areas were mildly abraded with an alcohol soaked gauze pad. The EEG was recorded from electrodes positioned over the midline parietal area and referenced to the right mastoid. Silver-silver chloride electrodes manufactured by Del Mar Avionics were held in place with collodion and filled with conductive electrode gel. Impedance was kept below 5k ohms. The EOG was recorded from two electrodes positioned above and below the right eye. Position was determined by the fit of each individual pilot's helmet and oxygen mask. The ECG was recorded from two chest leads with the negative electrode positioned at the manubrium and the positive electrode positioned at the fifth rib at the anterior axillary line. A common ground electrode was positioned on the right side approximately at the level of the seventh rib. The EOG, ECG, and ground electrodes were 3M Infant Red Dot disposable silver-silver chloride.

For each channel of data, 20 minutes of standard calibration signals generated by Del Mar equipment were recorded prior to subject hook-up. After the subject cable was connected to the recorder, all signals were visually checked on a battery operated oscilloscope before cables and amplifiers were secured inside the pilot's flight suit.

After pilots were suited and the recording unit placed in the leg pocket of the G-suit, a SONY model M-205 micro-cassette recorder, used to record pilot voice communication inside the cockpit, was calibrated in 15 second increments to insure that any tape distortions would not affect accurate time synchronization. It was necessary to have audio recorders on board the aircraft so that we could obtain pilot narrative and time hacks associated with each mission event. These time designations were used later during data reduction to locate the mission events on the physiological data tapes.

The physiological recorder clock was synchronized prior to mission briefing, and once again after the briefing when all pilots synchronized their watches to the mission time. After time synchronization, pilots were taken to the aircraft where they prepared for launch. Once inside the cockpit, the audio recorders were positioned and secured to the pilot's knee pad and both recording units were tested prior to takeoff. The audio recorders were connected to the aircraft communication system.

Mission Scenario

The aircraft flown in this study were A-7D's, single seat fighter attack aircraft. The aircraft is equipped with cannons and missiles for air-to-air combat, with cannons and gravity weapons for air-to-ground. The aircraft is known for its very accurate attack system.

The mission we selected for the study was a battle area interdiction (BAI) mission profile. The BAI mission is a tactical Air Force mission which is designed to take aircraft deep into enemy territory, far behind the forward edge of the battle area (FEBA), to divert, disrupt, and destroy enemy targets. This kind of mission does not require extensive coordination with friendly forces, due to it's characteristics of being unescorted and independent in its operations. The BAI mission requires the pilot to fly fast for extended periods of time at low altitude. Navigation and weapons delivery require the flight to maneuver and employ countermeasures. Thus, for experimental purposes, this mission profile is desirable for it provides diversity of flying tasks within a structured training mission where the precise timing and location of mission events are known.

The selection of specific mission events for in-depth analysis was based on experimental procedures "tailored" to a mission effectiveness criteria (see Skelly and Purvis, (2) for methodology). The basic idea is to sample mission segments to minimize sampling periods without sacrificing information. This means selecting mission events that are critical to mission success based on the particular mission objectives (in this case, BAI objectives) and sampling these events across the mission in a manner that will provide adequate representation of mission routing complexity. Our mission was 90 minutes in length and is depicted in Figure 1. The route shows the mission events that were of primary interest. The following is a brief description of each mission event.

1. Formation Takeoff. A four ship formation takeoff from main operating base (MOB).

2. Low Altitude Awareness Training Area. The area depicted on the map as the military operating area (MOA). Pilots practice low level terrain avoidance/following in this area.

3. Flyover Update. Shown in Figure 1. at point C. This navigational update is the first in-flight baseline. This is used as a baseline sampling segment since all pilots are accomplishing the same sequence of flying tasks at this point.

4. Gun Jink Maneuver. This is where the aircraft maneuvers both vertically and horizontally to negate guns tracking. The maneuver is performed between points C and D.

5. Flyover Update. At point E on the map, this is the second in-flight baseline.

6. Slice Maneuver. This maneuver is a 360 degree level turn and is a high G relatively long duration maneuver performed between points E and F.

7. "9" left/"9" right maneuver. This maneuver is high G, short duration, turns of 90 degrees performed between points F and G.

8. Pre-IP Flyover Update. This is the third in-flight baseline at point G.

9. Flyover Update. This is the fourth and final in-flight baseline at point H performed before the initiation point (IP) of the bombing range.

10. IP Inbound. Pilots are entering the bombing range and workload is intense.

11. First Run Attack. At 2,000 ft (AGL) the first weapon delivery is accomplished with a 20 degree "pop-up." There is a formation separation into two ship elements. The bombing range is designated on the map.

12. Rejoin. The four ships then move out in a rectangular formation for second weapon delivery.

13. Weapons Delivery three and four are released at 800 ft (AGL).

14. Level Bomb Delivery. For weapons delivery five and six there is a 200-300 ft (AGL) release. This particular run is practice for poor visibility deliveries.

15. Switch Pattern Direction. This is mutual support strafing north to south.

16. Climb Out The four ships rejoin, accomplish bomb check, climb to cruising altitude back to MOB. This is shown on the map by the dotted line.

17. Formation Landing. During the final approach, workload is highest during gear down and final approach fix call.

These mission events were chosen to provide information about: (a) workload variability across different types of mission events, e.g., maneuvers vs. in-flight baselines; (b) cognitive and/or physical demands associated with levels of difficulty during bomb runs and maneuvers; and (c) comparability of cognitive demands during mission events between simulated and actual missions.

Data Sampling and Collection

Physiological measures were collected continuously throughout the 90 minute missions, but in order to create a manageable data base for analysis without sacrificing information, these measures were selectively sampled in the following manner: (a) Mission briefing prior to the flights was used as our pre-flight baseline data. We sampled this period for two minutes at the end of 30 minutes of briefing to permit acclimation to the recording equipment and the briefing environment. (b) Takeoff was sampled twice; two minutes continuously immediately prior to takeoff and two minutes during takeoff. (c) We sampled during low level awareness training after five minutes in the MOA, for a continuous period of two minutes. (d) Our in-flight baselines were sampled for one minute. (e) Maneuvers were sampled for one minute also. (f) The bomb runs over the range were sampled continuously for 15 minutes since it was impossible to separate the discrete bombing activities. (g) During the high altitude cruise leg of mission, samples were taken 10 minutes after achieving altitude for a period of two minutes. (h) And finally, the landing segment was sampled beginning one minute prior to touch down continuously until one minute after touch down. It should be noted that we recorded data from all pilots continuously for each 90 minute mission and selective sampling was done to achieve manageable data bases. There is always the available option to increase sampling sites and review data from unforeseen events during any part of the data analysis process.

Data Reduction Procedures

After the physiological data were collected, there was extensive preparation of the data prior to the data reduction and analysis procedures. The audio tape from each first mission was transcribed verbatim, then the elapsed time between each time hack given by the pilot was documented and converted into real time intervals. Finally, the time intervals were corrected for differences between the physiological recorders and the audio recorders.

The data reduction phase was also labor intensive due to the very nature of collecting these measures in operational environments. First the raw data were passed through the Del Mar playback unit to normalize the compressed analog signals. The signals were then passed through adjustable bandpass filters to permit elimination of artifacts associated with DC shifting and extraneous noise. The EEG was filtered from .1hz to 60hz to obtain comprehensive information associated with pertinent bandwidths. The ECG filter settings were 4hz to 50hz to permit measuring the R to R interval in the QRS waveform without unduly distorting the R wave. This setting eliminated high frequency noise and low frequency DC shifting. There was no additional filtering of the EOG signal over the Del Mar preset filtering of duration data.

After filtering, the data were digitized and analyzed according to the appropriate test parameters on AAMRL's Neurophysiological Test Battery (NWTB). These analyses provided descriptive statistics. Additional inferential data analyses were accomplished using the analysis of variance (ANOVA) procedures.

Data collection for this first study was over a six month period. In order to obtain data from two airborne flights for each of our eight pilot subjects, twenty-six actual missions were flown. Ten missions were aborted due to weather, aircraft equipment failures and late takeoffs. An additional eight missions were cancelled due to pilot scheduling problems. During the missions there were also instances where specific mission events were eliminated due to weather conditions, loss of audio communication, and range conditions. Thus, four of our pilots have missing data in at least one mission event per flight.

Simulated Mission

The simulator used in this study was an A-7 high fidelity Weapons Systems Trainer (WST) equipped with: (a) 135 degree night visual system, (the system could accommodate limited peripheral field of view, e.g., from 10 o'clock to 2 o'clock positions, but not 9 o'clock or 3 o'clock), (b) six degree of motion, (c) full emulation of cockpit instrumentation, (d) Heads Up Display (HUD), and (e) radar.

The pilots were instrumented with recording units at their fighter base approximately two hours prior to the simulator flight. They were then transported 45 miles to the simulator facility for a scheduled two hour simulator period.

Prior to entering the cockpit, pilots were outfitted with their standard flight gear, e.g., helmets with oxygen masks, parachute harness, G suit, flight gloves, and flight suit. All pilots were briefed on the mission and objectives, as well as the performance objectives of each phase of the mission. They were provided with a mission map and data card containing navigation destination data. Formal task direction was conducted by the experimenter at the simulator console.

The experimenter console contained the full complement of repeater cockpit instrumentation. Positioning of the simulator was controlled at the console by simulator support personnel. These personnel were always present to correct or analyze any abnormalities, answer experimenter questions, etc. A 25 inch CRT provided the experimenter with a repeater display of the pilot's visual scene out the front, through the HUD. Thus, the experimenter was able to monitor pilot performance in both switchology and flight performance.

The mission began with the pilot at the end of the runway preparing for takeoff. When the experimenter verbally cleared the pilot for takeoff, the engine was brought to full power and brakes were released. The pilots were directed throughout the mission by the experimenter to perform specific mission events, e.g., maneuvers at mission times comparable to their actual flights. Table 1 shows the time line comparison of mission flight times between the simulated and actual mission. The time line is shown in a cumulative manner with all events shown as time from start point.

TABLE 1. TIME LINE COMPARISON OF ACTUAL AND SIMULATED MISSIONS

Mission Segment	Aircraft	Simulator
Takeoff	0+00	0+00
Flyover Update	0+15-20 min.	0+15 min.
Slice Maneuver	0+27-34 min.	0+18-22 min.
9 left/9 right	0+32-34 min.	0+28-33 min.
Pre-IP Update	0+34-36 min.	0+31-36 min.
IP Flyover Update	0+38-47 min.	0+36-40 min.
Action Point	0+48 min.	0+40-48 min.
Pop-Up Attacks	0+49 min - 1 hr. 10 min.	0+41 min. - 1 hr. 25 min.
Approach Landing	1 hr. + 15 min.	1 hr. + 28 min.
Landing	1 hr. + 17-20 min.	1 hr. + 30 min.

After landing the pilot exited the cockpit and the physiological instrumentation was removed. All simulator missions were flown successfully according to the scheduled plan. It should be noted that because of the available visual system in the simulator, missions were flown in twilight conditions while actual flights occurred during daylight hours.

Performance Scoring

Each simulated mission event was scored against a specific set of performance criteria. An abbreviated list of these performance measures is shown in Table 2.

TABLE 2. SIMULATED MISSION PERFORMANCE MEASURES

EVENT	MEASURES
Takeoff	Airspeed/Climb Mach
Climb, Cruise	Airspeed, Altitude, & Heading
Descent	Correct Identification & Use AI symbol ECM Pod
Fence Checks	Accomplishment of Checks
Low Level Navigation	Maintenance of Appropriate Altitude
Position Updates	Switchology - Designation/Entry
Threat Countermeasures	Proper Identification ECM Pod Management Maneuvering Use of Chaff & Flares Control - Altitude/Airspeed Visual Acquisition (Missile)
Target Attack	Pop-up Point Identification Pop-up Parameters Altitude, Airspeed, & Climb Angle Target ID Weapons Release Accuracy
Target Egress/Reattack	Reattack Maneuvering Target ID Weapons Release Accuracy
Landing-Instrument Approach	Altitude, Airspeed, & Localizer Glideslope & Course

These data were then combined and used to rate pilots on a scale of 1-5 where 1 is poor performance and 5 is excellent. Pilot ratings were made in four categories of overall mission effectiveness: first pass effectiveness, consistent low level flying, low level maneuvering ability, and overall situation awareness.

First pass effectiveness refers to the pilot's ability to put bombs on target. A score of 5 indicates the pilot received no assistance from the experimenter and all bombs were on target; a score of 4 indicates there was a slight hesitation during the pop-up suggesting some planning error; a score of 3 indicates more hesitation, with searching for the target at the top of the pop-up maneuver, and not following the navigation equipment; a score of 2 indicates indecisiveness by an initial turn to the left, followed by a weak

execution; a score of 1 indicates a lack of planning, turning during pop-up, disregard for the bearing pointer, and finally, experimenter input required to complete the bomb run. The second category, consistent low level flying, was evaluated according to an altitude criterion of 100-300 ft. AGL during terrain avoidance/following portions of the mission. A score of 5 was flight at 50-150 ft. AGL; a score of 4 was 150-250 ft. AGL; a score of 3 was 250-350 ft. AGL; a score of 2 was 350-450 ft. AGL; and a score of 1 indicated altitude above 450 ft. AGL. The third category was also scored on low level flying ability, however, this category relates to the pilot's ability to stay low during defensive actions, maintain orientation control, and accomplish all maneuvers at 300 ft. A score of 5 in this category is maneuvering at 300 ft. AGL or below (the exception is pitch back because this is a climbing maneuver); a score of 4 is 300-500 ft.; a score of 3 is 500-700 ft.; a score of 2 is 700-900 ft.; and a score of 1 is altitude above 900 ft. AGL. The final category refers to the pilot's general situation awareness including: navigation, after maneuver recovery and return to low level altitude of 100-300 ft., cockpit switchology, and in-flight checks. A score of 5 indicates consistent situational awareness, that is, no apparent lapses in attention (e.g., slowing of airspeed, altitude rise, turning in the wrong direction, etc.) and aggressive return to low level after maneuvering; a score of 4 indicates a rare lapse of attention and a less than maximum recovery performance during return to low level; a score of 3 indicates multiple lapses of attention as shown by airspeed, altitude, turning, etc.; a score of 2 indicates the pilot experiencing frequent lapses in attention; and a score of 1 indicates complete loss of orientation and/or a crash.

RESULTS

Simulator Performance

During the simulator missions, two of the eight pilots crashed and one pilot had a near crash incident during a pop-up maneuver. Pilot overall mission effectiveness ratings appear in Table 3.

TABLE 3. SIMULATOR MISSION EFFECTIVENESS RATINGS

Pilot #	First Pass	Low Level Maint.	L L Maneuver	Sit. Awr.
1 (H-H)	5	4	4	4
2 (H-H)	4	2	1	3
3 (H-M)	2	2	4	3
4 (H-H)	2	5	4	4
5 (H-H)	4	4	3	4
6 (M-H)	2	4	3	3
7 (H-H)	4	4	2	4
8 (L-L)	4	5	5	5

Overall simulator performance showed that in the simulator, pilots had the most difficulty maintaining consistent low level flying and accomplishing effective first pass weapons delivery. Pilots scoring below average in this category exhibited weak execution, indecisiveness, and initially turning the wrong direction resulting in prompting from the experimenter. Poor performance in this category may be due to the limits of the visual system, and pilots using a backup heading reference due to an inoperative moving map display.

The designation beside the pilot number shows their relative experience level, a combination of total aircraft hours and hours flown in fighter aircraft. The first letter indicates level of experience according to the total number of aircraft hours where High is 1500 hours or more, Medium is 500-1500 hours, and Low is less than 500 hours. The second letter indicates the number of hours flown in fighter aircraft, where High is 1000 hours or more, Medium is 500-1000, and Low is less than 500 hours. In general, the mission effectiveness ratings reflect overall flying experience. The exception was pilot #8, with relatively low flying experience. This pilot was the only one out of the eight pilot subjects to have completed an intensive special Air Force training program in low level flying.

Physiological Measures of Performance

At this time, data reduction is complete for four of our eight subjects, thus the statistical analyses we are reporting are based only on these four subjects.

In general, the physiological data obtained in the simulator did not exhibit as much artifact contamination as did the flight data. We were able to obtain useful information regarding our planned comparisons. For example, the physiological measures did discriminate between: (a) flight position (wing vs. lead), (b) actual and simulated flight, (c) type of mission event (e.g., in-flight baseline, maneuvers, weapons delivery, takeoff/landing, etc.), and (d) individual pilots. In addition to our planned comparisons, we were able to obtain interesting data regarding two unforeseen events, a "bird strike" of one aircraft and the mid-air incident, where the lead pilot turned into his wing.

Descriptive information was first obtained from the physiological data by: examining the ECG in terms of beats per minute (BPM) and interval beat intervals (IBI); performing a spectral analysis of EEG data, where the amplitude for respective bands are reported independently and not as a proportion of total power; and examining the EOG data in terms of blink rate (blinks per minute) and eyeblink duration (see Stern et al. (5) for technical description of measurement procedure). A repeated measures analysis of variance procedure (ANOVA) was applied to all descriptive data.

Mission Events. All physiological measures discriminated among type of mission event (e.g., briefing, takeoff, maneuvers, weapons delivery, etc.). For example, ECG (BPM) showed a significant change in heart rate across the fourteen mission events [F(13,39)=8.55,p<.0001]; EOG, eyeblink duration showed a similar change, [F(13,39)=3.03,p<.003] although not as powerful as the heart rate changes. The EEG bands were analyzed separately as four bands where Band 1=4-8hz, Band 2=8-13hz, Band 3=13-20hz, and Band 4=20-30hz. The change across events was significant for Band 1 [F(13,39)=5.49,p<.001]; for Band 2 [F(13,39)=3.39,p<.0016]; for Band 3 [F(13,39)=2.25,p<.02]; and Band 4 [F(13,39)=2.46,p<.015]. Bonferroni contrast tests were applied to the data to determine how the events differed. Weapons delivery produced the highest BPM (mean=104.45 BPM), this event was significantly different from the briefing and cruise segments (76.79 BPM and 88.48 BPM respectively). All EEG bands showed the highest activation for the guns jink maneuver and the lowest for briefing (e.g., Band 2, 6 μv at guns jink and 3.3 μv at brief). Figure 2. shows changes in the EEG Band 2 (a) and Band 3 (b) over selected mission events. The high activation associated with guns jink is typical of all four pilots. Events associated with G stress generally produced more intensive activation. Eyeblink duration seems to also have been affected by high G events, the longest average duration was 152.5 msec. during the 9 left/9 right maneuver and the shortest durations were landing and pre-takeoff at 124 msec. and 126 msec. respectively, Generally, eyeblink duration decreases as attentional demands increase, indicating higher workload. In this case, the 9 left/9 right maneuver was the highest G event (between 5-6 G's) as well as a visually demanding maneuver. It appears that the EEG and the eyeblink duration measures are more sensitive to the G stress than heart rate. Blink rate did not discriminate between mission events.

Flight Position. Heart rate and EEG measures discriminated between the airborne missions and the simulator mission, with the actual flights significantly different from the simulator missions. Heart rate averages for the lead position were 100.7 BPM, 95.5 BPM for the wing position, and 84 BPM for the simulator [F(2,6)=5.17,p<.04]. EEG activation discriminated the actual missions from the simulator mission across all four bands, with Band 1 and Band 2 exhibiting the most change [F(2,6)=11.47,p<.008], [F(2,6)=9.93,p<.01] with an average amplitude in Band 2 of 2.5 μv for the simulator mission and 5.2 μv for wing and 4.9 μv for lead during the actual missions. While the EOG measures did not produce significant differences between actual and simulator missions, eyeblink duration [F(2,6)=1.98,p<.2] averages were longer for simulator missions, (149 msec.) than actual missions (125 msec.) indicating overall higher workload during actual flight.

Flight Position and Mission Events. All physiological measures showed a significant interaction between mission events and flight position (lead, wing, simulator). The EEG Bands 3 and 4 showed the most significant change [F(24,63)=2.85,p<.0005] and [F(24,63)=3.25,p<.0001] where activation intensity was higher during all mission events in the aircraft as compared to the simulator (e.g., Band 3 mean amplitude for simulator events was 2.9 μv, and 5.7 μv for the aircraft) with the exception of the pre-mission briefing. The simulator briefing produced an enhanced activation compared to the lead and wing briefings (e.g., Band 3 mean amplitude for simulator brief was 3.7 μv, 2.8 μv for lead and 1.9 μv for wing). Nine of the mission events: pre-takeoff, takeoff, low level training, first flyover update, slice and 9 left/9 right maneuvers, cruise, and landing showed higher activation in the wing position as compared to the lead position. The four remaining events: guns jink maneuver, three flyover updates, and weapons delivery, showed higher activation in the lead position. Differences in all cases were approximately 1 1/2-2 μv in both Band 3 and 4. This suggests that EEG activation may be a reflection of overall workload, a combination of cognitive and physical demands.

Eyeblink duration data agree with the EEG results in discriminating among mission events as a function of flight position. Durations were shorter during most mission events (the exception was the flyover update approaching the bombing range) when pilots were flying in the wing position (mean=125 msec.), as compared to the lead position (mean=140 msec.) and the simulator missions (mean=150 msec.) [F(24,63)= 1.98,p<.016]. This suggests that flying in the wing position demands a higher level of visual attention than either the lead or simulator positions. Eyeblink rate also showed a similar significant interaction pattern [F(24,63)=1.67,p<.05].

There was no significant difference in heart rate between lead and wing flights during mission events with the exception of the flyover update events [F(24,63)=3.69,p<.0001] where early updates produced a decrease in heart rate in the lead position (lead=89 BPM vs. wing=100 BPM) and later updates produced a decrease in the wing position (lead=100 BPM vs. wing=87 BPM).

Individual Differences. Physiological response patterns of individual pilots differed significantly in two ways: across mission events and by pilot flight position. In both cases, our four pilots can be categorized into two pattern types. The first pattern type seems to reflect the overall workload imposed by the flight position, call this pattern Type P. The other category is a pattern of response intensity that appears within the position pattern, call this pattern Type I. For example, pattern Type P is most clearly illustrated by our heart rate data where two pilots exhibit highest heart rate in the lead position and lowest rate in the wing position (93 BPM vs. 82 BPM and 77 BPM vs. 68 BPM). Their simulator heart rate is most similar to their wing data, 84 BPM and 71 BPM respectively, For the other two pilots, heart rate was lowest in their simulator runs (85 BPM and 80 BPM), but in one case, the lead position was higher than the wing (117 BPM vs. 114 BPM) and just the reverse with the other pilot (116 BPM vs. 114 BPM). These two pilots' airborne rates are similar, but significantly different from their simulator runs. This interaction of individual pilot by their flight position was statistically significant [F(6,63)=27.07.p<.0001].

Both EEG and EOG measures reflect this interaction pattern as well. For example EEG Band 4 [F(6,63)=14.89,p<.0001] and eyeblink duration [F(6,63)=9.52,p<.0001]. For two pilots, EEG activation was higher in the lead position as compared to the wing position and vice versa for the other two pilots. All four pilots showed the lowest activation in the simulator position. Eyeblink duration also discriminated between pilot groups in the same manner, with two pilots exhibiting overall longer durations in the lead position as compared to the wing position, and two pilots showing overall longer durations in the wing position. Figure 3. shows eyeblink duration over selected mission events for pilot #1. This pilot showed a pattern of generally longer eyeblinks when flying in the lead position. Figure 4. shows eyeblink durations for pilot #5, indicating longer eyeblink durations occur most often in the wing position. For three pilots, the simulator produced the overall longest eyeblink durations, the exception was pilot #1.

In general, a decrease in eyeblink duration is indicative of increased attentional demands, however, eyeblink duration also appears to be affected by high G stress.

The physiological profile of pattern Type I, associated with patterns of response intensity, is most clearly represented by heart rate data. This pattern is seen in the significant interaction between individual pilots and mission events [F(39,63)=2.40,p<.001]. All pilots showed distinct peaks across mission events where heart rate was significantly higher compared to other events. Two pilots (pilots #1 & #2) showed peak heart rate at pre-takeoff, takeoff, and weapons delivery. The other two pilots (pilots #4 & #5) showed peak heart rate at pre-takeoff, takeoff, slice maneuver, and weapons delivery. Two distinct intensity profiles emerge for these pilots. Pilots #1 and #2 show a pattern of heart rate that increases sharply at pre-takeoff, then decreases at takeoff. Heart rate for these two pilots remains relatively low and stable throughout the mission until weapons delivery, where the increase is again at takeoff levels. After weapons delivery, their heart rates return to previous levels. The other two pilots show a much different profile. There is an initial rise at pre-takeoff and another rise at takeoff. After takeoff their heart rates remain relatively high throughout the mission, peaking again at the slice and weapons delivery. These data can be seen in Table 4. where heart rate in BPM is shown across the fourteen mission events. The data is averaged over lead and wing positions. Mission events are listed as B=brief, PT=pre-takeoff, T=takeoff, LL=low level training, F1=first flyover update, J=guns jink, F2=second flyover, S=slice, 9L/9R=9left/9 right, F3=third flyover, F4=fourth flyover, WD=weapons delivery, C=cruise, and LA=landing. The asterisks denote peak heart rate events.

TABLE 4. HEART RATE DURING MISSION EVENTS

Pilot #	B	PT	T	LL	F1	J	F2	S	9L/R	F3	F4	WD	C	LA
1	60	85*	78*	74	74	74	73	78	73	71	78	87*	76	77
2	79	107*	101*	83	87	85	82	83	81	86	86	101*	81	72
4	82	114*	125*	112	119	125	111	129*	122	114	112	130*	102	117
5	86	123*	124*	109	111	119	117	125*	117	110	113	129*	112	112

Unplanned Events. Since we collected our data continuously throughout all missions, we were able to record and later review some unique mission data regarding two unforeseen airborne situations; a bird striking one of the aircraft, and a mid-air incident where the lead pilot turned into the wingman. Figure 5 (a). shows heart rate and blink data of the wingman involved in the mid-air incident. The data show low stable heart rate just prior to when the pilot perceived danger and called, "Look out!"; then a sharp increase, followed by a three minute recovery to prior heart rate levels. This pilot was the most experienced one in the group, and while the incident was perceived as serious, note his recovery time.

The other incident, a bird strike is shown in Figure 5 (b). The pilot had just cleared some power lines when he was struck by the bird. During the time segment shown, the pilot was evaluating damage to his aircraft. Again, this was a very experienced pilot, note the recovery time to previous baseline levels, approximately one minute. In both cases, the pilots were two of the most experienced in the group and their responses to those situations were physiologically and behaviorally remarkable.

DISCUSSION

Physiological Measures

All physiological measures used in this study provided useful information about pilot workload throughout a mission, and how a pilot's cognitive demands change from flying in the lead position to flying the wing position. In addition, we gained important information about how pilot response to workload during a simulated mission differed from workload imposed during actual missions.

EEG. The data showed that the EEG is a useful measure in this environment. The EEG data is notable for several reasons. First, these data discriminated overall workload associated with flight position changes, as well as discrete changes in workload specific to each mission event. During high G events, the EEG 8-13hz band (Band 2) showed increased activation. This result is in accord with the findings of Berkhout et al. (6) where pilots received repeated exposure to +Gs acceleration. Their data show alpha activation to increase under real or perceived stress. Finally, the higher frequency bands appear to reflect subtle changes associated with processing routine information, as opposed to new or novel information. For example, the EEG beta bands (Bands 3 & 4) showed increased activation to the simulator brief as compared to both lead and wing briefing sessions. Between the lead and wing, activation was higher for the lead brief. EEG enhancement for the simulator brief may be explained by the unfamiliar and novel experimental situation at the simulator site. When the pilot flew his simulated mission, the information conveyed to the pilot was new and the mission circumstances were quite different from the typical simulator sessions pilots were accustomed to. That is, the briefer provided the pilot with a different set of instructions and flight performance criteria. The simulator brief was the only event during the simulated mission where EEG activation in the beta frequency bands (Band 3 and 4) was higher than either lead or wing missions. Thus, these data suggest processing demands were different across the three briefing sessions. In a laboratory situation, Ray and Cole (7) also found beta frequencies were enhanced in the parietal areas during performance of cognitive tasks.

ECG. The ECG data show that the type of mission event produced significant effects on the pilot's heart rate. Since each subject served as his own control due to the normal between-subject variability, the one hour pre-flight briefing served as the control condition. All flight events were associated with higher pilot heart rate than was found during the briefing segment. Heart rate appears to reflect overall workload, but without the sensitivity to G stress exhibited by other measures. The in-flight workload

studies of Roscoe (8) and Lindholm and Sisson (9) note that heart rate was less affected by G stress than other physiological measures. Further, Roscoe states that heart rate was an especially sensitive measure of workload when the situation was demanding and pilots were highly experienced.

A final important aspect of the ECG measures was the discrimination among pilots according to physiological response patterning. Heart rate provided the clearest discrimination among individual patterns of effort expenditure associated with pilot response to changes in flight responsibility and the workload demands of specific mission events.

EOG. The EOG eyeblink frequency data was found to be more variable between subjects than the ECG data. In general, mission segments which were highly demanding on the pilots' visual-perceptual system were associated with significantly fewer blinks. Blink frequency did not show the same degree of correlation with event difficulty as did the ECG and EEG data. However, the eyeblink duration data proved to be a sensitive indicator of discrete changes in pilots' attentional state. In general, segments where visual attentional demands were high showed a decrease in blink duration, while blink durations increased during segments associated with lower workload. The exception was an event where pilots sustained the highest Gs (+6 Gs) during a maneuver (9 left/9 right). Eyeblink durations were longer during this period than any other event in the missions. This occurred in both lead and wing flights. This lengthening effect on eyeblink duration was negligible during the other two maneuvers, guns jink and slice. The Gs sustained during those maneuvers were approximately +4Gs to +5Gs. This seems to suggest that above +4Gs, eyeblink duration is compromised as a sensitive measure of visual attention.

There are also some problems with obtaining and accurately interpreting eyeblink rates. First, blink rate can often increase during high workload situations when normally one would expect a decrease. For that reason, it is advisable to examine the pattern of eyeblink occurrence. In high workload situations there are often instances when the pilot does not blink for long periods (e.g., 20-30 seconds) followed by rapid periods of blinking. The "flutter" blinking may result in a paradoxical increase in blink rate during high workload events. In our study, blink rate data is confounded for two pilots due to weather and late afternoon sunlight conditions. The lead flight of pilot #1 was made during difficult haze conditions where visibility was often only 45 miles. It is quite possible that this haze condition contributed to an overall enhancement of blink rate during his lead flight. The situation was different for pilot #2, here blink rate data was lost due to head movements and squinting during late afternoon, bright sunlight, flight conditions. In both cases, blink rate may not accurately reflect actual workload conditions.

While these data were reduced off-line, this does not preclude data reduction in the aircraft for the future. In fact, our laboratory is in the process of developing more efficient data reduction capabilities for eventual airborne usage. Under development consideration are automatic analysis and artifact detection routines to be developed so that on-line analysis can be accomplished. When a sufficient physiological data base has been obtained from operational environments, these routines would allow the researcher to specify levels from the various measures that indicate high and low workload conditions.

CONCLUSIONS

We conclude from our data that physiological measures can be a practical and efficient tool for measuring performance in terms of a crewmember's response to workload imposed by various operational situations. They provide data not otherwise available thrcugh more tranditional techniques on a near real-time basis. The nonintrusiveness and continuous nature of these recordings make them excellent candidates for more widespread use in both military and civilian flight.

We believe this first study is an important first step to understanding the behavioral requirements that are necessary to produce the same behavioral outcomes in a simulator that occur in the actual operational situation. In this study we found that flight responsibility and type of operational environment (simulator/aircraft) were important factors that differentially affected pilot physiological responses during the missions. We believe physiological measures can be important tools for identifying and ultimately quantifying other factors as well.

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MOB TO POINT A	8:00
POINT A TO POINT B	2:00
POINT B TO POINT C	2:50
POINT C TO POINT D	10:00
POINT D TO POINT E	5:18
POINT E TO POINT F	6:30
POINT F TO POINT G	2:30
POINT G TO POINT H	8:20
POINT H TO IP	3:30
IP TO RANGE	1:40

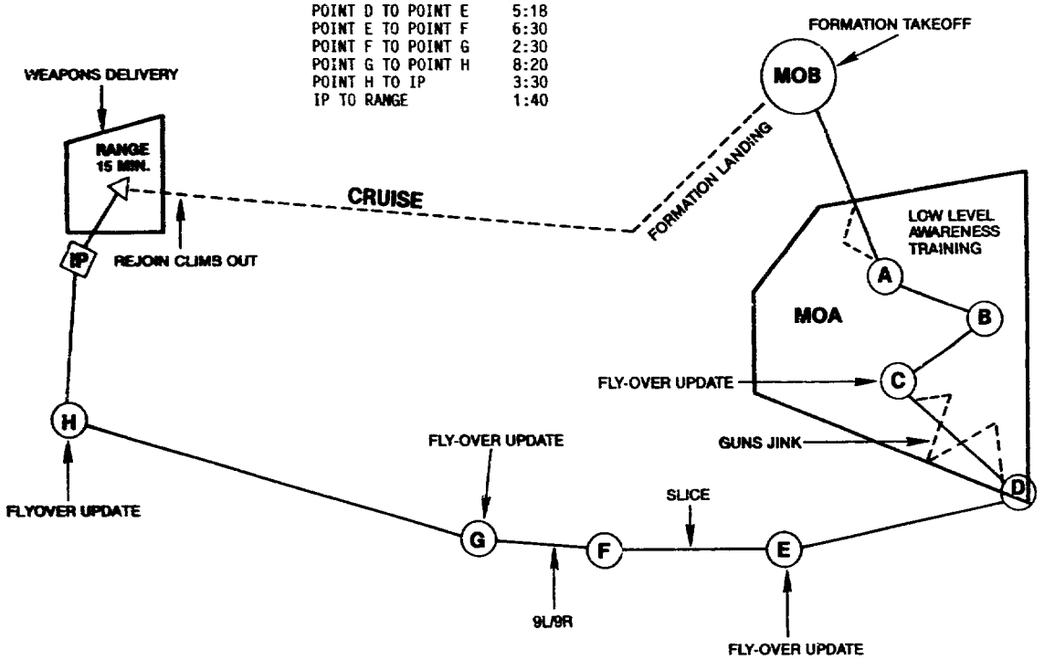

FIGURE 1. MISSION EVENTS.

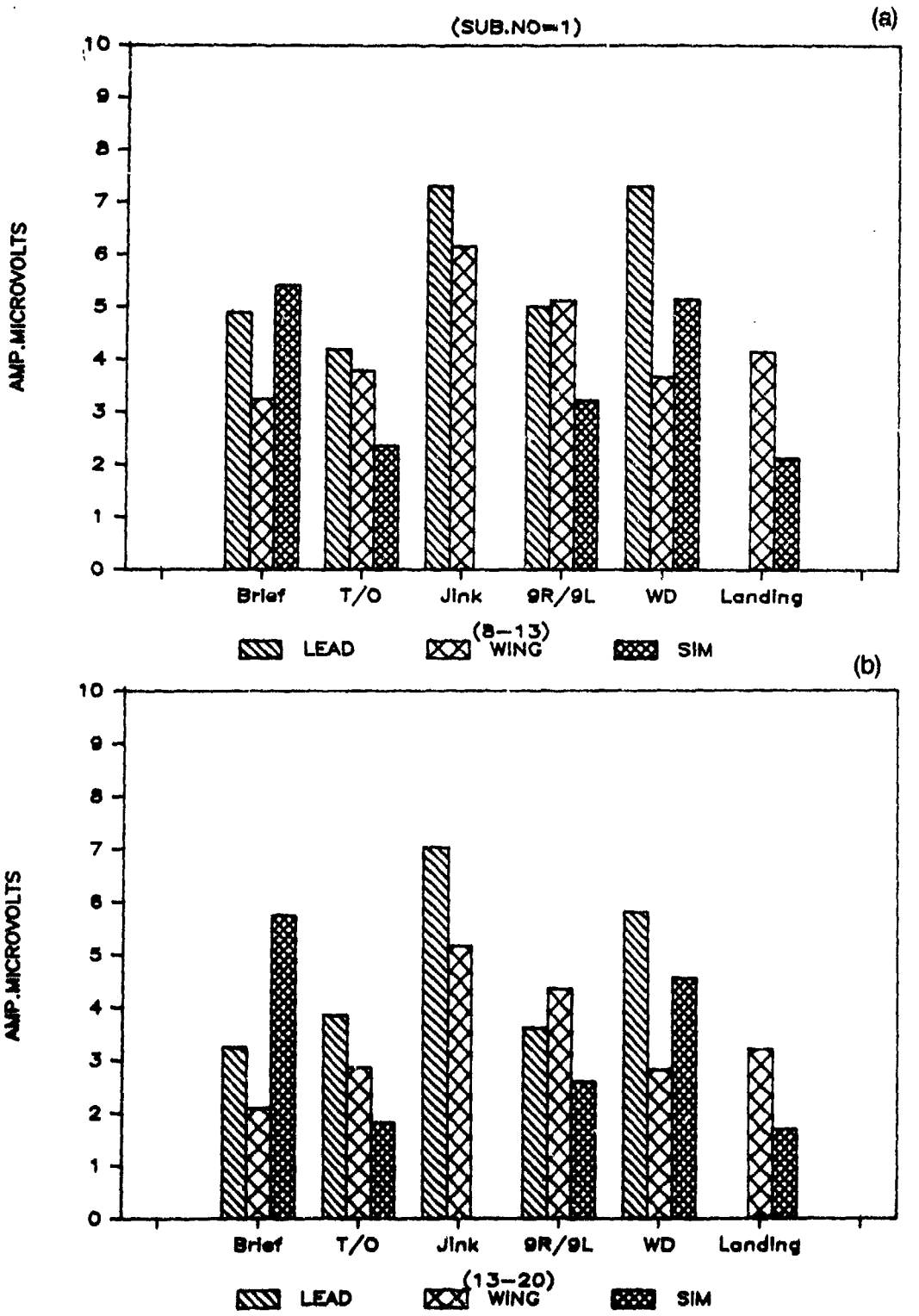

FIGURE 2. EEG CHANGE IN 8-13HZ BAND (a) AND 13-20HZ BAND OVER SELECTED MISSION EVENTS.

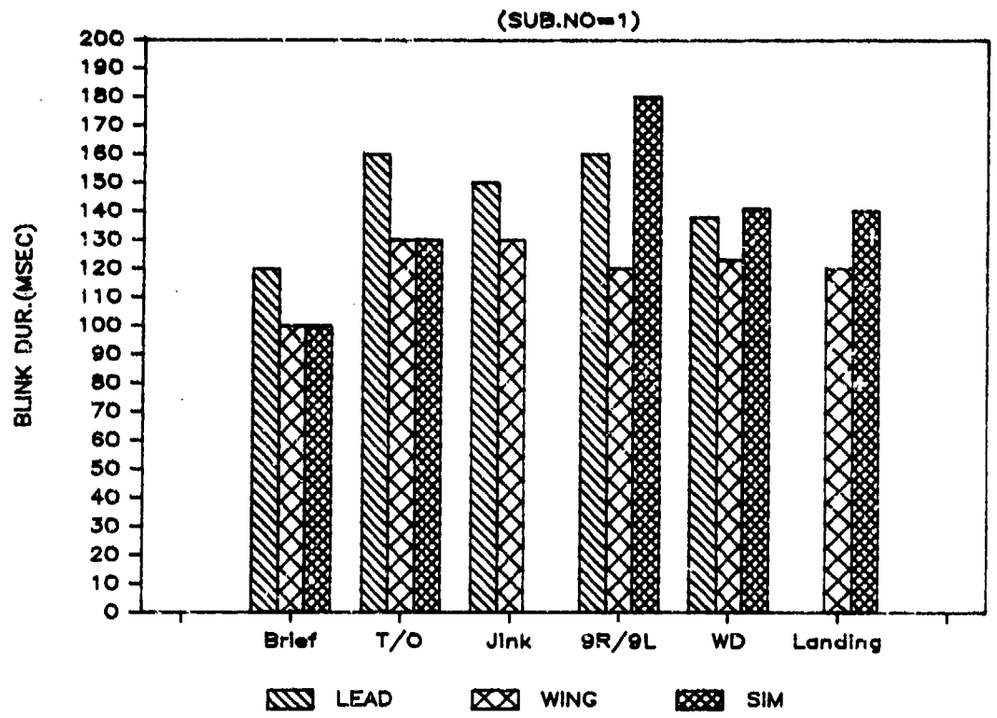

FIGURE 3. PILOT #1 EYEDLINK DURATION CHANGES OVER SELECTED MISSION EVENTS AS A FUNCTION OF FLIGHT POSITION.

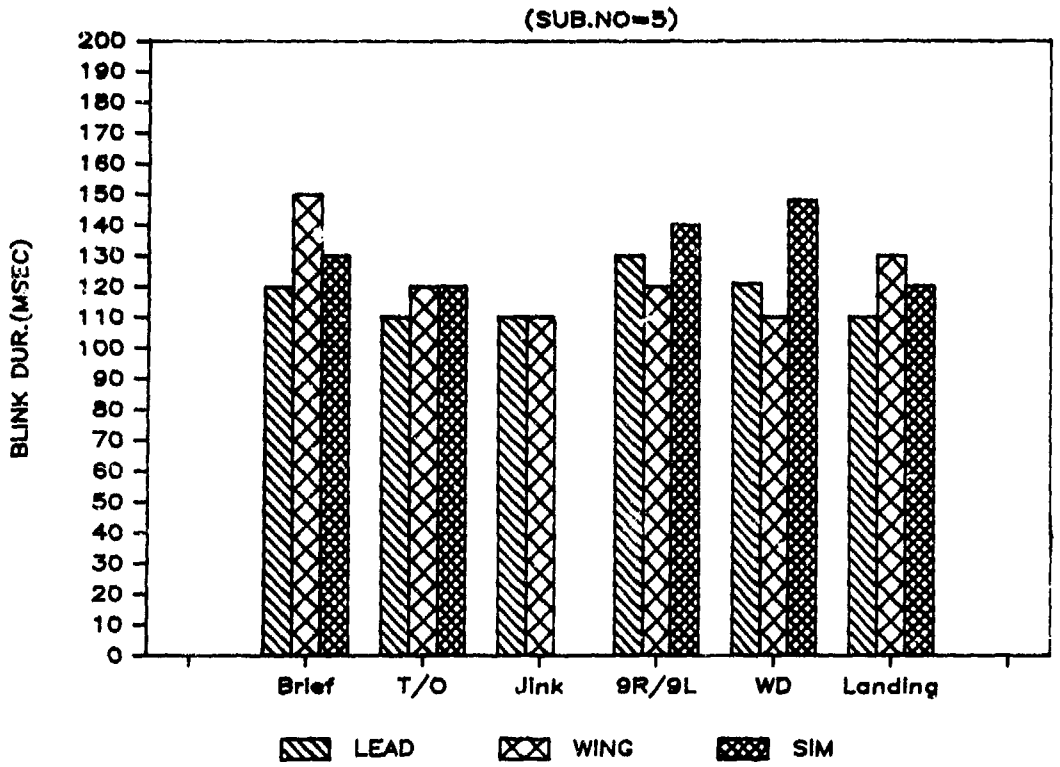

FIGURE 4. PILOT #5 EYEBLINK DURATION CHANGES OVER SELECTED MISSION EVENTS AS A FUNCTION OF FLIGHT POSITION.

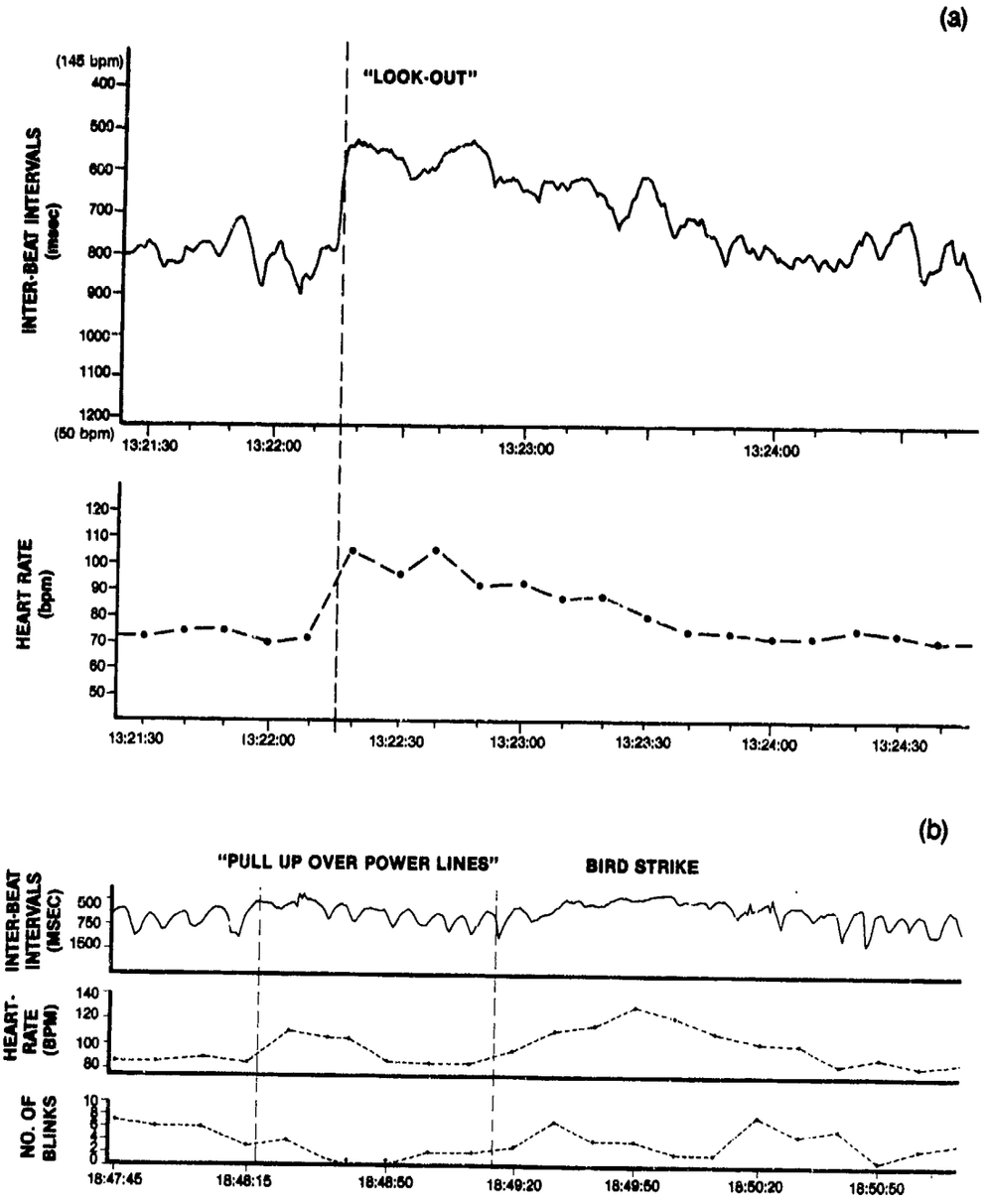

FIGURE 5. AIRBORNE EMERGENCIES (a) MID AIR INCIDENT AND (b) BIRD STRIKE.

DISCUSSION

OFFENLOCH, GE: You are to be commended for the way in which you made your physiological measurements in an operational setting. To make physiology airborne, by arranging equipment which is small, and by placing oscilloscopes and on-line frequency analyzers on an aircraft allows you to obtain results that are truly astonishing. We have done similar work with senior test pilots doing aerobatic manoeuvres in specially-arranged planes in which a suddenly-appearing engine failure had been incorporated. The spectral second-to-second EEG changes that take place are so convincing that if you discuss them later on with the test pilots they will tell you that they didn't think it was possible. You can readily tell whether or not visual information is being analysed; which instruments are being fixated and for how long. You can see whether there is motor activity in controlling the stick, or whether there is more in observing the flight instruments.

VOGT, GE: I admire the work you did because I know what it means to collect these data in the noisy environment of an aircraft. However, I wonder how you are going to interpret the data? If you apply physiological measures, then you will require a second measure to interpret them in terms of task performance. For example, if you increase the difficulty of a task, then you can keep performance constant by increasing arousal, which will show up in your physiological measurement. Do you think that the task of flying the aircraft, which is a very complex task, was constant enough in its difficulty to follow these paradigms?

SKELLY, US: We selected the events that I reported, as based on a mission-effectiveness criteria, and with a lot of consultation with the operational commands about what they viewed subjectively to be a very difficult high workload. We would have liked to have had on-board recorders, but those particular units were not available. The best we can do is to look at differences in the physiological responses to the overall mission tasking within events. Some maneuvres were selected on the basis of the slice being a high-G sustained period of time; the others, as high-G short duration maneuvres. The eight weapons deliveries were selected with various altitudes at the "pop up"; viz., they started at 2000 feet AGL and went down to 500 feet (therefore, the overall workload should have increased dramatically). The same was true for the level events. Given the operational constraints, we feel that we have differences in workload or difficulty in the tasks. The only time that we knew that the pilots were doing the same thing at the same time was during the in-flight baselines so we tracked those. We had takeoff and landing done as a 4-shift formation rather than in the technically easier single-shift formation. We feel that each time the flight path was flown, whether in the lead or wing position, it was as constant as we could make it, given that we had very little control.

KRAMER, US: I wonder if you could speculate on the relative sensitivity of specific components of the physiological measures to specific components of workload? It seems that they are fairly diffuse; i.e., that they might reflect effective perceptual, cognitive and motor commands of the tasks.

SKELLY, US: We feel that heart rate especially seems to be an overall measure of both physical and cognitive load. I tried to demonstrate that, even though the physical load was constant with G-stress environment, we did see a constant difference between flying lead and flying wing that must include a cognitive aspect. In contrast, the eye blink duration was picking up something different. (Eye blink duration also discriminates between wing and lead positions.) When the pilots were flying in the wing position, then at a particular point in the mission at which they were required to maintain a constant formation spacing, then eye blink duration was much shorter than that in pilots in the lead position. The eye blink rate was a very disappointing measure; we lost a lot of data here. The causes for this are that you have huge movements under G-stress, pilots squint when flying into the sun, and so on and so forth. In previous high-fidelity simulator missions, the eye blink measure was the best one but there we didn't have any gross movements. In contrast to EEG and heart rate measures, I think the eye-blink-duration measure seems to be very sensitive to visual attentional demands.

EVENT-RELATED AND STEADY POTENTIAL CHANGES IN THE BRAIN RELATED TO WORKLOAD DURING TRACKING

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SUMMARY

In two experiments ERPs and slow potential changes have been recorded from normal subjects performing a visual tracking task in which the level of difficulty was systematically varied. In the second experiment a secondary discrimination task was added to increase the level of operator load and to probe the allocation of cerebral processing resources.

The most notable feature to emerge was a protracted slow potential shift, associated with the primary task. The amplitude of this shift proved to be sensitive to the difficulty manipulations such that increased difficulty resulted in increased negativity. However, a memory task introduced in the early part of each trial tended progressively to decrease the amplitude of the shift as the memory demand increased. ERPs to the individual points of decision and response during the course of a trial were also found to be sensitive to the level of task loading.

The introduction of the secondary task resulted in a possible further increase in the negative shift to tracking, but in reductions in the amplitude of late cognitive components of tne secondary task ERPs compared with their levels when this task was presented on its own.

INTRODUCTION

Studies of varying levels of task demand and the consequent allocation of processing resources, using brain electrophysiological changes as indices of the processing concerned, have been carried out by a number of workers. Among the most extensive have been those of the group working at the University of Illinois at Urbana/Champaign. This group has tended to concentrate upon the late positive components of the event-related potential - particularly the P300 component - as the physiological index of principal interest (1,2,3,4). Typical experimental paradigms have involved the use of dual tasks, in which spare processing capacity during a relatively demanding primary task has been probed by the use of a secondary task of the classical "oddball" kind favoured in P300 experimentation. Such experiments have successfully demonstrated resource reciprocity between the tasks such that, as the demands of the primary task increase, the amplitude of P300s associated with that task increase whereas those associated with the concomitant secondary task decrease (5,6,7).

Our own group has also demonstrated the sensitivity of P300 to task demand (8), but has in addition shown that the amplitude of the slower potential changes (SPs) is also sensitive to varying levels of demand. Most of these effects have been revealed through changes in the amplitude of the contingent negative variation (CNV) which increased with increased task complexity (9). The CNV is normally viewed as a preparatory phenomenon, but one which is closely related to the level of involvement of the individual with the task concerned. This involvement factor has been described under a number of different headings, such as motivation (10,11), anticipated energy output (12) and attention (13,14,15,16).

Most CNV experimentation has tended to investigate preparatory intervals of at most a few seconds. There are, however, strong indications that comparable negative shifts may extend over considerably longer periods of time in appropriate circumstances. These may reflect more sustained changes of state closely associated with the level of processing resources being deployed on the task which is currently focal for the individual. Investigation of these protracted changes necessitates the use of DC recording; that is to say amplifiers must be directly coupled and no time constants, as normally used in EEG recording, allowed to offset the slowly changing potential differences.

DC recording from the human scalp at the usual levels of EEG amplification has been notoriously difficult for a variety of reasons. However, with improvements in technology, particularly in the design and stability of amplifiers and electrodes, such recording has become possible over extended periods of time. Using these developments we have been able to study DC shifts associated with continuous involvement tasks in which the level of load on the operator could be systematically varied. We have, at the same time, been able to investigate the more transient ERPs recorded to discrete individual events requiring decisions or action within the course of the task.

The principal task used in these studies has been a visual tracking task. In the first of the series of studies, the results of which will be reported in this paper, several factors affecting task difficulty - but all intrinsic to the task - were manipulated to vary the level of load on the operator. In a second study we have added to this primary task a secondary task to enable us to investigate the additional issues of capacity and resource reciprocity. Preliminary findings from this study will be reported briefly. In further studies we are currently seeking to separate the contributions made to the overall load by the cognitive and motor aspects of task demand.

METHODS

Experiment 1

Twenty-four right-handed, normal subjects performed the tracking task; seven were female. All were in good health and their ages ranged from 20 to 47 years.

Each subject sat at a table facing, at a distance of 90 cm, a video monitor on which the task generated by a microcomputer was presented.

On the table was mounted a joystick, operated by the subject's right hand, and a series of buttons, operated by the left hand. The tracking trials each had a duration of approximately 28 seconds. Prior to the start of a trial a fixation spot appeared in the centre of the previously blank screen. Subjects were required to fixate this spot whenever it was present. An auditory warning signal of rising and falling frequency announced the beginning of the trial proper. One second after the onset of this signal the fixation spot was replaced in the centre of the screen by either one, three or six letters. These remained on for 3 seconds and were memorised by the subjects as potential "targets" operating during the current trial. Two seconds after their disappearance the object to be tracked, a letter "X" appeared moving across the screen. This letter was "neutral" in that it was never included among the memory set target letters. Its onset was responded to as rapidly as possible by the subject pressing the first of the left hand buttons. This produced on the screen crosswires with which, using the joystick, the subject began to track the "X". After a period of time, which could vary between 1 and 10 seconds from trial to trial, the "X" changed into another letter of the alphabet. The subject had then to decide whether the new letter was a target - i.e. was included in his current memory set - or not. If it were a target he pressed the left hand of his second pair of buttons to engage it; if not he pressed the right hand button of this pair. In either case he continued to track the letter.

After 11 seconds from letter onset a small flashing rectangle appeared at the bottom of the screen, indicating that the letter was then "in range". If it were a target the left hand button of the next pair had to be pressed to "fire" at it; if not the right hand button was pressed. This latter action erased the crosswires and terminated tracking. For targets tracking continued for a further 2 or 4 seconds until either the sound of an explosion indicated that a "hit" had been achieved or all movement simply halted, indicating a "miss". A second or two later the fixation spot reappeared, eye fixation then being held until the end of the trial, approximately 3 seconds later. Between trials the screen remained blank.

Forty-eight such trials constituted the experimental set for each subject. They were preceded by a comparable, but not identical, training set, also of 48 trials. Trials varied in difficulty, based on changes in a number of parameters. The first of these related to the speed of movement and linear distance travelled by the letter. This could be either rapid and over a relatively long distance or slow and over a short distance. The second parameter was movement perturbation; the letter could either move smoothly along its linear track or be subject to irregular lateral movements. Memory load was, as already indicated, varied by requiring subjects to remember 1, 3 or 6 letters on each trial, along the lines of a Sternberg-type memory task (17). A further factor affecting trial difficulty in a more limited way was the timing of letter "unmask"; that is the time at which the letter revealed itself as a target or non-target. This was at one of six different times after initial letter onset. The first of these times (1.0s) was experienced by subjects as more difficult than the others because it generally occurred at the stage during which the target was being acquired. Of the remaining times, the last (10.0s) was slightly more difficult subjectively than the others because of its proximity to the in-range signal. The factors affecting difficulty were balanced across trials, with the exception of unmask times, which were varied in a less structured way as their function was primarily to prevent this time from being readily predictable. Instructions given prior to each series of 48 trials laid emphasis on the need for both accuracy of tracking and speed of button pressing responses.

EEG was recorded continuously throughout the 48 experimental trials, but not during the training set. Recording was from specially prepared silver-silver chloride scalp electrodes located at Fz, Cz, Pz and Oz. Each was referred to a linked pair of similar electrodes at the mastoids. Vertical electro-oculogram (VEOG) was recorded from a pair of silver-silver chloride electrodes above and below the right eye. Horizontal electro-oculogram (HEOG) was recorded from a pair of similar electrodes at the outer canthi.

All recording was with directly coupled amplifiers, a filter setting of 70 Hz and recording gains of 50 μV/cm for EEG channels and 200 μV/cm for EOG. A further VEOG channel was recorded in parallel with a time constant of 1.2 sec. This was used as part of a procedure to compensate the EEG channels for eye blinks without making compensations for slower changes at the EOG electrodes. It was considered that no safe assumptions could be made about the origins of the latter if present. The procedure entailed using potentiometer adjustments to feed back a proportion of the VEOG to the neutral (white) side of the EEG input until it exactly compensated for - i.e. eliminated - any eyeblink contribution. Each EEG channel was separately compensated in this way.

No adjustments of DC recording levels was permitted during trials. Where necessary such adjustments were made during the period of eye fixation immediately prior to a trial. Amplified EEG and EOG from all channels was sampled continuously by a PDP-12 computer and digitized at a rate of 5 ms per point. Samples for a period of 28.16 seconds, beginning 7 seconds before letter onset, were stored on digital tape for all error- and artefact-free trials. Any rejected trials were repeated at the end of the set to ensure that data on all 48 trials were collected from all subjects.

Speed and accuracy of performance were measured by taking reaction times for each button pressing response and by sampling tracking error - i.e. the distance of the tracking crosswires from the letter - every 100 ms. A mean tracking error was also computed for the time between the "acquisition" of the letter and termination of tracking.

From the EEG and EOG data, 28.16 second samples were computed both within and across subjects. Within subjects the averages were for (a) all trials; (b) all targets and all non-targets; (c) all long/fast and all short/slow trials; (d) all perturbed and all non-perturbed movements; (e) for each of the three memory set sizes; (f) for each of the six unmask times. Similar grand averages were computed across subjects and, additionally, across-subject grand averages were computed for each individual trial. All amplitude measurements were made with respect to a baseline established as the mean level of activity over 0.5 second prior to the auditory warning stimulus.

Experiment 2

Ten normal adult subjects have so far been tested in this experiment which is still in progress. In form it is similar to Experiment 1, although the primary tracking task has been modified in some minor respects and further conditions added in which that task is combined with a secondary task. The secondary task has both a visual and an auditory version, all subjects experiencing both. The new sequence of conditions is as follows:

Condition 1 Secondary Task A (alone)
Condition 2 Primary Task (alone)
Condition 3 Primary Task plus Secondary Task A
Condition 4 Secondary Task B (alone)
Condition 5 Primary Task plus Secondary Task B

The primary task has the following differences from that already described. The auditory warning signal is replaced by a visual signal, achieved by causing the eye fixation spot to flash for 1 second prior to display of the letter sets. Letter unmask times have been reduced from 6 to 3 and now occur at 3.0, 5.5 and 8.0 seconds after letter onset. To each linear track followed by the letter crossing the screen has now been added a reciprocal track; the overall design has been balanced for these new tracks, which were added to ensure no systematic bias by virtue of eye movements. The midpoint of each track now lies on the mid horizontal axis of the monitor screen.

The visual form of the secondary task is based on a circular array of eight light emitting diodes (LEDs) which surround the screen. These light up for 200 ms in one of three patterns: a four diode square, a four diode diamond, or a circle of all diodes. Each pattern can occur in either red or green, giving a possibility of 6 separate stimulus conditions. When the secondary task is combined with the primary task 12 such stimuli (2 of each combination) are delivered, beginning with the advent of the primary task warning stimulus and ending 26 seconds later. Inter stimulus intervals range between 2.0 and 2.75 seconds and stimuli occur in a pseudo-random order which varies on each trial. With the exception of the first, no secondary task stimulus is coincident with a discrete primary task stimulus. One secondary task stimulus combination (the red square) is designated a target. Its occurrence has to be responded to as rapidly as possible by the subject pressing an additional bar-switch operated by the left thumb.

The auditory form of the secondary task also entails the presentation of six separate stimulus combinations in a similar manner and at the same times as for the visual version. In this case the stimuli are high (1850 Hz), medium (1250 Hz) or low (850 Hz) tone pips of 200 ms duration delivered to either the left or right ear via headphones. The high tone in the left ear is designated as the target.

In Conditions 1 and 4, one of the secondary tasks is presented on its own. That is to say 48 sets of 12 stimuli are presented exactly as described above, but without the presence of the primary task. Half of the subjects undertake the visual version first and half the auditory. In all cases the secondary task data is sampled at the same rate (5ms/pt) as the primary data and averages are computed for all of the first eleven stimuli within a given trial and for each of these stimuli individually across the 48 trials. These averages are for 2.56 seconds, beginning 500 ms prior to stimulus onset.

RESULTS

Experiment 1

The averaged waveforms revealed a consistent pattern of DC shift throughout each trial, the amplitude of the shift being related to the difficulty factors present in a given trial. An example of a typical trial is given in Figure 1.

Following the ERP to the onset of the warning stimulus there was a rising, CNV-like, negativity as the subject prepared for the onset of the letters to be memorised. Letter onset elicited a further ERP complex and the negativity was generally sustained throughout the exposure period. After letter offset a further negative rise occurred in preparation for the appearance of the letter to be tracked. The ERP complex to this event was characterised by a prominent posterior late positive component and an anterior negative component apparently linked to the subject "enabling" the tracking system. A sustained negative shift then accompanied the first stage of tracking to the point at which the "X" changed to a target or non-target. A prominent ERP complex was elicited by this unmask, the principal feature being a series of late positive components with latencies extending to 700 msec or longer. These led to an accelerated negative rise which reached its peak at the time of the in range signal, the response to which was followed by yet another rise in negativity when the letter was a target. This culminated in a variable response complex depending upon whether a hit or miss occurred. For non-targets the negative shift stabilized following the in range signal and the consequent terminating button. A final small response occurred to the reappearance of the fixation point and generally the negativity began to subside by the end of the averaged epoch, although in most instances it was still showing substantial negativity at this time, relative to its pre-trial baseline.

The DC shifts were found to be sensitive to the experimental manipulations in the following ways: (a) The average of all "long/fast" trials showed a significantly increased negative shift from the time of appearance of the letter "X" (see Fig. 2) compared with the "short/slow" trials (Fig. 2). These differences became highly significant ($p<.001$) from 2-4 seconds onwards and were widespread; (b) Over a similar period all trials with movement perturbation showed a significantly increased negative amplitude compared with those without such perturbation (Fig. 3). However, in this instance the difference was essentially confined to the vertex; (c) The three levels of memory set - i.e. 1, 3 or 6 letters - showed DC amplitude differences beginning immediately after the onset of the letters on the screen (Fig. 4). The negative shift during this phase, which extended until 2 or 3 seconds after onset of the "X", was largest for the 1 letter set and progressively decreased over the 3 and 6 letter sets, actually becoming positive for the 6 letter set at posterior electrodes. The amplitude differences between letter sets 1 and 3, and between 1 and 6 were highly significant, but those between sets 3 and 6 reached significance only at electrode Oz. Not surprisingly, targets and non-targets showed no significant DC differences prior to the in range signal; both had to be

tracked in an identical fashion up to that point. Thereafter the negative shift continued to rise only to the target, the difference between targets and non-targets being significant over the centro-parietal region at this stage.

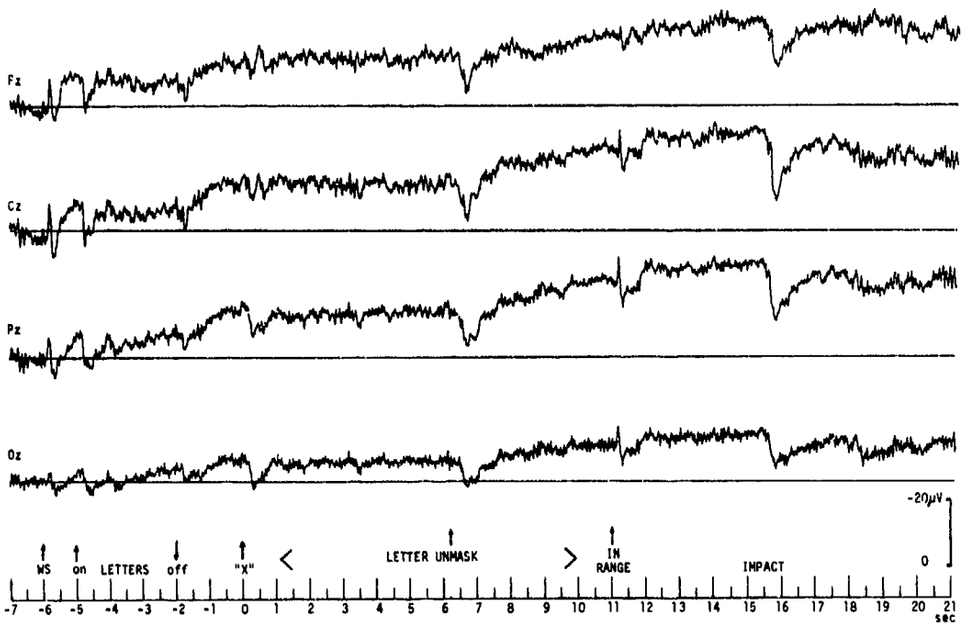

Figure 1: Grand average waveforms across all subjects for a typical single trial in which the tracked letter was a target moving rapidly over a relatively long distance, but without movement perturbation.

Each of the stimuli conveying discrete experimental information resulted in a clearly defined ERP complex. With the exception of the auditory warning stimulus, these events were visual. Nevertheless, the morphology of the resultant ERPs varied substantially, their form being as follows:

letter onset:	N100; P220; N280; P350; N550/P475*
object onset:	N160; P220; N270; P320; N470
letter unmask:	N160; P230; N260; P320; N360; P430; P500; N600; P730
in range signal:	N200; P290; N350; P400; N/P530

The amplitude and peak latency of each of these components was measured from the grand average of each trial for each electrode. The measures were made with respect to a pre-stimulus baseline, represented by the mean level of activity over the 250 msec immediately prior to the stimulus. ERP differences resulting from the various difficulty factors were then examined.

Significant amplitude differences were found between all of the ERP components to letter onset on short/slow trials and those on long/fast trials. Difference waveforms, derived by subtracting the latter from the former, revealed the presence of an extended negative shift of around -3.0 uV, having its onset about 80 ms after the appearance of the object. Closer inspection determined that this was in fact the onset of the sustained DC difference already reported between long/fast and short/slow trials. Anteriorly its onset appeared to be delayed slightly - or temporarily occluded - by a response complex associated with the making the "enable" response.

ERP latency differences associated with the presence of movement perturbation occurred to both object onset and the in range signal. Movement perturbation significantly lengthened the latency of N160, P220, N270 and P320 at Fz and Cz of P220 and N270 at Pz for object onset. At Oz only N160, P220 and P320 showed significant delays. To the in range signal, perturbed trials had significantly longer latencies for P290 and P400 at all electrodes and for N350 at electrodes Pz and Oz only.

The principal effect of target stimuli was associated with the unmask stimulus. The latencies of N160 (at Fz, Cz and Pz) and P430 (at Cz and Pz) were significantly longer and the amplitude of N600 (at Fz, Cz and Pz) was significantly smaller for targets compared with non-targets.

Footnote: *Indicates an anteriorly negative/posteriorly positive component of the kind usually referred to as Slow Wave.

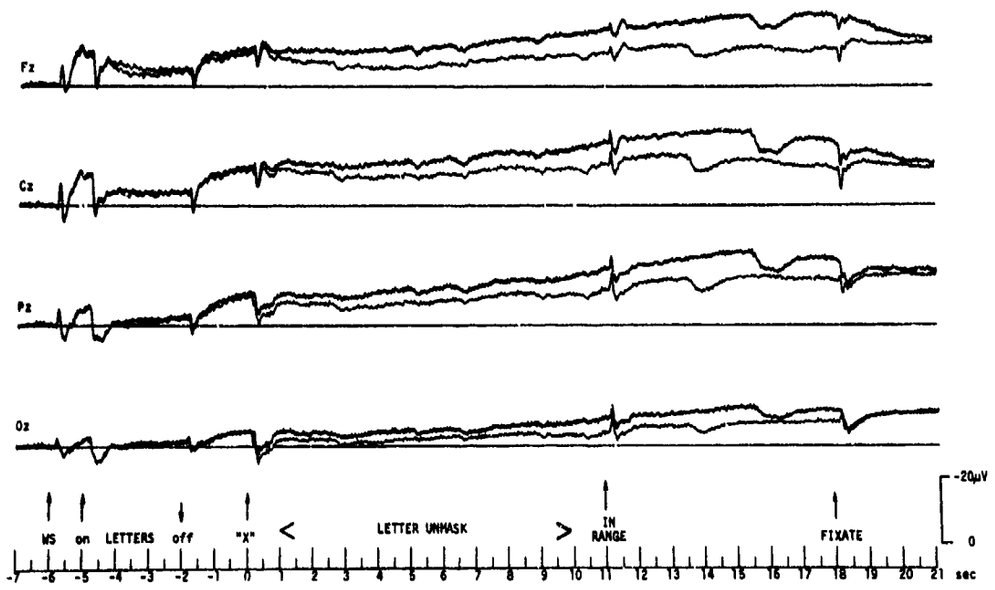

Figure 2: Grand averages of all trials in which the tracked letter moved rapidly over a long distance (thick trace) compared with those in which it moved slowly over a short distance (thin trace).

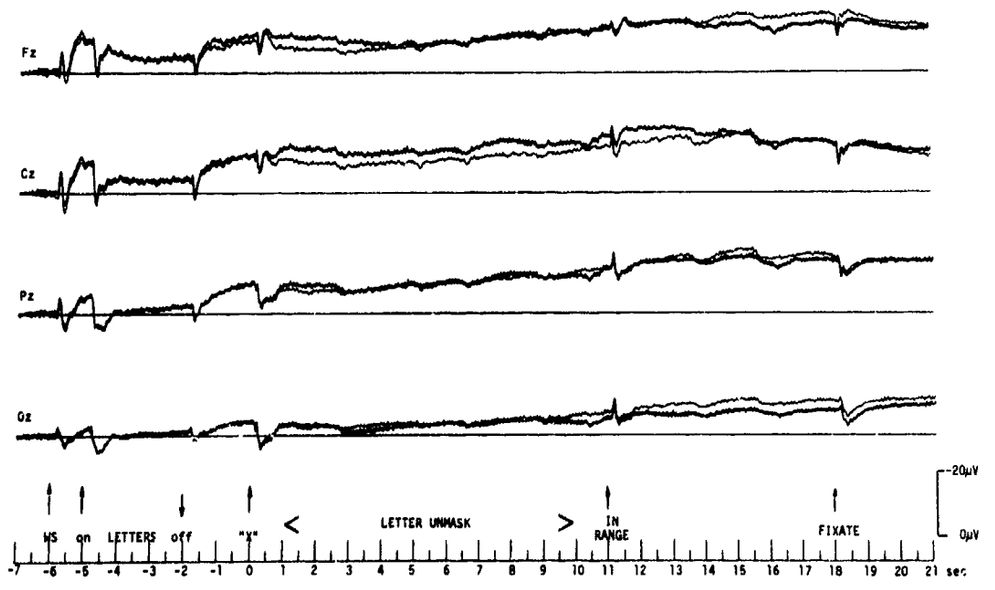

Figure 3: Grand averages of all trials in which the tracked letter was subject to movement perturbation (thick trace) compared with those in which there was no perturbation (thin trace).

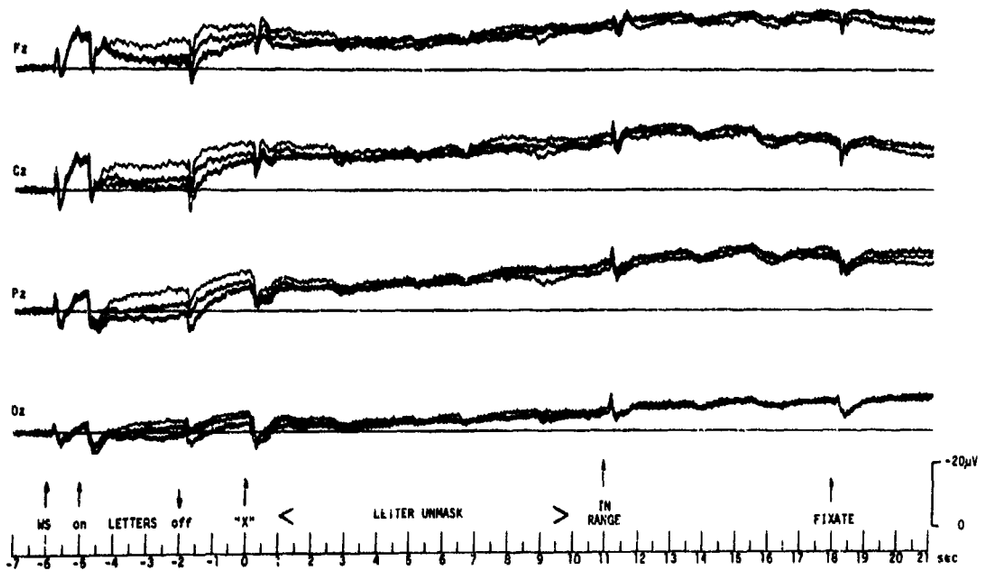

Figure 4: Grand averages of all trials in which the memory set size was 6 letters (thick trace), 3 letters (medium thickness trace), and 1 letter (thin trace).

The effects of letter set size manifested themselves principally as amplitude differences in the ERPs to object onset and letter unmask. For object onset the amplitudes of N270 and P320 were least negative/most positive to the single letter set and most negative/least positive to the six letter set. The differences between letter sets 1 and 6 were significant at all electrodes. The amplitude of these components to the three letter set invariably occupied an intermediate position, but only at Pz were P320 differences significant between all three letter set sizes; for N270 at Pz the differences between sets 3 and 6 failed to reach significance. For the unmask stimulus, the amplitude of P430, P500, N600 and P700 were all less positive/more negative at electrodes Cz, Pz and Oz to the 6 letter set compared with the one letter set and with the three letter set. Of these, only the N600 difference at Oz failed to reach significance.

A one-way ANOVA performed on the ERPs to letter unmask showed a significant effect of unmask time on the amplitude of P320, N430, P500 and N600 at electrodes Pz and Oz, with the single exception of P430 amplitude at Oz.

Speed of performance, as measured by RT to the main experimental events, showed a mean of 507 ms to letter onset, 1152 ms to letter unmask and 922 ms to the in range signal. None of the difficulty factors manipulated during the experiment resulted in significant differences in RT, with the exception of movement perturbation, which rosulted in significantly increased RT to the in range signal, and letter set size, which showed significant RT differences to both letter onset and letter unmask. RTs were shortest for the 1 letter set and longest for the 6 letter set.

Significant correlations were found between RT and certain ERP components - particularly late components - to the same event. For object onset there were significant correlations between RT and the amplitude of N270 at Fz and Pz, and the amplitude of P320 at Pz and Oz. For unmask there were significant correlations between RT and amplitude of P320, P430, P500, N600 and P730. For P430 these were significant at all electrodes and, for P500, at all electrodes except Fz. The remainder were significant only at posterior electrodes. For the in range signal, RT correlated significantly with both amplitude and latency of P290, N350, P400 and N/P530. The latency correlations did not reach significance at Oz for P290 or at Fz and Cz for N350. For the remaining components, only at Fz were there no significant correlations (except for P400 latency). Where significant correlations occurred, increased latency of RT was associated with decreases in the amplitude of positive components and increases in the amplitude of negative components. Where ERP latency correlations occurred, longer RTs were invariably associated with longer ERP component latencies.

Accuracy of performance, as measured by mean tracking error, showed highly significant differences between perturbed and non-perturbed trials ($p<.0001$), perturbed trials not surprisingly showing the higher error. There were no significant differences in tracking accuracy dependent upon other manipulations of trial difficulty. A comparison of the across-subject grand averages of the 12 trials showing the highest tracking error with the 12 trials showing the lowest tracking error showed DC differences very similar to those between perturbed and non-perturbed trials. Those with the higher error showed the more negative DC

amplitudes. Mean tracking error was found to correlate significantly with a number of individual ERP components. The significant correlations for letter onset were principally with N160, P220, N270 and P320 latencies at all electrodes except Fz and Cz for N160, Oz for N270 and Pz for P320. The other main pattern of correlation was with the P290, N350 and P400 components to the in range signal. In the case of P290 this correlation was at all electrodes, but for latency only. For N350, correlations were significant for amplitude at Fz, Cz and Oz and for latency at Pz and Oz only. For P400, both amplitude and latency were significantly correlated with tracking error at all electrodes except Fz. For N350 and P400, decreased accuracy (increased tracking error) was associated with increased negativity or decreased positivity. Increased tracking error was invariably associated with increased ERP latencies in the components concerned.

An evaluation of the EOG evidence and of the contribution of possible sources of artefact will be dealt with later in the discussion of results.

Experiment 2

Results have so far been obtained from 10 subjects. Data from the first two subjects were treated as pilot data and resulted in minor adjustments being made to experimental procedures. Their data has therefore been excluded from our preliminary evaluation which has been carried out on 8 subjects. Because it is too early for a comprehensive statistical analysis of results, we will confine ourselves to a brief description of the results obtained so far and the light they shed upon Experiment 1.

The waveform pattern produced by the primary task alone is similar to that seen in Experiment 1. In the limited number of subjects so far tested it has been less prominent posteriorly than previously, but otherwise the protracted negative DC shift has emerged as a robust and consistent phenomenon. The use of reciprocal tracks has virtually eliminated any residual possibility that such shifts can be attributed to eye movement artefacts. Nevertheless, in this second experiment the waveform differences between long/fast and short/slow tracks have largely disappeared, which must leave open the question that these particular differences were influenced by unidirectional eye movements of different magnitude, even though the EOG data from the original experiment did not obviously support this explanation and their distribution was not that of the normal eye field. More reassuringly the DC differences between perturbed and non-perturbed trials are very similar to those recorded in the first experiment, as are those between the three letter set sizes. Once again there are no marked differences between DC levels for trials in which the letter was a target compared with those in which it was a non-target, except for the period following the in range signal.

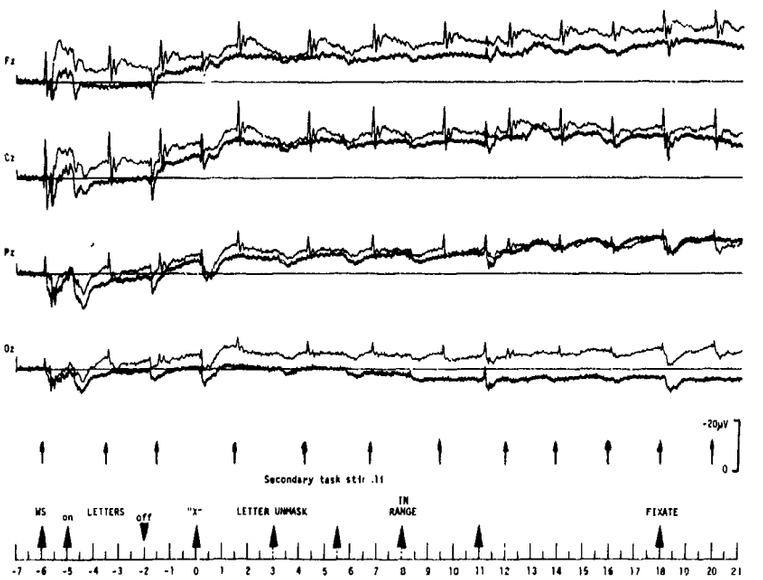

Figure 5: Grand averages from Experiment 2 for 8 subjects. The thick trace is for all trials in Condition 2 (Primary - tracking - task only). The thin trace is for all trials in which the auditory version of the secondary task was combined with the primary task. Time scale is in seconds.

The presence of the secondary task in the combined trials - Conditions 3 and 5 - does not greatly change the basic pattern of the DC waveform extending through trial. There are, however, tentative indications that the negative DC shift itself may be larger in amplitude, particularly in the case of the auditory secondary task (see Fig. 5), which was reported by all subjects to be subjectively the more difficult of the two when combined with the primary task. Nevertheless, even with the presence of the secondary task, the differences

of DC level due to the various difficulty manipulations persist in much the same form as in the primary task alone. ERP complexes, superimposed on the DC shift, are clearly discernible for each secondary task stimulus.

ERPs to secondary task stimuli showed the characteristic range of components associated with auditory and visual stimuli in an odd-ball discrimination task - viz. N1, P2, N2, P3 and Slow Wave. The actual latency structure for target stimuli in the visual task presented alone was N150, P180, N275, P410, P680 (a protracted positivity extending over several hundred milliseconds). For the equivalent auditory targets the structure was N100, P180, N275, P325, N/P600 (an anteriorly negative, posteriorly positive protracted slow wave).

The use of 6-way discrimination tasks resulted in the whole range of components being visible both to targets and non-targets. Late components to targets were generally larger than those to non-targets, although latencies to both were, with the exception of the N2 component, very similar. When the secondary task was presented on its own the peak latency of N2 to visual targets was 275 ms and to non-targets 305 ms. When this task was combined with the primary task, the latency lengthened to 330 ms to both targets and non-targets. N2 was also exceptional in that it increased in amplitude in both primary + secondary task conditions. Most other late components showed a marked amplitude reduction in these combined conditions (see Fig. 6). The one exception was the late frontal Slow Wave (N600) to auditory stimuli, which was equal in amplitude (or even larger in the case of non-targets), but its duration extended for several hundred milliseconds in the combined condition. Interestingly, this anterior slow wave was also of rather longer duration to non-targets than to targets in the secondary task only condition.

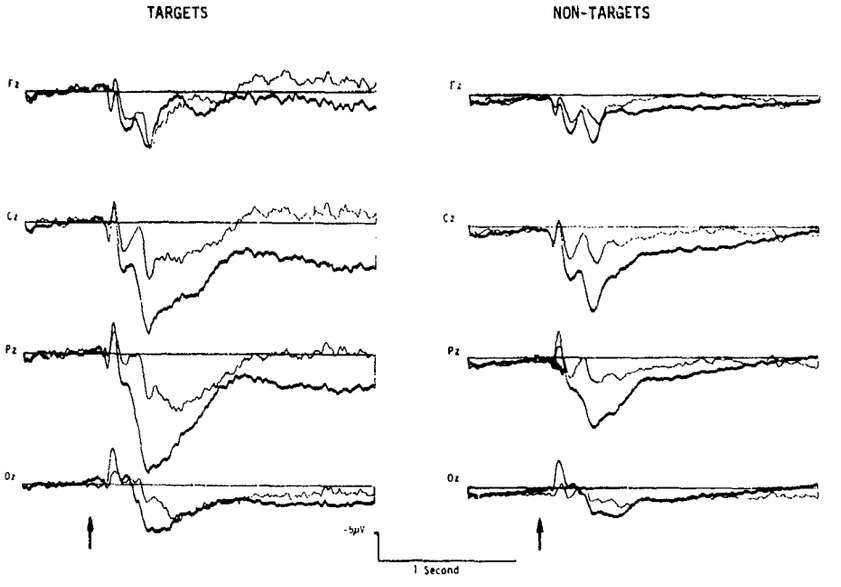

Figure 6: Grand averages of all visual secondary task trials which were targets, necessitating a button press (left column) or non-targets (right column). Thick traces are for the condition in which the secondary task was presented on its own; thin traces are for the condition in which it was combined with the primary task. Stimulus onset is indicated by arrows.

The description and values quoted above apply to the mean values of all secondary task stimuli. A preliminary examination of stimuli according to their position in the sequence suggests that the degree of reduction in amplitude in the combined conditions is dependent upon that position. That is to say, stimuli occurring during phases in which the primary task tracking and processing demand was high show a proportionately greater level of reduction. Those stimuli which occur after tracking has ended show relatively little reduction when compared with those for which no primary task was present.

DISCUSSION

This series of studies has successfully demonstrated systematic DC shifts in the brain that extend over many seconds, are behaviourally linked and appear to be sensitive in their amplitude to the level of task difficulty and hence to the processing load on the operator. The basic DC pattern of change emerges as being remarkably consistent across both trials and subjects.

The evidence points to there being more than one type of slow potential process contributing to the steady negative shift of the DC. The rising negativity which follows the warning stimulus and extends to the

onset of the letter to be tracked can be considered as a preparatory process having much in common with the contingent negative variation. Its function can perhaps be thought of as progressively mobilising the processing system such that it reaches its peak of readiness at the time it is called upon to enable the tracking system and begin tracking with maximum speed and efficiency. The negative shift between the warning stimulus and the onset of the letters to be remembered is almost classically CNV-like in character. It can be considered either as an early phase of the overall preparation for the appearance of the letter to be tracked or as a secondary CNV concerned specifically with preparation for the onset of the memory set letters. In either case memorization of the letter set appears to constitute a distraction from the preparatory build-up for tracking. The relatively low demands of the single letter result in a temporary levelling off of the rising negativity; the 3-letter set results in reduced negativity and the most demanding 6-letter set reduces the negativity even further with the result that over parietal and occipital regions the shift becomes temporarily positive.

From the time of the appearance on the screen of the letter to be tracked, the negative rise is resumed; it persists for the remainder of the trial. This shift seems to have less to do with timed preparation and more to do with the level of task involvement, although it can still be considered goal oriented. It can clearly be related to levels of workload and its early onset raises the question of whether it might bear a relationship to the shift described by Näätänen and Michie (18) as Processing Negativity and by Hillyard (19) as Nd. The circumstances of its appearance are admittedly different from the attended vs non-attended channel differences giving rise to the original processing negativity. One of the features noted is that its onset latency centrally and posteriorly is earlier than that found anteriorly. Processing Negativity has been described by Näätänen (20) as also having this characteristic. Possibly both kinds of shift are examples of a family of negativities that appear when focal attention is selectively recruited.

The virtual disappearance in Experiment 2 of the DC differences found in Experiment 1 between long/fast and short/slow trials raises questions about the source of the original differences. It was never entirely clear why the relatively modest increase in difficulty set by the longer and slightly faster movement should in the first experiment have given rise to such a pronounced and widespread increase of negativity. As already indicated, the distribution of the differences seen did not match at all closely those of the eye fields, nor did their general pattern conform to that of the VEOG. It was also the case that a significant DC difference developed very soon after onset of the letter to be tracked. Nevertheless, the difference does increase over the duration of the track, which could be consistent with an increased angle of eye movement due to a longer track. In the second experiment, the only modification of importance was the introduction of reciprocal tracks; for every downward movement there was, on another trial, an equivalent upward movement, balanced in all other respects for its level of difficulty. This inevitably suggests that at least part, if not all, of the original speed/distance differences may have been due to ocular contamination. The perturbation differences are clearly not in this category; in the second experiment they remain remarkably similar to those seen in the first experiment, despite controls introduced to eliminate systematic eye movements.

Although one must remain cautious in the interpretation of results from only eight subjects, the finding of an increased negative shift when the secondary task is added to the primary provides additional support for the notion that increased work load manifests itself in this form. At the same time the reduction in amplitude of the late ERP components to secondary task stimuli delivered during the tracking task (compared with their control values), would seem to constitute an example of resource reciprocity. That is to say, amplitudes drop on this task as resources are withdrawn, while amplitudes increase on the tracking task as additional resources are deployed to meet the increased demand.

The finding in Experiment 2 that the sensory modality in which the secondary task is presented can make a difference to performance, to the size of the negative shift and to the perceived level of difficulty by the subject is of some interest. Intuitively, and in the light of the existing literature, we had expected that the auditory secondary task, being in a different modality from the primary task, would be less demanding. In the event the increase in RT tended to be longer in this modality; all subjects reported the auditory combination to be more demanding and it resulted in higher negative shifts than the visual equivalent. It seems that when such a strong basic visual set is operating it takes more effort to switch to and from another modality. Typical subjective accounts were that it was not that the auditory targets were less readily perceived, but that it took longer for their significance to be registered and dealt with. This was borne out by the performance data. Normally one might have expected auditory RT to be shorter than visual RT, but in this instance it was much longer.

In summary, the two experiments reported have resulted in several important findings. They have, for the first time to our knowledge, demonstrated in human subjects task dependent, behaviourally linked, DC shifts extending over tens of seconds. They have revealed that the amplitude of these shifts provides a sensitive indicator of the level of load on the operator and have confirmed the ability of both ERPs and slow potentials to shed light on issues of resource reciprocity. So far it has not been possible to separate the cognitive from the motor elements of workload but further experiments in this series are already addressing these issues. Finally, we consider that the present evidence offers support for the notion that negative DC or SP shifts may be closely linked with that part of cerebral processing for which there is focal awareness - i.e. is at the forefront of consciousness - as distinct from those background elements of processing which are dealt with on a more automated basis that makes less demand on the available resources.

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DISCUSSION

KRIEBEL, GE: I have a question regarding your baseline. If one of your subjects was a bit drowsy, and you get a shift in slow potential, what would be the outcome if you correlated workload with vigilance? Perhaps, there would be something like a "ceiling effect". If so, what would happen to the amplitudes of the late components of the ERPs to different stimuli if you are near such a ceiling?

McCALLUM, UK: Our subjects vary a little in state; they vary very little in the size of the negative potential shifts that they generate over the periods of time of the experiment. One of the objectives in introducing the additional load of a secondary task was to see if these potentials could be pushed to and beyond this ceiling. We haven't "hit" the ceiling in the current set of experiments; but I agree that it's an important issue to pursue. In previous experiments, we have looked at increasingly-difficult tasks in which we have gone beyond this ceiling; i.e., beyond a certain workload, and the slow potential has started to drop. This has occurred with CNV experiments and also with the late components of the ERPs; e.g., P300 amplitude. So these effects do operate over certain loads of complexity.

OFFENLOCH, GE: Your sequence of CNVs, which were recorded anteriorly to posteriorly, show greater DC shifts to negativity than to positivity in the more frontal leads. Is this a general physiological rule, or was it the result that in your experimental paradigm motor responses were involved?

McCALLUM, UK: You are right; the distribution of slow potentials changes. In the situation that we were looking at, it is a fairly flat field; quite an anterior field. The interesting feature for me pertains to the fact that the late anterior negative slow potentials from the frontal lobes are the definitive ones; and not always the posterior positive ones. The activity from the frontal lobes is becoming much more important again, after many years of neglect, and this should be a consideration of investigators in the ERP field.

NEUROPHYSIOLOGICAL PRECURSORS OF ACCURATE VISUOMOTOR PERFORMANCE

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SUMMARY

Using advanced, novel signal processing techniques, we have measured the rapidly changing, spatial mass neuroelectric patterns associated with preparation and execution of precise right- and left-hand finger pressures in response to visual numeric stimuli in seven healthy right-handed adult male subjects. Previously unseen pre-stimulus differences between patterns associated with subsequently accurate and inaccurate performance were revealed. A spatially specific, multi-component neural preparatory set, composed of invariant left frontal and midline precentral components and hand-specific central and posterior parietal components, appear to be essential for accurate performance of certain types of difficult visuomotor tasks. When this preparatory set is weakened, or inappropriate, subsequent performance is likely to be inaccurate.

INTRODUCTION

We have been advancing the measurement of neuroelectric substrates of human cognitive functions in relation to quality of performance. We analyzed data from healthy volunteers who performed a task that manipulated basic cognitive and visuomotor functions, such as those critical for flying high performance aircraft, and established the existence of complex "preparatory neural networks" that appear to be prerequisite to accurate performance.

Preparatory set for human visuomotor performance, defined as a state of readiness to receive a stimulus or make a response [1], has been studied by a variety of disciplines. Temporal properties of preparatory sets have been measured in information-processing studies, but such studies have not focused on the underlying neural systems [2]. Spatial properties of preparatory sets have been measured in cerebral blood flow studies, revealing increased metabolic activity for sensory-specific focus of attention in superior prefrontal, midfrontal and anterior parietal cortices [3]. These studies, however, have been limited by the temporal resolution (1 minute or longer) of blood flow measurement techniques. Clinical neuropsychological studies have demonstrated that behaviors requiring preparatory sets rely on intact lateral frontal regions [4-7], but variability in size and location of lesions has limited the spatial specificity of such studies in localizing normal function. And although scalp-recorded brain electrical and magnetic recordings provide both spatial and temporal information on neural activity underlying preparatory sets, studies of the Contingent Negative Variation (CNV), an event-related brain potential component thought to be related to preparatory set, have often yielded controversial or ambiguous results (reviewed in [8-10]).

By recording from an increased number of electrodes, and by using several signal enhancing procedures, we have measured the rapidly changing spatial patterns of mass neuroelectric activity associated with preparation and execution of precise right- and left-hand finger pressures in response to visual numeric stimuli. During the prestimulus period, we found differences between patterns associated with subsequently accurate and inaccurate performance. The results suggest, therefore, that a spatially specific, multi-component neural preparatory set, composed of an invariant left frontal component and hand-specific contralateral central and parietal components, may be essential for accurate performance of certain types of difficult visuomotor tasks.

METHODS

Seven healthy, right-handed male adults were recruited from the community, informed of the risks and benefits of the study, and paid for participation.

The subjects were required to exert rapid, precisely graded pressures (forces from 0.1 to 0.9 Kg) followed by immediate release, with right- and left-hand index fingers in response to visual numeric stimuli (numbers 1 to 9). Each stimulus was presented 1 second after the appearance of a cue, which was the letter "V" slanted at a fixed angle (30 degrees) to the right or left to indicate the required response hand. The direction of the slant was determined randomly for successive trials. The cue, stimulus and feedback about performance were presented on a Videographics-II CRT monitor located 70 cm from the subject, and were all controlled for duration and visual angle.

Eighty percent of the trials were response trials, in which the stimulus was slanted in the same direction as the cue and the subject was to respond quickly with finger pressure of the indicated hand. In a random 20 percent of the trials, the stimulus was slanted opposite to the cue and the subject was to make no response. These miscued "catch" trials ensured that subjects attended to the cues and stimuli. Monetary bonuses (5 cents) were paid for "win" trials and monetary penalties (10 cents) were deducted for responding to miscued "catch" trials.

In order to help subjects calibrate their responses, the pressure produced was displayed after completion of each response. This feedback was presented as a two-digit number 1 second after the peak of response. The feedback number was underlined to indicate a "win" when the response error was less than the recent performance level, which was updated on-line after each trial as the average error from the preceding five trials for each hand separately. This criterion, together with frequent rest breaks, minimized possible systematic changes in arousal level.

Subjects practiced the task, learning the motor control and the conditions of reward and penalty, in a pretesting session that continued until the performance level approached a stable asymptote. Each subject performed between 900 and 1000 trials over 5 to 6 hours, with frequent rest breaks.

Electrodes were placed according to an expanded version of the Ten-Twenty Electrode System in which additional coronal rows of electrodes were interposed between the original rows. The anterior midline parietal electrode was used as reference. Brain potentials from 26 scalp electrodes, vertical and horizontal eye movement potentials, and flexor digitori muscle potentials of both hands were recorded onto magnetic tape at 128 Hz from 0.75 sec before the cue to one second after feedback.

The Laplacian operator, a spatial pattern enhancement technique, was applied to the brain potentials at every time point to reduce the blur distortion that results as potentials are transmitted from the brain to scalp [11-14]. This operation removed the effect of the reference channel. Peripheral channels were not transformed because application of the Laplacian operator to an electrode requires surrounding electrodes, which are absent for channels at the edge of the recording array. Sixteen channels remained.

Two independent raters edited the data for artifacts by visual inspection of brain, eye movement and muscle potential polygraph channels. Trials with artifacts due to eye movement, head or electrode movement, or scalp muscle contamination were eliminated, as were trials with slow, bimodal, or delayed responses, or with flexor digitorum activity between the cue and the stimulus. Remaining trials (60%) were then sorted for response accuracy. Accurate and inaccurate performance data sets consisted of trials in which the error (deviation from required pressure) for each subject was less and greater, respectively, than his mean error over the entire recording session. Both sets of trials were balanced according to a number of criteria in order to avoid confounding inaccuracy per se with possible variations due to transitory and longer-lasting changes in arousal and learning.

Classifying performance separately for each individual compensated for between-subject performance differences. Hence each data set contained trials from each subject. Outlying trials on the distribution of recent performance level were eliminated to ensure that accurate and inaccurate data sets did not differ from each other in this variable. This correction eliminated the possibility that inaccuracy would be confounded by performance variations due to transitory changes in arousal. Furthermore, accurate and inaccurate trials were evenly distributed throughout the recording session in order to eliminate confounds due to learning and tonic arousal.

To quantitate the electrical activity of the brain, we measured the covariance (similarity of waveshape) between different pairs of electrodes over brief segments (187 or 375 msec) of event-related (cue, stimulus, response, feedback) waveforms averaged from the seven subjects. This approach is based on the hypothesis that when areas of the brain are functionally related, there is a consistent pattern of waveshape similarity between their macropotentials [15-23]. Covariances between each of the 120 combinations of the 16 Laplacian-transformed channels were computed from enhanced and filtered average waveforms. Covariance for each electrode pair was determined by computing the

crosscovariance function between their waveform segments, lagging one channel with respect to the other from 0 to 125 msec. The value of covariance was the maximum value of that function.

The statistical significance of each event-related covariance was assessed by reference to a noise distribution computed from the same data. For the CNV interval, data were "delta-band" filtered, while for the other intervals, "theta-band"-filtered, enhanced averages were used [24,25].

RESULTS

For right- and left-hand accurate performance, mean error (deviation from the required pressure) was .35 (range =.24 to .52) and .39 (range =.28 to .51), respectively. For right- and left-hand inaccurate performance, mean error was 1.62 (range =1.18 to 1.96) and 1.68 (range= 1.40 to 2.18), respectively. Mean reaction time, averaged across all subjects, was consistent among hand and accuracy conditions (610-618 msec).

To validate the covariance analysis in a known case, the above procedure was applied to waveforms time-registered to the onset of the finger pressure response [26-31]. Because the major peak in the Laplacian waveform during the response was centered 62 msec after response onset and was about 190 msec wide, a 4- to 7-Hz bandpass filter and a covariance interval of 187 msec were used. The most significant left- and right-hand covariances occurred between electrodes overlying cortical regions involved in motor execution (Figure 1).

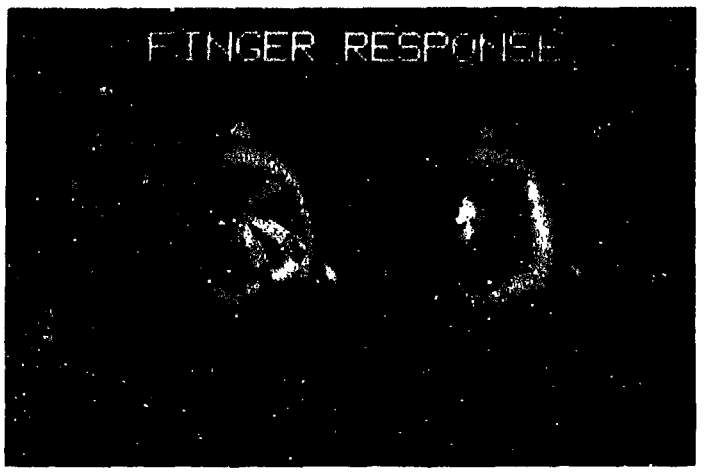


Fig. 1. View of the most significant between-channel covariance patterns (colored lines) from the wave at the peak of the finger response. The motor-related wave was measured during a 187-msec interval centered on the peak of left-hand and right-hand index finger pressures from seven right-handed men. The thickness of a covariance line is proportional to the negative log of its significance (from .05 to .00005). The arrow points from the leading to the lagging channel. The color scale at the left, representing wave amplitude, covers the range from the minimal to maximal values of the two maps. All covariances involve the site overlying supplementary and premotor cortices. There is a strong lateralization of frontal, central and antero-parietal covariances over the hemisphere contralateral to the responding hand.

The patterns of covariance shown in Figure 1 presented more spatially discrete information than did their corresponding "BEAM" amplitude maps [21,23]. In the 187-msec interval centered on the peak of the response (82 msec after response onset), right- and left-hand covariance patterns were near mirror-images. Considering all significant covariances, left-sided covariances were significantly greater than the comparable right-sided ones by the Student's t-test at $p<<.0001$ ($t=18.5$) for the right-hand response. Significant right-sided covariances were significantly greater than the left at $p<<.0001$ ($t=21.5$) for the left-hand response. In both patterns, all covariances involved the midline antero-central site overlying the premotor and supplementary motor cortices. Covariances between this site and the left frontal, antero-central, central and antero-parietal sites for right hand responses, and between corresponding right hemisphere sites (except right antero-central) for the left hand, were all consistent with known motor-related cortical areas.

The procedure was then applied to the cue-to-stimulus period to study preparatory sets. A delta (up to 3 Hz) lowpass filter and a covariance interval width of 375 msec were used to study the low-frequency CNV component (Figure 2).

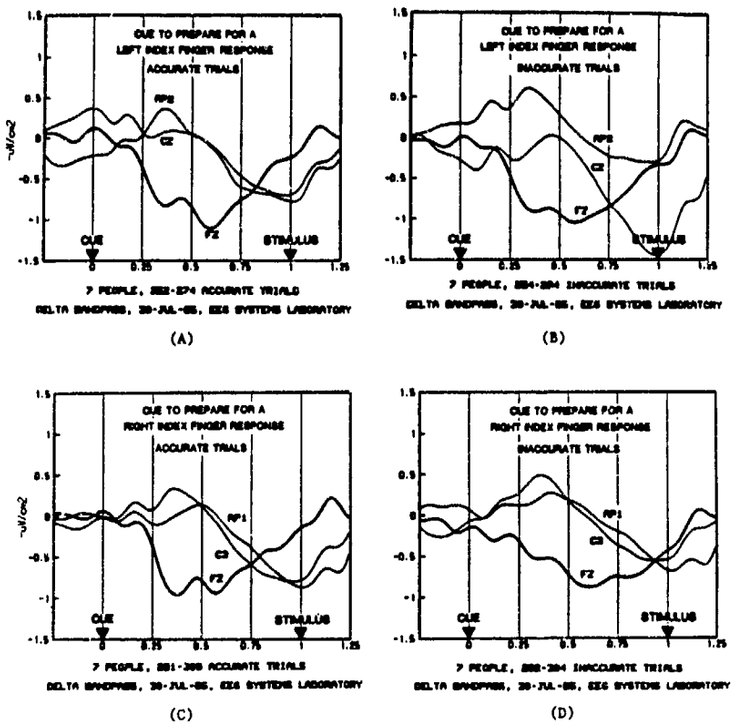
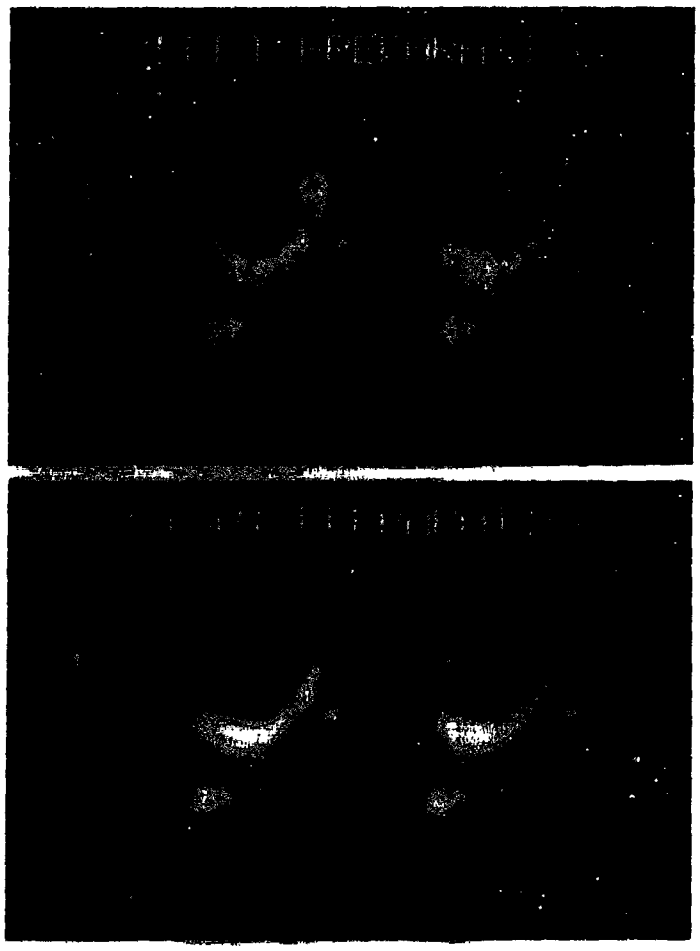


Fig. 2. Amplitudes of the contingent negative variation (CNV) computed during the cue-to-stimulus period. Amplitudes between filtered (below 3 Hz), event-related Laplacian waveforms, averaged from seven subjects, are not significantly different for the comparison of left-accurate (A) with left-inaccurate (B) conditions, or right-accurate (C) with right-inaccurate (D) conditions.

Comparison by the Student's t-test of mean squared amplitude, measured on each Laplacian waveform (over the same 500 to 875 msec post-cue interval as was used for the covariance) between subsequently accurate and inaccurate conditions of each hand was not significant ($p>0.05$) [21,25].

Similarity between the sets of CNV amplitudes, or between covariance maps, was measured with an estimate of the correlation and its confidence interval. For the small number of repeated measures, a normal distribution could not be confirmed. Therefore, robust, resistant estimates were calculated using a distribution-independent "bootstrap" Monte Carlo procedure [32], that generates an ensemble of correlation values from randomly selected choices of the repeated measures. When the distributions of CNV amplitudes from subsequently accurate and inaccurate conditions were compared by this procedure, the correlations were 0.84 +/- 0.16 preceding right hand performance, and 0.83 +/- 0.14 preceding left hand performance. These results indicate that discriminating between subsequently accurate and inaccurate waveforms based on the mean squared amplitude of the averaged event-related CNV waveforms is not possible.

During this same period, however, well-defined between-channel covariance patterns related to subsequent accuracy were discovered. They first appeared in the interval centered 500 msec after the cue and became well-differentiated between accurate and inaccurate conditions in the 500 to 875 msec interval (centered 313 msec before stimulus onset) spanning the late component of the CNV. The lack of muscle potential and eye movement signals in these intervals confirm that these patterns are neural in origin [21,25]. Covariance patterns during the period between the cue and stimulus (Figure 3) were distinct from those related to overt finger responses.



(A)

(B)

Fig. 3. View of the significant ($p<0.05$) between-channel Contingent Negative Variation (CNV) covariance patterns (colored lines). Measurements are from an interval 500 to 875 msec after the cue for subsequently accurate and inaccurate left-hand (A) and right-hand (B) visuomotor task performance by seven right-handed men. The thickness of a covariance line is proportional to its significance (from .05 to .005). The color scale at the left, representing wave amplitude, covers the range from the minimal to maximal values of the two maps. Covariances involving left frontal and appropriately contralateral central and parietal electrode sites are prominent in patterns for subsequently accurate performance of both hands. The magnitude and number of covariances are greater preceding subsequently inaccurate left-hand performance and are more widely distributed compared with the left-hand accurate pattern. For the right-hand, fewer and weaker covariances characterize subsequently inaccurate performance.

During the interval from 500 msec to 875 msec after the cue onset, covariance patterns associated with subsequently accurate right-hand performance involved predominantly left hemisphere sites, particularly left frontal, central, parietal, and antero-parietal sites. These 4 sites were the most prominent in that the numbers of significant covariances in which they were involved each exceeded one half of the maximum number at any site (9 for the antero-parietal site). The other sites in the pattern were involved in one third, or less, of that maximum. The same criterion was used to judge which sites were prominent in the left-hand pattern. All 24 significant covariances involved sites on the left side and 18 (75%) were exclusively on the left side. The covariance pattern preceding subsequently accurate left-hand performance for this interval involved predominantly right-sided sites. Of 18 significant covariances in this pattern, 13 (72%) involved right hemispheric sites. The right-sided central, parietal and antero-parietal sites were most prominent, compared to corresponding prominent contralateral sites for the right-hand accurate pattern. The left frontal site was prominent preceding both left- and right-hand performance. The midline central and antero-central sites were prominent in the left-hand pattern, but were not among the most prominent in the right-hand pattern.

Only two significant covariances were related to subsequently inaccurate right-hand performance in this interval, namely, left parietal and antero-parietal to left frontal. In contrast, the subsequently inaccurate covariance pattern for the left hand was more bilateral and complex than the subsequently accurate pattern. In addition to the cue-to-stimulus period, the post-stimulus and post-feedback periods also showed differences related to accuracy, but the response period did not [24,25].

The signal strength of pre-stimulus covariances was much smaller than those during overt responses, that is, the scale of significance was three orders of magnitude smaller. The smaller number of pre-stimulus covariances allowed all significant covariances to be shown in Figure 3. Comparison by the Student's t-test of the sets of subsequently accurate and inaccurate covariances was significant at $p<.001$ for both left- ($t=5.57$) and right-hand ($t=7.70$) comparisons. The "bootstrap" correlation between covariance patterns preceding subsequently accurate and inaccurate performance from channel pairs that were significant for either condition was 0.57 +/-0.09 for the right hand, and 0.10 +/-0.14 for the left hand. The t-test and "bootstrap" correlation results, taken together, suggest that the left-hand accurate and inaccurate conditions differ both in scale and in pattern, while the right-hand results differ only in scale. Unlike the between-channel covariance patterns, the CNV amplitude maps were highly similar for both accuracy conditions and hands, and were not useful in determining what areas would covary [21,25].

Using statistical pattern classification procedures, covariances shown in Figure 3 were considered as possible variables to distinguish subsequent performance accuracy. The classifier was a nonlinear, adaptive, two-layered decision network [18-21,33-35] that decided whether subsequent performance was accurate or inaccurate from CNV-interval between-channel covariances of each trial. This algorithm produced, by a recursive procedure, classification equations consisting of weighted combinations of the decisions of discriminant functions, which themselves consisted of weighted combinations of a subset of the covariance values of Figure 3. Cross-validation of the equations was performed by testing equations on data that were not used to derive them. Significance was determined according to the binomial distribution.

When the trials of each of the 7 subjects were classified by equations developed on the trials of the other 6 subjects, the overall discrimination was 59% ($p<0.01$) for right hand and 57% ($p<0.01$) for left-hand performance. Discrimination of subsequent right-hand performance accuracy was above 57% for 6 subjects and was 50% for the seventh. For left-hand performance, discrimination for 3 subjects ranged from 56% to 67%, and was 53% or below for 4 subjects (who had fewer trials overall). Average classification of each fifth of the trials from the 4 subjects with lowest left-hand discrimination, using equations from the other four fifths, was 61% ($p<0.001$). This suggests that the 4 subjects had similar covariance patterns preceding left-hand performance, which were different from the other 3 subjects. The greater uniformity for right- over left-hand discrimination suggests that there are similar covariance patterns among the strongly right-handed subjects preceding accurate and inaccurate right-hand performance, and a divergence of patterns preceding left-hand performance. While there were differences in discriminative power between individuals, overall the group preparation patterns were clearly effective in deciding an individual's subsequent performance accuracy. For the one subject with the most trials, average classification of 68% ($p<.001$) for subsequent right- and 62% ($p<.01$) for subsequent left-hand performance was achieved by testing a separate equation on each fifth of his trials, formed from the other four fifths.

DISCUSSION

Although the origin of these event-related between-channel covariance patterns of preparatory sets is not known, our results suggest that preparation for accurate performance in a visuomotor task involves several brain components [36]: a cognitive component manifested by invariant activity at the left frontal covariance site, a hand-specific somesthetic-motor component manifested by the contralateral central and parietal sites, and an integrative motor component manifested by activity at the midline central and antero-central sites. The last component was strong in the pattern preceding accurate left-hand performance and weaker in that preceding accurate right-hand performance. For both hands, preparatory covariance patterns were different from those accompanying actual response execution. Covariance patterns preceding inaccurate performance by each hand differed markedly. The relative lack of significant covariances preceding inaccurate right-hand performance may be interpreted as evidence for a weakened preparatory set. By contrast, the complex, anatomically diffuse but strong patterns in the left-hand condition suggest that inaccurate performance by the nondominant hand of strongly right-handed subjects may result from erroneous, possibly confounded, preparatory sets.

Our evidence for distributed, coordinated, preparatory components of human visuomotor performance is consistent with previous studies of this aspect of behavior. The involvement of the left frontal site is consistent with evidence that preparatory sets in humans are synthesized and integrated in left dorsolateral prefrontal cortices [4-7,37,38]. The finding of an appropriately lateralized parieto-central somesthetic-motor component is consistent with data that show neuronal firing patterns in the motor cortex of nonhuman primates, and localized potentials in the somesthetic cortex of humans, preceding motor responses [1,39,40]. Finally, a midline antero-central integrative motor component is consistent with involvement of premotor and supplementary motor regions in initiating existing motor schemes and establishing new ones [3,41,42].

Our results demonstrate that the human brain, unlike a fixed-program computer, dynamically "programs" its distributed, specialized subsystems in anticipation of the need to process certain types of information and take certain types of action. When these preparatory sets are incomplete or incorrect, subsequent performance is likely to be inaccurate. The fact that classification of performance accuracy improved when equations were formed and tested on the same subjects suggests that single-subject equations formed from large numbers of normative trials may make covariance patterns useful for on-line prediction of subsequent behavior.

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DISCUSSION

KAUFMAN, US: In the late 1920's, Wolfgang Köhler presented an apparent motion stimulus, which was physically biased so that people tended to see the motion in one direction. However, by giving them prior instructions or exposures to other stimuli, he was subsequently able to cause these people to see the motion in the direction for which the stimuli were not biased. He called this an "objective set" or "einstellung", and I guess you can consider that as a kind of preparatory set. The 1938 edition of Woodsworth's Experimental Psychology includes a chapter on the a, b, and c types of reaction time, and he discusses the effect of preparation on reaction time at great length. There is a wide domain of phenomena in which preparation affects perception, performance, attention, interpretation, etc., and we see, once again, in your presentation the effects of preparation. Additionally, we see electrical activity on one side of the head that was not there when the performance was "accurate". As psychologists, one of the fatal flaws in all of this work is that we are telling people what they already know. People already know that preparation is affected, that they can get surprised, and that there are cognitive processes -- behavioural procedures -- that reveal a lot about these things. What else are we learning from what you are doing?

GEVINS, US: What is new from this study is that these are the first measurements that show the preparatory sets in the brain. If you put aside source localisation and pretend that the electrodes are measuring the immediately underlying activity during the state of preparation, then what we have shown is that preparation in the brain consists of four completely separate and distinguishable components that can be resolved. In the case of right-handed people, the left pre-frontal cortex has to be exactly tuned to the pre-motor and the supplementary motor cortex, which is known to be the highest level of motor control in the brain. (It is well known from patient data that the pre-frontal cortex is involved in the temporal sequencing of activity.) So those are the first two components which may be described as cognitive components in preparation. The other two are a sensory component and a motor component which "switches" with the hand that is about to be used. When there is a subsequent accurate performance for a right-handed response, then this distributed preparatory set (which seems to involve the synchronisation of these separate cortical systems) diminishes if the subjects do not maintain concentration on the task (which has a specific cortical tuning in advance). Correspondingly, for left-handed responses in strongly right-handed people, the sources of error are different. If they subsequently respond correctly with the left hand, then we see the same preparatory set -- the cognitive component, the motor control component, the somesthetic component and then the motor tuning component which shifts with the hand about to be used. When subjects are preparing the left hand and they are going to make a subsequent mistake, then there seems to be a variety of sources of error. It's as if the instantaneous tuning of the brain to a specific task is turned off. This new technology has allowed us, for the first time to begin to dissect in real-time the specific tuning of localized cortical areas which make up these preparatory sets, and to explain the sources of error in terms of the tuning of specific cortical systems. What is new about all of this is that we are saying something about the actual neural basis of preparation; we know it exists, what it is, and how it is modulated.

LANDOLT, CA: The work that you presented relates only to right-handed people. Have you done similar studies with left-handed or ambidextrous individuals? I wouldn't expect the CNV covariance significance patterns in left-handed subjects to be mirror images of those in right-handed subjects. However, I believe that such studies should be done to clarify the importance of the dominant hand in performing complex visuomotor tasks. I feel the question is also important because an answer may give an indication of the importance of hand-dominance in the ergonomics of future aircraft cockpit systems if maximum performance is to be achieved. It would also have implications in aircrew selection.

GEVINS, US: No, I haven't looked at left-handed people, and I certainly think that the experiment should be done with them. Part of the reason we haven't done such studies relates to the fact that it takes a long time -- about one trillion arithmetic operations -- to produce the results in this simple experiment.

LANDOLT, CA: Is there any correlation in the spatial sense between the movement-related "readiness potentials" and your CNV responses? If there is, you might be able to use the readiness potentials as a preparatory set by itself in regard to accurate versus inaccurate performance as a mechanism for aircraft control purposes; e.g., in weapons firing.

GEVINS, US: Yes, we examined all of the data from the time of the cue right up until the response for the intervals which had the most predictive ability for the subsequent accuracy of the response. Curiously, for this experimental paradigm, the most predictive power came from the CNV in the interval between the cue and the stimulus. The readiness potential showed some relationship to subsequent accuracy, but was much stronger. However, I wouldn't want to generalize beyond the context of this particular experiment. In terms of using the readiness potential to gain a couple of extra milliseconds; you know, the time it takes to actually twitch the finger -- in a sort of biocybernetic way -- I don't know that it's that important. The brain and the body have evolved over a long period of time. It's a very efficient set up for communicating between the brain and finger wiggling with a very high reliability of success. I don't think the reliability in picking up the readiness potential, even under the best of circumstances, would be as high as the finger twitch, in spite of the fact that it is a very clear and strong signal. I see these types of measurement as those you can use to study the brain in order to make better airplanes. I don't see putting them in a real-time biocybernetic loop.

KRAMER, US: It seems to me that event-related brain potential components and your neural account of pattern analysis seem to provide a nice set of complementary data; especially in respect to the parallel processing model that you indicated in your presentation. There has been a recent paper by Coles, Gratton et al. (J. Exp. Psychol.: Human Perception and Performance, 11:529-553, 1985) on a continuous flow model that has come to similar conclusions on parallel processing. In fact, those conclusions were derived from readiness potentials in terms of speed, accuracy, and trade-off paradigms. The results complement each other nicely, and provide converging support for the parallel processing model that you presented.

KRIEBEL, GE: If you compare readiness and CNV potentials, you will find differences in the motor actions. It's very different whether you initiate a motor action yourself -- a self-based motor action --

or if you respond with a motor action to a stimulus. We did some experiments in Dr. McCallum's labratory in 1974, in which we combined both CNV and readiness potentials. We started the readiness potential paradigm with a finger movement; and, using the finger movement as the stimulus for the CNV condition, we found the topographical scalp distributions to be very different. For the readiness-potential situation, there were clear pre-central and central maxima of activities which show motor cortex action; especially, the supplementary motor area. The CNV condition showed much more frontal activity. The readiness-potential condition also showed parietal activities while the CNV situation did not.

GEVINS, US: Some years ago, there was quite a controversy about whether or not the CNV and the readiness potential were the same phenomena. I think the confusion came about because investigators were not using comparable experimental conditions. They didn't have the same types of stimuli and the same types of paradigms. Some effects came about from the choice of the reference electrode; e.g., the topographic scalp distribution of readiness potentials and CNVs are tremendously influenced by whether a single ear, a "linked" ear, or a nose reference is used. My own choice has been to make derivations which are independent of the reference electrode by taking the Laplacian of the scalp potential distribution. Doing this allows one to see a very sharp classification of the potentials involved in the execution of preparation and movement. For example, the actual motor potentials that I showed were extremely lateralized when looked at with the Laplacian. When they were looked at with linked ears, or an average reference, or a nose reference, then they looked much more bilaterally distributed. In any case, the CNV and readiness potentials are quite distinct.

KRIEBEL, GE: We did quite a number of experiments with different reference electrodes using the same readiness-potential paradigms to measure pre-speech potentials, and potentials prior to finger movement. Mostly, we used linked ears as the reference electrode, but we also used the nose tip and the sternal prominence. We found that the topographical distributions of the readiness potentials did not change very much.

GEVINS, US: I have to take exception to that statement. I had shown the difference between a right-index finger movement recorded with 51 channels (which is necessary to see its distribution clearly) with a linked-ear reference and with Laplacian "deblurring". Quite clearly, though the general features were similar, the location and focalization were extremely clear with the Laplacian derivation, suggesting that the underlying dipole generators were "buried" within the central sulcus. So, I think it is very clear, both from theory and from actual measurements, that the topographic distribution of most components will change with the referencing.

JOHNSON, GE: I have a word of caution about the time at which a stimulus really begins. It's important for those working with evoked potentials with constant intervals between stimuli. If you use a particular interval, say 1 to 2 seconds, you are effectively working with two different baselines. This is something that we often tend to forget. Maybe, we have the wrong definition for time zero; maybe, time zero is really the time of the cue which is itself the stimulus; or, if you prefer, the previous stimulus. Your comments please?

GEVINS, US: I guess the issue is whether the stimulus should be randomized or made more specific. In our paradigm, the intertrial interval was random, but the timing of events between cue and stimulus was fixed, as was the time for completion of response until feedback was initiated. In experimenting with the randomization of time between cue and stimulus, we found that all that occurred was a "blurring" of the preparatory process of the CNV along with a change in degree of accuracy of response. I concluded that to have the clearest signal and the best understanding of what was happening, it was best to have a fixed interval and not introduce any "blur". In these experiments, we are not using the pre-stimulus activity as a baseline. The idea of randomization is to make the average across trials -- the pre-stimulus activity — equal to zero. That wasn't the intent in these experiments. We were effectively making a baseline statistically, by taking the file and randomizing it over time and obtaining estimates of how well things correlated. So the idea of randomization is used to have a zero average of the pre-stimulus activity from which peak amplitude measurements can be obtained. However, if the purpose is otherwise, then I would suggest that you bring your variance under control by using a fixed interval.

THE NEUROELECTRIC SELECTION OF NAVAL AVIATION PERSONNEL: AN EVALUATION

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SUMMARY

We are examining the value of using event related potentials to predict success in naval aviation. In this paper we discuss the background of the project, some methodological considerations, and our approach to the problem. Some early results have become available and are encouraging.

INTRODUCTION

The Selection Problem

The problem of devising rational means to select candidates for flight has been with us for over 75 years now. It has become more important as aircraft have become more complicated and training more expensive. Selection for flight in the U.S. Navy is based on considerations of academic histories, written tests, physical examinations, and biographical information. The net effect is a substantial improvement over random selection. Nevertheless, perhaps 30% of those who enter flight training do not finish (1). Hence there is continuing interest in improving the selection process.

Possibly the first attempt to use the EEG to forecast the performance of naval aviators was carried out by Alexander Forbes and Hallowell Davis as a part of the Pensacola Study of Naval Aviators of 1940-1941 (2,3).[1] Forbes and Davis examined the electroencephalograms (EEGs) of several hundred Navy flight candidates for signs of epilepsy. They found no reliable association between the presence of minor EEG abnormalities and later flight performance. In fact, those subjects who later became very good pilots were slightly more likely to have displayed minor EEG abnormalities than those who failed.[2]

The data of Forbes and Davis were contradicted by the findings of a study carried out at about the same time by Thorner, Gibbs, and Gibbs, at Randolph Field, Texas (4). Harlow Ades examined the question again at Pensacola in 1962 (5), and again failed to obtain clear evidence of an association between minor EEG abnormalities and flight performance.

The emphasis on detecting low-level epilepsy in these studies was logical. The g-forces of tactical flight can cause susceptible individuals to experience vertigo, blank states, and, occasionally, motor seizures; and epilepsy diagnosis was one of the first successful uses of the EEG (e.g., 6). Nevertheless, the weight of the evidence seemed to indicate that routine electroencephalography provided little information beyond that obtained by simply watching students for signs of confusion during the dual flight period of training (5).

Several years ago, the Naval Medical Research and Development Command undertook an exploratory development program, 'Neuroelectric Selection,' to evaluate the use of evoked response electroencephalography in selecting sonar operators and aviation personnel. The sonar work is being carried out by the Naval Health Research Center and the Naval Submarine Medical Research Laboratory. The aviator project grew from a collaboration between the Naval Aerospace Medical Research Laboratory (NAMRL), in Pensacola, and the Navy Personnel Research and Development Center (NPRDC), San Diego. Here we present an outline of the work with aviation personnel.

During the first phase of the project, we evaluated a set of event related potential (ERP) tests and analytical software developed jointly by NAMRL and NPRDC. The ERP tests, developed by NPRDC and examined there in several contexts (7), were designed to provide measures of sensory and attentional mechanisms. The analytical routines developed at NAMRL for this project were designed to automate the processes of artifact detection, data reduction, and response measurement, and to make it possible to handle large data sets efficiently. Some early results from this study will be described presently.

[1] According to Thorner, Gibbs, and Gibbs (4), the first electroencephalographic study of student aviators was performed in Canada, by Goodwin and co-workers.

[2] Gastaut, Lee, and Laboureur (18), in France, examined the possibility that the hazards of naval aviation attract individuals with abnormal EEGs, and concluded not.

We are currently engaged in a second evaluation, of an ERP testing system developed by the the U.S. Air Force and others: the 'Neuropsychological Workload Test Battery' (NWTB). This evaluation involves recording ERPs under conditions thought to assess memory, attention, vigilance, and multiple-task performance abilities. A more complete description of the NWTB system can be found in reference 8. The results of our study of the NWTB will be described in later reports.

METHODS

Experimental Design

We are interested in using ERP-based tests to forecast performance. Hence we are interested in the tests' predictive validities. The 'predictive validity' of a test is the accuracy with which it predicts some future behavior. This can be estimated by (1) giving the test to candidates, before they enter a job and (2) comparing test scores and performance, after the candidates have developed work histories. Our approach has been to administer the ERP tests to students before they enter flight training, and then compare the test data with their performance, after they complete the various stages of flight training.

By the time they arrive at our laboratory in Pensacola, our subjects have met all the requirements of the aviation screening process, save flight training itself. Testing at this point in time is perhaps the optimal way to judge a test that would be added to an existing battery, because it controls for the fact that techniques already in use produce useful information (see also reference 9, pp. 33-35). Evidence that a test forecasts well in populations of pre-screened subjects means not only that it predicts, but that it makes information the screening procedure now in use does not pick up.

Thus far we have obtained data from about 205 naval pilot and flight officer candidates, overall; we are continuing to obtain ERP measurements from new subjects. A total of 150 subjects participated in the study we will discuss here. The data we will describe are from 135 of the 150. The missing 15 subjects' data were lost due to equipment failure or test protocol violations, or were too noisy to analyze. No data were rejected by eye (we will discuss our artifact rejection techniques, presently).

Recording Procedures

The ERP data we will discuss here were recorded from 8 scalp locations. These comprised 2 symmetrically located frontal sites, F3 and F4 in International 10/20 notation; 2 symmetrical temporal sites, T3 and T4; a central scalp site, CZ; 2 symmetrical parietal sites, P3 and P4; and an occipital site just left of midline, O1. The EEG reference electrode was placed at nasion; a central frontal electrode served as ground. Eye movements were monitored by recording the electro-oculogram (EOG) from two sets of electrodes: A vertical EOG derivation was recorded in bipolar fashion from electrodes placed above and below the outer canthus of the left eye; an oblique-horizontal derivation was recorded between nasion and a point below the outer canthus. We will call the latter derivation 'horizontal' in the remainder of this report, for brevity.

The 8 channels of EEG were amplified by a factor of 20,000 and led to analog filters with attenuation rates of 6 dB/octave and passbands extending from .1 to 100 Hz. The EOG was amplified by 2,000, but otherwise treated like the EEG. The amplified and filtered signals were converted to digital format at 256 Hz.

ERP Test Protocols

Each subject was told the purpose and nature of the tests and, after electrode placement, seated in a comfortable chair in a dimly lit, IAC sound attenuated room.

The stimuli used in the test were checkerboard flashes, tones, and flash-tone compounds. The compound ('bimodal') stimuli were created by turning on the flash and the tone at the same time.

The visual stimulus was black and white checkerboard (16x16) located 1 m in front of the subject, subtending an overall visual angle of 4.6 degrees. To produce a flash, the checkerboard was back illuminated for 5 ms at approximately 5ft-L.

The auditory stimulus was a 10-ms segment of 1,000 Hz sinusoid, delivered to both ears through headphones at 80 dB SPL (A-weighted). A background of continuous, 40-dB, Gaussian noise was presented over the headphones, to provide an acoustical noise floor.

The three stimulus types were presented in random order, in 4 blocks of 30 trials each. Each stimulus was turned on at the midpoint of a 2-sec EEG recording interval; successive recording intervals followed one another after .5 to 1.5 s, at random.

Each subject served in 2 attentional conditions, divided and focused. In the divided attention conditions, the subject was asked to mentally count each stimulus delivered. In the focused attention conditions, the subject was asked to count each tone that occurred without an accompanying flash. The order in which the two attentional conditions were distributed across the four blocks of trials was: divided, focused, focused, divided.

Analysis of the ERP data

As was mentioned previously, a substantial part of our work has been concerned with developing procedures for analyzing evoked response data. McFarland and Franzen (3, p. 68) questioned the reliability of EEG measurements in their summary of Forbes and Davis's study.[3] Their concerns retain some validity. The strategy of eliminating suspect data by eye, for example, is not unknown in contemporary ERP research, and is a potential source of bias.

The approach we have used has been to submit the data to a set of computer programs that first examine the raw EEG and EOG for voltage-by-time patterns resembling several types of electrical artifacts (eye movements, transients, large absolute amplitudes, and large and small RMS amplitudes). Sampling intervals that contain artifacts judged uncorrectable, by one of the programs, are marked at this point and disregarded later. The remaining EEG is then digitally filtered by calculating a 3-point moving average (which is a zero phase shift filter). Segments of EEG that were identified as containing eye movement artifacts are then "corrected" by subtracting appropriately scaled portions of the vertical and horizontal EOG from the EEG, using a modified version of the time domain procedure described by Gratton et al. (10). Then the corrected EEG is checked again, using the routines previously described, and any records that still contain artifacts are rejected permanently. Data surviving the foregoing are then signal averaged in the conventional way. The averaged ERPs and the original data are saved, along with a record of the artifacts encountered along the way.

RESULTS

Waveform Descriptions

Figures 1 through 3 show grand average ERPs calculated using data from 135 subjects. The averaged responses from a given recording site are superimposed in the figures, with their voltage excursions drawn relative to the mean voltage during the 500 ms preceding the stimulus. Responses from different sites are drawn with their ordinates offset to make them more visible.

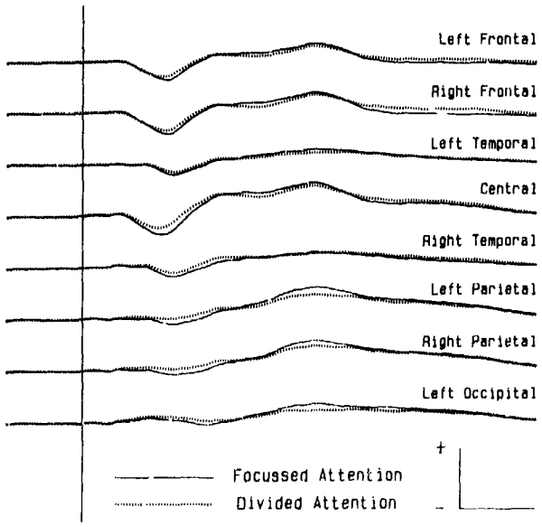

Figure 1. Auditory responses averaged across 135 subjects. The stimulus is turned on at the vertical line. The calibration mark shows 100 ms and 20 μV.

[3] McFarland and Franzen (3) noted that an analysis of a subset of the Forbes and Davis data using Forbes' modification of Mary Brazier's scoring technique did produce a low correlation that did not hold up in replication.

The surface topographies of the auditory and visual responses appear to be conventional. The major negative peak between about 70-170 ms poststimulus, N1, is largest at central and frontal sites in responses to auditory stimuli (Figure 1). The visually evoked N1 is largest occipitally and parietally and occurs somewhat later (Figure 2). Regardless of modality, the major positive peak between 300 and 450 ms poststimulus, P3, is largest parietally and centrally.

The topographies of responses to the auditory-visual compounds are more symmetrical from front to rear during, roughly, the first 150 ms poststimulus. This is consistent with the idea that much of the "bimodal" responding recorded from the surface in this latency range represents the summed activities of cells that respond to light or sound, but not both. By about 300 ms the activity has resolved, nonadditively, into conventional central-parietal P3 distributions.

Shifts of attention among the stimulus classes are associated with changes in N1 amplitudes (cf. reference 11). The greatest change in the auditory N1 occurs at vertex; the absolute amplitudes of these responses are larger when attention is directed toward tones.

Bimodal stimuli, like auditory stimuli, produce larger N1s at most sites when attention is focused on tones (Figure 3). The simplest explanation is that the auditory N1 is at least partly generated by neurons whose acoustical responses vary with attention, but whose photic responses are sluggish or nil.

Visual responses in the N1 latency range are also relatively negative, at some sites, when attention is focused on the tones (see Figure 2). It is possible that the visual N1 is actually driven positive in the divided attention condition, making the focused attention N1 negative by comparison: The visual N1, which has a relatively long latency, may overlap the initial segment of P3 and, as might be expected, the visual P3 is more positive when attention is divided and, hence, partly directed toward vision. Thus the larger P3 may shift the superimposed, divided attention N1 upward, producing the apparent negativity of the focused attention N1.

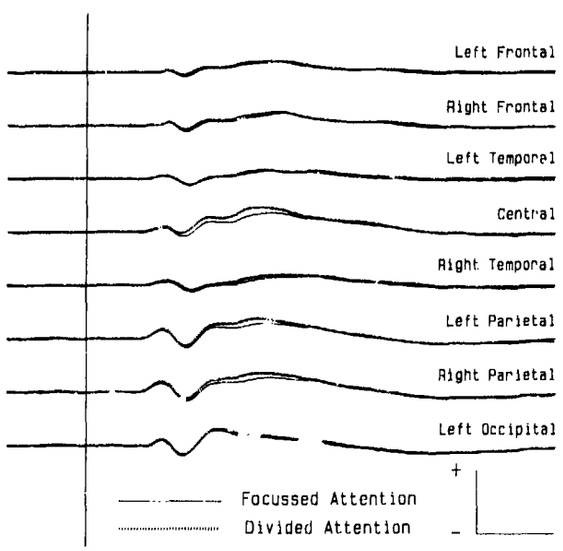

Figure 2. Visual responses averaged across 135 subjects. The calibrations are 100 ms and 20 μV.

Changes in auditory and visual P3 responses accompanying shifts of attention are consistent with accepted descriptions of the wave's behavior (see reference 12, for a review). The largest changes occur at parietal and central sites. Auditory P3 responses tend to be larger and earlier when attention is focused on tones, smaller and later when attention is withdrawn from tones and distributed among all stimuli. Visual P3 responses are larger when attention is distributed across all stimuli and smaller when it is focused on tones.

The bimodal P3 responses are more complicated, differing somewhat at the central and parietal recording sites. We will discuss their behavior in a subsequent report.

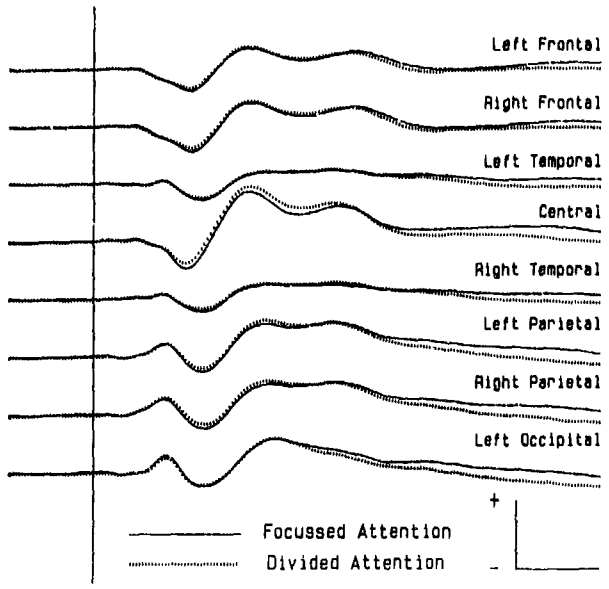

Figure 3. Responses to auditory-visual compounds averaged across 135 subjects. The calibrations are 100 ms and 20 μV.

The Relation between Flight Performance and ERPs

The best predictions of flight performance we have observed thus far were derived from frontal N1 responses. Figure 4 illustrates what appears to be the most robust of these. The ordinate in Figure 4 is primary flight grade. The abcissa is the difference between N1 latencies at the left and right frontal recording sites.

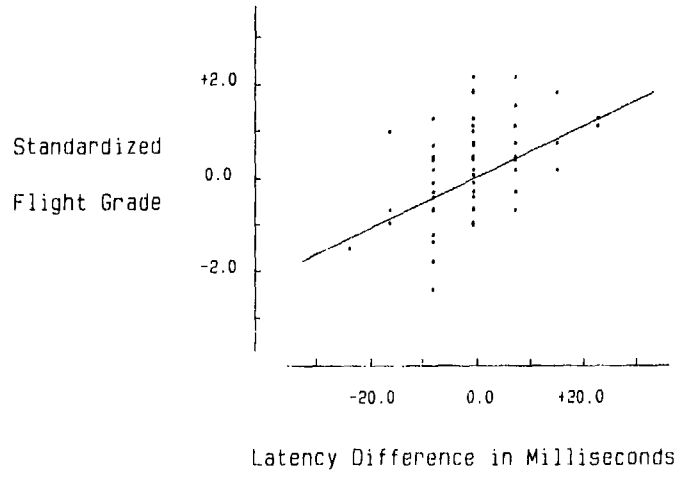

Figure 4. Flight performance versus the difference in N1 latencies at left and right frontal electrodes. Positive differences indicate the right hemisphere leads.

The responses whose measurements are plotted in Figure 4 were evoked by tones, in the condition in which attention was focused on the tones. The subjects are a combined group of student naval aviators (SNAs, pilot trainees) and student flight officers (SNFOs, who, for the most part, will become bombadier/navigators and weapons officers). The SNA and SNFO grades have been standardized by subtracting the appropriate group mean from each grade and dividing by that group's standard deviation. The 89 subjects whose data are shown in Figure 4 are the entire subset of individuals for whom complete sets of both ERP and primary flight data have become available to date. The striated appearance of the data swarm is due to a somewhat coarse binning of the latencies.

The correlation between flight performance and the ERP measurements of Figure 4 is about .45. Its single-test statistical significance level is $p<.000025$. Multiplying p by 72, to account for the 72 correlations between hemispheric difference measurements we examined, yields a conservatively corrected significance level of .0018, for this family of tests (see reference 13 for a discussion of the Bonferroni correction of significance levels). The data of Figure 4 were the only ERP response peak measurements that predicted well enough to survive such an adjustment of significance levels.

We cross validated this result by predicting each student's flight grade, in each case using an equation derived from all of the data except his (14). The value of the correlation coefficient implied by the resulting prediction errors was .43, very near the original estimate of .45. A conventional formula adjustment of the correlation coefficient, taking into account its expected decrease in new samples, produced a "shrunken" correlation of .44, midway between the original and cross-validation estimates.

DISCUSSION

The magnitudes of the performance-ERP correlations we have observed thus far compare well with values reported for many conventional psychometric tests. They are, however, not extremely large. A correlation of .45 implies that the overall prediction error will be reduced 11% when the test is used. This is relative to the RMS error associated with guessing that each student will perform at the mean, the best one can do when there is no other information. However, a correlation of this magnitude does approach an economically useful level, because the absolute cost of flight training makes even small percentage savings worthwhile. We have, so far, looked only at performance in the first stage of flight training; the economics will improve if our predictors can forecast events still farther in the future.

The magnitude of the correlation between performance and the hemispheric difference measurements was something of a surprise to us, because lateralized effects in ERP data tend to be small, and not always reliable. It is not unprecedented, however. Our decision to examine hemispheric differences was based on Lewis and Rimland's report (15) that asymmetries in visual response RMS amplitudes were associated with performance differences in a sample of experienced pilots and flight officers. We have not yet found clear evidence of correlations between performance levels and either peak or RMS amplitude measurements. Nor were the visual responses in our data significantly related to flight performance. Nor have we found systematic differences between the surface topographies of responses from pilots and flight officers, as did Lewis and Rimland.

Our failure to observe these effects could be due to noise in our data or, perhaps, to differences in experimental design. The Lewis and Rimland study (15) had the form of a 'concurrent' validation design, in which subjects' performance levels are known at the time of testing. This is usually the design of choice for validating achievement and diagnostic tests (16). An advantage of the concurrent design is that it can be more powerful than the prediction design used here. This is because subjects can be selected to concentrate observations on high and low performing individuals. We have used a prediction design instead, because it is generally the most appropriate way to evaluate selection tests (16). This is because it protects against biases that tend to occur when the quality of the subject's work is known in advance and, more fundamentally, because the only way to find out whether a test actually forecasts is to try using it to forecast

Measurements of P3 have not yet proven useful, something of a disappointment as P3 is comparatively large and easy to detect, and because theoretical reasons can be given for why it should predict. This could be a failing of our test protocols. The differences between focused and divided attention responses are not very large, and perhaps a genuine relation between P3 and performance is simply masked by noise. It could also be that we have not yet analyzed the data in the right way. Also, recall that our experimental design does not estimate the ability of ERP measurements to predict performance *per se*, but their ability to predict performance after existing prediction techniques have been applied; perhaps P3 adds nothing useful to the available information.

In light of the immediately preceding remarks, it seems appropriate to comment on a methodological problem in applied EEG research. The comment applies to multiple channel EEG research in general.

The wealth of numbers the technique generates renders conventional statistical analysis extremely difficult. The experiment described here, for example, produced a set of averaged evoked responses consisting of 12,288 mean data points for each subject, not an especially large number by current standards. A predictor set this large affords many opportunities to be misled by chance properties of the data: Given a sufficient number of subjects, a stepwise multiple regression analysis would implicitly consider as many as 12,288! different prediction equations (fewer if the predictors happened to be uncorrelated).

Reducing the data to a few amplitude and latency measurements per electrode helps, but only to a degree. For example, we need about 180 subjects if we obtain 4 measurements from each of 8 electrodes and want to detect correlations of .4, using arbitrary subsets of 4 predictors each. This assumes that a false positive rate of 5% is tolerable. About 230 subjects are required for the same analysis if we use 16 electrodes; about 285 if we use 32. Several times this number may be necessary if we cannot specify the number of measurements in a "pattern" before looking at the data.[4]

The required sample size also becomes larger if we want to detect genuine correlations of .4 with odds much better than chance. This is because sample variation will cause tests for a phenomenon that is just detectable at, for example, p=.05 to fail about half the time (17). This fact has almost certainly contributed to difficulties in replicating EEG and ERP studies (recall McFarland and Franzen's criticism (3).

Although sample sizes amounting to large fractions of 1,000 subjects are not common in contemporary EEG research, they are not unknown. Forbes and Davis's Pensacola study was based on recordings from just under 1,000 subjects (2); Ades' was based on data from nearly 1400 (5). Gastaut et al. recorded from over 1300 (18). Studies of this size can produce extremely useful information. This is especially true for negative results, which are useful, and which are convincingly demonstrated only in very powerful experiments.

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[4] These values are for the case in which all possible subsets of 4 predictors are examined. They were calculated by iteration, using Diehr and Hoflin's technique for approximating critical values of multiple R^2 in Best Subset multiple regression (19).

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DISCLAIMERS

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Volunteer subjects were recruited, evaluated, and employed in accordance with the procedures specified in Department of Defense Directive 3216.2 and Secretary of the Navy Instruction 3900.39 series. These instructions are based upon voluntary informed consent and meet or exceed the provisions of prevailing national and international guidelines.

DISCUSSION

KAUFMAN, US: It's extremely interesting that Dr. McCallum and Dr. Gevins point to the late components and slow phenomena as being the most labile and affected by cognitive processes; whereas, the earlier components seem to be so little affected that they are less interesting. If the slow activity tells us most about cognitive phenomena — higher-order processes — then why do you feel that you have any hope of providing us with some practical ways for selecting personnel for aircrew. Your primary effects seem to be sensory evoked potentials — evoked by checkerboards, tone bursts, etc. The probability of getting anything, even hypothetically, from your technique that would tell us whether or not a pilot could be more-or-less likely to land effectively on an aircraft carrier seems to be very remote. I would suggest, constructively, that you shift focus toward the later components and look at ways in which these components interact with task variables that are more strict. That is, study those task variables that have more face validity in terms of the actual cognitive requirements of piloting an aircraft.

STANNY, US: With regard to the point about N100: That just happened; it was there in the data when we looked at P300. P300 was not significant in the analysis that we ran. Regarding the possibility of looking at measurements with more face validity, it is our intention to do so. The present study was an evaluation of a set of protocols that someone else had developed and allowed us to use.

KAUFMAN, US: Yes, P300 was in your data, but the manipulations weren't such as to make P300 do anything, or N100. I think the sensory evoked response as a rather primitive construct of neural efficiency has seen its day in some of this work.

EVOKED POTENTIAL ANALYSIS OF IMPACT ACCELERATION EXPERIMENTS

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SUMMARY

This report focuses on the use of somatosensory evoked potentials (SEPs) as an assessment tool for transient injury in rhesus macaques undergoing impact acceleration in the -Gx direction. Adult male rhesus macaques, seated on a sled and restrained (except for the head and neck), were accelerated at peak sled accelerations ranging from 95.8 to 1039.6 m/sec2. The sled was decelerated by friction forces ranging from 0.7 to 3.0 m/sec2. Somatosensory stimuli were delivered prior to, during, and after impact. Amplified SEP activity was telemetered and recorded on magnetic tape. The raw SEP data were digitized and analyzed off-line.

Results for cortical SEPs are consistent with and extend previous analyses, suggesting a threshold for transitory changes in cervical SEP latencies in macaques at peak -Gx sled accelerations below 550 m/sec2. This threshold is below the threshold for single impact -Gx neuropathological injury in macaques (800 m/sec2), and suggests a role for cortical SEPs in establishing injury criteria for humans.

INTRODUCTION

A primary mission of the Naval Biodynamics Laboratory (NBDL) is to investigate the biomechanical and physiological effects of impact on human and non-human primates. Impact injuries to the head and neck are a major trauma problem for both military and civilian populations. These injuries can result from direct impact (collision of the head or neck with another object) or indirect impact (impact acceleration which is transmitted from the torso to the head via the neck). Evoked potentials have proved useful in investigating impact injuries since the early work with monkeys (1). This research, combined with the experiments of Friede (2) using cats, has implicated the cervico-medullary junction as the vulnerable site for cervical stretch and impact. Since then, SEPs have become a primary tool of research in impact injury research at NBDL (3, 4) and other laboratories (5). In particular, much has been learned about indirect impact injuries in the rhesus macaque through the use of SEPs. Previous results (4) showed that the latency of cervical spine SEPs were significantly increased after indirect impact in the -Gx direction. Since that report, additional data have been analyzed using a revised evoked potential analysis system. The initial results of this analysis are reported here and extend previous results (4) to include cortical SEPs measured before and after indirect impact.

METHOD

Baseline hematology, biochemistry and clinical evaluations (including radiography) were completed prior to surgically implanting electrodes in eight adult male rhesus macaques. All surgery was performed under general barbiturate anesthesia. An array of three spinal cord stimulating electrodes was placed in the epidural space of the L1-L2 area. A similar array of three cervical recording electrodes was placed in the epidural space of the atlanto-occipital area. Two cortical recording electrode arrays, consisting of five electrodes each, were placed bilaterally in the epidural space over the primary somatosensory cortex. Final placement of the cervical and cortical electrodes were guided by interpretation of evoked potentials produced by stimulating the L1-L2 electrode. The cranial and cervical leads were brought out through an implanted cranial pedestal. Post-surgical radiographs of all implants were then taken, followed by a three month post surgical recovery period. Details of the surgical procedure are provided in Appendix I.

The macaques (restrained except for the head and neck) were seated on a standard NBDL sled and accelerated down a 213 meter horizontal track by a Bendix 12 inch HYGE system with a piston stroke ranging from 0.7 to 1.62 meters. This system is capable of generating 996,750 newtons of thrust, imparting forces up to 200 Gs (1958 m/sec2) for durations as long as 90 milliseconds to the 410 kilogram sled. In this series of experiments the peak acceleration was 1039.6 m/sec2. An environmentally controlled housing surrounds the track and the sled was decelerated by friction forces ranging from 0.7 to 3 m/sec2. Amplified EKG and SEP signals were telemetered, along with stimulus markers and precision time codes, through an FM multiplex system. The 3 db bandpasses were 0.1 to 100 Hz for EKG and 10 to 1500 Hz for cortical SEP data. Somatosensory stimuli (0.2 millisecond rectangular constant current pulses) were delivered prior to, during, and after impact. The raw SEP data were digitized and analyzed off-line.

Linear and angular acceleration were determined using six linear accelerometers locked to the cranial pedestal (see Appendix I) which was bolted to the calvarium.

Biplanar x-ray anthropometry gave precise three-dimensional spatial coordinates of the instrumentation relative to the head anatomical coordinate system (6, 7, 8). An inertial data acquisition system sampled each of the 24 channels of inertial data at 2000 samples/second and stored the digitized data on a magnetic disc in real time. The digitized data were then scaled and transferred to a digital tape for off-line analysis. Head-mounted photo targets were filmed using three high-speed rotary prism cameras operating at 1000 frames/second (9, 10). All cameras were calibrated with respect to a known point on the sled (11). Target location with respect to the sled reference was digitized, producing three-dimensional head trajectory information (6, 12, 13, 14).

The eight rhesus macaques were subjected to a total of sixteen runs with sled accelerations ranging from 95.5 to 1039.6 m/sec2 in the -Gx vector. Each animal made two runs a day; a low level control run of approximately 100 m/sec2, and a higher level test run. Any clinical signs were noted, and post-run x-rays taken. The animals were maintained for 28 days before being sacrificed. Necropsy reports were prepared for all animals. Averaged evoked potentials for right and left cortical and cervical electrode sites were computed. However, only cortically recorded data are reported here. Averaged evoked potentials were computed for each two-second segment starting two minutes prior to impact until five minutes post impact. The stimulus presentation rate was five/second, which meant averages were composed of 7 to 10 sweeps each. A sweep lasted from 40 milliseconds pre-stimulus to 40 milliseconds post-stimulus. Sweeps (750 points) with more than 38 clips were rejected. Additionally, a pre-impact super-average was computed from all data in the two minute period preceding impact. Normalized (amplitude independent) cross-correlations were computed using a template to determine latency shifts produced by impact (15). The templates were chosen from each individual pre-impact super-average to include the components around 10 milliseconds. The windows for the cross-correlations extended from -0.5 to +3.0 milliseconds of the individual templates.

RESULTS

Only one of the animals showed any clinical signs during the twenty-eight days following the last run. This animal seemed reluctant to sit up or use his left arm. Necropsy findings revealed posterior damage around the spinous process C1 attributable to the experimental impact. A second animal showed no clinical signs, but the necropsy findings revealed demyelination secondary to atlanto-occipital damage due to impact. This extended into the lateral tracts, through the thoracic cord to L1, where massive glial scar tissue appeared. A third animal seemed to be having respiratory trouble during the 30 minute post run recording time. Doxapram was administered, but the animal died 22 minutes post impact. The cause was attributed to the restraint straps being too tight for breathing. In addition, the necropsy revealed scattered minimal subdural and subarachnoid hemorrhages around the T12 to L1 area of the spinal cord.

Photographic documentation of the position of the head at the moment of impact showed unexpected variations from the intended head-up neck-up position. This variability in initial conditions may explain the difference between injured and uninjured animals run at the same impact levels.

Figures 1 to 6 illustrate the effects of impact acceleration on cortical evoked potentials. Odd numbered figures represent low-level control runs. The following figure is the higher impact run for that animal. Each of the three pairs is from a different animal, with the pairs arranged in ascending level of impact acceleration. These impact levels were chosen, based on years of research with the animal sled and restraint system, to include: a moderate level, a borderline level and a probable injury level. The top evoked potential in each column is a super-average of all averages for the two minutes preceding impact. The other averages (n=10) are taken at the indicated time intervals relative to impact. One animal (runs LX4792 and LX4795) did not have a right cortical recording.

Figure 7 illustrates the results of the cross-correlations for all eight test level runs, with two control level runs at the bottom for comparison. The injured animals were runs LX4799, LX4803 and LX4812. Higher levels of impact show greater latency offset and longer recovery times than lower levels of impact, while the control level runs showed no changes.

DISCUSSION

The present work confirms earlier reports (4) that latency shifts due to impact occur at levels of acceleration below the threshold for pathological injury (16), and substantiates the neuropathology findings of others that the cervico-medullary junction is the most sensitive site in comparable impact situations. For this component set, latency shifts were found at all levels of impact above 100 m/sec2. This increased sensitivity reflects improvements in data acquisition and analysis made since the earlier work.

Amplitudes were not examined here because previously (4) it was found that cortical EP amplitudes were not useful for indicating the threshold of injury. Future analysis will include amplitude variables.

Follow-up experiments have been conducted to assess the effects of anesthetics on these EP changes. If the results are comparable, then the confounding problem of variability in initial head-neck positions revealed by the photo data for this series can be eliminated.

The major implication of these results is that SEPs continue to show great promise as an index of pre-pathological injury levels in impact research. Application of these techniques in the human impact injury research program at NBDL is now in progress, along with the enlargement of the borderline impact level database for animals.

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The opinions and interpretations contained herein are those of the authors and do not necessarily represent the views, policies, or endorsement of the Department of the Navy or any other government agency.

The animals used in this study were handled in accordance with the principles outlined in the 'Guide for the Care and Use of Laboratory Animals (National Institutes of Health Document No. NIH 80-23),' established by the Institute of Laboratory Animal Resources, National Research Council, Bethesda, MD.

Trade names of materials and/or products of commercial or nongovernment organizations are cited as needed for precision. These citations do not constitute official endorsement or approval of the use of such commercial materials and/or products.

Projects conducted at NBDL are a team effort, reflecting work by many members of the staff. In addition to those people, thanks are due to Mr. Jerry Vandergrift for extensive programming assistance.

LX4809 $-G_x$: 100.6 M/S^2

CORTICAL

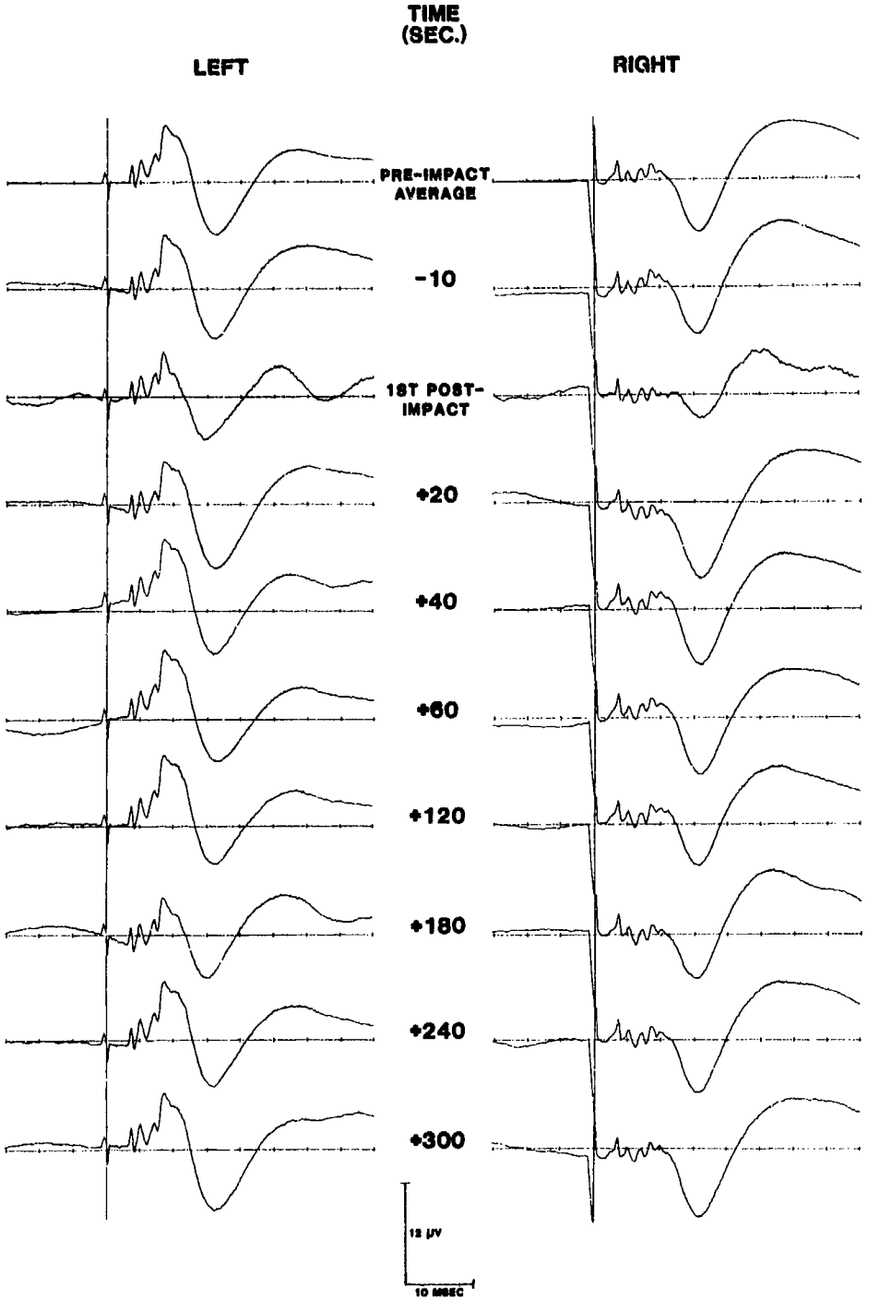

FIGURE 1

LX4810

$-G_x$: 545.2 M/S^2

CORTICAL

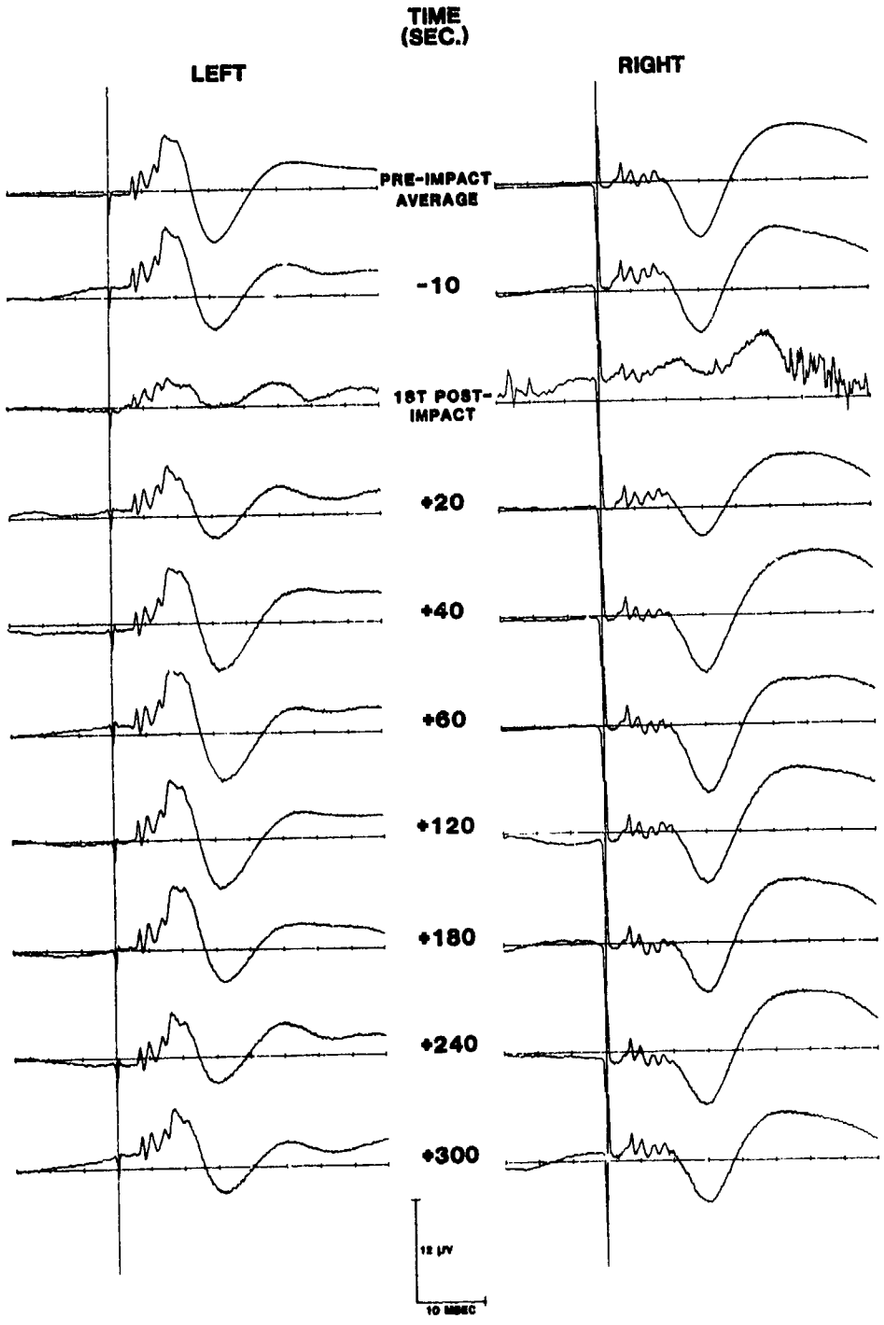

FIGURE 2

LX4815

$-G_x$: 101.0 M/S^2

CORTICAL

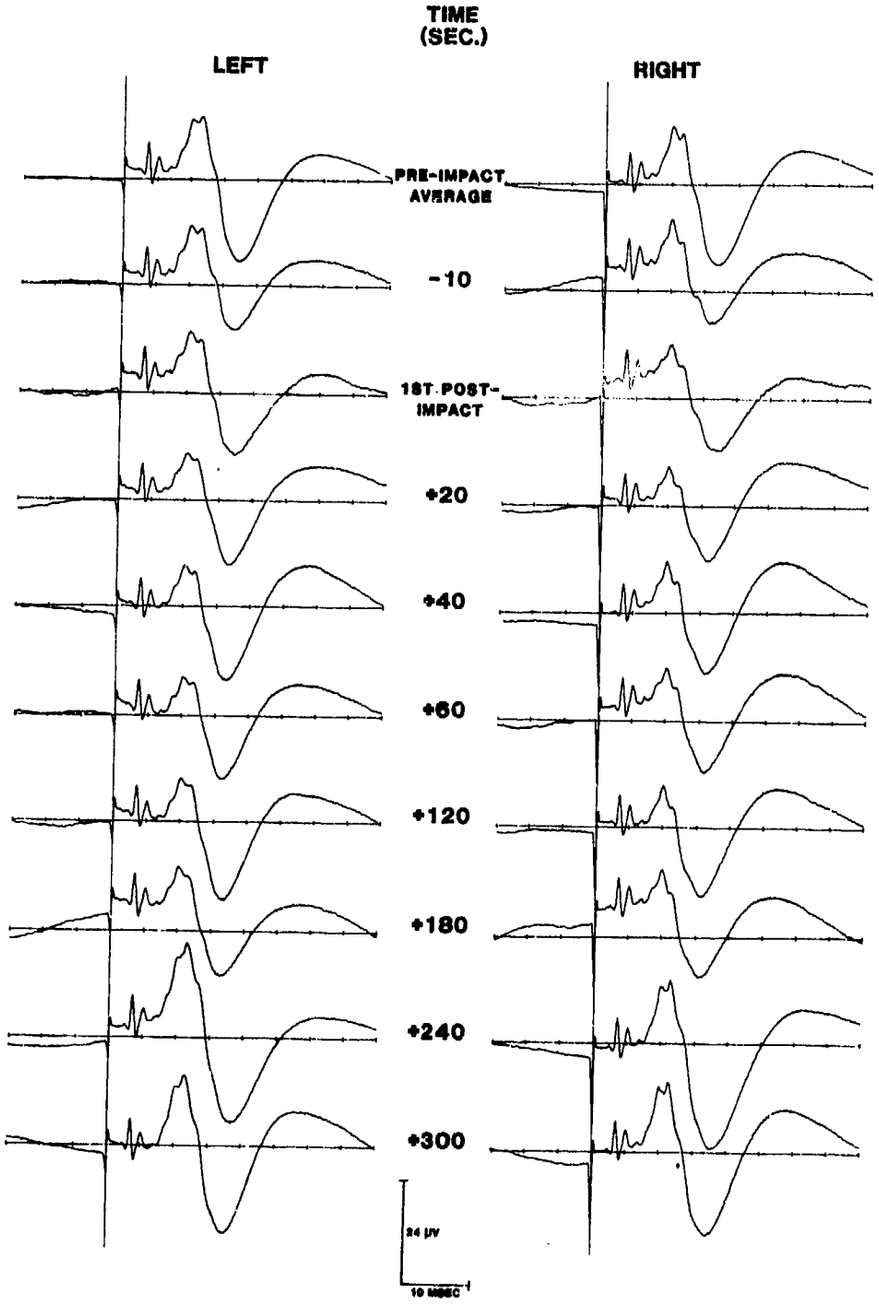

FIGURE 3

LX4816

$-G_x$: 700.3 M/S^2

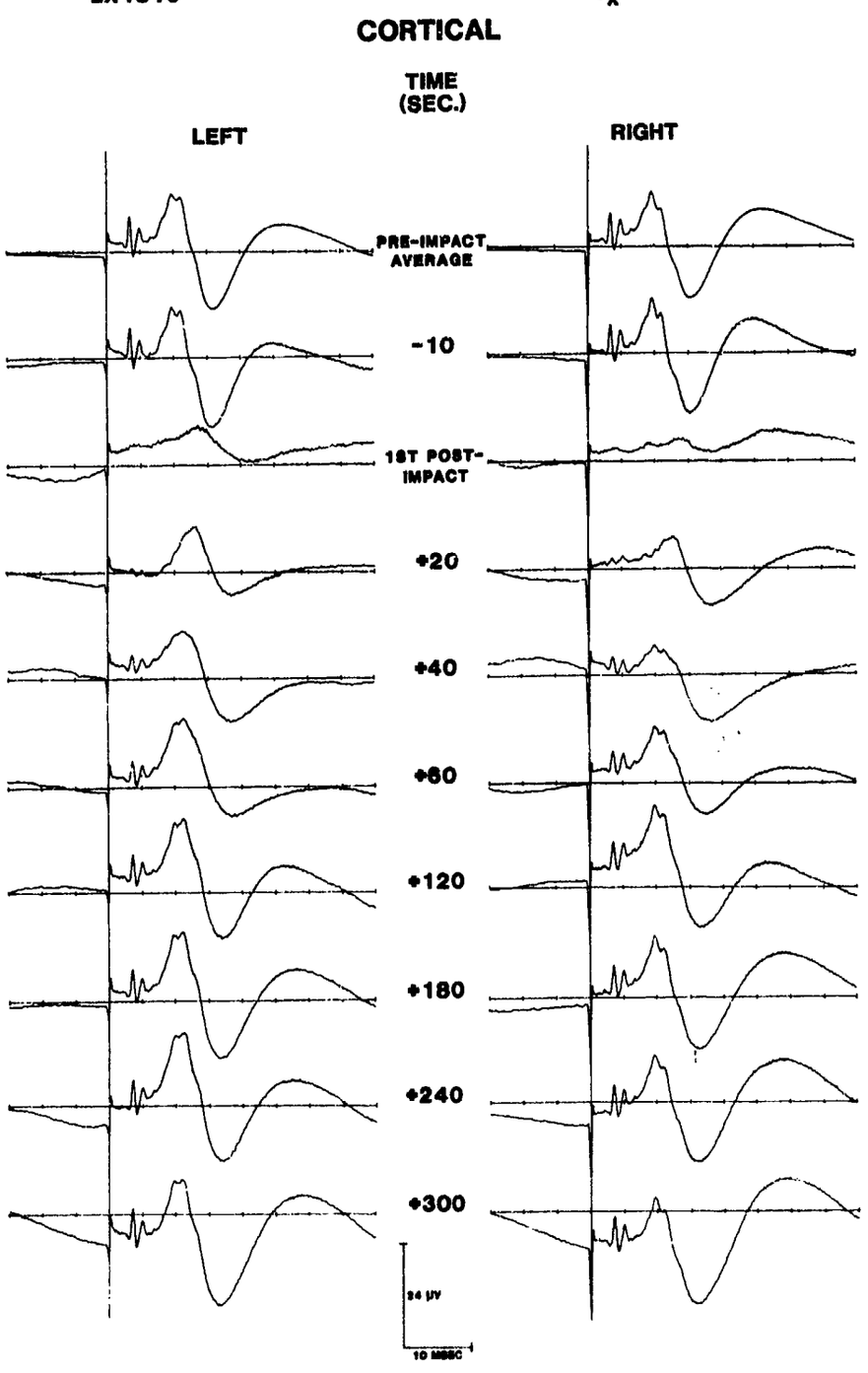

FIGURE 4

LX4792

$-G_x$: 95.5 M/S^2

CORTICAL

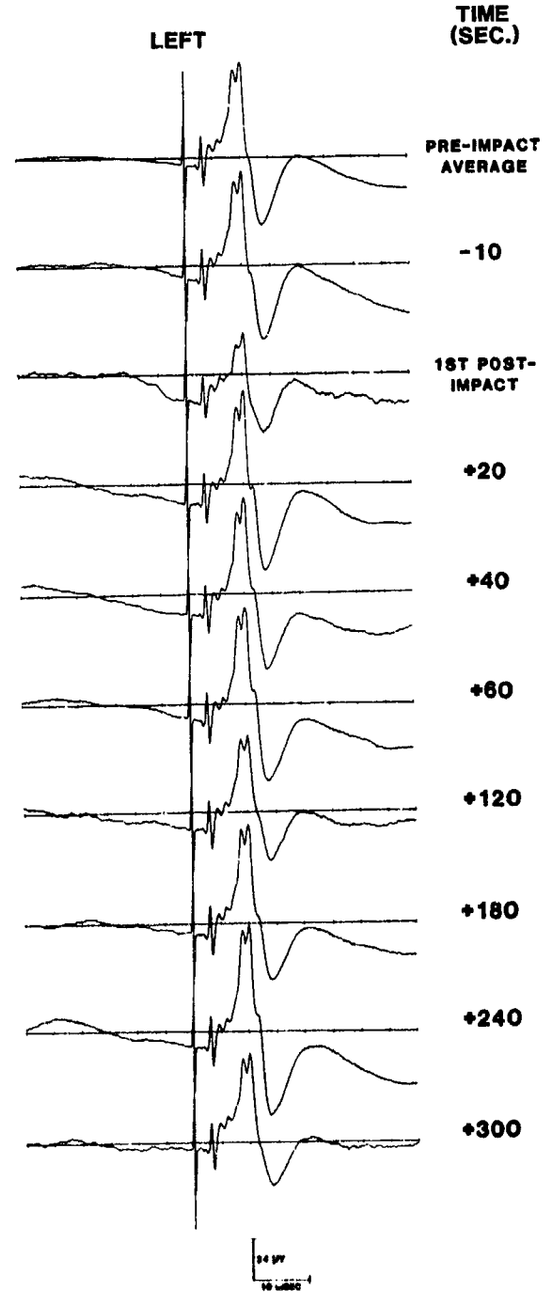

FIGURE 5

LX4795

$-G_x$: 985.1 M/S^2

CORTICAL

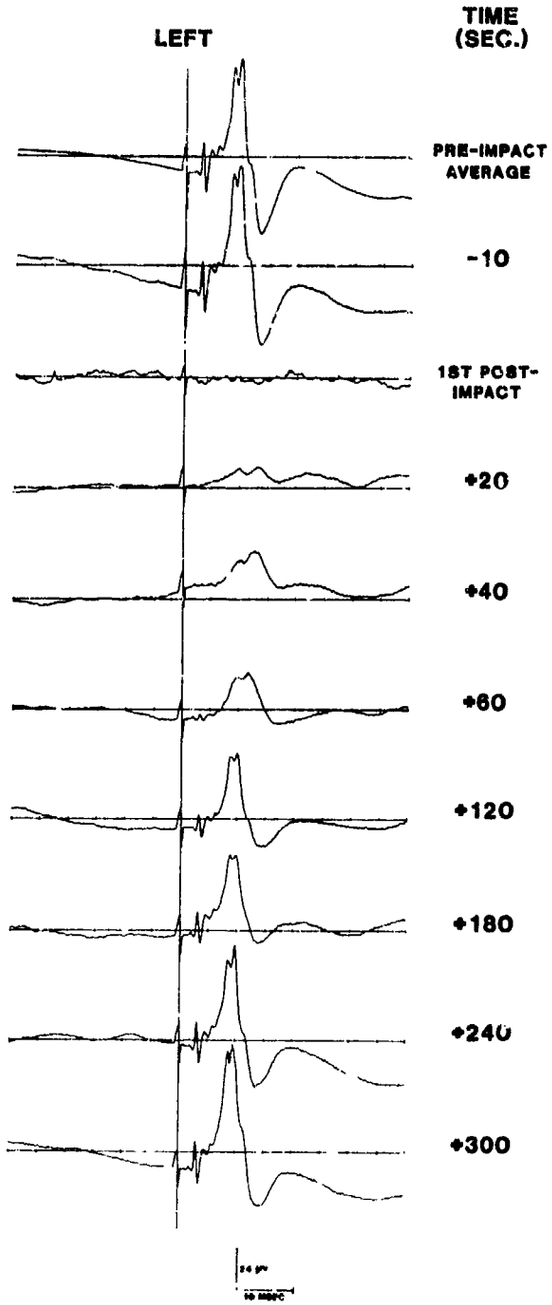

FIGURE 6

LATENCY OFFSETS

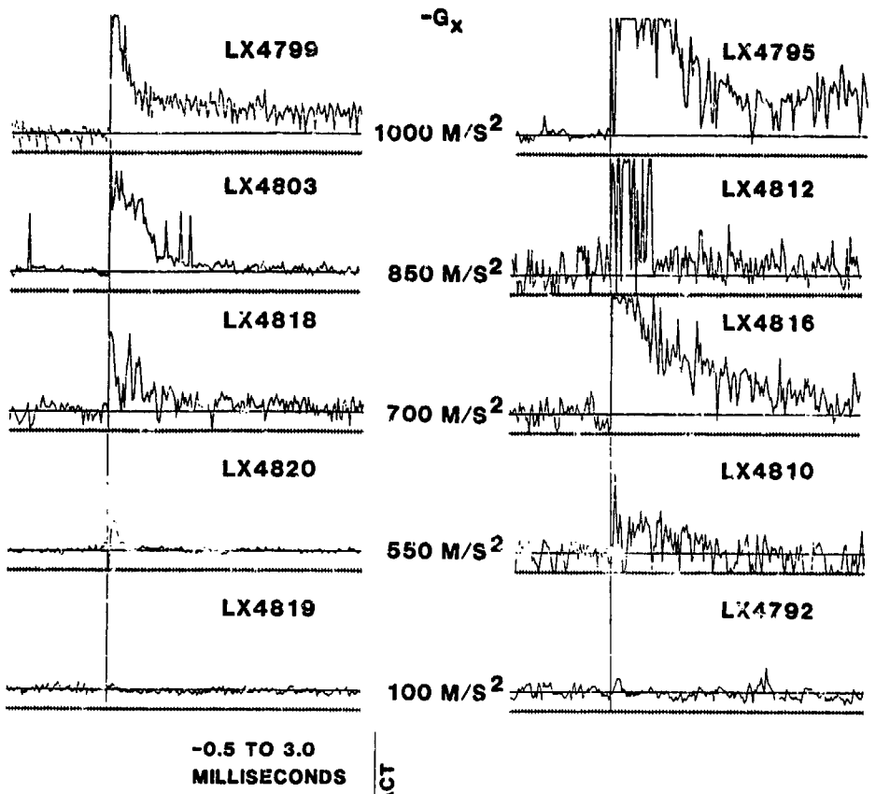

FIGURE 7

APPENDIX I

The animals were tranquilized with Ketamine, I.M., given atropine, S.Q., and transported to the surgical prep room. An indwelling catheter was placed in the saphenous vein and the monkeys brought to a surgical anesthetic level with Surital, I.V. They were then endotracheally intubated and maintained on halothane, nitrous oxide and oxygen. Following clipping and shaving of the head and spinal cord areas, and an initial surgical scrub, the animals were placed prone on the surgical table with the head restrained in a stereotaxic unit. After a final surgical scrub of the head and cervical and lumbar surgical sites, the head and cervical sites were covered with sterile drapes and the lumbar site was covered with a windowed sterile drape for the first surgical procedure.

Using electrocautery, a midline incision (1.0 to 1.5 inches) was made over the L1-L2 area and the fascia and muscle reflected laterally by blunt dissection. Electrocautery was used to expose the spinous process and body of vertebrae L1. The spinous process was then rongeured away to expose the dorsal epidural surface of the cord. A triplicate electrode was placed on the surface of the cord with the attached wire extending outside the muscle and fascia. The electrode was anchored in place and the muscle and fascia closed with 4-0 Dexon suture. The skin was then closed over the connecting wires which were left in place. For the cervical electrode placement the head was rotated toward the chest to place the neck area in a flexed position. Using electrocautery, a 1.5 to 2.0 inch midline incision was made distal to the occipital crest in the skin of the neck. Fascia and muscles were reflected laterally by blunt dissection to expose the area of the atlanto-occipital interface. A triplicate, keel electrode was placed epidurally in the foramen magnum and anchored in place. Muscle and fascia were closed with 4-0 Dexon. The skin of the upper neck and occipital area was then bluntly undermined for placing the electrode connecting wire in the subcutaneous tissue of the occipital area. The skin incision was then temporarily closed and the electrode tested by stimulating the L1-L2 electrode with a 0.2 millisecond rectangular electrical pulse and monitoring the cervical electrode for an adequate SEP. Following testing of the electrodes, the skin incision was closed with 4-0 Dexon.

Two weeks after the above procedure, using similar anesthetic and surgical preparation procedures, the cortical electrodes were impianted. Using electrocautery, an elliptical window, approximately 1.5 by 2.0 inches, was cut in the skin of the head in the median line posterior to the orbital ridge, with the long axis running anterior-posterior. The incised skin was removed by blunt dissection and hemorrhaging was controlled by electrocautery. The exposed fascia and periosteum were then removed with periosteal elevators and the muscle reflected laterally by blunt dissection. The exposed skull was scraped and any prominent mid-sagittal crest was removed with a carbide dental burr. A trephine hole, approximately 12 to 16 mm in diameter, was made on each side of the midline and centered on the ear line (anterior-posterior). When trephining, extreme care was taken not to injure the dura or epidural vessels. Following trephining, the holes were covered with sterile cotton pads until it was time to place the cortical electrodes. Six to eight especially prepared stainless steel bolts were then placed in the skull with the threads and nuts on the outside of the skull using drilled "T" slots to provide an anchor for the pedestal to be formed later. The "T" slots were drilled with the carbide dental burr, and the crossbars of the "T"s were faced in different directions to strengthen the anchoring mechanism. The nuts were tightened until they were snug but not excessively tight. The bolts were shortened as necessary to allow placement of a female Amphenol connector and the threaded cylinders in the pedestal. The openings in the bone around the bolts were packed with gel foam.

At this point, the connecting wire from the cervical electrodes, previously left in the subcutaneous tissue, was located and bluntly dissected until exposed through the cranial window. The connectors on the wires were then plugged into an Amphenol connector. All wires were then sealed to the connector with sterile medical Silastic adhesive.

The cortical electrodes were then placed on the epidural surface of the brain through the trephined holes with electrodes #2 (anterior) through #6 (posterior) on the right side and electrodes #7 (posterior) through #11 (anterior) on the left side. One depth electrode (parallel bipolar type) was positioned in the area of the right thalamus. Following SEP testing to insure proper placement, the stimulating electrode connectors were sealed in plastic tubing, buried in the subcutaneous tissue, and the skin closed with 4-0 Dexon. The trephined holes were then packed with gel foam. A sterile circular dam constructed of 0.75 inch autoclave tape approximately 1.5 to 2.0 inches in diameter was placed on the skull in such a manner as to encircle all the anchoring bolts and the wires from the electrodes. A thin layer of freshly prepared dental acrylic was poured to form the base of the pedestal and hold the wires to the skull. The Amphenol connector was then placed inside the dam on the right side and the three small threaded cylinders, which were attached to a triangular jig, were placed with the apex of the triangle anterior and on the midline. These cylinders were used during the impact runs to attach the accelerometer and photo targets to the animal. Dental acrylic was then added in thin layers (to minimize exothermic effects) until the cylinders and the Amphenol connector were covered, and a smooth, flat pedestal was formed. The skin of the head was then closed around the pedestal and a protective cap placed on the pedestal. The cervical and lumbar skin incisions were then closed with 4-0 Dexon.

DISCUSSION

KAUFMAN, US: I remember 6 to 7 years ago, your laboratory conducted sled tests with monkeys using very large G-forces in an attempt to assay the effects of impact on humans while landing on aircraft carriers or some related operations. (The monkeys showed a 1-ms increase for components of somatosensory evoked potentials to such high G-forces.) The laboratory then ran humans in a totally different domain of G-forces, because you cannot endanger them in these experiments. What are the linking hypotheses to go from human results to monkey results? How do you justify the monkey experiments in terms of their effect on how you would handle humans?

WEISS, US: What we are reporting in this paper are the results from cortical evoked potentials. The results that you are referring to relate to cervical studies, in which we showed a threshold effect for injury precursors at the cervical level. Obviously, we cannot make these kinds of studies on humans. Our intent and concern in our human volunteer experiments, which are at the heart of our laboratory's work, are the safety of the human being. We have established safe guidelines for human exposures which are very conservative. We have had no serious or significant injuries in our human experiments which involve a number of different vector exposures. Our intent is to reach the limit of voluntary human impact tolerance. (In the experiments, the maximal exposure level is the level beyond which a subject refuses to experience further increases in G-force.) We do not want to exceed our guidelines — which are based on historic data and a number of sources of information — without having adequate physiological monitoring in place on our humans. The thrust of the animal work, in addition to establishing injury modes, is to identify physiological indices of incipient injury; viz., to study the events which occur before there is any pathology — what we call the precursors of injury. By extending our work to the analysis of the cortical potentials from the animals, we are beginning what we hope will lead to an analytical scheme for recording cortical evoked potentials on our human volunteers. The intent is to have these procedures in place before we exceed our current limits of G-forces with volunteers.

KAUFMAN, US: You have answered my second question. The first question relates to the fact that you use very high levels of G-forces with monkeys, and you produce noticeable injury. It reveals itself in the evoked potential as roughly a 0.8-ms increase in latency at the cortex, and, similarly, at the cervical junction. With such a small difference in latency between the early pathological and the normal states — which only occurs with extraordinary strong stimuli — how do you expect to link these to what you can hope to do with the human subject?

WEISS, US: We see latency shifts at all levels in the cortex, and that is the important point. With cervical recordings, we find a threshold effect. In the cortex, there appears not to be a specific threshold effect; but, rather, a more monotonic graded effect (a dose-dependent effect). So, we anticipate that, at the lower levels, we will see shifts in our human population. The challenge is to develop some kind of scaling criteria which will enable us to predict when latency shifts are entering a danger zone. (Because of the differential mass in subjects , we have to subject smaller subjects to higher loads than we like, so the issue is one of scaling.) Let me point out that there are instances, currently, in operational aircraft maneuvres involving F16's and other aircraft which lead to severe neck injuries in pilots. The operational situation is compounded by the fact that pilots have additional loading on their heads; and that's another issue we are addressing in our laboratory — the effect of increased head mass. So when these other factors are taken into account, the levels at which we are exposing our animals as an injury model are not unrealistic in terms of the forces that are encountered in the operational environment of these aircraft.

EEG INDICES OF G-INDUCED LOSS OF CONSCIOUSNESS (G-LOC)

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SUMMARY

To investigate the utility of the electroencephalogram (EEG) as an indicator of state of consciousness, we recorded human brain activity during exposure to rapid onset (6 G/sec) centrifugation (+7G). Eight healthy volunteers (mean age 31 years ± 7.65) were given at least two sessions of sustained acceleration (+7G_z) on the USAFSAM human centrifuge. The sessions were conducted without G-suits and subjects were instructed to relax and not attempt anti-G straining maneuvers. Six subjects each experienced two episodes of G-induced loss of consciousness (G-LOC) while one subject lost consciousness once and experienced visual blackout once. One subject remained conscious but experienced visual greyout in both sessions.

EEG signals were recorded with EEG Grass gold-cup electrodes which were held in place by using gauze and collodion. Data were digitized at 256 samples per second and transferred to a DEC PDP-11/55 computer for analysis.

Results demonstrated a shift from beta to delta activity with pronounced absence of beta activity during unconsciousness. These results are in keeping with findings in the anesthesia and aerospace medicine literature. EEG can be useful in detecting unconsciousness during acceleration.

LIST OF SYMBOLS

LOC: loss of consciousness

G-LOC: acceleration-induced loss of consciousness

EEG: electroencephalogram

EOG: electrooculogram

CSA: compressed spectral array

delta: EEG activity from 0.5 to 3.5 Hz

theta: EEG activity between 4 and 8 Hz

alpha: EEG activity between 8 and 12 Hz

beta: EEG activity over 12 Hz

RATIONALE

The environment posed by high performance fighter aircraft offers a serious challenge to the limits of human tolerance to acceleration. Mishaps due to acceleration-induced loss of consciousness (G-LOC) have been reported for several types of aircraft in the current NATO inventory. Centrifuge training and educating aviators about G-tolerance are attempts to address this problem. Survey results from both the US Air Force and US Navy tactical air forces (Pluta, 1984, Johansson, et al., 1986) indicate a recognition of the problem with 12% of respondents reporting at least one episode of G-LOC while flying. These data may not fully represent the magnitude of the hazard posed by G-LOC since amnesia and confusion are frequently associated with such episodes.

With the advent of advanced fighter aircraft which can sustain higher G levels for longer periods of time, machine capabilities will increasingly surpass human G-tolerance limits and G-LOC will become an even more crucial issue. Monitoring the state of consciousness of pilots of high performance aircraft is one potential means for improving flying safety.

BACKGROUND

A number of researchers have studied EEG in the centrifuge and operationally in flight. As early as 1945, reports were made of changes in the EEG during LOC episodes experienced while undergoing centrifugation. Franks, Kerr and Rose (1945) observed that during increased G, alpha waves were replaced by high frequency, low amplitude waves in

fully conscious subjects. Progressively slower waves of higher amplitude usually appeared with deep blackout and onset of unconsciousness. This pattern remained until shortly before subjects regained consciousness.

Sem-Jacobsen (1959) recorded EEG in subjects during simulated combat flight maneuvers. A correlation between the EEG during flight and the aviators' flight performance records was found; pilots with no change in EEG pattern with high G had very good histories with no accidents in flight. Changes in the inflight EEG correlated with poor performance records and flight mishaps which had been attributed to pilot error or undetermined reasons. Nonpilots under similar conditions reflected analogous group differences based on their in-flight EEGs, demonstrating a generalizability of the EEG pattern to other populations. Further studies (Sem-Jacobsen, Nilsing, Patten, and Eriksen, 1959) found EEG changes to some high performance aircraft maneuvers and at "landing brake."

Extending this research, Sem-Jacobsen (1961) included aircraft flight dynamics recording and in-flight filming of the pilot. These data confirmed the earlier results and revealed that some pilots were unconscious for up to 30 seconds while "pulling up" from a simulated bombing dive.

In 1961, Browne and Howard exposed subjects to centrifugal acceleration until blackout or unconsciousness to demonstrate EEG changes with gradually increasing hypoxia. They found no abnormal EEG waveform changes with blackout. However, with unconsciousness, the EEG yielded slow (1-3 Hz), high voltage (70-130 uV) activity. The observed LOC episodes occurred 4-6 seconds after arterial blood pressure reached 30 mm Hg. Convulsions were evident (either minor spasms or major epileptiform seizures) during LOC in some subjects.

Ades (1961) tested pilots in the back seat of high performance aircraft to determine if nonclinical (i.e., less stringent) EEG analyses would yield features which correlated with flight events and cerebral metabolism. G forces during aerobatic flight appeared to precede abrupt EEG changes (high voltage bursts of slow wave activity). The authors hypothesized this activity was related to an increase in cerebral blood flow because it followed G offset, rather than G onset, by as much as 30 seconds.

The same year Jensen et al. exposed 15 subjects to centrifugal acceleration until blackout. While subjects attempted to counteract cerebral hypotension with a straining maneuver, their EEGs showed increasing beta amplitudes. With increased cerebral hypotension the amplitudes in the delta range increased. This beta to delta shift during acceleration was marked and Jensen et al. suggested that the appearance of high amplitude delta and loss of beta indicates imminent LOC.

In 1962, similar changes due to $+G_z$ were reported by French researchers studying unconsciousness. Dell, Hugelin, and Bonvallet described the phasic nature of the effects of hypoxia on electrocortical activity. In phase one, no definite changes are seen. Phase two is characterized by a generalized high frequency cortical activation. Phase three, described as classical cortical depression, is heralded by spindles and slow waves. Phase four, which occurs when air is readmitted is typically 5-10 minutes long with cortical activation. Phases 3 and 4 were compared to the EEG changes which occur during the process of falling asleep and awakening.

In another centrituge study, Gazenko et al., 1963, found EEG effects were similar in both negative and positive acceleration. At the beginning of the run, before what the authors termed "phase one", beta rhythm was prevalent. Phase one is reflected by the desynchronization of the EEG. In phase two, theta and delta activities predominate. These frequencies precede visual grey-out. In the final phase (phase three) resynchronization of the EEG occurs. The EEG returns to its normal resting state 5 to 7 minutes after acceleration stops. The authors suggested that the EEG changes were related to cerebral arterial pressure.

McNutt et al. (1963) found high voltage slow wave activity during unconsciousness in acrobatic flight as determined by EEG and filming of the pilot. The subjects under study were divided into three groups: inexperienced (no flight time); experienced (300 hrs flight time); and clinical referrals (subjects grounded for exhibiting neurological symptoms in the air or on the ground). They found no flight-induced EEG changes in either the experienced or the inexperienced groups. In the clinical referral group, however, high voltage, slow wave activity in the EEG was evident 11-15 seconds after G onset. This finding indicates that EEG changes (specifically, a shift from high amplitude beta activity to high amplitude delta activity) result not from the exposure to acceleration but rather from the loss of consciousness.

The use of inflight EEG for the selection and evaluation of pilots was suggested by Sem-Jacobsen and Sem-Jacobsen (1963) in a follow-up of Sem-Jacobsen's 1959 work. Again, pilots were divided into three groups based on their inflight EEG. Subjects who had moderate or severe EEG changes also showed behavioral responses to stress (e.g., eyes turning and rolling upward, loss of facial muscle tone followed by convulsive jerking of the head). The EEG traces revealed a very short period of flattening which preceded high voltage delta and theta activity. These subjects demonstrated rapid recovery of the EEG to normal resting activity. These episodes of high voltage activity lasted from 4 to 90 seconds.

In 1964, Squires et al. exposed subjects to centrifugal acceleration in order to evaluate the use of the EEG as an index of consciousness or depth of blackout. With visual greyout there were increases in the high frequency bands (16-32 Hz) as well as the appearance of alpha (8-13 Hz). In early visual blackout, low frequency beta (16-19 Hz) leveled out in conjunction with increases in the lower frequency components. Alpha disappeared in deep visual blackout. Ernsting (1966) found similar EEG changes (appearance of alpha with subsequent delta presence) in his study of the EEG during rapid decompression.

Berkhout et al. (1973) performed a centrifuge study designed to minimize motion artifact in the EEG recording while also providing a balanced design for the presentation of G forces. EEG was altered by $+G_z$ even without blackout. The authors proposed that these changes did not alter performance at +6 or +7Gz if central vision was maintained.

Dumermuth et al. (1976) presented a clinical study of beta activity. Their purpose included the further study of what is regarded as a regular finding in routine EEG recording. Their research focused on the categorization of beta activity during various neuro-cognitive states. The beta patterns that they reported during conditions of excitation and arousal and during sleep could have major applications to G-LOC identification.

Recent studies reported in the literature have relied on self-report questionnaires to collect demographic and subjective data on incidence of inflight loss of consciousness episodes. While these data are useful and reflect the pilot recognition of G-LOC and its consequences, a more reliable means for determining LOC needs to be developed.

EXPERIMENTAL DESIGN

Experiments were designed to test the hypothesis that indicators of blackout and G-LOC can be derived from brain wave activity recorded from the scalp. Eight volunteers were subjected to rapid onset (6G/second) sustained $+G_z$ (7G) in the USAFSAM human centrifuge. All subjects underwent at least two consecutive sessions of centrifugation with seven of the eight subjects experiencing loss of consciousness (LOC). In six of these subjects, two episodes of LOC were recorded.

Monopolar electroencephalograms were recorded from C_z to A_2 and O_2 to A_1, (sites from the 10/20 Electrode System). Grass gold cup electrodes were held in place with gauze and collodion. Two channels of electrooculogram (EOG) were recorded using standard five lead set-up allowing the collection of both vertical and horizontal eye movement signals. EOG was collected to aid in EEG artifact identification and rejection. Other parameters recorded during $+G_z$ acceleration include electrocardiogram (Forster, et al. 1986) and stick force (Whinnery, et al., 1986).

To minimize slip-ring noise, pre-amplification was accomplished in the centrifuge gondola by use of a bank of Data Incorporated Model 2124 differential amplifiers set at a high pass filter of 0.05-Hz and a low pass filter of 30-Hz. Signals were collected through slip rings on the centrifuge and recorded on analog tape, AMPEX Model 3020.

DATA ANALYSIS

Data were digitized at 256 samples per second and divided into non-overlapping, one-second epochs. Fourier power spectral densities (PSDs) were tracked and plotted for approximately one minute of data encompassing the acceleratory period. The processing algorithm removed the best-fit linear trend and baseline for each epoch. This process removed the effects of baseline and very low frequency shifts from the data. Windowing the data was accomplished by multiplying the first and last 0.1 seconds of each one-second epoch by a split cosine bell. This tapering helps prevent aliasing in the Fourier transform step to follow. Fourier coefficients resulted from applying the FAST routine from the IEEE "Programs for Digital Signal Processing" collection (IEEE press, 1979).

FINDINGS

The power spectral densities (PSDs) were then computed from the Fourier coefficients. The PSDs were plotted as compressed spectral arrays (CSAs) which present power spectral density referenced to the first one-second epoch. See Figures 1 through 6. This presentation allows comparison of frequency changes across the acceleratory period. Time in seconds is represented on the vertical axis and power is represented on the horizontal axis. The onset of acceleration is noted on the vertical axis by " ". Cessation of acceleration (G offset) is indicated by " ". The dotted line on the vertical axis shows the total acceleratory period. Unconsciousness, determined by viewing the videotape of the subject, usually occurred one second prior to G offset. Subjects typically required 15-20 seconds to recover purposeful consciousness.

Visual inspection of the CSAs yielded these findings:
a) a significant increase in power in the delta range following unconsciousness; concomitantly,
b) a substantial reduction in power in the beta range coincident with LOC. These findings are evident for several seconds following G-LOC onset. These shifts can be seen in Figures 1 through 6.

Moments of the power spectral density also reflected a relative shift to low frequency activity during LOC as compared to the pre-LOC recording.

Pattern Recognition Procedure

Five experts familiar with reading power spectral plots attempted to classify the compressed spectral arrays (CSAs) resulting from each subject's data. They examined the epochs immediately prior to and after the termination of the acceleration exposure. Four levels of frequency spread for each EEG channel were provided as the visual stimuli. The judges classified the CSAs as either: a) showing a difference between pre and post Gz exposure or b) not able to discern a difference between pre and post conditions. Judges had no knowledge of the subject or his state of consciousness during the acceleration exposure and/or its aftermath. Judges were able to accurately determine unconsciousness 86 percent of the time. See Table 1.

TABLE 1

Expert Judgements from Compressed Spectral Arrays

Subject Number	Run Number	Expert Judgement Yes	No	Event LOC/Blackout
1	32	5	Ø	LOC
1	33	5	Ø	LOC
2	34	Ø	5	LOC
2	35	4	1	LOC
3	36	Ø	5	Blackout
3	37	-	-	Data Dropout
3	38	-	-	Data Dropout
4	39	4	1	LOC
4	310	5	Ø	LOC
5	311	5	Ø	LOC
5	312	5	Ø	LOC
6	41	3	2	Blackout
6	42	5	Ø	LOC
7	43	Ø	5	Blackout
7	44	-	-	Data Dropout
8	45	5	Ø	LOC
8	46	-	-	Data Dropout
	Totals	43	7	86% Correct LOC

The analysis of these data is incomplete. We are applying more sophisticated analytic techniques to the data such as pattern recognition and inferential statistics. Further, these preliminary data, which suffered some contamination by movement artifact, will be replicated in new studies of greyout, blackout, and LOC.

RECOMMENDATIONS

We recommend that studies be continued to validate and replicate these early findings which indicate that EEG measures may provide early warning information on loss of consciousness. Much additional work needs to be done to obtain robust and sensitive EEG measures which are specific to G-induced loss of consciousness. Intensive efforts should

be focused on the period immediately preceding unconsciousness to identify reliable premonitory changes in the EEG. We think that the EEG can be a valuable tool for determining state of consciousness in the aviation environment.

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Mrs. Irma Giesberg typed the manuscript and the staff in Technical Visual Services helped in preparation of video and still photography.

Fig.1 S1 run 32 lead 4.
G-onset at 15s, G-offset at 21s. Dotted line on the Y-axis defines the total acceleratory period. LOC at 20s.

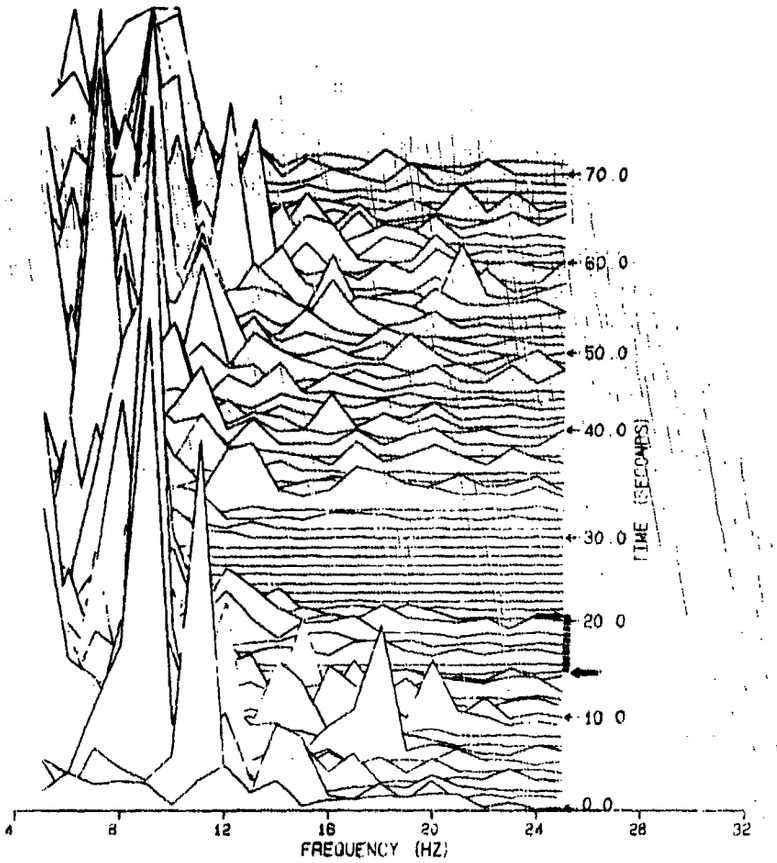


Fig.2 S1 run 32 lead 5.
G-onset at 15s, G-offset at 21s. Dotted line on the Y-axis defines the total acceleratory period. LOC at 20s.

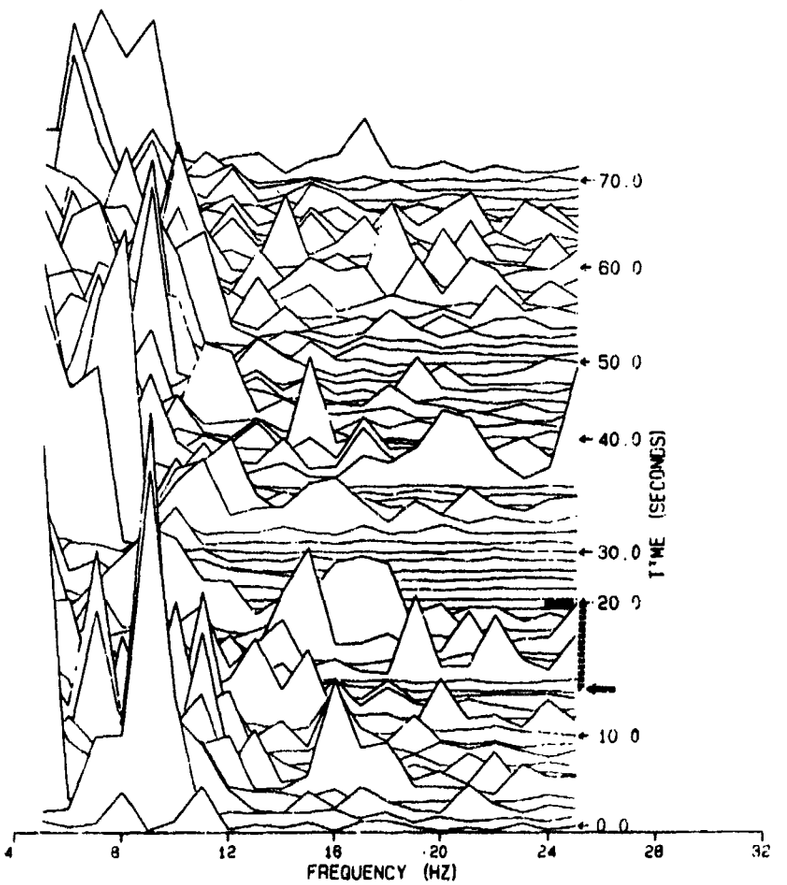


Fig.3 S4 run 39.
G-onset at 23s, G-offset at 31s. Dotted line on the Y-axis defines the total acceleratory period. LOC at 30s.

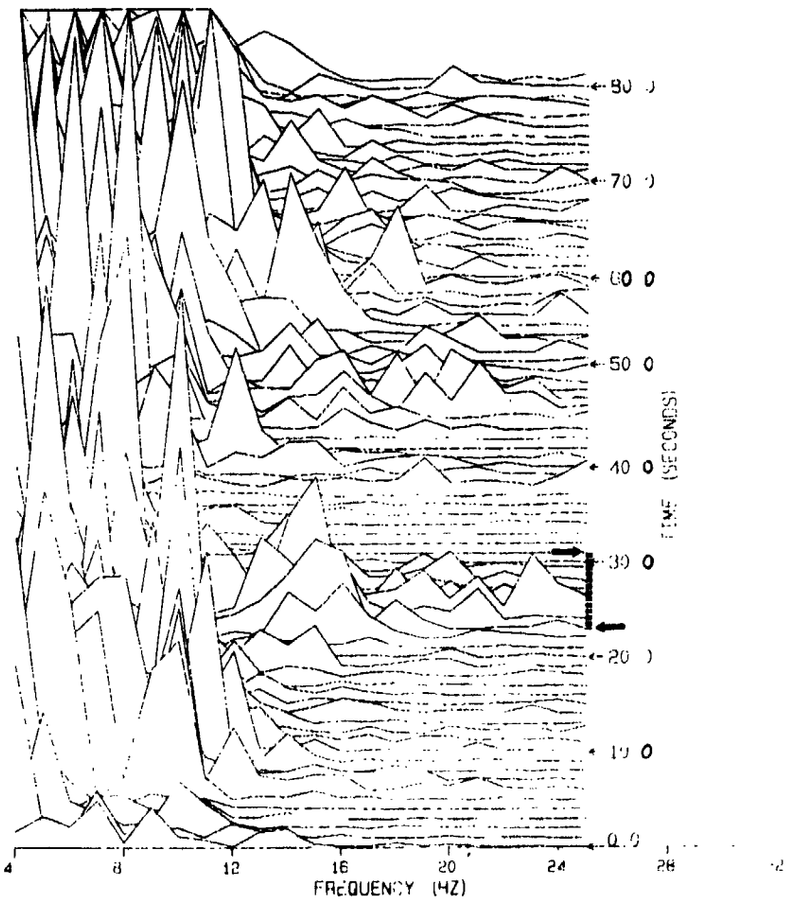


Fig.5 S5 run 311.
G-onset at 35s, G-offset at 42s. Dotted line on the Y-axis defines the total acceleratory period. LOC at 41s.

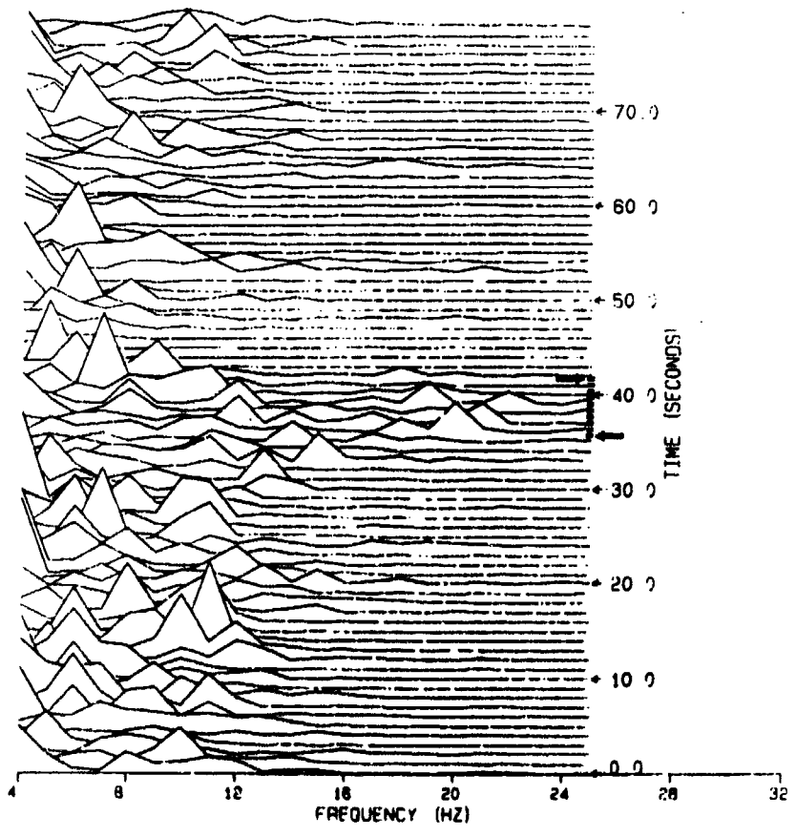
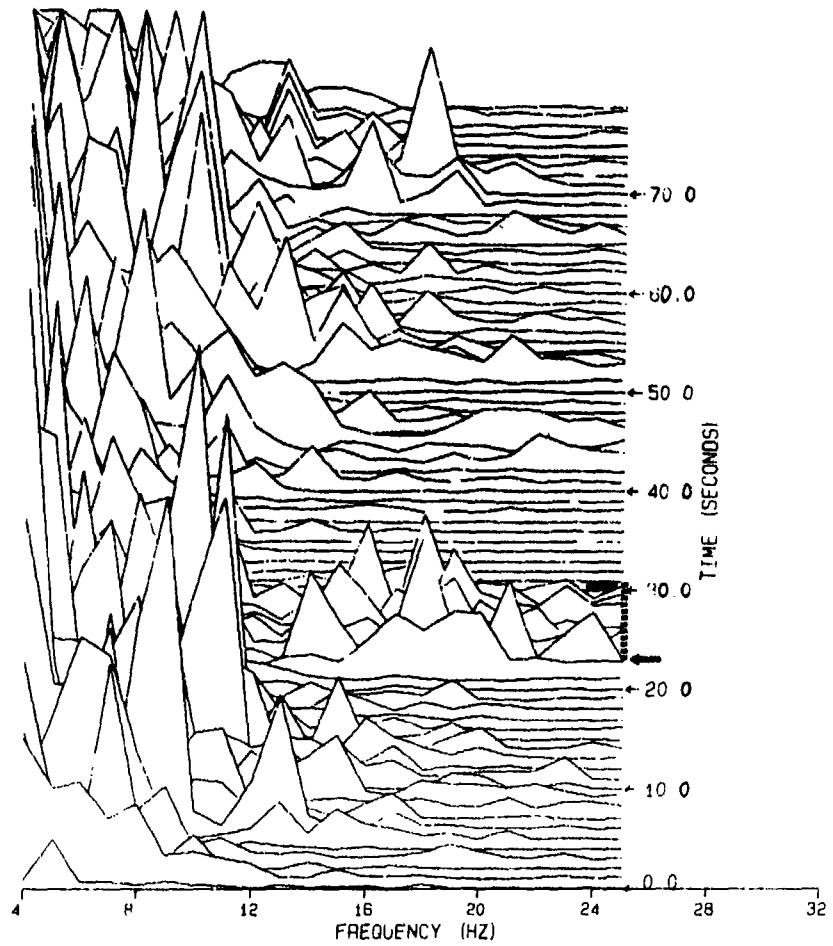


Fig.6 S6 run 42.
G-onset at 22s, G-offset at 32s. Dotted line on the Y-axis defines the total acceleratory period. LOC at 31s.



DISCUSSION

SKELLY, US: How many trials did you have per session for each subject? Did you find any cumulative effects? Were there changes in the duration and latency of your high frequency components as you approached loss of consciousness (LOC)?

LEWIS, US: We tried to complete all of our runs at one time, so we had 2 LOCs that occurred within a period of 25 - 30 minutes. We didn't find any cumulative effects; this has been raised before as a safety concern. We were studying recoveries to 1G- and 2G-forces, the trials of which we counterbalanced — one-half the subjects were tested first at 1G; half at 2G. We didn't find any differences there. Bear in mind that we had a very small sample size; only 6 subjects with LOC.

GEVINS, US: The data that you have shown look encouraging. They indicate that there may be a chance of recording good electrophysiological signals — EEGs and evoked potentials — which may be useful in predicting pilot blackout. The major problem will be the issue of artifacts, and there isn't really anyway of avoiding it. What I would suggest is that all investigators should be ultra cautious in interpreting the phenomena that they record from the scalp in simulators and in flight. It needs to be determined whether it is purely an electrical brain activity or whether it is contaminated with artifacts from muscles, eyeball rolling, etc.

WEISS, US: Your Run #34 stood out as a unique case. What was different about the spectral analysis in that particular instance?

LEWIS, US: Almost all of his results were movement artifacts. He was one of our LOC subjects.

WEISS, US: That reinforces Dr. Gevins' conjecture that artifacts must be considered in any study of this type. You didn't mention that you monitored neck EMG which would be the most obvious physiological signal to measure if you are concerned with LOC.

LEWIS, US: In this first study that we reported on, we did not record EMG. However, in our next study we are scheduled to record 5 channels of EMG, which will also be taken during anti-G straining maneuvres. We will also be using sensors for detecting head lull.

GAILLARD, NE: As I understand it, you brought your subjects rather quickly to 7G. If you had done it slower or kept your subjects at a lower G-level — say 6G — then the process of going into unconsciousness would also be much slower and you would have more time to study it and collect more data.

LEWIS, US: We wanted to have the subjects lose consciousness as quickly as possible, as we felt this to be the safest practise. In our next study, we will be collecting data to gray-out, blackout and unconsciousness during rapid G-onsets. We will repeat the experiments for gradual G-onsets, except for studying the state of unconsciousness, which would mean that the brain was deprived of oxygen for an extended period, and would be dangerous to the subject. We will also introduce realism into that flight by having some subjects perform the anti-G straining maneuvre while their responses are recorded.

DETECTION OF ACCELERATION (+Gz) INDUCED BLACKOUT BY MATCHED-FILTERING OF VISUAL EVOKED POTENTIALS

by
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SUMMARY

In air-combat-maneuvering and on human centrifuges, moderate levels of positive acceleration (+Gz), coupled with moderate rates of onset, produce visual symptoms which are ordinarily progressive: Decreasing visual sensitivity, dimming of the visual field, peripheral light-loss, and central light-loss (black-out). Since these symptoms provide warning of impending loss of consciousness, subjective visual symptoms are the most commonly used tolerance end point in acceleration research.

In order to provide an objective indication of the integrity of the visual system, we have developed a method for real-time monitoring of the steady-state visual evoked potential (VEP). Since significant degradation of visual functioning must be recognized in approximately three seconds, we required a previously unattained efficiency in producing and measuring the VEP. Using the Fast Fourier Transform (FFT), we developed a method for maximizing the signal-to-noise ratio: A digital, frequency domain, non-white-noise matched filter, with evaluation only at the expected response peak. The coefficients of the matched filter are determined empirically by analysis of test data obtained in a static run, just prior to the dynamic (+Gz) run.

Experiments on the U.S. Naval Air Development Center's Human Centrifuge demonstrated that the response does progressively decrease, disappearing at black-out. Improved computer facilities have permitted evaluation of alternative methods of processing, and the effectiveness of such processing.

Data from a static (non-centrifuge) experiment using four stimulus repetition rates and two electrode positions showed that windowing of the time record prior to FFT does not necessarily improve detection. In addition, it was found that the intial signal-to-noise ratio (S/N) of the VEP was -20 db. Matched-filtering, using a 3-second sliding average, gave an improvement in S/N of 30 to 33 db.

INTRODUCTION

During exposure to sufficiently high +Gz acceleration, subjects on human centrifuges (and pilots of high-performance aircraft) will experience the ordinarily progressive symptoms of peripheral light loss, gray-out, black-out, and ultimately loss of consciousness (LOC), due to the reduction or elimination of blood supply to the eye and brain (Duane, 1954, Leverett et al., 1966). With moderate rates of acceleration onset, each stage of visual loss is usually premonitory of the next, providing a margin of safety with respect to inadvertent LOC. Therefore, measures of visual functioning are the usual end-points in acceleration research (Burton et al., 1974; Coburn, 1970; Duane et al., 1962, Krutz et al., 1975) and visual symptoms are also the cue used by pilots to adjust "G-dosage" to tolerable limits. On the human centrifuge, we ordinarily use the NAVAIRDEVCEN Light-Bar (Cohen, 1981), as shown in Figure 1. With this, the subject uses a control stick to keep right and left Lights (Light Emitting Diodes in a continuous string) at the edge of what remains of his peripheral vision. The test run is terminated when vision has tunneled to a 60 degree cone.

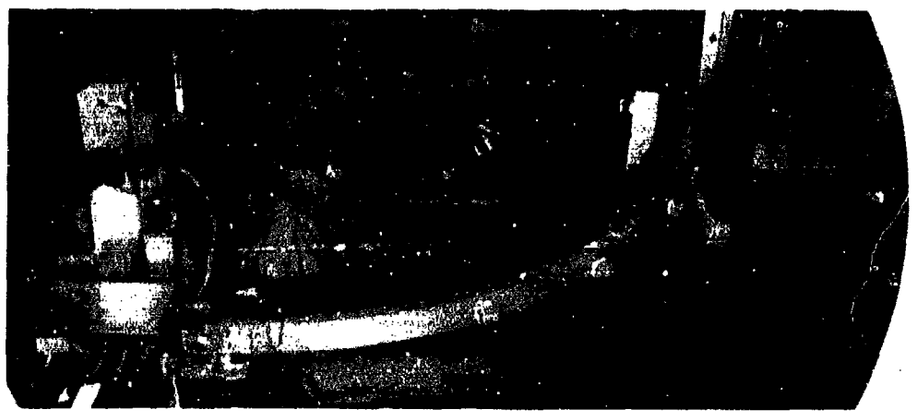


Figure 1. Naval Air Development Center light bar, used to track dynamically the loss of peripheral vision under +Gz acceleration.

Since the experimentally determined end-point is the basic datum for our comparions of G-protective devices and methods, an objective indication of the integrity of the visual system is very desirable. The fleet requirement which we address is improved G-tolerance, and this requires the best methods for evaluating proposed improvements. Better methods increase the precision of the experiment, and/or decrease the number of tests required to reach a decision at an acceptable level of confidence.

In order to provide this objective indication, we have developed a method for real-time monitoring of the steady-state visual evoked potential (VEP). (Nelson, et al., 1980-1984). The VEP is a small signal measured by surface electrodes on the back of the head, and is produced by viewing a flashing light (Regan, 1972 & 1977). (Figure 1 also shows our strobe light mounted at the center of the light bar). Since significant degradation of visual functioning must be recognized by us in less than four to five seconds, and since the VEP has a signal-to-noise ratio (S/N) of the order of -20 db, we required a previously unattained efficiency in producing and measuring it. (Note that the noise is the basic background electroencephalogram, not electronic noise). Time-averaging, which is the most commonly used method for S/N improvements in VEP studies, is definitely not adequate for our requirements for speed of response (Donchin and Lindsley, 1969).

While many other noise reductive methods for real-time monitoring or off-line analysis of the VEP have been used (Regan, 1977, Eisenstein & Morgan, 1982, J. I. Nelson 1984, McGillem and Aunon, 1983), our method appears to be the only one to attempt a formal maximization of S/N, with both signal and noise characterized empirically. In brief, we use the Fast Fourier Transform (FFT) to implement a non-white-noise matched filter to detect the VEP. This method was applied in an experiment on the Navy's Dynamic Flight Simulator (Human Centrifuge), and presented at the 1983 Annual Meeting of the Aerospace Medical Association (Nelson, Hrebien, Palumbo, and Cohen, 1983). That experiment showed that the VEP decreased as the tolerance limit is approached, and probably disappears at CLL, confirming earlier work by Duane et al., 1962. Figure 2 shows a specimen real-time run, and Figure 3 shows the weighted mean for all such runs from that study. For slow onset-rate +Gz ramps to relaxed tolerance, compensation appears adequate to prevent visual problems for the first 60% of the acceleration ramp, as shown in Figure 3. Beyond that point, increases in acceleration result in a rather regular and progressive decrease in this measure of visual functioning. This decrease occurs over approximately 22 sec. under these conditions. In a previous (static) study (Nelson and Hrebien, 1982(b)), mechanical occlusion of the stimulus resulted in a precipitous loss of response.

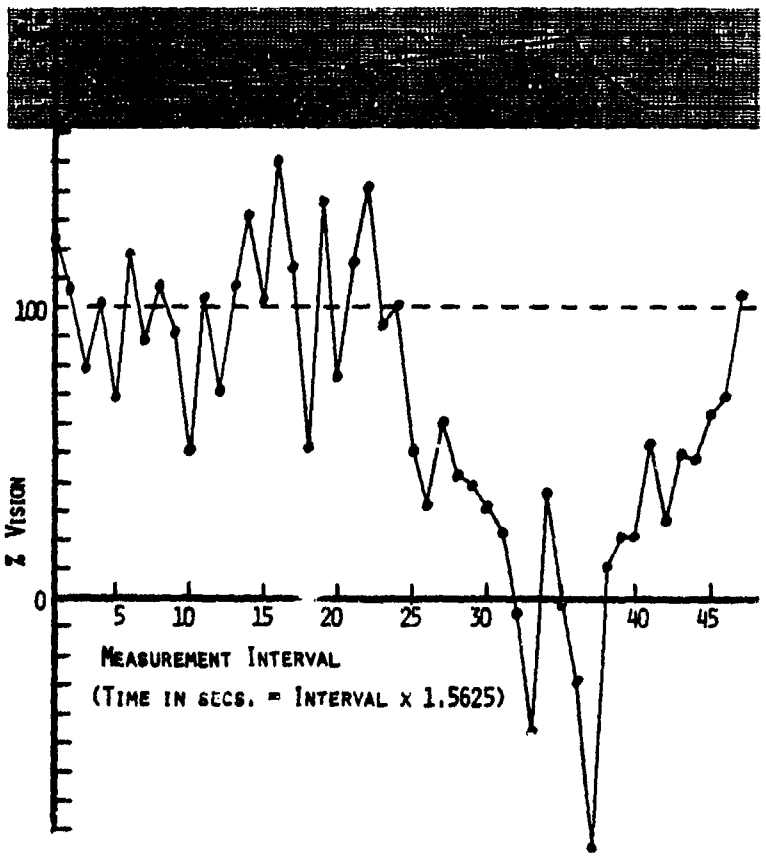


Figure 2. Specimen real-time run showing % vision as a function of +Gz acceleration.

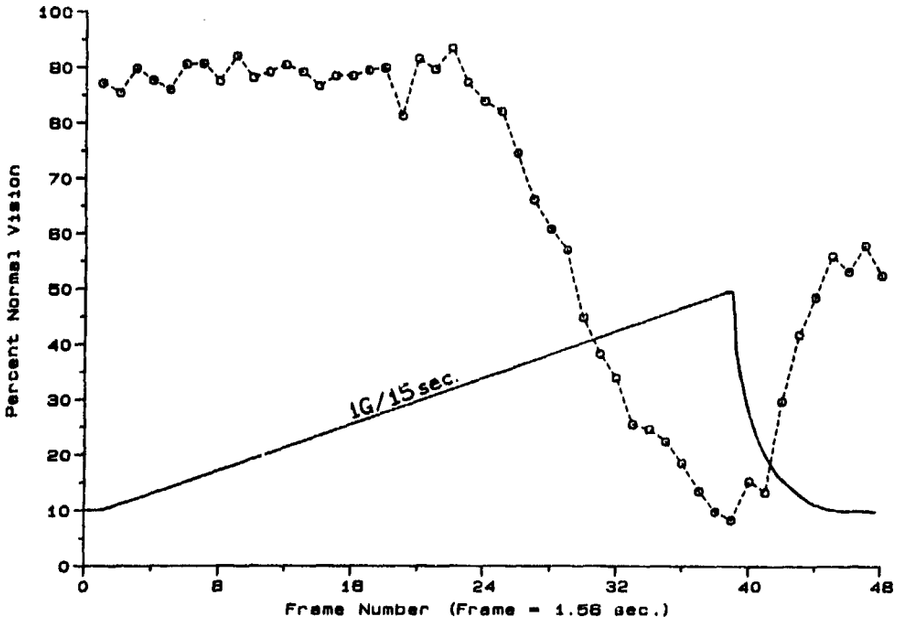


Figure 3. Weighted mean of % Base Vision for all +Gz acceleration runs, with 1 G/15 sec. acceleration ramp.

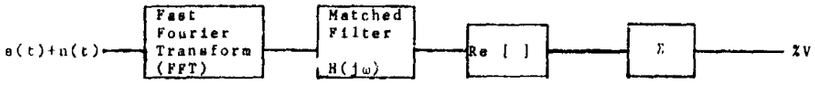
We now have a new computer system which gives us greatly expanded capabilities. It consists of a Digital Equipment Corp MINC (LSI-11/23) computer, two 10.2-megabyte cartridge discs, an 800 & 1600 bpi magnetic tape transport, analog to digital converter (A/D) with direct memory access (DMA), digital to analog conversion (D/A), IEEE-488 interface with DMA, digital plotter, printer, and a Sky Computer vector processor. The vector processor is capable of one million floating-point operations per second (1 megaflop), using DMA.

This system permits us to calculate FFTs and other functions much more rapidly, and therefore more frequently, in real-time and off-line. (As a bench-mark example, a 1024 pt. complex floating point FFT requires 60 msec). The discs and magnetic tape permit the recording of all raw data, so that alternative processing methods can be applied to the same data set. The industry-standard mag-tape permits data processing on other systems, such as the NADC Central Computer, which have extensive hardware and software resources.

In an analysis directed toward simplification of the computations required by our VEP signal detection technique (Nelson and Hrebien, (1982(a)), it became apparent that this method, which was derived from elementary compound variables theory (Guilford and Fruchter, 1978), is an implementation of a non-white noise (NWN) matched filter, which originated in the processing of radar signals. As in many signal detection techniques, we desired to operate on an input of signal plus noise (VEP + background EEG) with a linear filter to produce an output, whose S/N is maximum at a selected time. It has been shown that this maximization is only achieved by the use of a NWN matched filter (Turin, 1960).

A detailed examination of the application of the rotations and the optimal weights computed in the previous method revealed that they performed the same linear operations that a NWN matched filter would have performed, given the same signal and noise conditions. Realizing this, we save considerable computation time by the direct implementation of the NWN matched filter. The description of the method is also much more compact.

This filtering process is indicated:



With definitions being:

$s(t)$	= VEP (as function of time)
$n(t)$	= background EEG
$S(j\omega)$	= Fourier transform of $s(t)$
$\|N(j\omega)\|^2$	= Power spectral density of $n(t)$
$H(j\omega)$	= Filter transfer function
% V	= percent base vision

The filter transfer function is given by:

$$H(j\omega) = \frac{K\ S^*(j\omega)\ e^{-j\omega\tau}}{|N(j\omega)|^2},$$

where K is an arbitrary scaling constant and τ is a time delay, necessary to make the filter realizable (τ is inherent in the sampling process).

A direct implementation of this filter would start with the estimation of $S^*(j\omega)$, $|N(j\omega)|^2$, using the parameter estimation runs. Computations in the real-time runs then consist of taking the Fourier Transform of the VEP + EEG, multiplying this by $H(j\omega)$, then summing the real components of this product to obtain a single quantity indicating percent base vision.

The matched filter's coefficients are determined by analysis of data obtained in a static run, just prior to the dynamic (+Gz) run on the centrifuge, thereby adapting the filter to the unique combination of subject, electrode placement, stimulating frequency, and other variables, including some uncontrolled factors.

Given the new computer capability, we designed and completed an experiment to investigate some of the questions which had accummulated from our prior analysis and experiments: Is "windowing" beneficial, what is the underlying S/N, what improvement in S/N is achieved, what is the effect of electrode position, etc? An additional purpose of the experiment was to provide an archived database where some new questions might be investigated without the requirement to collect new data.

Since our last acquisition of computer data processing capability for this effort (Sky Vector Processor, 1983), significant progress has been made in price and performance of such equipment and software. At the lower end of the price-performance continuum, our methods to date can be replicated at lower cost. Further along the continuum, the proposed improvements can now be implemented at moderate cost.

METHOD

Using a repeated measures design, eight subjects (Ss) were tested with four strobe repetition rates (2, 4, 8, and 16Hz), with three test runs per S at each rate. The test runs were two minutes in duration, with one minute rest periods interspersed. The visual evoked potential (VEP) was measured at two electrode locations (primary and secondary visual projection areas).

Subjects were male Navy enlisted (seven) and officer (one) volunteers from the laboratory's medical support contingent. Informed consent was obtained as required by the laboratory's Committee for the Protection of Human Subjects. The Committee also approved the experimental protocol.

Tests were conducted in a sound-attenuating chamber, which also provided electrical shielding, and Ss wore both ear-plugs and ear-defenders to attenuate strobe sound, in order to avoid contamination of the VEP by an auditory EP. No Ss reported being able to hear the strobe. An aircraft seat with lap-belt fastened was used by the Ss. The chamber was lighted with 2 hooded DC peanut bulbs, with intensity adjusted by the safety observer to be able to see the subjects eyes, face, and posture. While we have never observed strobe-induced seizure, Ss were informed of the risk, a medical corpsman was in attendance, and a flight surgeon was on call.

Primary electrodes were placed at positions due to Drasdo (1980), who reported an anatomical study of the location of the visual projection areas. The first electrode was positioned on the midline at 5% (of the inion-nasion distance) above the inion. This is midway between the inion and Oz in the international 10-20 system (Jasper, 1958). The second primary electrode was located 20% (of the inion-nasion distance) to the right of the first electrode. Both electrodes were referred to Pz (in the 10-20 system), with right mastoid as ground.

The electrodes were Beckman miniature silver/silver-chloride, stored in normal saline. These electrodes were modified to permit injection of electrode paste (Signa gel) after application. This modification was made after observation of EEG lab procedures. Electrode sites were cleaned with Omni-Prep, rubbed with paste, and the electrodes were secured with collodion (non-flexible) and blown dry. This procedure is fast, reliable, and the electrodes are much more securely attached. Electrode-pair impedence was held to less than 4K ohms.

The strobe-light stimulus, a General Radio Model 1538-A, was enclosed in a grounded metal box, with copper screen over the light output. The light was routed through an L shaped box, painted flat-white internally, to a frosted 14 cm. diameter screen, with a one cm. fixation mark. The eye-to-screen distance was 1.17 meters, given a visual angle of 7 degrees. When the strobe was set at a nominal 4170 flashes per minute, no additional attenuation was required to provde a viewing intensity which was acceptable to the subjects.

An infra-red eye-blink detector was constructed, tested, and abandoned. The strobe-light pulsed the detector, which induced coherent noise in the electrode leads. Without the eye-blink detector, coherent noise was un-detectable in runs in which the subject was blindfolded. Figure 4 shows % vision during such a run, while Figure 5 shows a specimen standard run without the blindfold.

Both of the data channels were low-pass filtered (100 Hz, 40db/decade), sampled at 1024 samples. sec. and the data stored on digital magnetic tape. Figure 6 shows the general connections of the system elements: Strobe light with trigger generator, the low-pass filtered EEG, the A/D, clock, mag tape, and DECLAB/MNC-23 computer.

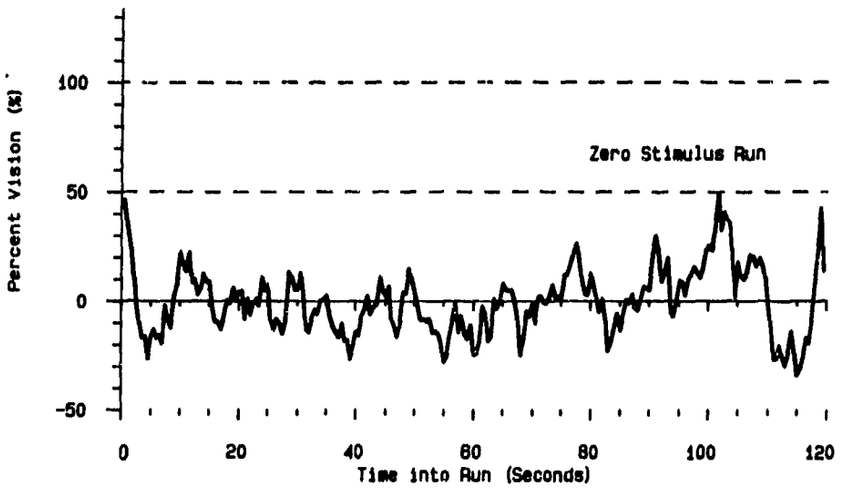


Figure 4. Blindfolded (zero-stimulus) static run, showing absence of response.

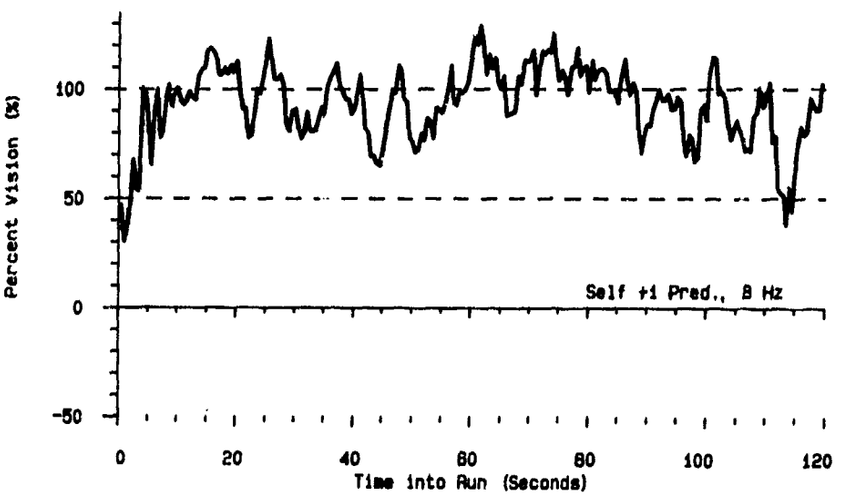


Figure 5. Static run, showing presence of response.

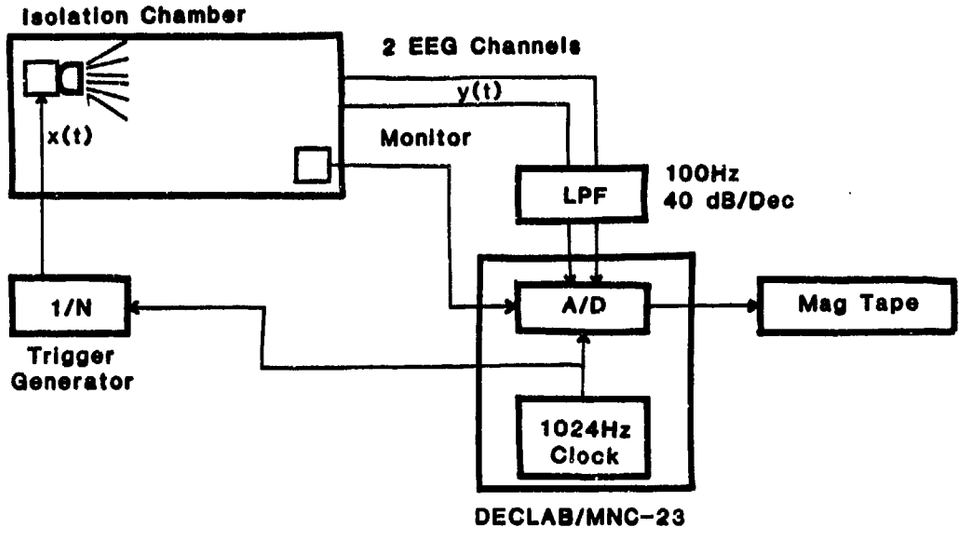


Figure 6. Interconnection of system elements.

RESULTS and DISCUSSION

In all of our earlier work on the VEP, we made a somewhat arbitrary decision to use a uniform weighting (rectangular window) for the time-function data as opposed to using the von Hann, Hamming, or other window (Harris, 1978). Non-uniform windows are symetric weighting functions with weights smoothly decreasing, closely approaching zero as the function nears its beginning and end. The choice of the uniform window was based upon the fact that all of our signal components have been selected to be whole-cycle within the selected time frame, with noise in general not being whole cycle. A uniform window will be maximally sensitive to such signals, and will distort only the spectral estimates of the noise, not the estimates of the signal.

Our new computer system, with its data collection, storage and processing capabilities, permitted us to evaluate our previous choice of window. The data were processed twice, with two solutions per second, with the percent vision variable being output at the same rate, with each % vision estimate the mean of the last six solutions, giving a three-second running average. A 3-second average was chosen, since detection of loss of vision within 3 seconds would be satisfactory for our application. When processing with the uniform window, 1/2 sec. time frames were used. When processing with the non-uniform window, one-second time frames were used, with 50% overlap.

The non-uniform window selected was the minimum 3-term Blackman-Harris (B-H) (Harris, 1978), This window has an equivalent noise bandwidth of 1.71, with its first sidelobe at -67db. With 50% overlap, estimates are essentially independent, since the shared variance (correlation squared) is only 1%, since r = .096. Also, the level of the first sidelobe of the window is nearly down to the -72 db resolution noise-floor of our A/D converter.

For each run, for each window, matched filters were derived and used to output % Vision for that run. Coefficients of variation (CV:standard error of % vision, divided by mean % vision, scaled as %) were calculated. A chi-square evaluation of the relative frequency of superiority of the two windows showed the uniform window to be slightly (but quite non-significantly) superior.

Using the ratio of the two CVs resulting from application of the two windows, an analysis of variance showed frequency of stimulation to be marginally significant ($p < .05$). An examination of the mean values showed that the B-H window improved mean performance for the 2Hz stimulus (10% improvement) and for 4Hz (7% improvement), with the uniform window superior (by only 2%) at 8 and 16Hz. When correlations of CVs between the three runs in each set were examined, the B-H window was found to produce moderately higher correlations between runs. A further ANOVA of CVs, with uniform window for run #1, and B-H windowing for run #2, showed frequency again to be only marginally significant ($p < .05$), but the window-by-frequency effect was significant at the 1% level.

Since the B-H window did not show clear advantages for this set of data, particularly at those stimulation frequencies giving better detectability, the uniform window was used in further analysis. However, since window choice did affect results, choice of window will continue to be evaluated in future applications, to determine what is best for that particular data set.

Using the CV derived with the uniform window, an ANOVA showed frequency of stimulation to be significant ($p < .01$). The mean values of CV for 2, 4, 8, and 16 Hz stimulus repetition rate were 70, 51, 44, and 56 respectively, with 8 Hz being the best stimulus overall.

In this and other comparisons, electrode position was non-significant. Since even visual inspection of the signals at the two electrode sites indicated gross differences in frequency composition, as shown in Figure 7, the approximate equality of the two sites is encouraging in that combining channels in future applications should give a useful improvement in detection. This is due to the fact that while there are moderate correlations of the noises at the two sites at the same frequencies, the noises at different frequencies are independent.

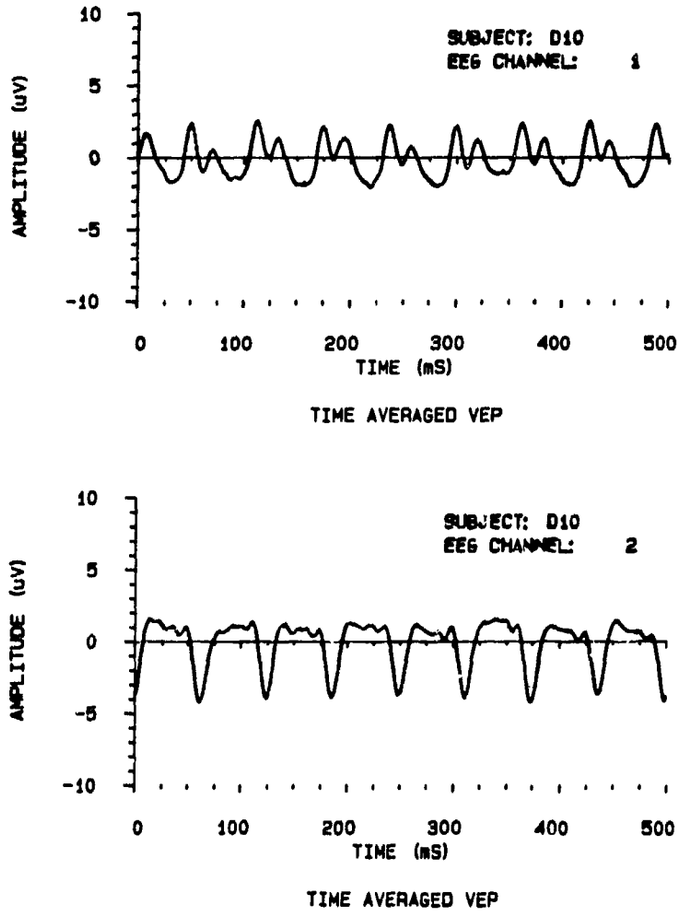


Figure 7. Time average of VEP for one subject, 15 Hz stimulus, showing difference in signals at two electrode sites.

The simplest method for combining the data from, for example, two electrode sites, would be to use the two values of ΣV, determine the simple noise correlation, and form an optimum weighted sum using the expectation for the variance of a weighted sum of correlated variables (Guilford and Fruchter, 1978, p. 390) to maximize the S/N of the resulting compound. Improved detection would result, but the approach is sub-optimal. The optimal approach will require determination of the correlation between the two noises at a spectral point, after both signals have been rotated to positive real. Following the optimal combination (as above for ΣV) at each spectral point, matched-filter theory (Turin, 1960), specifically the Cauchy-Schwarz inequality, will provide the weights to form the final compound variable, ΣV. If the noise correlations at the different spectral points differ significantly from each other, then a significant improvement in detection performance will result from using this second (more computationally intensive) method.

The formal model of the VEP (signal) combined with background EEG (noise) required by matched filter theory is one of independent additivity. In this, as in previous studies, we have found only small deviations of data from model. Figure 8, from a previous study with a strobe repetition rate of 3.2 Hz, shows a slight but consistent elevation of noise power at the harmonic points, relative to the adjacent non-harmonic points. This was also found in the present study. The most parsimonious interpretation of this is that it is due to a small degree of signal instability, contrary to the model. The data definintely do not support any photic-driving or capture theory (Regan, 1972, p. 77), wherein it is postulated that the background EEG is brought into syncronization with the stimulus, thereby producing the VEP. If capture occurred, it would decrease the noise at the harmonic points. The additive-independent model appears to provide an adequate approximation.

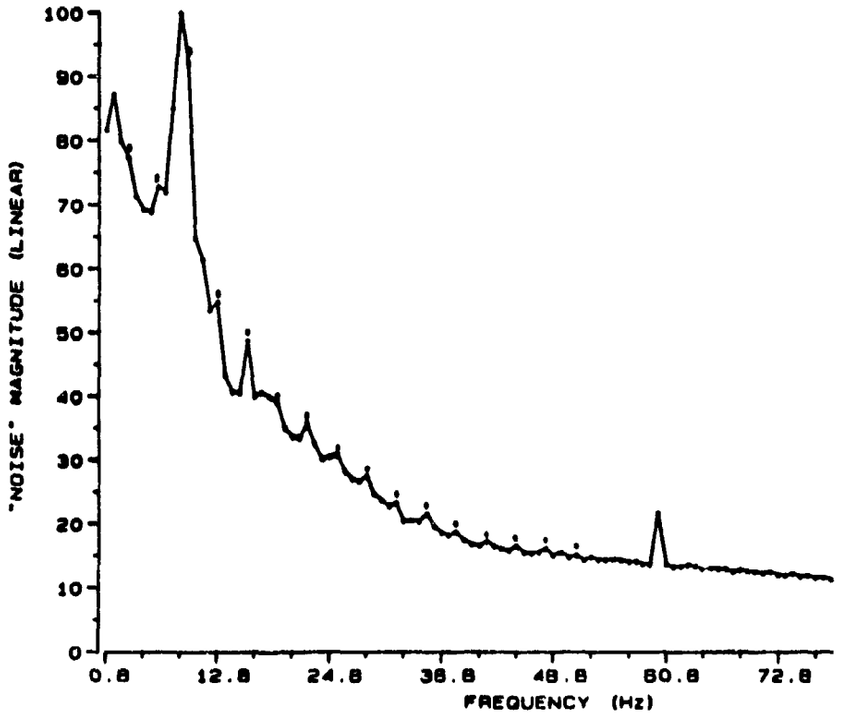


Figure 8. Noise (RMS) residue after removal of signal, with markers at harmonic points (3.2 Hz stimulus).

Since the reason for applying a matched filter to VEP data is to maximize the signal-to-noise ratio (S/N), an analysis in S/N terms was conducted. A S/N was calculated for each run, using the un-weighted, un-processed ensemble of time-functions. The over-all median for this initial S/N was -19.4 db. The median S/N of the % vision variable, using the 3-second running average, and applying the filter to the data set from which it was derived, was +14.3 db, for an improvement of 33.8 db. When the filter was derived from a run, then applied to the next run, the median shrinkage was 3.8 db, for a net 30 db improvement. This shrinkage indicates that adaptive estimation procedures may provide a worthwhile improvement in detection, particularly when shifts in background EEG are expected.

Shifts in the background EEG spectrum are to be expected under conditions of +Gz acceleration (Berkhout, et al., 1973; Duane, et al., 1962; the Sem-Jacobsens, 1963; Squires, et al., 1964), and the noise term of the matched filter should therefore adjust dynamically to reflect this.

Prior to the dynamic (+Gz acceleration) run, all spectral points are fully useable for noise spectra estimation. During the run, when %V may have decreased, the spectral points which contain no signal (adjacent points) are fully useable for estimation of the envelope of the spectrum. In addition, quadrature (to the signal) noise may also be used to update the spectral estimates of noise and/or the envelope of the noise spectrum. These quadrature estimates have but one degree-of-freedom, rather than the two (real and quadrature) available at each conventional spectral point, but they are estimates of the only noises of direct interest. Noise estimates at adjacent spectral points are useful

only to the extent that they can be used to estimate noise at those spectral points where there is (normally) also signal.

When new data are available from acceleration runs, we will then be able to evaluate the trade-off between lags in dynamic estimates and instability of the estimates. It should also be noted that these shifts in the EEG spectrum will, in themselves, be of interest (Lewis & Miller, 1987).

To express the obtained 30 db improvement in S/N in other terms, conventional sampling theory indicates that a sample size of 1000 is required to give this degree of reduction in error variance. In a 3-second time frame, with stimulus repetition rates varying from 2 to 16 Hz, the available sample size for time averaging ranges from 6 to 48 (whole cycles of the fundamental).

Looking at the results of the best stimulating frequency for each S we find 8 Hz is best for 4 Ss, with 4 and 16 Hz best for 2 Ss each. The 2 Hz rate was not the best for any S. Figure 9 illustrates that subjects differed in frequency composition of the response, as well as resulting S/N. Selecting the best stimulus for each S gave an improvement of the order of 2 db. However, selecting the best frequency for each S gave a 4.4 db difference between the Ss with the highest and lowest S/N, while one S showed an 8.2 db difference between this best and worst frequency of stimulation. Since it is likely that all of the stimulating frequencies were non-optimal for the indivual Ss, and in some cases grossly so, the use of a swept-frequency technique to determine a genuine optimum for each S should improve overall results, with radical improvement for Ss with highly peaked responses (Spekreijse, 1966). A swept-frequency search is required, since system non-linearities prevent a more analytic approach to determining an optimum. Figure 10, the time averages of the response for one subject at three stimulus repetitions rates, shows the strong non-linearity of the response.

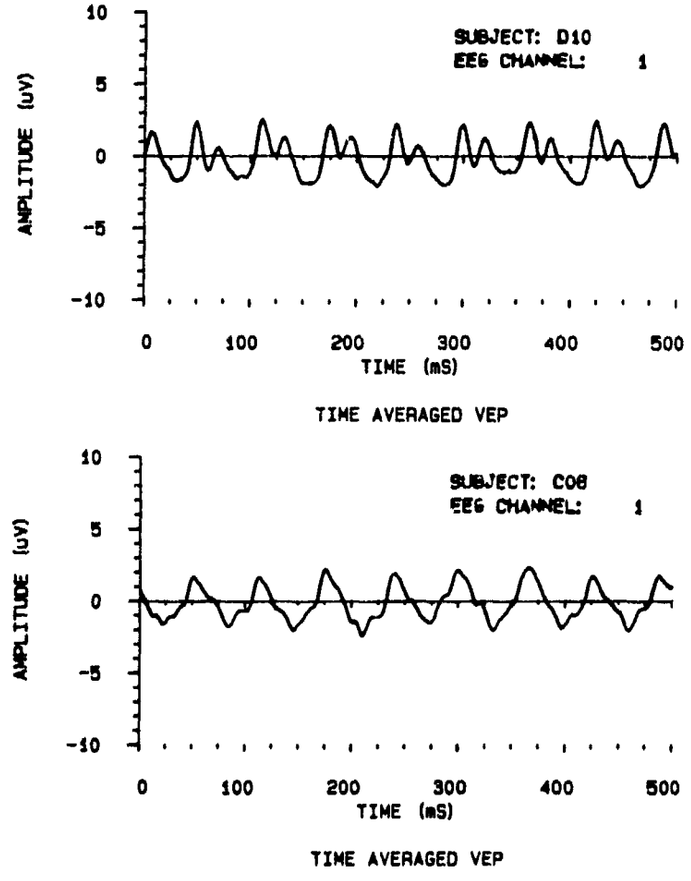
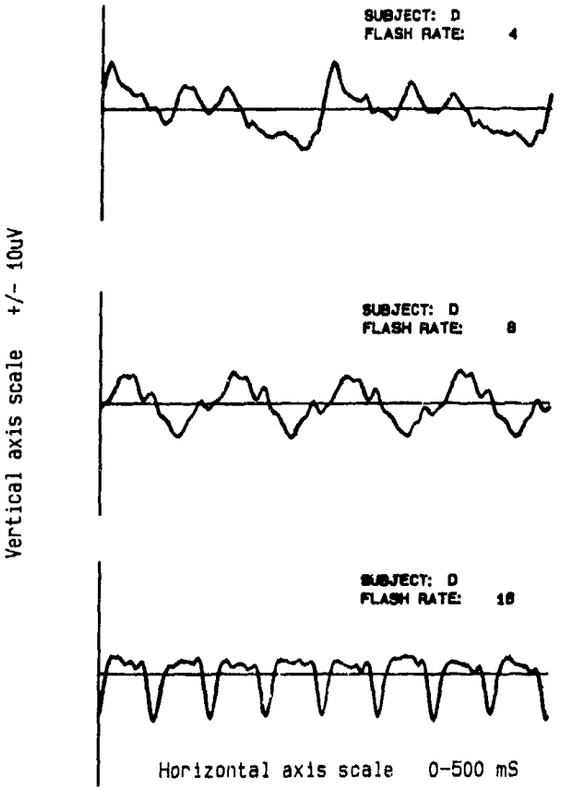


Figure 9. Time averages of VEP for two subjects, same stimulus and electrode sites for both.



Non-Linearity of VEP

Figure 10. Time averages of VEP for one subject at three flash rates, showing non-linearity of response.

In Figure 11, we show an analysis of all of the runs made with an 8 Hz strobe rate, summarizing the total normalized power and coherence as functions of frequency. (Coherence is the proportion of total power that is due to signal (VEP) power) (Bendat and Piersol, 1971). The 18 db range of noise demonstrates the requirement for non-white-noise assumptions when implementing the filter. The distribution of the coherence across many harmonic points demonstrates the advantages of processing the full harmonic content of the response. Single frequency filters, even of the (expensive) precision phase-sensitive lock-amplifier type, (J. I. Nelson, 1984) can only look at one, out of approximately eight, of the significant components of the signal.

The plot of the maximum coherence achieved in any run indicates that individual cases of useable components occur out to 100 Hz, so selection of a frequency cut-off should not be based upon average results. The nulls in the coherence function, which occur at the non-harmonic points, indicate that one of the functions of the matched filter is to serve as a comb filter, having zero gain at the non-harmonic points.

The large S/N improvements achieved to date have provided a measure which is a valuable adjunct to other measures, such as the light-bar or doppler blood flow to the brain. For use as a reliable end-point, the present improvement in S/N of approximately 33 db will need to be increased by an additional 5 to 6 db. This goal may be achievable.

The signal processing methods developed during this effort, while directed toward the solution of our particular problem, the detection of loss of VEP under acceleration, could be applied to considerable advantage in other VEP research efforts, and to processing of psychophysiological data in general. Improved monitoring of VEP during cranial surgery would be an example of a practical clinical application (Feinsod et al., 1976). The elimination of any frequency components which are entirely noise, and the differential weighting in terms of S/N at the other frequencies would give much more sensitive measures, and could reveal important components of the response which would otherwise remain undetected. Large signal components with large associated noise can completely

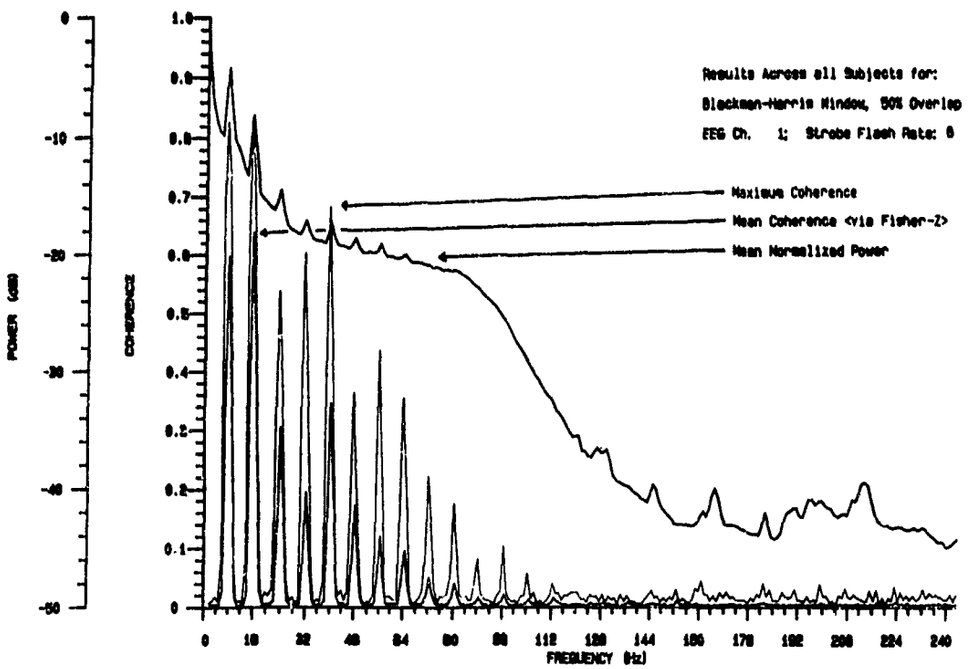


Figure 11. Power, mean coherence, and maximum coherence, for all 8 Hz flash rate runs.

obscure small signal components, which may have the same or superior S/N, as compared to the large components. Phase information could be retained, and the processed signal could be viewed in the time domain, with a specified level of confidence that all of the features of the waveform represent non-random effects.

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Electroencephalographic Correlates of Pilot Performance: Simulation and In-Flight Studies

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Summary

Both laboratory and in-flight studies were carried out in order to evaluate the utility and feasibility of EEG monitoring as a means of identifying central nervous system correlates of performance and G-force effects during military flight operations. Four studies were conducted, two with controlled laboratory simulation, and two in actual flight during military training missions. Data analysis focused on EEG power-spectral density characteristics and their temporal modulation, specifically in sensorimotor and visual cortical areas. Several consistent findings emerged. During competent performance, a highly unique discrepancy appeared between left and right hemispheres in central 8-15 Hz activity. This pattern disappeared as performance degraded. The temporal modulation of this activity also reflected these changes. During high G-force situations, power at frequencies below 8 Hz was progressively and non-specifically enhanced. Continued competent performance, however, was still reflected by the pattern described above. These findings are discussed in terms of their neurophysiological implications.

I. Introduction

The challenge of central nervous system assessment in relation to the physiological and cognitive demands of modern military flight has several distinct components. First, the data collected must accurately identify a relevant index of brain physiology. Second, the methods used to obtain requisite biological signs must not interfere with pilot comfort or performance. Finally, the information derived must ultimately provide the pilot with extended capability and/or response alternatives. From the beginning of our work in this area we have addressed this challenge from the perspective dictated by these considerations.

In order to properly encompass all of these requirements, we initiated parallel programs of laboratory and field studies. The laboratory experiments focused on a search for relevant measures which could be applied to an on-line assessment of CNS function. The field studies, on the other hand, addressed the problems of eventual applications in light of real operational demands. Additionally, the field studies provided for an assessment of G-force influences which could not be simulated in the laboratory.

The functional orientation for all of these studies was directed by past experience in studies of sleep physiology. The perspective which this background provides is somewhat unique in the area represented by this conference. Our emphasis is on the concept of "physiological state" which differs significantly from a consideration of moment-to-moment fluctuations in neural activity or performance capability. The concept of recurring physiological states is best understood through reference to the states of sleep and wakefulness. Clearly, brain physiology and associated behavioral manifestations are different in these two states. However, it is today well documented that sub-states exist within both sleep and wakefulness (1,2) and that these can be both intrinsically or situationally determined (3,4). That is, both physiological organization and behavioral response characteristics are continuously modulated by an interaction of internal biological periodicities and external environmental circumstances. This modulation determines the background "set" or functional framework within which a given response occurs.

In seeking to track this modulation within the context of CNS assessment, we have focused upon the spontaneous electrical activity of the cerebral cortex, the electroencephalogram or EEG. This measure provides a continuous, real-time, dynamically modulated and totally non-invasive index of the "background state" of CNS organization. Because functional topography and frequency modulation are important attributes of this measure, our emphasis was on the activity recorded from task-appropriate cortical regions from which frequency patterns were at least partially clarified in the neurophysiology literature. Thus, electrodes were placed over visual and sensorimotor cortical areas to evaluate the putative command functions involved in the visual-motor tasks associated with aircraft control. Additionally, our analysis focused on the frequency components of these signals as they related to the theoretical basis of thalamocortical substrates for EEG rhythmic activity in the visual and somatosensory pathways.

Years of neurophysiological investigation have established the fact that naturally occurring rhythmic patterns in the waking EEG from sensorimotor and visual cortical areas arise from thalamic neuronal generator mechanisms and their gated discharges to localized cortical projection areas (5,6). These generators are intrinsic to thalamus (7,8), reflect the status of specific sensory pathways (7,9,10,11), and result in cortical rhythmic patterns the characteristics of which are determined by the independent, functional modulation of cortical excitability (12,13,14). For example, the occurrence of rhythmic 8-15 Hz patterns recorded from central cortex (the so-called sensorimotor

rhythms) are facilitated by immobility and can be altered or blocked by arousal or gross movements, respectively (15,16,17). Moreover, at least in relation to sensorimotor rhythms, hemispheric laterality differences are seen in the waking state (18).

Our strategy was to examine the interplay between visual and sensorimotor cortical EEG frequency patterns in relation to the type and quality of flight-related control performance required and demonstrated. Our initial studies involved laboratory simulation of relatively simple flight scenarios in order to document functional predictions in an optimal situation for recording and experimental control. Subsequent studies involved in-flight recordings from Air Force pilots undergoing target acquisition training in a multi-engine aircraft, and typical training maneuvers in high-performance fighter aircraft, in which high G-force stress was a factor.

II. Methods: General Overview

All of the studies to be described here utilized similar EEG recording and analysis procedures. Signals were recorded from gold-plated, cup-type electrodes (Grass Instruments) placed in bipolar arrays on the scalp according to the standardized International 10-20 System (19). Placements included bilateral central cortex (C1-C5 and C2-C6) and unilateral or bilateral parietal-occipital cortex (P3-O1 and P4-O2). A ground lead was placed also over the mastoid bone behind the left ear. The skin was cleansed and abraded prior to electrode attachment with a high viscosity electroconductive paste (Grass EC-2). Electrodes were further secured by various methods (see below). In all cases, electrode resistance measurement readings below 2000 ohms were required prior to and after recording sessions in order for the data to be considered valid. Except for a few cases of failed connections or damaged preamplifiers, no data were lost as a result of this convention.

Since the ultimate evaluation of recorded EEG data would involve power-spectral analysis, the issue of artifact reduction and anti-aliasing measures was significant. Scalp electrodes were attached to miniature preamplifier units (Oxford Medilog) at close proximity to the high impedance recording source. These amplifiers increased signal-to-noise ratio by approximately 10:1, thus greatly reducing potential cable noise. In laboratory studies the signal was fed directly to post-amplifiers in a Grass model 78 polygraph and from these to a pre-filtering and scaling unit on the front end of our VAX model 11/750 computer (Digital Equipment Corporation). Pre-filtering by this unit provided a rolloff of 6db (50% attentuation) below 0.5 Hz and above 40 Hz. In-flight studies utilized a specially designed flight vest which contained a pre-filtering unit providing a 6db rolloff below 2 and above 30 Hz. The signal was then fed to a post-amplifier unit in the vest which also provided a second-stage rolloff of 6 db below 1 and above 60 Hz. Finally, the filtered and amplified signal was led to a miniature 4-channel FM tape recorder (TEAC, Model HR-10G). These extra filtering measures were introduced in recognition of the fact that in-flight recordings would be subject to greater movement and muscle artifacts than those obtained in the stationary laboratory setting. Data recorded on the FM tape unit were subsequently played-back in parallel to the laboratory polygraph and pre-processing equipment described above, thus providing a third stage of artifact reduction for this context.

In all studies, a 3 min. calibration signal, consisting of a 9.5 Hz sine wave of 50 uv peak-to-peak, was played into the recording system prior to each data collection session. This signal provided a calibration reference for a standardized 50 uv scaling of one volt peak-to-peak at the time of computer analysis. The analog data were then digitized and subjected to Fast Fourier Transform using the algorithm of Jennrich (20) as modified by Pacheco et al. (21) and Mason (22). Successive 16-second epochs (2048 data points) were analyzed with 128 coefficients summed to provide a resolution of 0.5 sec from 0-40 Hz. Calculated spectral estimates were sorted into seven consecutive 4 Hz frequency bands between 0-27 Hz, thus dividing power into bands corresponding to functionally meaningful frequencies within the human EEG (ie; 0-3 Hz=delta, 4-7 Hz=theta, 8-11 Hz=alpha, etc.). The spectral densities of these frequency bands were computed by calculating the area under the spectral distribution generated for each 16 sec. epoch. Values were log transformed and simultaneously stored on the VAX hard disc and down-loaded to a hard disc on a laboratory PC computer. Adjusted data files were then subjected to graphic and statistical analysis through use of Lotus and Matlab software programs.

III. Findings

The program to be reviewed here was initiated several years ago and includes both laboratory and actual in-flight studies. Except for the initial laboratory study, which represented our inauguration to this field, all of our other investigations are still ongoing. In most instances, the data have all been collected within the context of more or less strict research protocols, depending upon the circumstances of the study. However, we were to discover that the analysis of consecutive 16 sec. epochs of EEG activity from multiple cortical recording sites in many subjects across extended protocols was to generate both exciting opportunities and frustrating problems. The opportunities stemmed from the fact that extensive, high quality EEG data were successfully obtained from a variety of flight-related contexts. The problems were created by the vast amounts of data so obtained and the many analytic options one might choose in seeking common and relevant trends. Accordingly, data analysis is still underway and it appears that this effort will continue for some time. What we present here are the initial, consistent findings which hold promise for providing insight and guidance in our search for meaningful indicies of function.

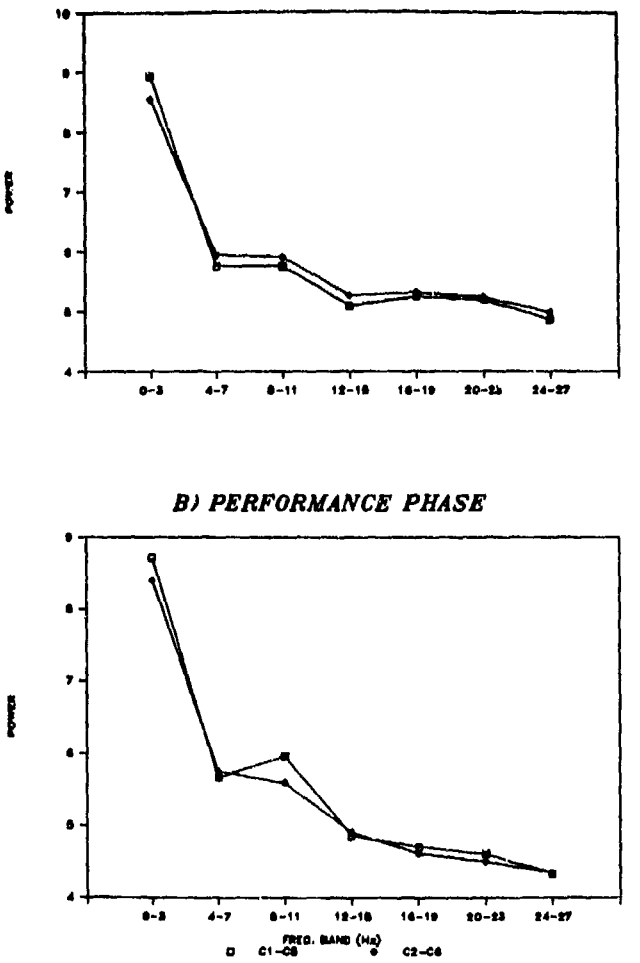


Figure 1. Mean power-spectral density distributions derived from three subjects and comparing EEG data from non-performance epochs (A) with correspponding data from performance epochs (B). Note that only during performance of the F-16 flight simulation task was left central 8-11 Hz activity enhanced.

A. Laboratory Studies

1. F-16 Simulation: Performance versus Non-Performance

This study employed six male volunteers between the ages of 25 and 45 years. Three of these subjects were pilots, one a senior flight officer with the California Air National Guard, and two with civilian licenses. The other three had no formal flight training. Each was provided with several brief practice sessions on a video game involving a rudimentary flight simulation of an F-16 fighter aircraft. An authentic aircraft seat was used in front of a video display and was fitted with left and right hand controls for velocity and attitude, respectively.

After familiarity with the task was achieved, each subject participated in a six-hour protocol involving successive 10 min. flight legs during which specific instructions regarding aircraft positioning and speed were to be followed. After each leg, the subject was allowed 5 min. to read, make notes or simply consider the requirements of the task. Breaks or rest periods were provided for 15 min. each hour. Bilateral central and parietal-occipital EEG activity was recorded continuously during these sessions, as described above, except for the break periods. In this case, electrodes were secured in place by collodion-soaked pads. EEG data were subjected to power-spectral analysis as detailed above.

The performance tasks in this study were well within the capabilities of the subjects but the primitive nature of the program made control of the aircraft rather

difficult. Thus, subjects worked hard to perform the instructed flight profiles. Unfortunately, however, we were unable to obtain quantitative performance data in this context. Accordingly, our analysis was limited to an evaluation of EEG changes with the alternation of flight-performance versus non-flight-performance epochs. Since our interest in this communication is focused on a search for discriminating variables in sensorimotor and visual cortical EEG patterns, we shall consider this dimension here. Other findings from this study have been reported elsewhere (23).

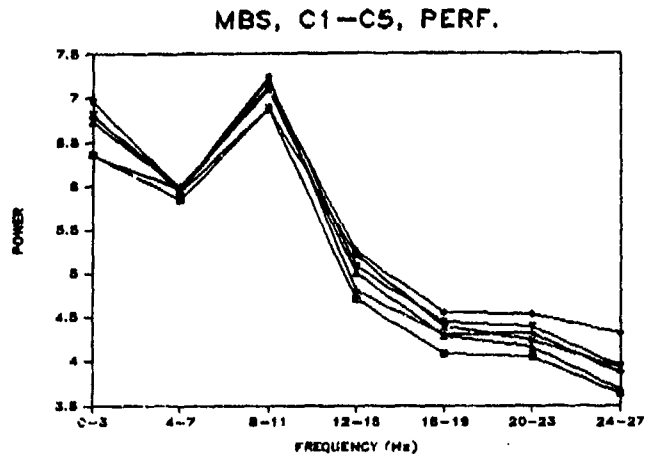


Figure 2. Power-spectral density distributions averaged over three 10 min. flight performance epochs in each of six consecutive hours of our F-16 flight simulation task. Data are from one subject, and compare spectral profiles from left sensorimotor cortex EEG recordings (top) and left visual cortex recordings (bottom). One data block was lost from the P3-O1 recordings due to electrode failure. Note the extremely consistent elevation of activity at 8-11 Hz from left sensorimotor cortex during this performance and its absence in visual cortex. This subject showed unusually low 0-3 Hz activity in central recordings.

The most consistent finding in this regard was a significant increase in 8-11 Hz activity in sensorimotor cortex exclusively during flight-related performance (Fig. 1). Moreover, this increase occurred differentially in left central recordings (C1-C5) in four of the six subjects and across the entire protocol. This enhancement of left central 8-11 Hz activity was extremely consistent, and was not reflected in simultaneously recorded data from parieto-occipital cortex (Fig. 2). Of the four subjects showing this effect, two were right-handed and the other two were left-handed. While performance comparisons were difficult in this study, the data obtained suggested that these four subjects, three of whom were the trained pilots in this group, performed better than the remaining two subjects.

2. Cessna Simulation: Good versus Poor Performance

Ten subjects were recruited from the U.C.L.A. Air Force R.O.T.C. program for this

study. Each had at least 50 hours of solo flying experience and all were healthy males ranging in age from 19 to 25 years. Subjects were called at random from a master list provided by the local R.O.T.C. coordinator. They were told that participation would require 10 to 15 hours and that the time commitment would vary depending on how quickly each acquired the skills necessary to fly the simulator. Training and testing took place over a period of six months.

The video P.C. program "Flight Simulator II" (Microsoft Corporation) was chosen because it offered realistic performance features with which most Air Force R.O.T.C. cadets would be familiar. This program simulates the instruments and flight characteristics of a Cessna 182 class, single engine, 148 MPH, retractable gear aircraft. Subjects were provided with up to four one-hour practice trials on the simulator in order to assure standard familiarity and mastery of its various features.

Subjects were monitored electroencephalographically during approximately five hours in the final test session. EEG placements included bipolar and bilateral central and parieto-occipital leads, as described above. Electrodes were fixed to the prepared scalp with collodion adhesive and attached to the Oxford Medilog miniature preamplifiers. These leads, together with that from the mastoid ground, were fed to a Grass model 8-16 electroencephalograph, and an eight-channel Crown Vetter model A magnetic tape recorder. Leads from the EEG machine post-amplifiers fed EEG data directly into the VAX computer system for on-line data analysis.

A Mitsubishi Video Printer (model P50-U) printed hard copy of the video screen every thirty seconds during the flight legs. This printout yielded information concerning the plane's present position, heading, altitude, air speed, rate of ascent/descent, position of the throttle, yoke, and flaps, as well as the same view the subject saw through the "window" of the plane at that moment. Information tabulated from this printout was later utilized in the evaluation of subject performance.

Before testing, each subject was assessed for transient physiological factors which might affect their performance. The Stanford Sleepiness Scale was utilized along with questions designed to give a general overview of the subject's current activity level in order to discern if anything unusual had occurred on the day of testing. This assessment included: quantity and quality of sleep the previous night, naps taken that day, recent alcohol consumption, time of last meal, medications/drug use, and current physical complaints, if any.

After the subject was interfaced with the monitoring system, each was isolated and seated comfortably in front of the color video monitor and provided with manual control devices which controlled the air speed (utilizing the throttle) and the altitude and pitch (utilizing the control yoke). The video screen showed the instrument cluster of the airplane along with a view from the plane's cockpit in a split screen format. In each case, the investigator was seated in an adjacent room and acted as co-pilot, communicating with the subject via an earphone/microphone headset. An overhead camera monitor provided continuous visual information concerning posture, movement, and other behaviors relevant to the task, and those related to significant artifact were noted on the simultaneously recorded EEG tracing. Subjects were requested to maintain relaxed facial muscles, limit speaking to essential conversation, and adhere to the flight protocol as closely as possible.

Each subject was required to take off from a particular airport, fly to a designated location, turn to a new heading and land at a specified airport. Each of the flight legs were designed to be completed within thirty minutes. The subject was advised that he should have successfully landed within the thirty minutes alloted for each flight leg. They were free to ask how much time was remaining during any particular flight leg. After each flight leg, a twelve-minute rest period was provided. Rest periods were occasionally longer than twelve minutes if the subject landed or crashed the simulator before the thirty minutes alloted for the leg had expired. During the rest periods, the subject was given time to look over the protocol for the next flight leg. Resting EEG data were also collected for later analysis.

Each of the seven flight legs had its own protocol which differed in starting point, turning point, designated landing airport, and specific flight criteria. Each flight leg had three phases: a departure phase, an enroute phase, and an arrival/landing phase. After take-off, the protocol required the subject to maintain the take-off heading and climb at 90 knots to a specified altitude. Once they arrived at that altitude they executed a turn to a new heading. The enroute phase required the subject to climb to a new altitude and maintain it until they began the descent for landing. Once they were over the designated turning point, they turned to a new heading and flew to the designated airport for landing. For the arrival/landing phase they were required to land on a specified runway from a specified direction. After landing they were told to await further instructions. The rest period followed a description of the next flight leg.

Data analysis is still underway in this study. The focus of initial analysis was on the comparison of EEG characteristics during good versus poor performance in the simulated flying. The multiple flight legs with differing degrees of difficulty created a sufficient variation in performance for the evaluation of EEG correlations. Completed group data are not available at the present time but several consistent relationships have emerged.

As in the previous study, EEG activity from central cortical recording sites has

proven to [illegible]eful. In particular, activity in the 8-11 Hz frequency band from left central co[illegible] was again characterized by the most dynamic modulation in relation to performance. It was noted that the sequence of successive 16 sec. spectral density values at this frequency displayed a modulatory pattern over time approximating periodicities ranging from 0.2 to 2 cycles per minute. Moreover, this periodicity was clearly correlated with flight performance activity.

To explore this relationship systematically, profiles of the key performance variables, including air speed, altitude and heading, were compared with computer-derived templates based on actual instructions for a given flight leg. Deviations from this template exceeding a criterion level in either direction were scored as errors. Loss of control of the aircraft resulting in a "crash" led to one point in the error score for every epoch prior to expected landing. In this way, flight legs, and segments within each leg, were rated for each subject in a dimension of good to poor performance.

Corresponding periodicty in the 8-11 Hz band of EEG activity from left central cortex was displayed and subjected to both modulation and trend analysis. Modulation analysis was accomplished by subjecting the sequential spectral density values themselves to FFT analysis (Fig. 3). A consistent peak defining a periodicity between 0.2 and 0.4 cycles per minute was seen in data from vitually every subject. This periodicity was stronger and more consistent, however, during periods of good performance. Conversely, faster periodicities ranging from 1-2 cycles per minute, dominated periods of poor performance.

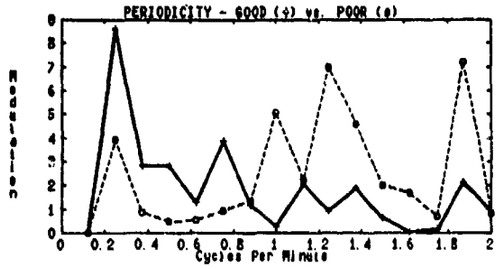


Figure 3. Modulation periodicity analysis based on FFT of successive spectral density values at 8-11 Hz from left central cortex in one subject during the enroute-landing phase of two flight legs in our Cessna simulation study. These legs were contrasted by the fact that one (solid) was rated as good performance whereas the other (dash) was rated as poor performance. Note the slower periodicity during good performance and an almost reciprocal relation to the faster periodicities during poor performance.

An additional discriminating variable was provided by regression analysis applied to the amplitude modulation of these periodicities (Fig. 4). During periods of good performance a significant positive trend was obtained. However, during poor performance, the trends observed were either negligible or negative in slope.

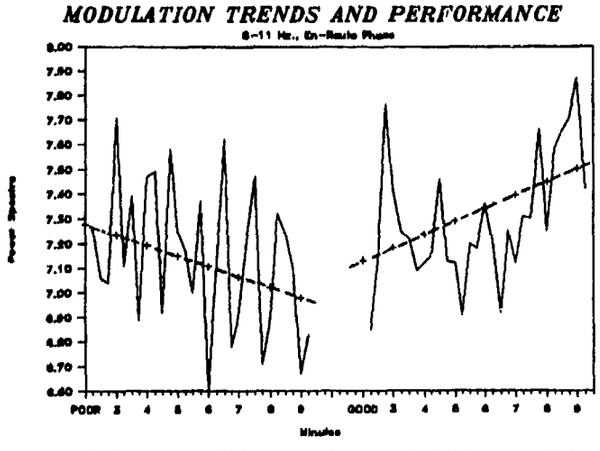


Figure 4. Power-spectral density modulation of central 8-11 Hz activity during good (segment on right) and poor (segment on left) performance in the Cessna simulation study. Modulation trends in these data were determined by linear regression analysis. A combination of slower modulation with a significant trend towards increasing amplitude (positive modulation slope) was consistently characteristic of good performance segments.)

B. In-flight Studies

1. NCH 131-H Study

Five USAF test pilots who were already part of an ongoing flight training and test program on the NC131-H Total In-flight Simulator (TIFS) were selected through the Test Pilot School (TPS) at Edwards Air Force Base (EAFB) to act as subjects in this study. All pilots were part of a TPS class that was scheduled to fly evaluation missions on the Avionics Systems Test Training Aircraft (ASTTA). All involvement with the current project was conducted on a minimal interference basis with the ongoing avionics evaluation and training program. For the current protocol, each subject was required to fly several missions, thereby providing repeated measures, albeit under different mission directives and at different times of day.

Before and after each flight, subjects completed the Profile of Mood States (POMS), which evaluates immediate subjective mood states. In addition, each subject completed questionnaire forms of a Cooper-Harper flight-oriented subjective workload assessment, as well as a card sort version of the Subjective Workload Assessment Test (SWAT) after each mission. In-flight three-point Cooper-Harper ratings were also conducted after each flight segment task was completed.

The EEG recordings employed in this study utilized the special flight vest arrangement described above. Additionally, a custom helmet liner with electrodes attached to retractable flaps over appropriate cortical sites was used. The scalp was prepared and electrode paste introduced to the site and the electrode. The flap was then closed and secured with a velcro trim. Leads from all electrodes were attached to Oxford miniature preamplifiers, also secured by velco at points between bipolar electrode sets, and cables from these units were fed into the processing and recording modules of the flight vest. A mesh cranial cap was then placed over the sealed electrode flaps, preamplifiers and cables, in order to further secure the whole assembly. This arrangement provided a fully portable monitoring system which in no way interfered with flight activity (Fig. 5). A flight helmet pre-molded to the scalp configuration for each pilot was then donned prior to takeoff. In-flight data collection included continuous EEG recordings, as well as several onboard measures. These provided recorded video images of the training station instrument panel and continuous data recordings of aircraft flight parameters.

Figure 5. In-Flight portable EEG data recording system is shown here on a pilot ready to put on his pre-molded flight helmet and step to the aircraft. The special flight helmet liner (A) containing permanently mounted EEG recording electrodes at standardized placements and adjacent miniature preamplifiers, and covered by a mesh cap, is connected via secured cables to a modified flight vest. This vest contains a power supply for the preamplifiers (B), a data filtering module (C), a post-amplifier unit and battery pack (D) and a miniature FM data recorder (E). The system is activated at will by connecting the post-amplifier/battery pack unit to the recorder.

After the hookup was complete, subjects entered the aircraft (most flights included two test subjects, one scientist/observer, and the requisite engineering/ technical crew) and went through the necessary preflight preparations. The observer from our staff made both voice and note recordings of activity changes, flight configuration changes, time sequence and other relevant events. All intercom dialogue was recorded on one channel of our microrecorder together with simultaneous EEG data.

Flight scenarios included either air-to-air or air-to-ground target detection, as well as the use of Instrument Navigation System (INS) and Infrared Detection System (IRDS) devices. Different scenarios involved different tasks, thereby varying workload considerably from one situation to another. All subjects were required to perform all other "normal" flight functions simultaneously with whatever additional workload tasks were involved in each scenario (i.e., there was no active copilot during data collection periods).

During the flight sequences, command pilot rotations typically occurred at least once. Thus, each flight contained several task segments and data on each of two subjects. When possible, each subject also flew different flights at different times of the day. In this way, we were able to collect data on four of the five subjects at three different points in time, morning (approx. 1000-1200 hrs.), afternoon (approx.1400-1700 hrs.) and evening (1730-2100 hrs.).

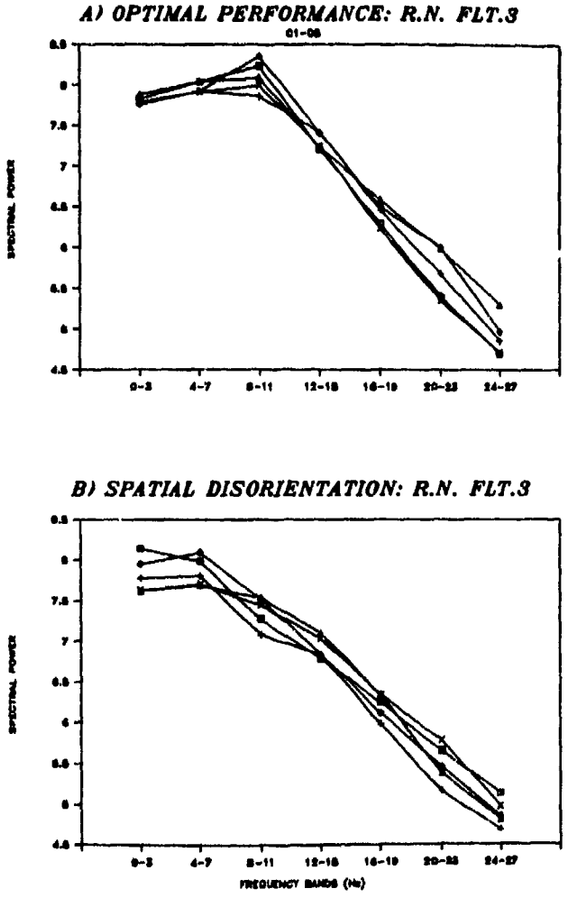


Figure 6. Power-spectral distribution curves each derived from the mean of four successive 16 sec left central cortex EEG epochs (approximately one minute of data) from a test pilot flying target missions in the NC131-H aircraft. Curves at A show data obtained during a target run lasting about five minutes where both flight and targeting functions were performed competently. Curves at B are data from the same pilot obtained during a later run. From the start of this run the pilot was confused as to the location of the target and eventually became totally disoriented.

When all of the data collected in this study are fully analyzed, it should be possible to evaluate such parameters as fatigue, time-of-day, and comprehensive performance correlations in relation to recorded EEG patterns. At present, we have succeeded in identifying specific flight segments in several pilots that were characterized by documented variations in performance, and in determining corresponding EEG configurations. For example, during an early morning flight, pilot R.N. completed a highly successful targeting run involving effective aircraft control and use of INS and IR guidance systems. Sequential 64-second spectral distribution profiles (based on the mean of four 16 sec. EEG epochs) were characterized in particular by a peak of activity at 8-11 Hz in left central cortex (Fig. 6A). Approximately one hour later, this same pilot experienced an unequivocal and verified period of spatial disorientation during an IR target identification run. Spectral profiles from left central cortex showed a marked and significant depression in 8-11 Hz activity during this sequence. (Fig. 6B). Activity in right central cortex (C2-C6) did not show significant differences in these two conditions nor did visual cortical recordings.

When data from a series of flight segments over several different flights were combined and rated on the basis of performance characteristics, several consistent findings emerged (Fig. 7). Activity in all frequency bands except 8-11 and 12-15 Hz showed no

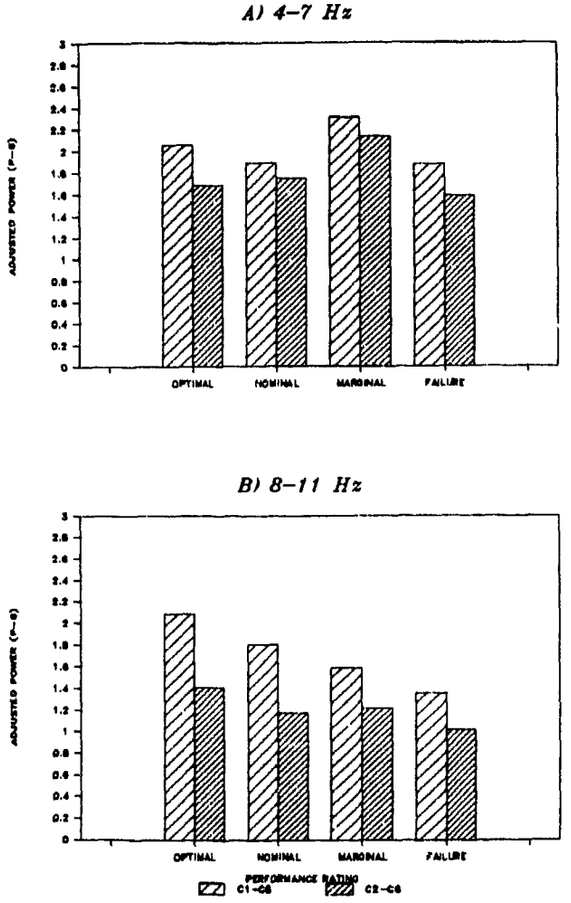


Figure 7. Mean EEG spectral power at 4-7 Hz (A) and 8-11 Hz (B) from both hemispheres is shown here for data segments recorded in four different targeting runs during which performance by the same pilot was rated from optimal to failed. Values at 4-7 Hz showed no systematic trend in relation to the dimension of performance, nor were there any significant differences between left and right hemispheres, although power on the left side tended to be higher. At 8-11 Hz, however, an essentially linear decline in power from the left hemisphere paralleled the dimension from good to poor performance. Power in right central cortex was significantly lower than that on the left during optimal and nominal performance only, and showed an overall difference only at the extremes of this dimension. The ordinate scale in this graph was adjusted to compensate for shortcomings in the Lotus graphic program.

related trends. However, in these two bands, a consistent relationship was observed. Activity at these frequencies from left central cortex (C1-C5) showed a significant linear decline from optimal to failed performance while right central activity did not. The previously noted discrepancy between left and right hemispheres was maintained across this dimension but was greatest during optimal and nominal performance.

Modulation analysis was applied also to these data (Fig. 8). Once again, optimal performance was associated with an increasing amplitude of temporal modulation in the 8-11 Hz frequency band, exclusively. Further, spectral analysis of power in this band over time indicated that intrinsic periodicity was generally slower during optimal versus failed performance. Left and right central hemisphere differences were again confirmed and were greatest during optimal performance.

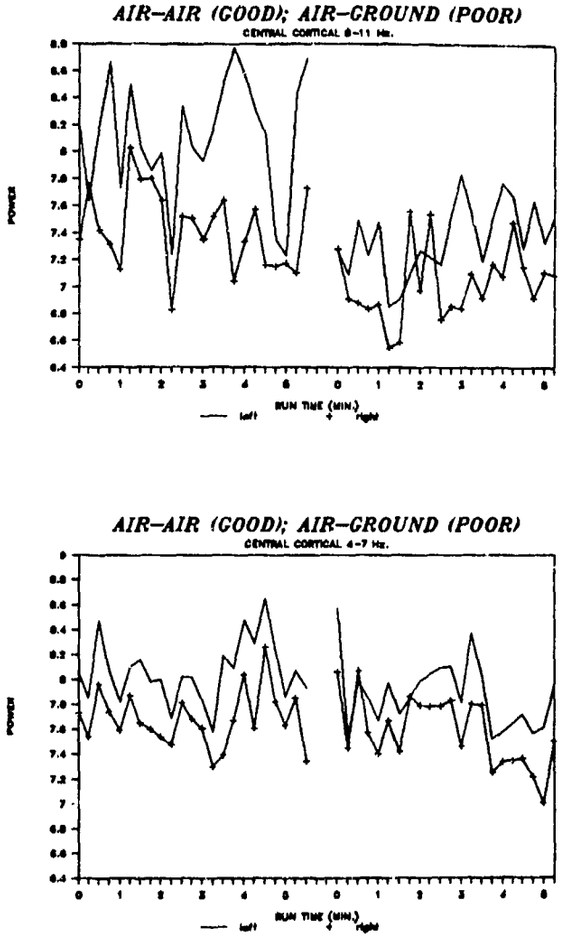


Figure 8. An example of the temporal display of EEG power modulation based on spectral density values derived from sequential 16 sec epochs of EEG data shown here for central cortical 8-11 Hz bands during good vs. poor performance samples. Both graphs show bilateral data from a good performance run (left portion of abscissa) compared with data from a different poor performance run (right portion). Note that during good performance 8-11 Hz power from the left central cortex is both elevated and more slowly modulated when compared with that from the right and with data from both hemispheres during poor performance. Hemispheric differences are reduced in the 4-7 Hz band and their amplitude and modulation do not discriminate quality of performance. These findings are functionally similar to those shown from our laboratory study in Fig. 4.

These in-flight findings support observations made in our laboratory studies suggesting that central cortical EEG patterns can be differentiated in optimal versus poor flight performance by virtue of a constellation of more-or-less consistent parameters.

These include: 1) relative power in left central 8-15 Hz activity; 2) differences in this activity between right and left hemispheres; and 3) the amplitude and period of temporal modulation in this frequency range.

2. T-38 In-flight Study

The effort to devise methods for the collection of valid EEG data in the highly dynamic environment of fighter plane operations has been a long-term component of our program. It was determined early-on that standard laboratory procedures were simply inappropriate. As suggested at the onset, the ultimate goal of this effort was to achieve a totally noninvasive, self-contained system which would provide a reliable index of pilot functional status. Over a progressive series of trials, using our own staff as passenger subjects, we were able to devise a methodology which achieved these goals within the current state of related technology, and to begin recently to collect appropriate data from Air Force pilots during actual flight operations. We are greatly indebted to the staff and officers at the Flight Test Center, Edwards Air Force Base, for this accomplishment.

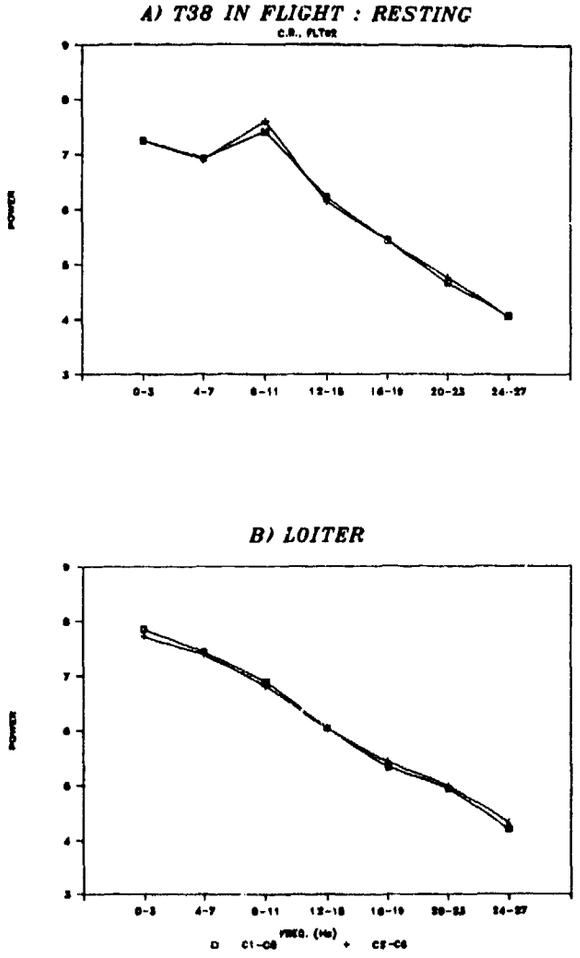


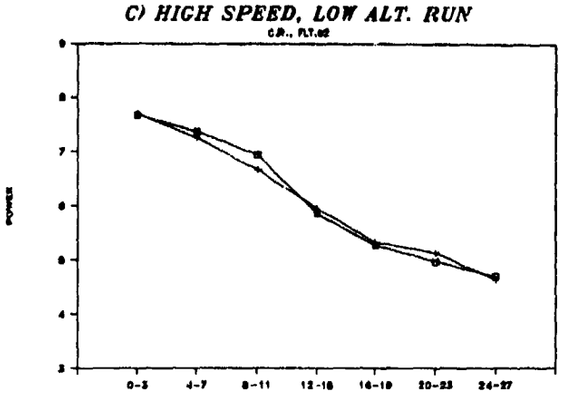
Figure 9. Mean power-spectral distribution curves calculated from left and right central cortical EEG data from an Air Force test pilot during flight segments (approximately 2-4 min. in duration) in a T-38 aircraft. During these segments the pilot was not flying the aircraft. Data at A are from a period of resting with eyes closed. Data at B are from a period of resting with eyes open during straight-and-level flight.

The system developed for this purpose was described in the previous section and used in the NC131-H study. Briefly, it consists of a specially configured flight-helmet liner cap with fixed electrodes at appropriate sites and adjacent miniature preamplifiers. Retractable flaps provide for rapid electrode attachment, with velcro seals and a mesh

overcap securing everything in place. A pre-molded helmet inner-liner pad prevents the occurrence of "hot spots" when the flight helmet is put on. Leads from the electrode cap are fed unobstrusively to the previously described flight vest which contains essential data collection electronic devices. The parachute and aircraft seat belts fit over this vest and the system is configured so as not to interfere with potential ejection requirements. This entire arrangement was evaluated and approved by an appropriate Safety Review Board at the base.

Since all data collection trials are on a non-interference basis, it is necessary to extract appropriate segments from established flight profiles. Pilots are briefed in advance as to our objectives and have made every effort to cooperate within the restraints of a given specified test mission. Again, only preliminary data are available at this time from actual pilot subjects.

During a given flight, data were obtained from periods of non-operation resting, with and without attention to ongoing events (Fig. 9). Spectral analysis of such data showed a selective increase in central 8-11 Hz activity from both hemispheres when eyes are closed (Fig. 9-A). This spectral distribution peak is absent on both sides of the brain during attentive periods when the other pilot is flying the aircraft (Fig. 9-B). However, when the subject pilot flies the plane through a difficult maneuver (Fig. 10-A) activity in the lower frequency bands is increased, and particularly at 8-11 Hz in left central cortex. With maneuvers creating high G-force effects (Fig. 10- B), this



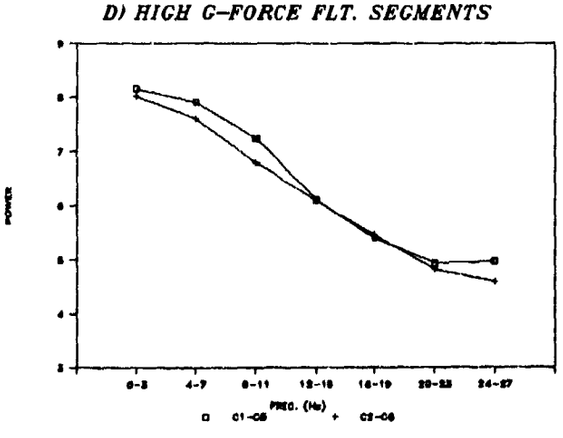


Figure 10. These graphs constitute a continuation of Fig. 9. In this case the subject pilot is flying the T-38 fighter aircraft. Data at C are from a low-altitude (approx. 100 ft.), high-speed (500 knots) flight segment, including turns with some increased G-force. Data at D are from four flight segments during which 4-5 G turns were being performed.

hemispheric discrepancy is increased as is power in the lower 4-7 and 0-3 Hz frequency bands. The latter increase is consistent with data obtained previously from non-pilot passenger subjects (23).

These findings are summarized using a different format in Figure 11. Resting activity during straight-and-level flight with eyes closed was associated with a decrease in power in the 4-7 Hz band and an increase in power at 8-11 Hz, bilaterally, in sensorimotor and visual (not shown) cortex. Demanding flight maneuvers, with some associated G-force effects, resulted in an increase in 4-7 Hz activity and a decrease in 8-11 Hz power with a discrepancy developing between left and right hemispheres in central cortex. This trend continued to some extent with high G-force maneuvers (4-5 Gs), in that power significantly increased bilaterally at 4-7 Hz and unilaterally at 8-11 Hz in left central cortex.

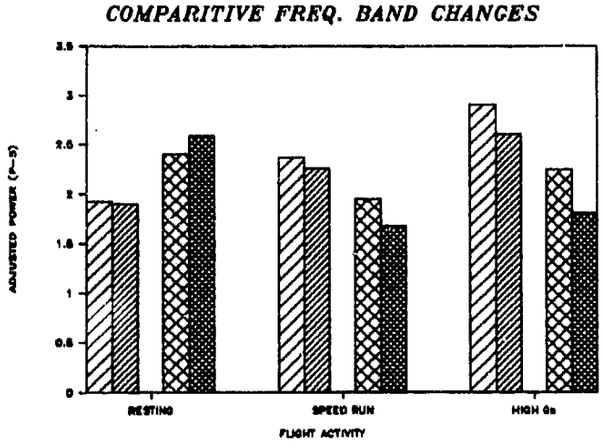


Figure 11. Comparative analysis of spectral densities at 4-7 and 8-11 Hz in left and right central cortex during three of the four flight conditions described in Figs. 9 and 10. Data from both hemispheres at 4-7 Hz are shown first during each condition (broad hatch left, close-hatch right). Data for 8-11 Hz are shown second (broad-cross left, close-cross right.). See text for discussion of these data.

Our findings to date suggest that a non-specific increase in frequencies between 1-7 Hz accompanies the imposition of significant G-force effects in a graded and parallel manner. To the extent that the pilot continues to effectively operate the aircraft, this is associated also by a specific discrepancy between left and right central cortical EEG patterns at 8-11 Hz, with power on the left greater than that on the right. Additionally, central cortical hemispheric differences appear only when the subject is actually flying the aircraft.

IV. Discussion

We have presented here a brief overview of a series of studies in various stages of completion. Accordingly, it was impossible to provide a comprehensive integration of findings. Preliminary observations, however, did disclose a consistent trend in a body of data which encompasses a number of diverse laboratory and field contexts.

As stated at the outset, our focus on the concept of background functional state and a reliance on neurophysiological constructs relating to the underlying substrates of EEG activity in task-specific neural systems is somewhat unique. It is difficult, therefore, to compare our findings with those of other groups interested in these problems. For example, studies examining event-related potentials within the EEG in relation to information processing and cognitive activity (24), while also directed to functional considerations, limit recordings to standardized midline electrode placements, a practice which precludes comparison with the hemispheric differences that proved so useful to the studies reported here. Further, EEG studies concerned with the increase in nonspecific, slower frequencies which parallels the decline of vigilance (25,26) cannot be compared with findings relating to specific frequency changes in association with increasing vigilance. Finally, there has been little in the way of extended and/or systematic EEG data collected in the context of actual military flight operations.

Data from the four EEG studies described here showed that most flight-trained individuals engaged in the visual-motor tasks associated with piloting aircraft develop a significant hemispheric discrepancy in the incidence of 8-11 Hz activity recorded from the sensorimotor (central) cortical areas, with activity in the left hemisphere exceeding that in the right. This discrepancy was present during such performance whether it occurred in the quiet, undynamic laboratory setting or in a T-38 traveling at 500 knots in a terrain-

following exercise. It was present in both left and right handed individuals and in both younger and older adults. It was not present during resting, cognitive activity or high-performance flight if the subject was not operating the controls. Most importantly, it was attenuated or abolished during poor or failed performance when the individual was operating the controls. Time-series and trend analysis of the incidence of central 8-15 Hz activity supported these observations. A more or less periodic modulation of this activity was documented under all circumstances. However, during good performance, modulation in left central cortex was uniquely dominated by slower cycles, ranging from 2-5 minutes in period and with increasing amplitudes. Conversely, during poor performance, this modulation was faster (1-2 cycles per minute) and showed stable or decreasing amplitudes. Both period and amplitude differences between hemispheres tended to disappear as performance deteriorated.

Although increased arousal or demand generally decreased activity at this frequency, it did not abolish hemispheric differences in central cortex if the task was being successfully performed. Moreover, this discrepancy was abolished in conditions of both low and high arousal if the subject was not operating the aircraft controls. Thus, one cannot attribute the attenuation of this pattern during poor performance or disorientation to a nonspecific arousal effect.

It is possible that the unilateral facilitation of 8-15 Hz patterns was related to the so-called "en arceau rhythme" (or mu rhythm) described by Gastaut (27). However, this rhythm is dependant on the absence or suppression of movement (27,28), an unlikely requirement for the hand operating attitude control in most of our studies. Moreover, as stated above, this hemispheric discrepancy disappeared during periods of non-performance. Nevertheless, the possible relationship of these findings to the mu rhythm concept bears further consideration.

It will be recalled from our initial comments that an extensive animal literature has shown that rhythmic EEG frequencies in sensorimotor cortex are produced by ascending volleys of intrinsic, gated discharge from neurons in the specific thalamic relay nucleus projecting to this area. The amplitude of resulting EEG patterns is determined by changing levels of cortical activation. Further, oscillatory thalamic discharge is increased by either the spontaneous or imposed reduction of afferent activity in related sensory pathways. Thus, it is reasonable to propose that a unilateral increase in sensorimotor EEG rhythmic patterns reflects a decrease in the processing of somatosensory information in that hemisphere. Conversely, the attenuation of such activity implies increased functional processing. Additionally, the modulation of these events over time can be interpreted as an index of the need for such information.

The present context does not allow for a detailed discussion of these neurophysiological dynamics. However, it can be seen that they provide a basis for some speculation concerning the present findings. We would suggest that competent flight performance requires a differentiation of right and left hemisphere sensorimotor functions. It is now generally accepted that the left hemisphere functions in a primary linear, sequental and logical fashion, and is specialized for symbolic comprehension and calculation, while the right hemisphere functions in a primarily holistic, simultaneous fashion and is specialized for visual-spatial and visual-perceptual activities (29,30). Given the nature of this division of labor, our data imply that high-performance flying is improved as these underlying neurophysiological functions become more clearly differentiated. Indeed, it appears that the actual psychomotor act of aircraft control is less relevant to adequate performance than the visual-spatial processing that is ongoing. We speculate that these psychomotor tasks must become highly overlearned or near automatic behaviors (probably even subcortically maintained) while the visual- spatial environment, and therefore visual-perceptual processing, remains novel and in need of constant adaptive response.

Borrowing from the analogy of Donchin et al (31), we would assign to the right hemisphere the task of "tactical" information processing and to the left the task of "strategic" information processing. Thus, in optimal performance circumstances, the right sensorimotor cortex is continuously engaged in the spatial-perceptual task of guiding flight operations. The left sensorimotor cortex, having specified the overall objectives, does not interfere with this process except to update on a periodic basis. The more often instructions must be updated or conscious calculations made (i.e., the shorter the period of amplitude modulation), the less competent the performance. When strategic and tactical efforts become simultaneous, the quality of performance may be compromised.

Our findings in the area of G-force effects on EEG patterns are very preliminary. Once again, however, they appear to be consistent. Data from both passenger and pilot subjects have shown that the onset and increment of significant G-force effects is accompanied by a nonspecific increase in lower frequency patterns. The present data for pilots operating the aircraft suggest that this is particularly true for the 4-7 Hz band. However, regardless of this effect, if central 8-15 Hz left-right hemisphere discrepancy is maintained, competent performance is continued. The ongoing collection and interpretation of data in this context should further clarify these relationships.

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DISCUSSION

KAUFMAN, US: It is well-known that when there is not too much demand on the alert but resting person, then there is a good bit of alpha activity, having some periodicity, which occurs in spindles in the range of 8 - 11 Hz. However, when the person is disturbed, he becomes alert and generates lots of beta activity. This used to be called desynchronization, sometimes alpha blockage, and is characterized by having less periodicity in the 8 - 11 Hz range. It may be hypothesized that you have a situation in which the pilot is presented with poor performance, which he perhaps senses; and he becomes more alert, he looks around more, his alpha activity is blocked, and he shows desynchronization. Similarly, under high-G, he becomes disturbed and displays the same kinds of characteristics. Given the fact that this can occur asymmetrically over the hemispheres, to what extent would such a hypothesis account for your data?

SCHUMMER, US: I cannot say that we have gone about asking all of the relevant questions pertaining to that hypothesis. Of course, if that were to occur, then we would expect to see increases in beta activity, which did not happen in our situation.

GEVINS, US: The beta band energy goes down with increased activation and performance of task. It does not increase as has been erroneously reported on numerous occasions. So Dr. Kaufman's account of your results is probably correct.

MOTION EVOKED VESTIBULAR POTENTIALS

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SUMMARY

Motion evoked potentials (MER) were collected from subjects while they were rotated from side to side in a seated position. The MERs were biphasic with major component mean latencies of 278 msec and 388 msec. It is concluded that the MERs are of brain origin and not due to artifacts from the recording environment. The latencies of the waveform components of the MER suggests that the MER results from the onset of the rotation stimulus. Differences between the MERs reported here and those of other published reports may be due to the added involvment of the saccule/utricle apparatus and the more rapid onset of the stimulus.

INTRODUCTION

The vestibular system is of crucial importance in establishing orientation in space and providing acceleration information. Numerous studies have been performed on lower animals which have provided much information concerning the anatomy and physiology of the vestibular system. However, little electrophysiological data is available from normal human subjects. This is in part due to the difficulty of providing adequate stimuli which permits the recording of electrical events associated with the stimuli. This is unfortunate because of the role played by the vestibular apparatus in normal situations as well as its hypothesized role in motion and space sickness.

Several investigators have recorded electrical activity from the human brain in response to motion stimulation (1)(2)(3). The results of these studies are inconsistent and inconclusive. The exact reason for this is not clear, but may be due to the nature of the stimuli used, or the state of their subjects (4)(5). However, Salamy et al (5) and Hood and Kayan (4) have taken systematic approaches to the methodological problems concerning vestibular stimulus presentation and status of subjects. These two studies focused on different aspects of the motion evoked response (MER). Salamy et al (5) were interested in the activity occurring within the first second following stimulus onset, while Hood and Kayan (4) investigated the later evoked activity (up to two seconds after stimulus onset). The subjects were seated in an upright position with their heads tilted 30 degrees forward. They were rotated about the vertical axis of the body, with the intention of maximally stimulating the horizontal semicircular canals. Salamy et al (5) reported biphasic MERs that exhibited prominent negative and positive components. The negative component had a mean latency of 193 msec after onset of the stimulus, and the positive component had a mean latency of 345 msec. The authors concluded that MERs were vestibular in origin, and not a result of somatosensory or ocular influences. The MERs were quite comparable to averaged scalp potentials obtained from the other sensory systems. Hood and Kayan (4) investigated the much longer latency MER components. These authors reported that they could not consistently find the short latency MER components found by earlier investigators. However, they reliably observed a slow, dome-shaped negative component reaching a peak at approximately 700 msec. This negative-going component was larger when visual input was present, indicating the influence of optokinetic effects from the visual system.

The differences in these two studies may be due to the experimental conditions. Salamy et al (5) used a fairly sudden onset motion, and the subjects were blindfolded and instructed to keep their eyes closed. Hood and Kayan (4) used a much slower onset motion, and subjects fixated on a spot at eye level that moved in conjunction with the subjects. Both studies positioned subjects so that only the semicircular canals were stimulated.

The purpose of the present study is to stimulate both the semicircular canals and the saccule/utricle apparatus. We examined the brain activity during the first second after stimulus onset to determine whether or not early components of the MER can be reliably recorded.

METHOD

Six young adult male subjects were used in this experiment. They were all healthy as ascertained by a physical examination. Silver-silver chloride electrodes were applied to the vertex (Cz) and both mastoid processes. One mastoid was used as reference, the other as ground. Electrode impedances were 5K ohms or less.

The Armstrong Aeromedical Research Laboratory Dynamic Environmental Simulator (DES) was used to provide the motion stimulus. The DES is a man-rated, three axis centrifuge with a 19 feet radius. It is controlled by a digital computer which operates a hydraulic and direct drive electric motor system. During this experiment, only the cab was rotated, not the main arm. The cab is a spherical gondola 10 feet in diameter and is rotated on the arm by a hydraulic drive system. Subjects were seated and strapped upright into an aircraft seat mounted at the center of the cab. From the upright, seated position the subjects were rotated approximately 90 degrees to their left along the Y-axis of the body. After several seconds in this position, they were rotated approximately 180 degrees in the same plane to the right side. The rotation took four seconds, which resulted in an acceleration of approximately pi/4 radians/sec^{-2} (45 degrees/sec^{-2}). They were then returned to the upright position and given several minutes to readapt, then the stimulus sequence was repeated for a total of six rotations. The EEG was sampled for one second at a rate of 250 Hz by a Nicolet CA 1000 averager beginning with the onset of rotation. Grass P511 AC amplifiers were used to amplify the EEG and had a gain of approximately 50K. The cab was illuminated and the subjects fixated a spot in front of their eyes during the rotation. A television camera mounted inside the cab provided visual monitoring of the subjects during the rotation and between rotations.

For two of the subjects, additional electrodes were attached at the center of the forehead approximately 1 cm above the nasion, and on the point of the cheek bone. This was done because the amplifiers were in the DES cab and also as a check on movement induced artifacts form the subjects. By positioning electrodes on the head at sites more distant from the brain, it was assumed that this would provide information as to whether or not motion artifacts were present. If the same electrical activity was found at the vertex, forehead and cheek sites, then one could conclude that motion artifacts were being recorded, as well as sensory activity from the brain. The forehead electrode also would register eye potentials that would be larger than those from the vertex due to the proximity to the eyes.

As a further test, this electrode configuration was applied to another subject who was presented with a stimulus situation that is known to result in a large, late positive component which is similar to the one found in this experiment(6). The so-called "odd-ball" paradigm was used in which 100 stimuli are presented that consist of 80 regular tones with 20 different, clearly discernable rare tones randomly interspersed. The subjects were asked to covertly count the rare tones that were heard. This would produce a large positive component approximately 300 msec following onset of the rare tone. Since this potential is of known brain origin, its relative size at the vertex, forehead and cheek would show the potential gradient distribution from brain-generated activity at these sites.

RESULTS

Figure 1 presents the motion evoked responses (MERs) from the six subjects. The MERs can be characterized as biphasic, starting with a negative-going component with a mean latency of 278 msec following the onset of rotation. This is followed by a large positive-going component that peaks at 388 msec (Table 1). The data taken from the forehead and cheek are depicted in Figure 2, and show that these biphasic components are attenuated at the forehead and essentially absent from the cheek recording. This indicates that the potentials recorded from the vertex were of brain origin. The data from the subject in the "oddball" paradigm are shown in Figure 3, and display the typical large late positive component which is quite similar to the MER in configuration. The positive component was evident, but smaller, at the forehead and essentially absent at the cheek. This was the same pattern found with the MERs.

Table I. Means and standard deviations of the major components of the motion evoked response. Latency in msec and amplitude in uv.

	Latency		Amplitude
Subject	Negative	Positive	Peak-to-Peak
1	288	372	14.3
2	280	360	10.2
3	284	400	9.2
4	264	396	13.8
5	284	420	12.0
6	268	380	12.8
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Mean	278	388	12.1
Std.Dev.	9.7	21.6	2.0

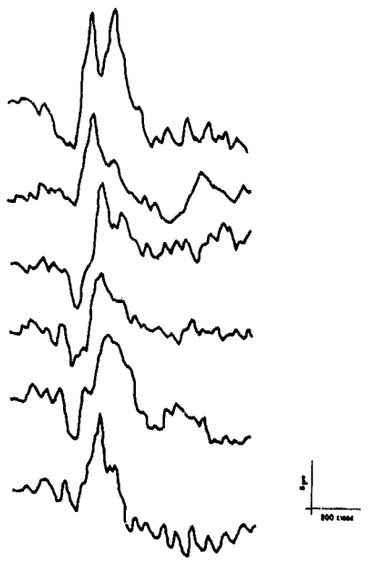

Figure 1. Average motion evoked responses from the six subjects. Positive plotted as an upward deflection.

In order to test for effects due to the movement of the electrode leads and amplifiers, a "dummy subject" consisting of 10K ohm resistors was placed in the position of the human subject's head. Analysis of these data taken during cab rotation resulted in a straight line recording, showing that the movement of the leads and amplifiers did not contribute to the MER.

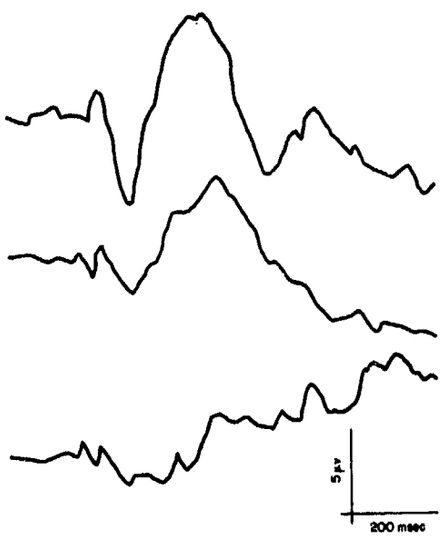

Figure 2. Averaged responses from one subject recorded from the vertex, forehead and cheek in response to six rotations.

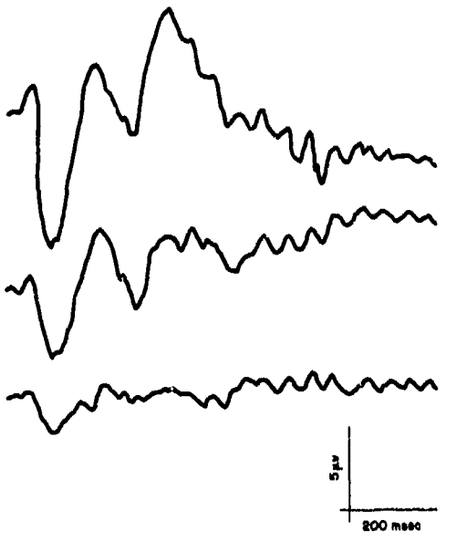

Figure 3. Responses from one subject in the "odd-ball" paradigm recorded from the vertex, forehead and cheek.

DISCUSSION

The MERs elicited in this study seem to be cortical in origin. They are quite similar from subject to subject and decrease in size as the recording site is moved away from the vertex. The similarity of the potentials between subjects indicates that they are due to vestibular stimulation. Identical MERs from all subjects would indicate that they were due to movement artifact and not neural in origin. The similarity found between subjects exhibited enough variability to argue for neural origins. Also, the finding that the amplitudes were much smaller at the forehead, and not evident at the cheek, further supports a neural origin and one which is probably located in the central regions of the brain. More precise localization is not possible with the present data. However, Salamy et al (5) reported that the largest amplitudes were recorded from the more central regions. Since the MERs from the forehead electrode were considerably smaller than those from vertex, ocular origins of the MER can be ruled out, or at least seen to have had a negligible influence on the MER.

Salamy et al (5) were concerned with possible somatosensory origins or influences on the MER. They convincingly argued that the time course of their records was not compatible to those found with somatosensory responses. The somatosensory system would produce much earlier components than those found. The same argument would seem to hold for the present data.

In contrast to Hood and Kayan (4) and in line with Salamy (5) we were able to record early components of the MER from our subjects. It is clear from Table I that the latencies of the two components were consistent across subjects. The standard deviations are similar to those reported from studies whose evoking stimuli are auditory or visual. It seems likely that the rate of onset of the stimuli was an important difference between Hood and Kayan (4) and Salamy et al (5) and the present study. The early components of the MER may well be sensitive to and directly responding to the initial onset of rotation. While the longer latency, dome like, response reported by Hood and Kayan (4) is produced by continuation of the rotation. These relationships should be investigated in a systematic fashion to provide better understanding of the mechanisms underlying the MER.

In regard to the data presented in Salamy et al (5), the latencies reported here are longer by approximately 100 msec for the negative component, and approximately 50 msec for the positive component. There are several possible reasons for these differences. Stimulus onset rate and body orientation are two good candidates though not the only ones. As discussed above stimulus characteristics are very important for the MER. While similar rates were used in the two studies the differences between them could well have produced the MER differences. The second factor was body orientation during the stimulus which determines the nature of the stimulation to the vestibular sensors. Salamy et al (5) purposely positioned their subjects so as to only stimulate

the semicircular canals. In the present study the subjects orientation was such so that the saccule/utricle apparatus would also be stimulated. The added input from these sense organs could be responsible for the later response latencies found in the MERs. Other variables may also have been responsible for the latency differences. While no conclusions can be drawn at this time concerning the origin of the reported differences, the data do suggest that studies be carried out which systematically vary these parameters in order to determine the variables responsible for the MER. Further, this sort of research would also permit the determination of the relationships between manipulations of these variables and exact changes in the MER.

In addition to manipulation of orientation and acceleration, the reliability of the MER should be tested. If these waveforms are stable over time, the differences between subjects could be investigated in terms of suseptibility to motion effects, such as nystagmus and motion sickness. It is possible that not only could suseptible individuals be identified but also the effects of medication and behavioral treatment could be monitored.

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DISCUSSION

GUEDRY, US: I gather that the tilt you used was from 90° left to 90° right or vice versa. To fully understand the nature of your stimulus you would also need to know the angular velocity profile. If you start your stimulus with a high angular acceleration to some constant velocity — probably 45°/s or so — then you would have a strong semicircular canal stimulus, and a more-or-less continuous change in stimulation of the otolithic organs. At the end of the stimulus period, you would have a reversed semicircular canal stimulation. Would you clarify exactly what is the condition of your stimulus?

WILSON, US: It was 45°/s. The entire motion took place in 4 seconds, but we only analyzed the first one-second of data because of equipment problems.

GUEDRY, US: So your stimulus at the beginning is, in fact, a semicircular canal stimulus which would persist for part of the time during which you were generating an otolithic stimulation.

JOHNSON, GE: Have you any idea of the reaction of the eyes during your experiments?

WILSON, US: We used a fixation light, but did not find large eye excursions. We had very small levels of activity, but we may have been picking up EEG. I don't think we had any eye movements that were detectable.

LANDOLT, CA: The stimulus that you used was asymmetrical in the sense that you tilted 90° one way from the upright position, and then tilted 180° in the opposite direction. If you evoked somatosensory potentials then, would these not show up as an asymmetric response? Did you check for this?

WILSON, US: We only recorded from the midline with this experiment, and only with one EEG channel. I think the way to check for this would be to record bilaterally.

WOLFE, US: I don't see how you can define your stimulus. If you move the whole body, then you will have a somatosensory stimulus, a cross-coupled semicircular canal stimulus, and otolithic stimulation; all taking place simultaneously.

THE EFFECT OF MILD HYPOXIA ON THE VESTIBULAR EVOKED RESPONSE

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SUMMARY

The effect of hypoxia on the long-latency vestibular evoked response (VsER) was examined in eight sitting subjects who underwent intermittent 0.1 Hz sinusoidal rotation in complete darkness, while fixating on a small target light that rotated with the subject. Evoked responses were recorded during 10 minutes of rotational stimulation after breathing each gas mixture for a minimum of 25 minutes. For intermittent clockwise (CW) rotation in the horizontal plane, a reproducible negative potential (-28.7 ± 2.3 μV) (mean ± SEM) developed at electrode sites located between the vertex and the "linked" ears during air breathing conditions. It peaked close to the point of maximum velocity of the sinusoidal stimulus. This negative cortical potential decreased (i.e., it became less negative) with respect to the air control by 25.4% ($P < 0.01$) when the subjects were exposed to a 16.7% oxygen breathing mixture (altitude equivalent of 1900 m). No effect was seen with 18.7% (910 m) and 14.4% (2780 m) oxygen breathing mixtures. For intermittent counterclockwise (CCW) rotation, a positive potential (30.1 ± 3.7 μV) developed, during air breathing, between the vertex and the linked ears. This amplitude decreased by 18.9% when breathing both the 18.7% and 16.6% oxygen gas mixtures ($P < 0.01$), and by 17.9% for a 14.4% oxygen mixture ($P < 0.05$) compared to the standard, air. These results indicate that the cortical processing of vestibular sensations may be affected even under very mildly hypoxic conditions. Animal studies have indicated that the levels of hypoxia used in this study can significantly alter neurotransmitter metabolism in brain tissue. Modifications in neurotransmitter synthesis and concentration by the hypoxic conditions may explain the susceptibility of cortical processing of sensory information to very mild hypoxia. Compensatory changes in cerebral blood flow and neurotransmitter synthesis may be responsible for the reduced effect under the more severe hypoxic conditions.

1. INTRODUCTION

Spatial disorientation in flight (SDF) occurs because of an incorrect conscious perception of the body's orientation in space. It is a contributing factor in up to 10% of all aircraft accidents [1]. Most research into the effects of environmental stressors on SDF has been concerned with the functional disruption of the vestibular and visual systems, either at the level of the end-organ or at the sub-cortical brainstem. However, it is in the cortex where conscious awareness of spatial orientation is processed [2,3,4,5]. Since inadequate or degraded vestibular and visual cues, and the failure to consciously detect changes in attitude or motion of the aircraft probably account for the most important causes of disorientation accidents [1], any disruption of the cortical processing of conscious perception of vestibular signals is also of critical concern. Although the correct functioning of the end-organ and brainstem is critical, SDF may still occur if cortical processing of vital information pertaining to spatial orientation is distorted or impaired.

The processing of both visual [6,7] and auditory [8,9] sensory information at the level of the cerebral cortex is more readily impaired by hypoxia than is the analogous sub-cortical primary processing [10]. A possible explanation for the sensitivity of the cerebral cortex to mild hypoxia is that even small changes in the concentration of oxygen in the breathing mixture can lead to dramatic changes in the functional metabolic state of the central nervous system [11,12,13,14] (see DISCUSSION). More severe hypoxia than that required to disrupt cortical function decreases the frequency of caloric-induced nystagmus [15], and increases the slow phase angular velocity of rotation-induced nystagmus [16]. However, in cats, complete anoxia of several minutes duration is required to effect the short-latency vestibular evoked response (VsER) [17], which arises from the vestibular nerve and the brainstem. Since the cortex is very sensitive to any changes in oxygen tension, one would expect that disruption of vestibular sensation may occur at levels of hypoxia that have little or no effect on the basic reflex mechanisms of the vestibulo-ocular system. Evidence of this has been reported by both Fraser *et al.* [18] and Yamasaki *et al.* [19], who found that mild hypoxia (oxyhemoglobin saturation >85%) affected the overall postural stability of standing human subjects.

Fredrickson *et al.* [3,4] have shown that there are primary cortical projections of the vestibular system to the parietal cortices of rhesus and squirrel monkeys, which are presumably associated with the conscious integration of sensory information for perception of body position. Several other groups have investigated the nature of the VsER in humans and also in animals [20,21,22,23,24]. Figure 1 summarizes the reported results on the long-latency cortical evoked responses to low frequency vestibular stimulation in conscious human subjects. In four of these studies, a slow negative potential developed during clockwise rotation that tracked the vestibular velocity stimulus. When the waveforms of the vestibular evoked response in all five studies are plotted on the same time axis, with the origin set to the point of maximum acceleration (large arrow, Figure 2), it is apparent that the negative evoked response lags the peak acceleration and leads or tracks the peak velocity, over a wide range of stimulus velocities.

Since this slow potential shift tracks the velocity stimulus, it is believed that it represents cortical processing of the vestibular stimulus [23]. Accordingly, the method was used in this study to examine the effects of mild hypoxia on the processing of vestibular information since this would have relevance in providing insight into pilot orientation and disorientation.

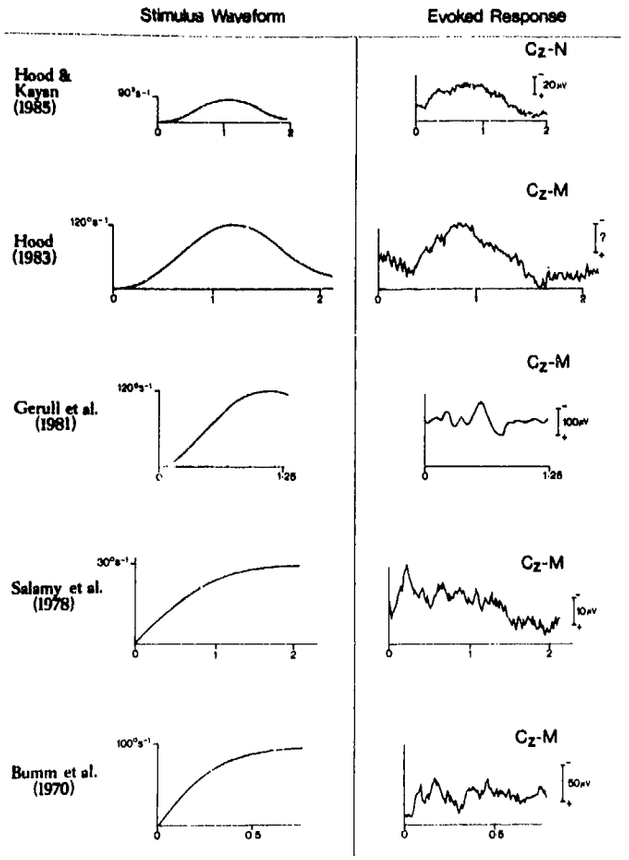

Figure 1. A summary of five studies on the long-latency cortical evoked response due to a vestibular stimulus (right column). The velocity stimulus is given in the left column. All evoked responses were recorded from human subjects with a vertex electrode referenced to a nose (Cz-N), or mastoid electrode (Cz-M) as cited. All plots are retracings made from the original figures provided in each reference. In Hood [22], no amplitude scale was provided. All abscissae are in units of seconds.

2. METHODS

The long-latency components of the VsER were recorded in eight sitting volunteer subjects (6 female, 2 male; mean age of 24 years), who underwent intermittent 0.1 Hz sinusoidal stimulation (angular displacement = 45°, angular velocity = $14°s^{-1}$, angular acceleration = $9°s^{-2}$; in the horizontal plane) in complete darkness using DCIEM's Precision Angular Mover (PAM). These angular accelerations are well above the reported threshold values for conscious perception ($0.035 - 4.0°s^{-2}$) [25], but below the levels used in the studies reported above [20,21,22,23,24], in order to minimize the possibility that the recorded evoked responses had a somatosensory origin. The intermittent rotations consisted of a half-wave sinusoidal rotation (of 5 seconds duration, every 15 seconds (Figure 3). The direction of rotation was alternated between clockwise (CW) and counterclockwise (CCW) rotations in each stimulus paradigm. Using the 10-20 International electrode position system, the cortical evoked responses were recorded from the Cz position, as referenced to the "linked" ears (referred to as "A" in text), and from the Cz site (as referenced to the Pz position) with silver-silver chloride miniature electrodes (Grass Instrument Co). Bipolar electrode configurations were chosen to conform to previous studies [20,21,22,23,24], as well as to examine potential changes over the primary vestibular cortex in the parietal lobe. Conjugate vertical and horizontal eye movements were recorded with silver-silver chloride electrodes to monitor the vestibulo-ocular reflex (VOR) and to detect blink artifacts. A common ground electrode was placed on the forehead. The signals were amplified with Gould Universal Pre-amplifiers (Model 11-5407-58) and Amplifiers (Model 13-4615-58), and stored on magnetic tape with an FM tape recorder (Hewlett-Packard Co., Model 3968A) along with the velocity profile from a tachometer coupled to the PAM. The Cz-Pz, Cz-A, VOR, and blink signals were bandpass filtered between 0.05 and 30 Hz, before they were taped.

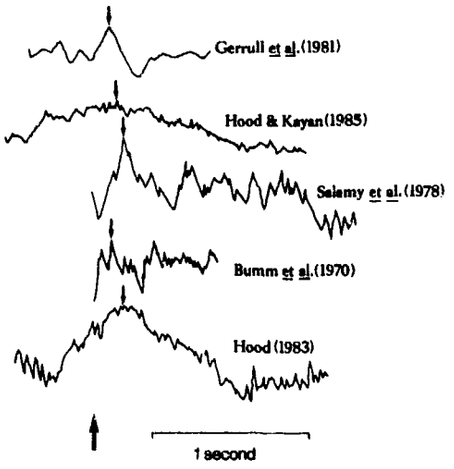

Figure 2.

The cortical responses shown in Figure 1 replotted relative to the point of maximum acceleration (large arrow). The smaller arrows on each waveform indicate the point of maximum negative response.

Each subject was exposed to each gas mixture for 35 minutes. The "resting" electroencephalogram (EEG) was recorded with the subject in the dark with the eyes open during the first 10 minutes of exposure to the gas mixture. Following ten minutes of other tests (not reported in this paper), the subject was then given 5 minutes of continuous 0.1 Hz sinusoidal rotation in complete darkness to record the VOR. The subject was asked to keep his/her eyes open and perform a subtraction task during this time. Following the VOR testing, the subject was exposed to 10 minutes of intermittent sinusoidal stimulation in the dark with the eyes open and fixed on a small light-emitting dioide placed 15 cm in front of the eyes, which rotated with the subject. Following the completion of the intermittent stimulation, the breathing gas mixture was switched, and the next set of readings were taken. Half of the subjects received the gas mixtures in the following order: air, 18.7% O_2 (altitude equivalent of 910 m), 15.6% O_2 (1900 m), 14.4% O_2 (2780 m), air; the remainder in the reverse order; none were aware of the order of gas presentation. All test gas mixtures were balanced with nitrogen. All subjects had refrained from alcohol and drugs for 48 hours, and food and caffeine for 12 hours prior to the experiment. Inspired oxygen partial pressure was monitored with a Beckman O_2 analyzer.

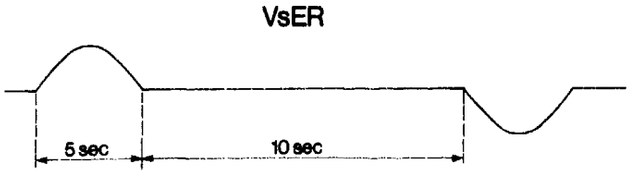

Figure 3.

Intermittent half-wave sinusoidal stimulus given to each subject. The intermittent stimuli consisted of one-half of a complete sinusoidal rotation (5 seconds duration) given at alternate CW and CCW rotations every 15 secs.

All FM tape data were transferred to a MASSCOMP 5700 computer (MASSCOMP Computer, Co.) The velocity, eye movement, and evoked response records were digitally filtered with a 3rd-order Butterworth filter, having a 3dB drop off in gain at a cutoff frequency of 0.2 Hz to remove high frequency components. The data files were reversed, refiltered, and reversed again to cancel the effects of phase shifting induced by the digital filters [26]. Individual 10-second segments of the intermittent stimulus and the VsER were averaged for each subject, stimulus, and gas (8 Ss x 2 stimuli x 5 gases = 80 conditions). The average amplitudes of the evoked responses were calculated only from those data segments that were uncontaminated by gross eye movement or other artifacts. A total of 10 to 15 stimuli were averaged for each condition. Amplitudes were calculated from the averaged EEG baseline activity that was recorded during the resting phase. Because of difficulties in accurately determining the starting point of the velocity profile, and the point of maximum amplitude, no latency measurements were attempted. Moreover, the concept of latency for long-latency VsER, is probably not meaningful in the context of the experiments described herein. Phase-plane plots of the stimulus velocity versus the averaged evoked response were compared with similar plots of stimulus velocity versus eye movement to test for eye-movement artifacts. The BMDP-2V software program [27] was used to perform a repeated measures analysis of variance on the data. Comparisons of the first air control versus the hypoxic gases and the second air exposure were performed with Dunnett's test. This test enables an examination for significant changes of effects of all four breathing gas mixtures as compared to the first air control [28,29]. All differences were considered significant when the probability exceeded the 95% confidence interval (i.e., $P < 0.05$).

3. RESULTS

A highly reproducible evoked response was recorded from all subjects. During intermittent sinusoidal stimulation, the VsER recorded from both the Cz-Pz and Cz-A montages was characterized by an initial evoked response (arrow, Figure 4) following the initial maximum acceleration (similar to the peaks seen by Bumm et al. [20], and Salamy et al. [24]. This was followed by a slow potential shift which closely tracked the stimulus velocity profile of the PAM. During CW rotation, a negative potential shift occurred; during CCW rotation, a strong positive potential. Figure 4 illustrates the average evoked response of subject "de" during CW stimulation under the condition of the second air control, along with a plot of the PAM velocity. A clear correlation between evoked response and stimulus velocity can be seen in the phase-plane plot (Figure 5). No correlation was observed between eye movement and stimulus velocity (Figure 6), indicating that the evoked responses were not an artifact due to eye movement. The average evoked response (under CW rotation) of subject "de" for each of the gas mixtures breathed over the course of the experiment is given in Figure 7. The average evoked response amplitudes for the intermittent stimulus for all eight subjects are given in Table 1 for CW, CCW, and combined conditions.

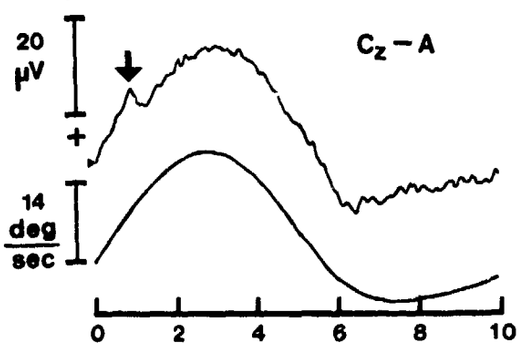

Figure 4.

Average VsER (for Cz-A montage) and stimulus velocity profile of subject "de" undergoing intermittent CW sinusoidal stimulation during air control. The arrow points to the initial evoked response following the maximum acceleration. There is an overshoot of the velocity stimulus in the CCW direction at the end of the CW rotation due to difficulties in controlling the PAM. Small arrowhead indicates baseline level.

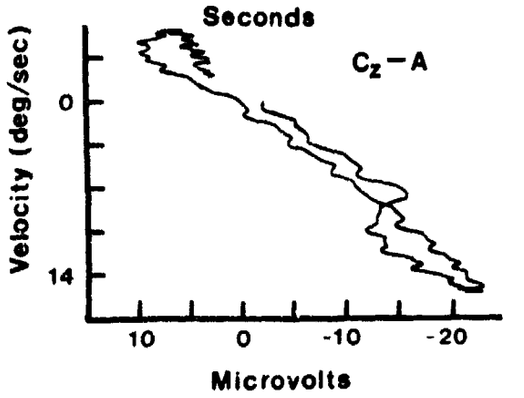

Figure 5.

Phase-plane plot of stimulus velocity (in deg/sec) versus the bipolar Cz-A cortical evoked response (in microvolts).

The mean negative cortical potentials recorded between Cz-A and Cz-Pz, during CW rotation, decreased (i.e., they became less negative) with respect to the first air control by 25.4% ($P < 0.01$) and 22.4% ($P < 0.01$), respectively, when the subjects were exposed to the 16.6% oxygen (equivalent altitude of 1900 m) hypoxic gas mixture. No significant changes were seen between the air control and the other hypoxic conditions. The mean positive cortical potentials between Cz-A decreased during CCW rotation by 18.9% when the subjects were exposed to the 18.7% (910 m) ($P < 0.05$) and 16.6% oxygen ($P < 0.01$) gas mixtures, and by 17.9% during exposure to the 14.4% oxygen (2780 m) mixture. When amplitude changes from the combined intermittent stimulations were compared, the mean Cz-A amplitudes decreased by 11.9% ($P < 0.05$) and 22.1% ($P < 0.01$) with the 18.7% and 16.6% oxygen gas mixtures, respectively. The mean Cz-Pz amplitudes decreased by 14.1% under the 16.6% mixture. No effect was seen due to exposure to the 14.4% oxygen mixture.

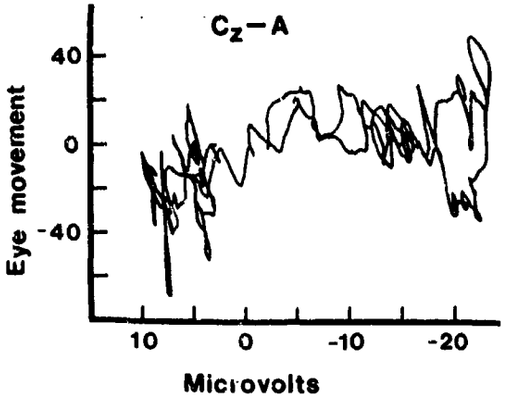

Figure 6.

Phase-plane plot of eye movement (in abitrary voltage units) versus evoked response (in microvolts).

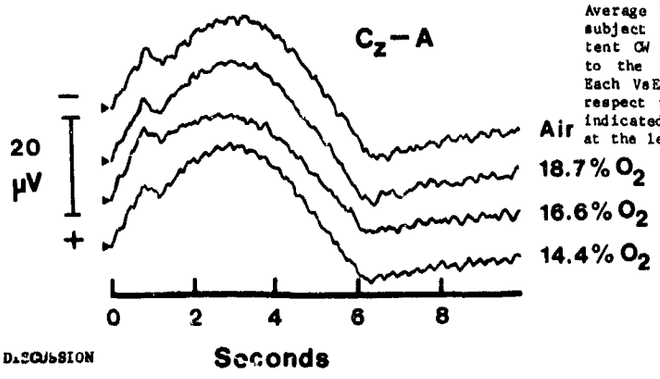

Figure 7.

Average VsER (for Cz-A sites) of subject "de" undergoing intermittent CW rotation, during exposure to the four gas mixtures shown. Each VsER waveform is drawn with respect to different baselines as indicated by the small arrowheads at the left of each tracing.

4. DISCUSSION

The shapes of the evoked response to the intermittent sinusoidal stimuli recorded in this study is similar to those observed by Hood [22] and Hood and Kayan [23]. However, they observed a negative potential under both CW and CCW stimulation. In this study, a positive potential, similar to the slow positive potential shift reported for CW rotation by Salamy et al. [24] was seen during the CCW rotation. A direct comparison of these different experiments is difficult since the choice of a bipolar montage affects the sign of the potential shift. The initial peak (arrow, Figure 4) is most likely the response evoked by the initial acceleration of the PAM, suggesting that the total waveform of the evoked response is due to a combination of evoked reponses in response to both acceleration and velocity stimuli.

The tracking of the velocity stimulus by the VsER is consistent with the velocity-stimulus tracking of cupular deflection in animal preparations for similar velocity profiles [30]. This suggests that the observed evoked response is, in fact, a mapping of cupular deflection output to the cortex.

TABLE 1.

BIPOLOR AMPLITUDES OF VESTIBULAR EVOKED RESPONSES
(in μV) UNDER AIR AND HYPOXIC CONDITIONS

Electrode Site	Rotary Condition	Gas Mixture				
		Air	18.7% O_2	16.6% O_2	14.7% O_2	Air
Cz-Pz	CW	-19.6	-16.1	-15.2*	-18.3	-17.3
±SEM		± 4.2	± 1.5	± 1.9	± 1.9	± 1.5
Cz-A	CW	-28.7	-27.5	-21.4**	-25.5	-23.4
±SEM		± 1.9	± 2.7	± 1.8	± 1.9	± 1.2
Cz-Pz	CCW	15.9	14.5	14.2	14.0	13.7
±SEM		± 1.9	± 1.4	± 1.3	± 1.2	± 1.7
Cz-A	CCW	30.1	24.4**	24.4**	24.7*	25.8
±SEM		± 3.7	± 1.7	± 1.4	± 1.6	± 2.7
Cz-Pz	Combined	17.4	15.3	14.7*	16.2	15.5
±SEM	(CW & CCW)	± 2.0	± 0.5	± 0.3	± 0.2	± 0.5
Cz-A	(CW & CCW)	29.4	25.9*	22.9**	26.9	24.7
±SEM		± 2.3	± 1.3	± 0.8	± 2.8	± 1.7

Values are given as the mean of eight subjects ± standard error of the mean (SEM).
Combined values are the means of the absolute values of the CW nd CCW results.
* Significantly different form first air control at $P < 0.05$.
** Significantly different from first air control at $P < 0.01$.

It is highly unlikely that the evoked responses observed in this experiment are due to artifacts. The sensations experienced under the conditions used in this study usually have been accepted as being entirely vestibular in origin [7]. Hood and Kayan [23] tested patients without vestibular end-organ function, and were unable to detect any VsER under stimulation velocities much larger than those used in the present study, thus confirming that the evoked responses are not of somatosensory origin (Figure 8). Morever, in both this study and that of Hood and Kayan [23], there were no detectable eye movements when the evoked responses were recorded, although strong eye movements were obtained when the fixation light was turned off. The decrease in the amplitude of the response with hypoxia would indicate that no electrical or mechanical artifact, due to movement of the subject or the PAM, was responsible for the recorded waveforms.

The change in evoked response amplitude indicates that the cortical processing of vestibular sensation is affected by even mild hypoxic conditions. This is in agreement with studies of other sensory modalities, where mild hypoxia had a detectable effect on dark adaptation [32,33,34], contrast discrimination [32], flicker fusion frequency [35], and on the generalized cortical activity [36]. The changes in evoked response amplitude seen in this study, and the effects on other sensory modalities, even under conditions of very mild hypoxia, are consistent with the biochemical changes seen in the brains of animal models, during exposure to similar levels of hypoxia. Table 2 summarizes the reported investigations into the effects of mild hypoxic conditions on various brain metabolites. The increased glucose utilization [11,12], increased lactate concentration [11], decreased acetylcholine synthesis [11,12], decreased norepinephrine and dopamine elimination rates [14], and an increase in cellular cytochrome aa_3 reduction [13] with increased levels of hypoxia, that are shown in Table 2, would be expected to attenuate total cortical potential changes in response to sensory stimuli, due to a decrease in neuronal activity.

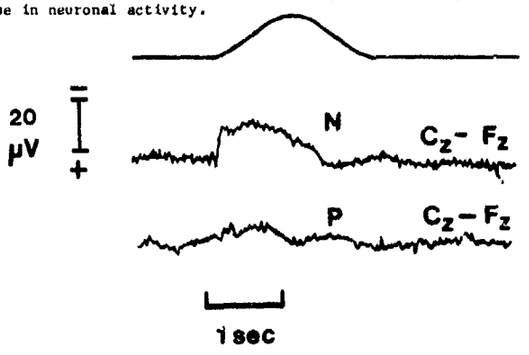

Figure 8.

Vestibular evoked response (at Cz-Fz sites) recorded from a normal subject (N) in response to CW rotational stimulation and the response from a patient (P) with absent end-organ vestibular function. Upper curve is the stimulus velocity. Redrawn from Hood and Kayan [23].

TABLE 2.

CEREBRAL BIOCHEMICAL CHANGES DUE TO MILD HYPOXIA

Altitude		Metabolic Changes									
Metres	$\%O_2$	Lactate Conc. $mol.g^{-1}$	Lactate[2] Conc. $nmol.mg^{-1}$ (protein)	Glucose[2] Utilization $nmol.mg^{-1}$ (protein) min^{-1}	ACh[2] Synthesis $nmol.100mg^{-1}$ (protein) min^{-1}	ACh[1] Synthesis $dpm.nmol^{-1}$	Serine[1] Synthesis $dpm.nmol^{-1}$	Aspartate[1] Synthesis $dpm.nmol^{-1}$	NE[3] Elim.Rate (Brain) h^{-1}	DA[3] Elim.Rate (Brain) h^{-1}	DA[3] Elim.Rate (Striatum) h^{-1}
-	30.0	-	13.1 ± 1.1	7.65 ± 1.09	1.81 ± 0.22	-	-	-	-	-	-
0	21.0	-	-	-	-	-	-	-	0.281 ± 0.027	0.226 ± 0.021	0.218 ± 0.017
396	20.0	0.85 ± 0.07	-	-	-	171.3 ± 10.6	9.2 ± 1.5	30.6 ± 4.8	-	-	-
1800	16.8	-	-	-	-	-	-	-	0.248 ± 0.026	0.428*** ± 0.043	0.317*** ± 0.025
2743	15.0	1.42** ± 0.12	19.0* ± 0.6	10.92* ± 1.24	1.18* ± 0.22	118.3** ± 5.7	4.1** ± 0.3	21.6** ± 1.3	- -	- -	- -
3800	13.1	-	-	-	-	-	-	-	0.204 ± 0.035	0.252 ± 0.011	0.269 ± 0.035

[1] Gibson et al. [12]. Metabolite concentrations were measured in the brains of male CD-1 mice after 17 minutes of hypoxia or control gases. Two minutes before sacrifice (U-^{14}C)glucose was injected intravenously. Acetylcholine (Ach), serine synthesis, and aspartate synthesis from labelled glucose is given in terms of recorded dpm per nmol of unlabelled neurotransmitter.

[2] Gibson and Duffy [11]. Metabolite concentrations were measured in brain of male Wistar rats after 15 minutes of hypoxia following exposure to 70% N_2/30% O_2 control gases. One minute before sacrifice, the rats were injected intravenously with isotopic tracer of acetylcholine synthesis (U-^{14}C) glucose and (1-$^2H_2$, 2-$^2H_2$)choline (20 $\mu mol.kg^{-1}$). Lactate concentration in nmol per mg of brain protein, glucose utilization given as nmol glucose utilized per mg brain protein per minute. Rate of acetylcholine synthesis is given as nmol per 100 mg of brain protein per minute.

[3] Prioux-Guyonneau et al. [14]. The norepinephrine (NE) and dopamine (DA) elimination rates from rat brains were determined by measuring the endogeneous concentration of norepinephrine and dopamine after inhibiting biosynthesis with α-methyl-para-tyrosine. Animals were sacrificed hourly for 4 hours during hypoxic exposure.

* Significantly different from value obtained under the control condition of 70% N_2/30% O_2 at $P \leq 0.05$ or better.

** Significantly different from value obtained under the control condition of 80% N_2/20% O_2 at $P \leq 0.05$ or better.

*** Significantly different from value obtained under the control condition of 79% N_2/21% O_2 at $P \leq 0.05$ or better.

The reduced response at the more severely hypoxic condition is in agreement with an earlier study in which human postural stability was affected at simulated altitudes of 1,500 m, 2,400 m, and 3,000 m, but was found to be normal at an altitude of 3,600 m [18]. Additionally, it is also consistent with alterations in the somatosensory evoked responses and EEG in rabbits during exposure to 12% O_2 [37], and with changes in serial choice reaction times during mild hypobaric exposures [32]. Figure 9 is a composite summary of the results of this study, the study on postural stability [18], and the results on reaction times from Paul et al. [38]. The dopamine elimination rate of hypoxic rat brains taken from a study by Prioux-Guyonneau et al. [14] (last column, Table 2) is also included in the graph. In all four studies, there is a biphasic response, which is highlighted by the fact that very mildly hypoxic conditions have a greater effect on the physiological, performance, and biochemical parameters, than does the more severe hypoxia. The high correlation between the dopamine elimination rates and the changes in the VsER, postural stability, and reaction time indicates that changes in dopamine neuotransmitter levels may account for these biphasic responses.

It is apparent that mild hypoxia may interfere with the processing of vestibular information in a manner similar to the disruption that occurs in the processing of visual and auditory stimulus information. Such disruption of sensory processing may be an important factor in pilot failure to perceive a change in aircraft orientation.

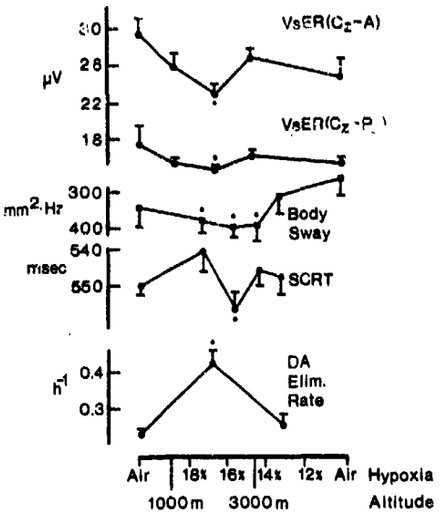

Figure 9.

Composite summary of results of studies on the physiological, performance, and biochemical responses to mild hypoxia. The first two plots are the VsER results taken from Table 1 of this study for the amplitude (in microvolts) of the combined (CW and CCW) rotations for the Cz-A and Cz-Pz electrode positions. The third plot shows the values of the power of the total body sway vector (in $mm^2.Hz$) measured with a balance platform, taken from the study by Fraser et al. [18] (decreased postural stability characterized by an increase in the total area under the power spectral curve). The fourth curve is the reaction times (in msec) for subjects performing a serial choice reaction time (SCRT) task under varying levels of hypoxia [38]. The fifth curve is the dopamine elimination (DA) rates (in inverse hours) from the rat striatum under different hypoxic conditions [14]. All error bars represent standard error of the mean (SEM). The asterisks indicate significant difference from control air at $P < 0.05$ or better.

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DISCUSSION

KAUFMAN, US: It is my impression that when the body is rotated about the vertical axis, the flow of endolymph in the horizontal semicircular canals exerts a mechanical deformation on the cupula;and the hair cells send signals, after a very short latency, to the vestibular nuclei, and, presumably, to the cortex as well. Since the latency can't be more than 20 - 40 ms, it follows that the response must be in step with long periods of stimulation such as the one you used; i.e., in step with the acceleration term. It couldn't be in step with the velocity term because it is the acceleration that produces the force. This may explain the puzzling fact that your data are out of phase by about 90° from those of Hood and Kayan (compare figs. 4 & 8 in text).

LANDOLT, CA: We feel that the "blip" in the evoked response occurs as a result of the sudden "jerk" as the direction of rotation of the PAM changes from CW to CCW. This was followed by a slow potential shift which closely tracked the stimulus velocity. Our stimulus frequency was 0.1 Hz, and that of Hood and Kayan was 0.5 Hz, which could account for the phase difference between the two results. Otherwise, both responses are tracking the velocity stimulus.

BENSON, UK: The point is that the primary afferent activity for stimuli of this type is primarily velocity information. Although the canals are stimulated by acceleration, the system is such that the afferent signal is related to instantaneous velocity, unless you have very long duration stimuli. That is well established from primary afferent activity, and even from basic considerations.

JOHNSON, GE: Were you stimulating the canal or the otolithic organs? Since your data were collected in complete darkness, I don't suppose you would have any way of knowing what the eyes were doing during that period?

LANDOLT, CA: Our rotations were solely in the horizontal plane so it is unlikely that there would be any otolithic stimulation. The subjects were fixating on a small luminous diode which rotated with the subject to minimize eye movements.

JOHNSON, GE: I was thinking more of counter rotation. Did you have any?

LANDOLT, CA: Since we did not stimulate the otoliths, we did not have counter-rolling. When the fixation light was turned off we did have strong nystagmic eye movements but the experiments reported here were conducted during light-diode fixation to avoid contamination of the cortical evoked response.

WOLFE, US: It is not clear to me that, if you use visual fixation in these experiments, whether or not you are really looking at an artifact of the visual system in response to the rotation. Have you done these experiments with no vision and obtained the same results?

LANDOLT, CA: We suppressed visual tracking by requiring the subjects to fixate on a light emitting diode that was attached to the rotating PAM. There was no correlation between eye movement and the stimulus under fixation conditions. If you keep the subjects in the dark, with no fixation, you observe a very strong eye movement; i.e., the classical vestibulo-ocular reflex, which will contaminate any evoked response waveform. Even blind subjects would have strong eye movements under vestibular stimulation.

WOLFE, US: You are suppressing the vestibulo-ocular reflex, and we know that there is an interaction with the visual-vestibular system. In part, what you may be looking at is the visual response to the rotation, rather than the vestibular response.

LANDOLT, CA: Any visual response would be in combination with vestibular sensory information to the cortex. It would not be an artifact due to eye movement.

BENSON, UK: I'd like to see all of these experiments done; firstly, on labyrinthine defective subjects, then on patients fully curarized, and then with people with high spinal transections. There may be a few problems there, but we still don't truly know if there is a vestibular evoked potential, or if this is secondary to vestibular-induced responses.

LANDOLT, CA: I would just like to counter one of your instances. Hood and Kayan have tried the method on labyrinthine defectives and found no detectable evoked response at the scalp electrodes.

Measurement and Classification of the Mode of Action of Antidepressant Drugs

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Summary

In a comparison of the chronic effects on the central nervous system of five new generation antidepressants, we performed a dose-response study with 5 - 7 healthy subjects per substance. Following standard medical screening, we made intraindividual comparisons after one week at each of the three dosages. We compared two MAO-inhibitors, a NA-reuptake inhibitor, a Serotonine-reuptake inhibitor and an α_1/α_2 adrenergic receptor and Serotonin S_2 - receptor - antagonist.
The visual evoked potentials were recorded from electrode position "O_z" between O_1 and O_2. The brightness, contrast and colour channels of the visual system were stimulated using on-off, checkerboard and colour changes respectively.
After digitizing, the evoked potentials were subjected to Fourier filtering and analysed in the standard EEG frequency ranges delta, theta, alpha and beta. This improved stability and precision of measurement without phase shifts. The beta and theta components indicated the best response. The latency changes of all components were measured and used to form attenuation and activation coefficients in each range. With the help of factor analysis, an activity profile of the effects of each of these drugs in the CNS was plotted in three dimensions. Both activation and attenuation coefficients were used to classify the effects of the antidepressants at the cortical level.
It is suggested that the complex modes of action of these drugs may be characterized by a local vector in the three-dimensional, common-factor space. Thus the mode of action measured in the CNS with these techniques shows promise in clinical and research applications including aerospace medicine.

Introduction

Depression as a symptom occurs in a wide range of human emotional and social states. As a clinical syndrome, affective disorders have been suggested to consist of heterogeneous groups of disorders with different etiologies and different responses to psychopharmacological treatments. In general, patients with an endogenous or major depression, who often need hospitalization due to severe impairment and suicidal risk, respond better to pharmacological therapies. There is increasing evidence from placebo controlled studies, however, that other forms of depression termed minor, secondary, reactive or atypical depression, and anxiety or panic disorders also bebefit from antidepressant therapy. As a result, neurophysiological characterisation of the different profiles of antidepressant drugs has become an important task.
It is commonly suggested that the primary neurophysiological effect of the classic antidepressant drugs, such as tricyclic inhibitors of monoamine neurotransmitters (reuptake blockers), and the irreversible and unselective monoamine oxidase (MAO) inhibitors, relates to their ability to increase the synaptic concentration of catecholamines and/or indolamines in the central nervous system <1>. Most antidepressants, however, are clinically effective only after chronic administration. Therefore research has focussed on the elucidation of adaptive changes of monoaminergic neurons in neurotransmission following subchronic administration. This raises the question of whether or not treatment with different types of antidepressants, including tetracyclic reuptake inhibitors and the newer generation of atypical antidepressants and selective MAO - type A inhibitors, leads to a common adaptive response in the CNS which, in turn, may represent the underlying neurobiological process leading to an improvement in the condition of the patients. Furthermore, the localisation of such compensatory responses to certain brain regions is of considerable importance. In search of such a method, we have combined a program of biochemistry, endocrinology and electrophysiology <5>. This report deals only with the results in the field of neurophysiology.
In visual evoked potential drug research, primarily the contrast channel of the visual system has been investigated. It seems,however, to be very difficult to classify various drugs when using only one channel. As a result, we investigated the three channels of the visual system - colour, luminance and contrast - and considered their frequency dynamics enabling us to describe the mode of action of each drug using 5 subsystems.

The frequency dynamics of the visual system were studied by Spekreijse and Regan in the 1970's <2,3>. They classified steady-state evoked potentials into 3 different frequency ranges:

1) a high frequency subsystem (40-60 Hz),
2) a medium frequency subsystem (14-20 Hz) and
3) a low frequency subsystem (9-12 Hz).

They found that the medium frequency visual evoked potential components were more dependent on colour than either the low or high frequency ranges. These findings could be supported by our own investigations. From the EEGs of normal awake persons, it is also known that dominant activity occurs in at least 4-5 frequency ranges. Here they are defined as :

1) 2 Hz (delta range 1- 4 Hz),
2) 5 Hz (theta range 4- 8 Hz),
3) 10 Hz (alpha range 8-14 Hz) and
4) 22 Hz (beta range 14-30 Hz) (compare also <2>.

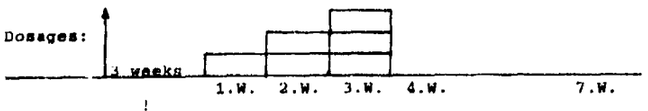
In this study the entire waveform was investigated including amplitudes and latencies of all components not only of the standard flash and checker-board evoked potentials but also of the colour-change evoked potentials. Using digital Fourier filtering (transformation and retransformation), we divided the transient evoked potential into the above-mentioned EEG ranges. The stabilization of the waveforms and latencies and the precision of measurement were quite good. This allowed a comparison of the frequency dynamics of the visual system in order to measure the effect of the psychoactive drugs on the system transfer function.
According to ANOVA it can be seen that one channel of the visual system is not adequate to differentiate all substances simultaneously. With the help of all channels and factor analysis, it is possible to simultaneously differentiate all antidepressants and other substances (compare Johnson et al in this book).

Subjects and Methods

29 healthy volunteers (15 men and 14 women, aged 32 ± 7, ranging from 20 to 45 years) participated in this study. All subjects gave their informed consent. They were free of any drugs for at least 4 weeks and a number of clinical-chemical, endocrinological, encephalographical and colour vision (Farnsworth-munsell and Ishihara) measures did not show any deviations from the norm. The dosage schedule and the composition of the subject groups are shown in figure 2.

SUBSTANCES		MECHANISMS OF ACTION:
Pirlindole:	Cassella	MAO Type A
(Euthym)		Reversible <6,7>
TRANYLCYPROMINE:	Röhm Pharma	MAO Type A, Type B,
(Parnate)		Irreversible
MAPROTILINE:	Ciba Geigy	Selective Noradrenaline
(Ludiomil)		Reuptake Inhibitor
MIANSERIN:	Organon	α_1/α_2 Adrenergic &
(Tolvin)		Serotonine S_2 Receptor
		Antagonist
FLUVOXAMINE:	Duphar	Selective Serotonine
(Fevarin)		Reuptake Inhibitor

Figure 1. Substances studied with their probable mechanisms of action in the CNS.



Time of Recording / Substance	Acute	1.W.	2.W.	3.W.	4.W.	7.W.	No.of Subjects	Age M ± S.D.	Range
	Acute Exp. in mg/die								
Pirlindole	225	75	150	225	-	-	N= 6 (3m/3f)	31 ± 6	25 - 39
Tranylcypromine	20	5	10	20	-	-	N= 6 (2m/4f)	33 ± 4	30 - 40
Maprotiline	75	25	50	75	-	-	N= 6 (3m/3f)	28 ± 8	20 - 44
Mianserin	60	20	40	60	-	-	N= 4 (4m)	34 ± 9	24 - 45
Fluvoxamine	150	50	100	150	-	-	N= 7 (3m/4f)	35 ± 8	25 - 44

m male, f female, W week

Figure 2 Dosage Schedule & Composition of the Subject Groups Receiving Antidepressants

Antidepressants with different pharmacological profiles were used. Since β-adrenergic receptor subsensitivity following the chronic administration of different types of antidepressants has been proposed to be one common mechanism of action of antidepressants, the effect of the above drugs was studied after a single dose or following chronic administration in weekly increasing dosages.
We studied three of the primary functions of the visual system by themselves - brightness vision, contrast vision and colour vision. For further details see Johnson and Wyrobnik <4>.In an earlier study Berdjes and Demisch <8> determined that the antidepressant Pirlindole had an effect on the visual evoked potential under one condition, i.e. on the latency of the P_{100}-component after flash stimulation but not after checkerboard reversal stimuli. This result was a first indication of various neuronal systems for brightness and contrast stimuli.
We used the conditions full field stimulation (Ganzfeld) on/off) and colour change. For these conditions the subjects wore a colour neutral, homogenous mask in order to avoid contrast effects. For the condition checker-board reversal the subjects fixated the centre of the screen. They sat upright, with their heads supported comfortably, 2 meters in front of a standard TV screen (Nordmende SK 2, 15625 hz line frequency, 625 lines, 67 cm diagonal screen) with a Videocolor tube (Hamburg,A 67 615X). The spectral maxima of the phosphors were 450 ±61.5, 540 ±78.2 and 625 ±20.5 nm ± half band widths. The intensities could be individually controlled and were set regularly to 1.2 (red), 0.6 (blue and checker-board) and 2.1 X 10^{-9} A (white screen, full average 1.2) (subjectively equal in brightness) and measured with a calibrated photocell (PIN10D, United Detector Technology) and a nanoamperemeter (Knick, Berlin, Model N 23). Under these experimental conditions for example, red corresponds to a specific luminance of 0.3 W/cm^2. The view field was 12°X8° visual angle. For each stimulus 160 repetitions were used. The standard interval was 2.7 s.
The evoked potential was recorded from the electrode position O_2 according to the international 10-20 system and the left ear served as reference. The recording equipment consisted of silver-silver chloride cup electrodes filled with a conducting paste and connected to EEG amplifiers (Helliger EE) with an input impedance of 10 MΩ (parallel to 1 µF). The output impedance was less than 10Ω . The maximum amplification factor was 33,000 at 30 µV. The highpass frequency was routinely 1 KHz (-3 dB) and the time constant was 1 s. The signal was stored after amplification on magnetic tape (recorder Ampex FR 1300).
The characteristics at the recording speed of 4.75 cm/s were as follows:

Frequency range	0 - 625 Hz
Signal/noise ratio (RMS)	40 dB
Harmonic destortion	<2%
Impedance-input	>20 KΩ
-output	1 KΩ

The calibration of the whole system took place with a 50 µV (± 1%) signal at the EEG input. The EEG was monitored on a 4 channel oscilloscope and artifacts were eliminated visually. The EEG was digitized at a sample frequency of 512 Hz, averaged and stored on floppy discs. Afterwards it was subdivided into the standerd EEG frequency ranges using a Fourier filter (no phase shifts) and the latencies of the peaks were measured in each of the 4 ranges.
In order to increase the precision of measurement, the evoked potentials were filtered into the standard EEG frequency ranges as mentioned above. Since the dominant activity of the brain lies in these ranges, these characteristics are also reflected in the visual evoked potential. In order to avoid the effects of eye movements (EOG, blink reflex) or the alpha rhythm on the VEP, only the results from the ranges theta and beta are reported. In both ranges we found characteristic latency changes of the evoked potentials with the different antidepressants.
The visual evoked potentials were measured before (control) and under chronic conditions at the end of each week (constant serum levels).

Results

In general the alpha and beta components of the VEP showed good correlations to stimulus wavelength while the theta components did not. In higher frequency ranges (30-60 Hz) no definite response was measurable (no details given in this report). Response in the delta range was likely due to the EOG blink reflex with a latency of 150-250 ms as described by Lowitsch et al <4>.
The latency changes were measured in the beta and theta ranges (figure 3). Changes in the alpha range were not included because these signals were too variable in themselves. Generalized and specific changes of the profiles were found for each substance (fig. 4).
Tranylcypromine and Fluvoxamine both showed a dose dependent, increasing activation (latency decrease) while Pirlindole and Maprotiline exhibited both activation as well as attenuation in the visual cortex. Mianserine showed the least differential effect.

Colour Channel / Beta Range:

	Dos. 1 Mean	Std.Err.		Dos. 2 Mean	Std.Err.		Dos. 3 Mean	Std.Err.	
Tra :	- 3.4	1.27	*	- 3.9	1.44	*	- 6.3	2.06	*
Pir :	6.2	1.05	*	6.2	1.19	*	7.8	1.25	*
Flx :	- 1.3	1.79	ns	- 6.6	1.90	*	-15.6	1.28	*
Mia :	1.9	1.29	ns	- 2.6	1.32	ns	- 0.2	1.12	ns
Map :	- 4.4	1.12	*	- 5.9	1.33	*	- 8.5	1.68	*
F-value:	10.48			12.78			33.78		
Groups :	Pir/Tra,Flx, Map/Mia			Pir/Tra,Flx,Map, /Mia			Pir/Flx/Tra,Map, /Mia		

Luminance Channel / Beta Range:

	Dos. 1 Mean	Std.Err.		Dos. 2 Mean	Std.Err.		Dos. 3 Mean	Std.Err.	
Tra :	-10.3	2.04	*	- 7.7	2.13	*	-10.3	2.01	*
Pir :	- 6.8	1.32	*	- 9.5	1.71	*	-11.4	1.53	*
Flx :	1.3	0.77	ns	1.5	1.17	ns	-15.2	1.40	*
Mia :	1.2	1.50	ns	2.4	1.32	ns	1.6	1.17	ns
Map :	- 3.5	1.53	*	- 6.9	1.64	*	- 7.3	1.80	*
F-value:	11.50			12.28			15.51		
Groups :	Tra,Pir/Pir,Map, /Mia,Flx			Pir,Tra,Map, /Flx,Mia			Flx/Tra,Pir,Map, /Mia		

Contrast Channel / Beta Range:

	Dos. 1 Mean	Std.Err.		Dos. 2 Mean	Std.Err.		Dos. 3 Mean	Std.Err.	
Tra :	- 7.7	1.17	*	- 8.8	1.52	*	- 9.9	1.68	*
Pir :	0.1	1.37	ns	- 1.4	1.15	ns	- 0.4	1.24	ns
Flx :	- 1.4	1.09	ns	- 1.2	1.15	ns	-10.8	2.03	*
Mia :	- 1.1	0.90	ns	- 1.3	1.19	ns	- 2.0	1.14	ns
Map :	1.5	0.87	ns	2.1	1.21	ns	0.2	0.89	ns
F-value:	10.56			11.38			13,48		
Groups :	Tra/Pir,Flx, Map,Mia			Tra/Flx,Pir,Mia, ,Map			Flx,Tra/Pir,Mia, ,Map		

Colour Channel / Theta Range:

	Dos. 1 Mean	Std.Err.		Dos. 2 Mean	Std.Err.		Dos. 3 Mean	Std.Err.	
Tra :	- 4.9	3.37	ns	-17.1	3.99	*	-21.2	4.22	*
Pir :	8.8	5.18	ns	0.1	4.49	ns	1.9	6.31	ns
Flx :	2.3	1.55	ns	- 3.7	3.39	ns	- 4.9	3.03	ns
Mia :	13.1	4.12	*	11.7	2.02	*	18.7	3.05	*
Map :	4.6	4.02	ns	8.4	4.97	ns	7.3	3.17	*
F-value:	3.14			8.42			12.78		
Groups :	Mia/Pir,Map, Flx,Tra			Mia,Map,Pir/Map, Flx,Pir/Tra			Mia,Map/Map,Pir, Flx/Tra		

Luminance Channel / Theta Range:

	Dos. 1 Mean	Std.Err.		Dos. 2 Mean	Std.Err.		Dos. 3 Mean	Std.Err.	
Tra :	- 7.1	2.06	*	-11.8	3.67	*	-15.3	2.71	*
Pir :	- 3.1	2.34	ns	-13.1	2.41	*	-10.3	3.45	*
Flx :	- 4.9	3.49	ns	3.7	3.97	ns	4.8	3.65	ns
Mia :	-14.1	5.98	*	-11.7	3.80	*	-16.1	3.35	*
Map :	1.7	5.87	ns	- 0.4	4.58	ns	8.9	3.63	*
F-value:	1.81			4.27			11.97		
Groups :	-			Pir,Tra,Mia,Map, /Map,Flx			Mia,Tra/Pir/Flx, Map		

Figure 3. The effects of antidepressant drugs on the visual evoked potential. Latency changes before and after drug administration in the beta- and theta-ranges of the EEG. The statistical evaluation consists of the t-test, One-Way-ANOVA and the Student-Neumann-Keuls-Procedure.
Mean: Mean latency changes in ms of all latencies of the VEP.
Std.Err: Standard Error (Standard deviation of the mean)
*: significant $p<0.05$
ns: not significant

Statistical Analysis

In order to show the changes in visual evoked potential, all peaks or components of this train wave were analysed according to latency changes. The latencies were much more dependable than the amplitude changes. The results of the studies were also averaged according to their own conditions and the dose response curve was formed. The data were then further compressed, computing the mean qualitative latency change (t -> sgn(t)) for each subsystem. This method allows a clear qualitative differentiation of the single components of the VEP according to latency and stimulus condition. The last stage of the analysis consists of forming the arithmetic means of the activation/attenuation-coefficients of each subsystem giving the total attenuation and activation coefficients. The qualitative latency changes were used as input variables for factor analysis. This is a method which forms mathematical hypotheses about a given set of data. If there are n variables measured with m persons, the result is an m x n data-matrix. Using this matrix, we can calculate all correlation-coefficients between two variables to get a symmetrical correlation-matrix. There may be some variables which show a high degree of correlation. We presume that they are interdependent or that there is another variable in the background, not directly measureable, which is responsible for the values of these variables. The factor-analysis model makes the last assumption, i.e. it tries to find those hypothetical variables , so-called "factors", which are able to reproduce the observed correlations in combination with a rule of calculation . The matrix A is the Factor-Matrix; its elements a are called Factor-Loadings. In the case of orthogonal factors , their values lie between -1 and +1. Every factor is characterized by an A-column. A factor is called general factor if all loadings are mainly different from 0; it then represents all variables. In the case of two or more loadings, we speak of common factors. In our case, three factors were extracted and each variable (the mode of action of each drug dosage on the CNS) was characterized by a point (local-vector) in the three dimensional factor-space. The length of this variable-vector in the common factor-space is identical with the the square root of the communality. The communality represents that part of the variance of one variable which is explained by the common-factors. The angle ϕ between two variable-vectors in the common factor-space is a measure of the correlation between two variables . The factor extraction leads to a factor-model which is in most cases not interpretable. It is strongly influenced by introducing new variables and changes from sample to sample. There are many positions of the coordinate-axes which reproduce the correlation-matrix. The task of rotation is to bring many of the variable-vectors near the coordinate-axes in order to get a so-called "simple-structure" which is in most cases easier to interpret.
The interpretation of the factors (coordinate-axes) is not an easy task because the meaning of the axes is not given but results from the structure of the data material.
In our case, drugs characterized by a differential mode of action were found near the plane defined by factors one and two (Pir,Mia,Map). Those mainly active in the beta-range of the EEG are on the left and those mainly active in the theta-range on the right side of the plane. The tendency towards activation (Tra,Flx3,CAS-997) or towards attenuation (Clo,Flx1) is determined by the distance of the drugs from this plane. This model is a first trial at classification of drugs by their mode of action on the CNS.

Discussion and Conclusions

Specific profiles of the efficacy of the action of different antidepressants in the CNS were found using the visual evoked potential. The clinically well established antidepressants showed both attenuation and activation properties. Mianserine and Maprotiline showed a stable profile of activation and attenuation as did the newer drug Pirlindole. This latter drug shows no anticholinergic activity, normal sleep profiles, little influence on psychometric parameters at this dosage, an increase in the alpha activity and a decrease in the other ranges of the EEG. All these data tend to show an attenuation of the CNS combined with a simultaneous activation. Tranylcypromine on the other hand, which is now recommended in atypical depressions charecterized by hypersomnolence, weight gain and retardation, showed a strong activation but a weak attenuation. The effect on the EEG is known to be thymoleptic in the acute phase with a peak around 5 hours - i.e. a decrease of alpha activity and an increase of beta and theta activity. Our results in the beta range of the evoked potential show a definite effect still after one or two weeks. This effect correlates well with the EEG effects. Both may be interpreted as a general activation of the CNS. Fluvoxamine in a higher dosage of 150 mg/die caused shortenings of the VEP latencies comparable to Tranylcypromine (see also <10,11>). This may correlate with sleep disturbances as has been reported by Berger et al <11>. This also led to drowsiness during our experiments. Our results with Pirlindole (figs. 5 & 6) show a latency decrease of several components already at a dosage of 75 mg/die especially in the beta and theta ranges of the brightness channel. On the other hand, Pirlindole causes a latency increase in the beta range for the colour channel. We were not able to measure any effect of the checker-board reversal stimuli. This result reminds us of that of Berdjes and Demisch <8> for flash stimuli. In other words flash stimuli and colour change show a similar effect with Pirlindole while the brightness channel showed opposite effects. This contrary effect of Pirlindole in the colour channel and the brightness channel in the beta range of the visual system is, however, a specific characteristic of Pirlindole. Mianserine showed a similar effect in the theta range as did Maprotiline in a weaker form. Pirlindole shows a profile in the middle range both for activation and attenuation. The question remains open whether the latency increases measured in the beta range with Pirlindole show a correlation to the antidepressant activity of the substance. A comparison to the EEG studies with Pirlindole shows a shift to the alpha range

(increase of power) and a corresponding decrease in the delta, theta and beta ranges (13). This is an indication for an attenuation in the CNS. Whether this is a specific effect just in the visual cortex or whether this effect is valid for the whole CNS cannot be decided upon with the present data. A localisation study would be necessary for this.

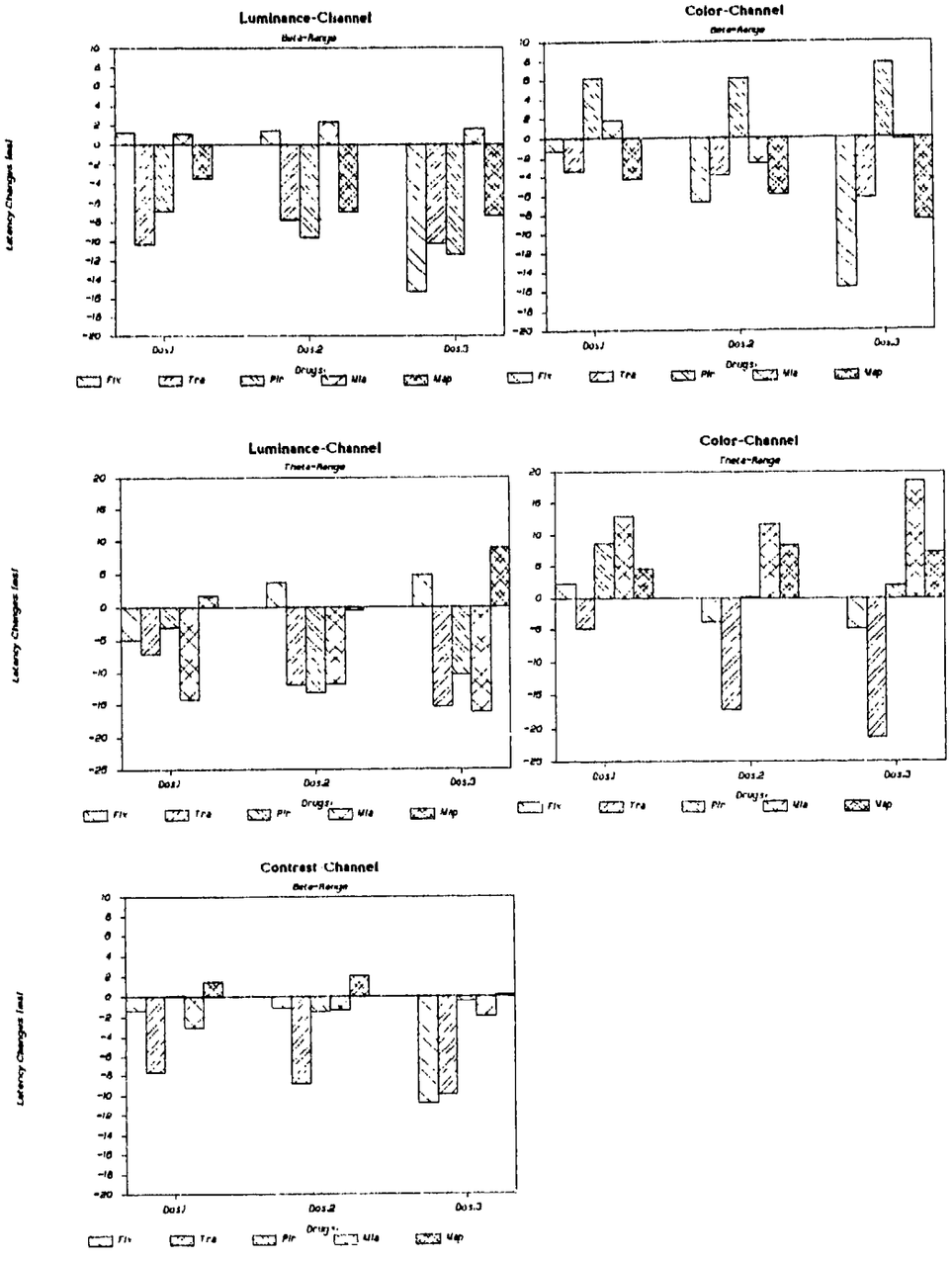


Figure 4. Histogramms of total latency changes in ms of all components in the beta and theta ranges. See fig. 3 for data. Other channels did not show any significant changes.

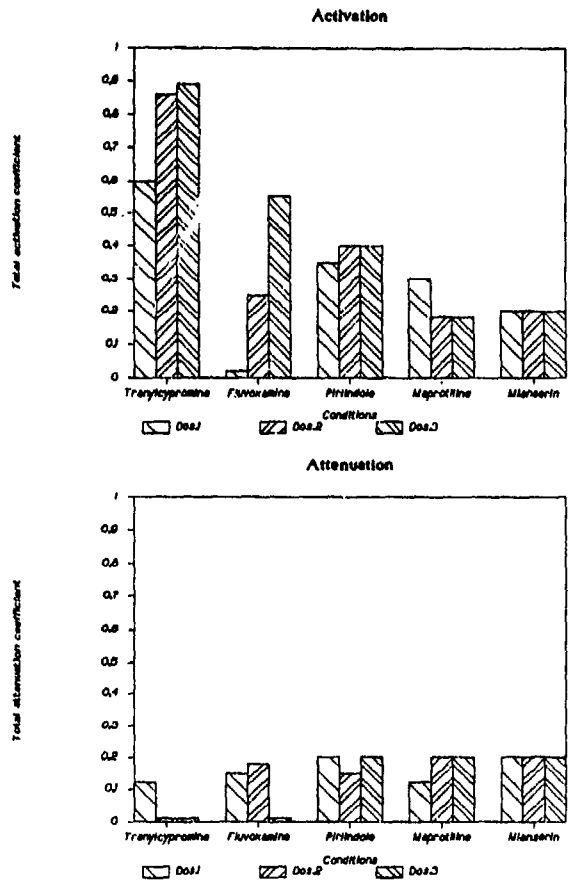


Figure 5. Activation and attenuation coefficients for the various antidepressants studied. These data are drawn from the data in figure 3.

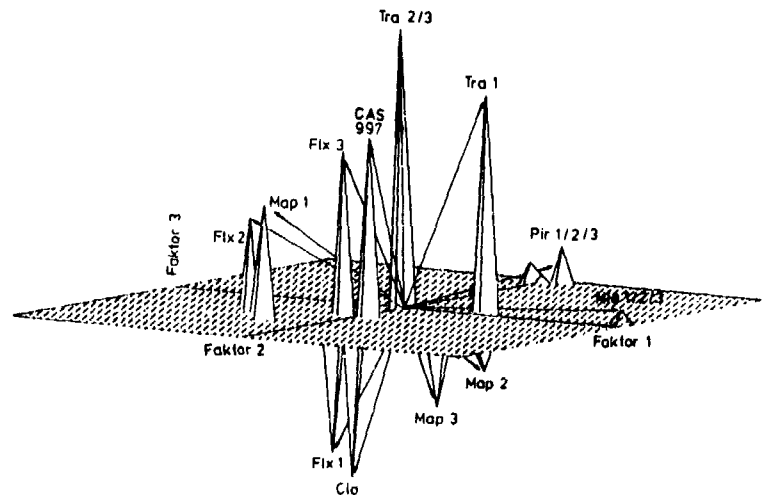


Figure 6. Trial classification of all drugs studied by the use of factor-analysis. See text for explanation

The visual evoked potential shows an activity profile of the effect of antidepressants in the CNS. This differential effect of attenuation and activation in the visual cortex seems to be reasonable for the characterization of the effects of antidepressants on the central nervous system. This expresses itself as an activation and an attenuation of various components of the evoked potentials. In the present stage of research the activation and attenuation coeffients (fig.6) have the greatest relevance. Different effects of these drugs on the frequency ranges analysed are an indication of the effects of the underlying mechanisms producing the evoked response in the beta- and theta-ranges. The coefficient of activation for the antidepressants may correspond to the elevation of mood and the attenutaion coefficient to the anxiolysis. With the help of these profiles the effects of the antidepressants and other drugs (compare Johnson et al in this book) in the central nervous system may be quantifiable with evoked potential recordings.

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DISCUSSION

KRIEBEL, GE: You offered us a very impressive amount of data. The clinician might wonder which of the data will be useful; e.g., in choosing the right antidepressant drug for the different kinds of depression. What will the equivalent dosage be to make these drugs comparable? I was astonished to see the different results that were obtained for Mianserin and Meprotiline. These belong to the tetracyclic group of antidepressants and are used by clinicians for the same kinds of depression in patients. So my second question relates to whether you measured widespread reactions on the cortex as being related with side effects, or did you measure correlations with the antidepressant effect of the drug? For example, an antidepressant drug does something entirely different during the first week of application than in the third week. Can you tell me something about the antidepressant profile?

JOHNSON, GE: The antidepressant profile is a matter of speculation right now. We've just measured effects in the brain and the only way we can compare these effects to the antidepressant effects is, of course, in patients. We did this work on healthy subjects, and they don't necessarily respond in the same manner as patients. However, our results with Tranylcypromine, especially at higher dosages, suggests that the correlation would be to the antidepressant activity. Your first question relates to the general effects in the brain. We measured it primarily in the visual cortex because we were studying the visual evoked potential. The subjective reports that we received; e.g., sedation and activation in the psychological sense, correlated quite well with the brain effects. For example, in the case of Fluvoxamine, the subjects were so highly activated at the highest dosages that they vomitted and had trouble sleeping. At the lower dosages, they didn't complain at all. This may indicate that we are measuring the total effects of the CNS; more specifically, maybe the antidepressant effects.

OFFENLOCH, GE: The main objective of this study was to show that "elaborate" messages also applied to the evoked potentials. You can differentiate among psychoactive drugs in a way which previously could only be done from spectral analysis of the normal EEG. This can now also be done for the evoked potential. For a strategy for the proper treatment of psychiatric patients, whatever their diagnosis, we would suggest the following procedure: First, analyze changes in EEG parameters in psychiatric patients before treatment in a manner similar to the method of Dr. Roy John. Ten years ago, we would have said that this was impossible; now we know it can be done. Also, the evoked potentials should be analyzed in all of their sensory channels. From the results, one can see which physiological or pathophysiological parameters have changed, and then apply our therapy to find the optimal dosage for the treatment.

JOHNSON, GE: For a given dosage of the newer generation of antidepressant drugs, we get a very stable profile of activity. This means that for those drugs that have a wide spectrum of dosage, we can pinpoint the profile; similarly, for drugs having maximal dosage.

Measurement of Electrical Activity in the CNS with Cortical Evoked Potentials and EEG: Efficacy Profiles of Drugs Using Factor Analysis

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Summary

In a series of experiments with 20 healthy, subjects per substance, the influences of a new nootropic drug and three cardiovascular agents on the CNS were measured and placebo controlled. The EEG and visual cortical evoked potentials were recorded from electrode position "O_z" between O_1 and O_2 according to the 10-20 system. Three channels of the visual system were selectively stimulated (contrast, brightness and colour using checkerboard, flash and colour change).
Acute and chronic studies are reported. Each VEP was filtered into the standard EEG-frequency ranges. Latency changes of the EP were evaluated in each range and analysed with the Fourier technique.
Both cardiovascular substances (an anti-hypertonic and a bradycardic agent) caused a significant latency increase ($P < 1\%$) of beta-components with apparent latencies of 80-100 ms. This attenuation was shown in the contrast and even stronger in the colour channel of the visual system. The results indicate a two-component effect, i.e on the central nervous and the cardiovascular systems.
For the nootropic substance, a significant latency decrease ($P < 1\%$) was found for three components of the visual evoked potential in the theta-range. Their latencies are from 170-360 ms. This activation of the CNS only occurred under acute conditions in the colour channel. The results of the EEG analysis are compared to the EP results.
Generalized changes for groups of substances and highly specific profiles of activity for individual substances may be measured using this set of stimulus and analysis techniques. Activation and attenuation of activity for one and the same substance also were measured indicating multiple modes of action. This may reflect cognitive processes and sensomotor activity.

Introduction

The measurement of the electrical activity of the central nervous system in man and the effects of external factors such as drugs and sensory inputs on this activity have often been investigated with the help of electroencephalographic (EEG) data (e.g.pharmaco-EEG) and cortical evoked potentials to sensory stimuli. Changes in the frequency spectrum were monitored and important information about the effects on the spontaneous and evoked activity in the CNS were obtained. For the EEG, the electrical activity is normally centered around the dominant frequency ranges of

2 Hz (delta range 1- 4 Hz),
5 Hz (theta range 4- 8 Hz),
10 Hz (alpha range 8-13 Hz) and
22 Hz (beta range 14-30 Hz).

The EEG is in general analysed in these frequency domains (Power Spectrum) but the cortical evoked potentials (EP) in the time domain. In this study we have combined both approaches as they provide complementary information <1>. During stimulation, certain frequency ranges were stabilised and time locked to the stimulus <2>. These dynamics were investigated by Spekreijse and Regan in the 1970s <3,4>. They classified steady-state evoked potentials into three frequency ranges:

1) a high frequency range (40-60 Hz),
2) a medium frequency range (14-20 Hz) and
3) a low frequency subsystem (9-12 Hz).

These authors found a strong colour dependency in the medium frequency VEP-components but less so in the low or high frequency components. Our own preliminary investigations supported these results <5>.
Transient evoked potentials are also part of the electrical activity of the CNS and reflect information processing from cortical and subcortical levels (e.g.awareness, perception, etc.). Since contrast and colour vision are the results of information processing in the cortex, evoked potentials are useful for studying contrast and colour coding in the brain. From the literature and previous studies in our laboratory we know that evoked potentials are also a sensitive measure of the effects of drugs on the CNS. Some components of the visual evoked potential (e.g. P_{300}) are closely correlated with cognitive functions. Using a digital frequency analyser, we divided the transient EP into various frequency ranges to investigate the different components of the visual evoked

potential. This procedure resulted in stabilised wave forms and latencies and increased the precision of measurement. The effects of a nootropic substance (Tenilsetam®, CAS 997, Cassella AG, Frankfurt) on the system transfer function of the colour luminance and contrast channels of the visual system were measured with the visual evoked potential data while considering their frequency dynamics.
It has been known for many years that Digoxin in high doses causes a deterioration of yellow colour vision. This was proven by the use of the Farnsworth-Munsell-100-Hue-Test <6>. In a pilot study <5> we measured the effects of cardiac glycosides on the visual system of man with cortical evoked potentials. We measured the effect of β-acetyldigoxin (Novodigal®, Beiersdorf, Hamburg) on the visual system after two weeks. Under subchronic conditions (plasma levels of digoxin 1.0-1.9 ng/ml), we compared the effects of this drug on the VEP and colour vision (days 15-19).
In a comparison of the effects of two further cardiovascular agents on the CNS, the effects of the well known Clonidine and its N-Allyl-derivative Alinidine, a new specific bradycardic agent whose site of action is the sino-auricular node, were tested with 20 healthy subjects. From previous studies it is known that Clonidine has the following effects on the CNS:

1) tiredness, peaking around 2-4 h
2) dry mouth
3) reduction of CNV-amplitude
4) increase of reaction times
5) reduction in amount of paradoxical sleep (REM-Phase)
6) sleep-EEG reduction in alpha level and an increase in the delta level.

As a whole, these reactions may be summarised as attenuation of activity in the CNS accompanied by an increase in the level of synchronisation of the EEG. There has been very little indication in the literature that Alinidine may have a specific effect on the central nervous system. In 1977 Stockhaus <7> reported an analgetic and a slight central depressive effect. The present study was undertaken to test the significance of the effects of Clonidine and Alinidine on the CNS.

Methods

Normal healthy subjects (35 male, 34 female, 20-50 years average age 28.3 years) took part in these studies. All gave their informed consent in writing. Additional medication was not allowed. Before testing they were examined with a standard medical check-up including EEG, clinical biochemical blood tests, circulatory parameters (blood pressure, pulse rate, ECG) and colour vision (Farnsworth-Munsell and Ishihara). The study design was double blind, in part placebo controlled, cross-over, intraindividual comparisons. The colour, luminance and contrast channels of the visual system were studied using a full field (Ganzfeld) blue/red and black/white reversal for the first two channels and checker-board reversal stimuli for the third channel. The subjects wore a colour neutral, homogenous mask for the first two parameters in order to avoid contrast effects and this mask was removed for the third parameter. The subjects sat upright, with their head supported comfortably, 2 meters in front of a standard TV screen (Nordmende SK2, line frequency of 15625 hz, 625 lines, diagonal of the screen 67 cm) equipped with a Videocolor (Hamburg) tube (A67 615X). The phosphors had spectral maxima at 450 ± 61.5, 540 ±78.2 and 625 ± 20.5 nm ± half-band widths. The intensity of each phosphor was controllable individually and was set for the colour red to $1.2X10^{-6}$, for blue and checker-board to 0.6 and for white to $2.1X10^{-5}$ A (average $1.2x10^{-6}$ for full screen) and were measured with a calibrated photocell (PIN 10 D, United Detector Technology, USA) and a nanoamperemeter (Knick, Berlin, Model N23). The specific luminance of the red reference was 0.3 W/cm². The entire field of view without the mask was 12°X8° visual angle. 160 repetitions of the stimuli were used for each condition. The interval between the stimuli was 2.7 s. For further details see Johnson and Wyrobnik <1>.
The EEG was routinely recorded from the electrode position "O_z", between O_1 and O_2 according to the international 10-20 system, and the left ear was used as reference electrode. The recording equipment constisted of silver-silver-chloride cup electrodes filled with a conducting paste, connected to EEG amplifiers (Hellige EE) which had an input inpedance of 10 mΩ (paralleal to 1 µF). The output impedance of this system was less than 10 Ω. The frequency range was routinely from 1000 Hz (-3 dB) to 1 Hz. After amplification, the signal was stored on a magnetic tape (recorder Ampex FR 1300). The standard speed of recording was 4.75 cm/s with the characteristics:

Frequency range	0 - 625 Hz
Signal/noise ratio (RMS)	40 dB
Harmonic distortion	< 2%
Impedance - input	> 20 kΩ
- output	1 kΩ

The entire system was calibrated using a 50 µV (± 1%) square wave signal at the EEG input. The EEG was monitored with a four channel oscilloscope and elimination of artifacts took place visually. The EEG was digitized with a sample frequency of 512 Hz, and was stored on floppy discs after averaging. Later the EP was subdivided into the standard frequency ranges mentioned above using a Fourier-filter technique (no phase shifts) and the latencies of the peaks were measured in each range. When necessary vision was corrected to 0.1 Dpt.
To introduce nootropic and cardiovascular drugs into the factor-analysis model of the

five antidepressants (for details compare Frauendorf,Johnson,Demisch in this book), the weighted arithmetic means of of all qualitative latency increases and decreases were computed to get coefficients of activation (latency decrease) and attenuation (latency increase). They were used as input variables for factor analysis. The Eigenvalues were calculated and three factors extracted. We performed a Varimax-rotation of these factors. In the cases of the drugs studied, the rotated structure showed a high stability against introduction of new drugs. This technique seems well suited as a means of classification of the effects of drugs on the CNS.

Results

In general the alpha- and beta-components of the VEP showed good correlations to stimulus wavelengths. On the other hand, the theta-components showed little correlation. In higher frequency ranges (30-60 hz) no definite response was measurable (no details given in this report). The response in the delta-range of the VEP was likely due to the EOG-blink-reflex having a latency in the range of 150-250 ms as described by Lowitzsch et al (8).

The Effects of the Nootropic Drug Tenilsetam on the CNS

In figure 1, a typical evoked potential is shown and compared to the control value. In this case as in the following the latencies in the studies were shown to be much more reliable than amplitude changes.

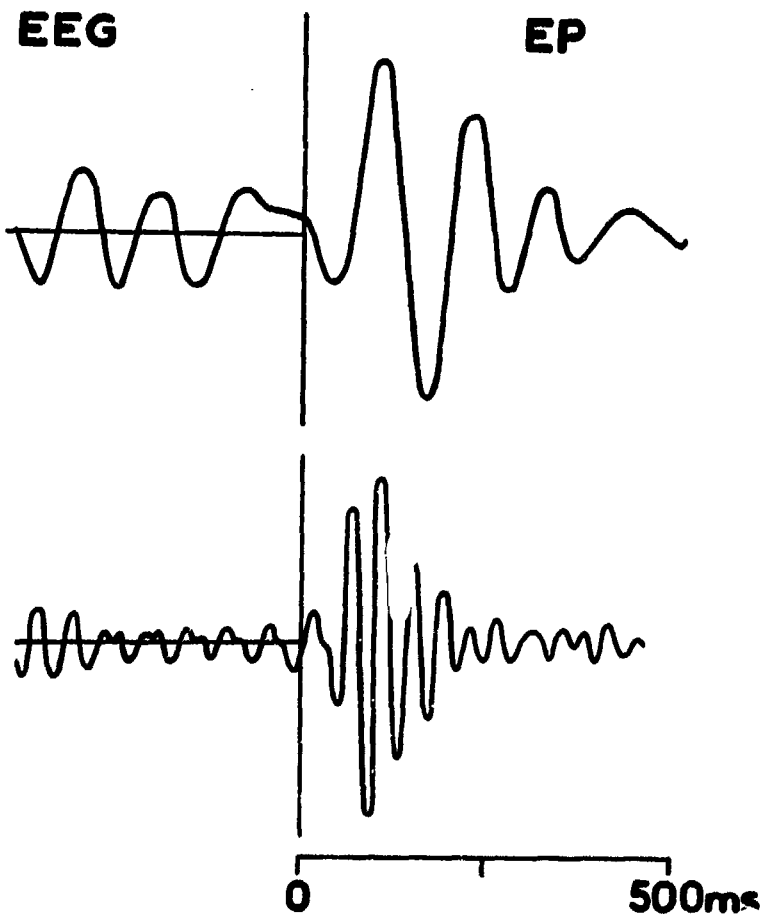

Figure 1. Typical recordings before (EEG) and after (EP) stimulation with colour change from blue to red. Upper curve filtered in theta-range and lower curve filtered in the beta-range.

Tenilsetam (150 mg/die) only caused an effect under acute conditions (figure 2). All three components of the evoked response in the theta-range (P_{100}, N_{141} and P_{322}) were decreased in latency (up to 10 ms) significantly ($p < 0.01$). This effect is presumably caused by an activation of the CNS by Tenilsetam. It was only found in the colour channel of the visual system and no significant effect could be measured either under placebo nor verum for both chronic (1 week) and rebound (after 1 week) conditions. Tenilsetam had no effects on physiological parameters like blood pressure, heart rate and multiple blood factors (SGPT, SGOT, GGT, AP, glu, bilirubin, creatine, albumin, hematocrit, BSR, urea, total protein, hemoglobin, triglycerides, glycosides, erythrocytes, T3, T4 and FT4). No subjective side-effects were found either. This substance, therefore, showed no measurable effect on the circulatory, blood or physiological parameters measured.
The statitics of the results for the colour change blue/red are shown in figure 3. The latency reductions of the peaks P_{100}, N_{141} and P_{322} may be classified as an activation in the visual cortex. The latencies of the peaks which are affected lie in a time range which is known from the literature to show a close correlation to concentration and perception. The third peak (P_{322}) corresponds in the unfiltered data to the well known peak P_{300} from the literature.

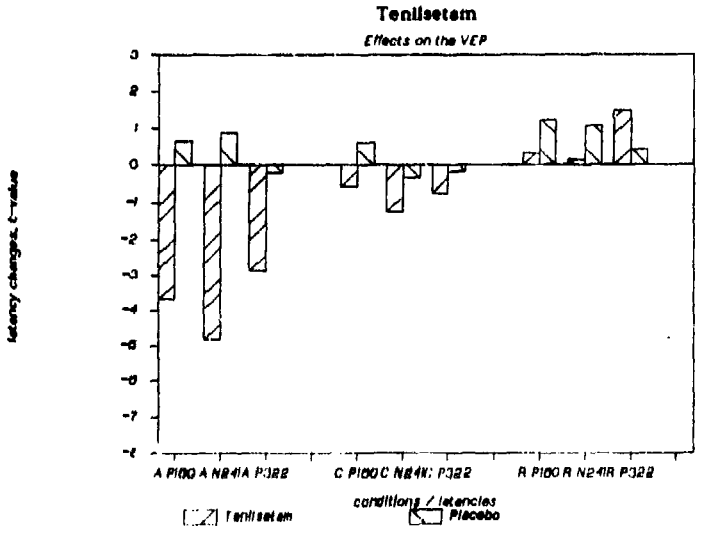

Figure 2. The effect of Tenilsetam on the VEP in the Theta-range. Average latency changes expressed as t-value under acute (A), chronic (C) and rebound (R) conditions. The results are expressed for the peaks P_{100}, N_{141} and P_{322}. Comparison of verum to placebo conditions.

The effect of Tenilsetam on the CNS is, however, decreased under chronic conditions (after 1 week). Neither under chronic conditions nor 1 week after medication were there any significant changes in the visual cortex. Placebo did not show any effect under these conditions either. Since it is known from the pilot study that an additional dosage under chronic conditions did not show any further effect on the visual cortex (in agreement with Saletu et al. <9>) the additional dosage was avoided at this stage. Under these conditions Tenilsetam showed no effect on the brightness channel of the visual system and is therefore not dealt with in detail. This finding agrees with our experience that in general this type of stimulation - colour change - is more sensitive for measuring changes in the visual system than brightness changes.

The Effects of Cardiovascular Drugs on the CNS

Effects of Digitalis <5>

In a pilot study from 1986, after subjects took Digitalis for two weeks, the subjective Farnsworth-Munsell colour test showed no significant increase in the number of errors, both of which lie in the normal range (compare also <6>), but the latency of one component of the VEP was significantly increased ($N_{144} \rightarrow N_{156}$, $P < 0.01$) at this low dosage (at 1.9 ng/ml but not significantly at 1.0 ng/ml). This was the first indication for a dose-dependency of the effect of Digitalis on the visual evoked potential. This indicated that the VEP method is more sensitive than the subjective Farnsworth-Munsell-100-Hue-Test. This pilot study was the basis for the following studies with cardiovascular drugs which have effects in the CNS as well.

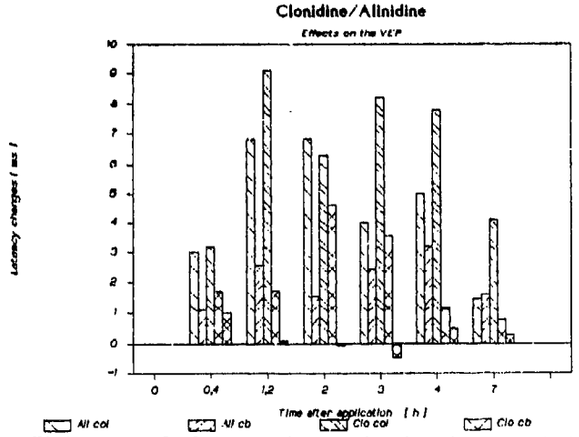

Figure 3. Histogram of latency changes in the visual evoked potential after ingesting Clonidine and Alinidine at time 0 h. Comparison of the effects on the colour and contrast channels using colour change (col) and checkerboard (cb) stimuli. Latency changes of the component P_{100}.

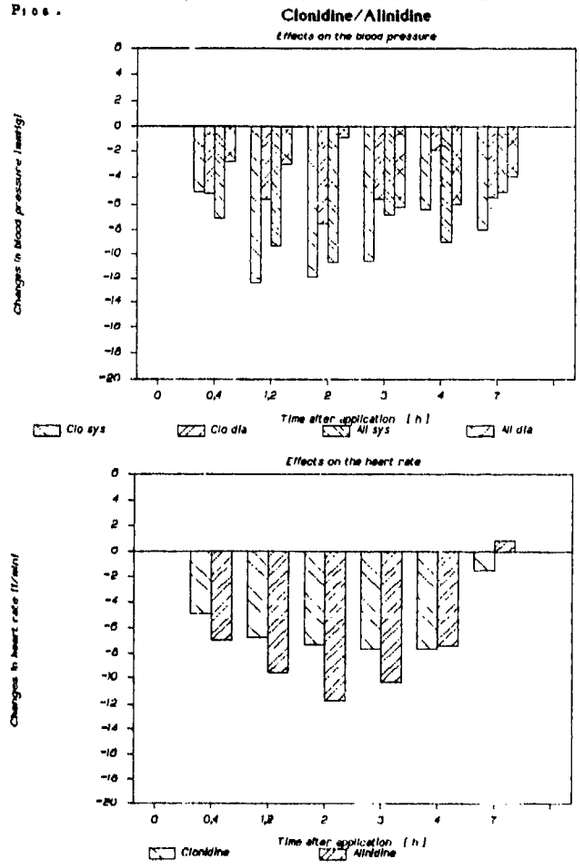

Figure 4. Histograms of the changes in blood pressure and pulse rate after taking Clonidine and Alinidine at time 0 h. Comparison of the effects on the systolic (sys) and diastolic (dia) pressures.

Effects of Clonidine and Alinidine

Both of these drugs showed a strong effect on the VEP component P100 under acute conditions (0.4-4.0 h. post.appl.) in the beta-range of the EEG after colour change and a more moderate effect under contrast conditions. In comparison to placebo, the latency of this peak is the best indicator for the time course of the effect of the two drugs (figure 3) in the CNS. The effect of Clonidine was monophasic with a maximum about 2 h and of Alinidine was biphasic at 2 h. and 4 h. Their effects on heart rate and blood pressure may be seen in figure 4.
Under pure chronic conditions there were also significant decreases in the blood pressure and heart rate, but no effect on the CNS was measurable (may not be seen in this figure). This may be due to adequate buffering of the brain. An additional effect of the drugs under chronic conditions was also shown 2-4 h.post.appl.
The effect of Alinidine on the visual cortex is less pronounced than that of Clonidine for colour changes and checker-board stimuli. The effects of Alinidine under acute and steady-state conditions are similar. Under no stimulus conditions nor at any point in time was a significant effect of placebo measurable. This applies both to contrast and colour vision as well. A slight difference between male and female subjects may be attributed to different serum levels due to body weight.

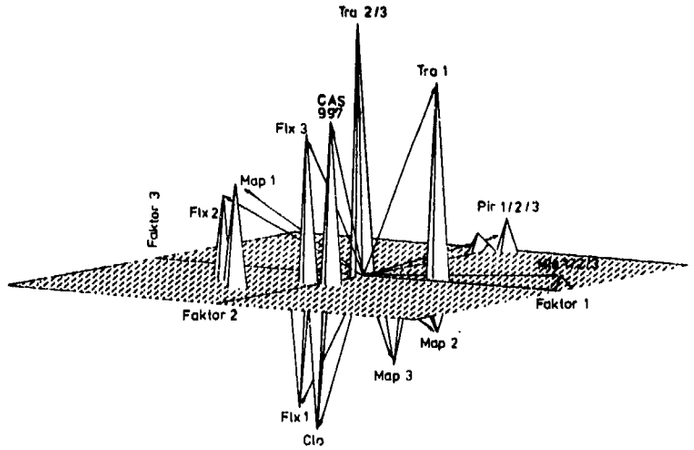

Figure 5. Trial classification of all drugs studied by the use of factor-analysis.

Discussion and Conclusions

We found specific profiles of activity in the CNS for each substance tested with the visual evoked potential. For the nootropic substance Tenilsetam, the strong latency decrease corresponds to the expected activation of the CNS. A subjective effect at this dosage is not known. In the case of the cardiovascular drugs, Digitalis showed a significant increase in latency of one component and the drugs Clonidine and Alinidine an increase in the latencies of several components. This indicates an attenuation in the CNS in the first 4 hours post-appl. No chronic effects were seen. These correlate well with the subjective effects in our subjects and the known central effects.
For Tenilsetam, the augmentation in the acute phase 1 hour after taking the substance is shown primarily in the colour channel of the visual system and after 1 week of intake the effect is not significant any more. One week after the last tablet, the effect of the substance is no longer measurable. A comparison of the effects of Tenilsetam on the EEG (9) shows a correlation to our results. Both studies speak for an increase in vigilance, attention, concentration ability, i.e. as a whole for an improvment in cognitive functions. Our results show a latency decrease for 3 components of the visual evoked potentials after taking 150 mg Tenilsetam in the theta-range of the colour system. In other ranges of the EEG, on the other hand, no effect was measurable. The fact that these results were measured only in the theta-range is still open to discussion.
Tenilsetam showed no significant effect on any of the biochemical and blood parameters studied. There was no subjective effect either. It must also remain open whether the measured changes in the latencies in the theta-range with Tenilsetam correlate directly with the nootropic properties of the substance. The acute effect in the visual cortex speaks for an activation in the central nervous system 1 hour after ingestion. These effects in the visual cortex show a clear correlation to the results from the pharmacokinetic and pharmacodynamic studies.
Our results show a highly significant effect in the brain. As a working hypothesis, we propose that the activity measured in the central nervous system corresponds to an improvement in the cognitive function, i.e. the activation measured in the central nervous system. This is a clear indication that Tenilsetam corresponds to an improvement in the brain function of man. A comparison to other dosages and in geriatric patients is planned at this stage of research.

In this project we were able to measure significant effects of Clonidine and Alinidine on the central nervous system. Both showed a latency increase of one beta-component with an apparent latency of about 100 ms in the visual evoked potential. This effect showed a close correlation to the known effects or side-effects on the central nervous system. After seven days (steady-state conditions), only the effects of Clonidine on the contrast channel of the visual system were attenuated. The colour channel was still dampened. Both substances had a stronger effect on the colour channel of the visual system than on the contrast channel. This is especially true for Clonidine. The form of the time course for Alinidine was biphasic while that of Clonidine was monophasic. We also know from a pilot study that both substances have no effect on the oculomotor syutem.

From studies of the effects of Clonidine on the EEG during sleep, it is known that it has a synchronising or sedating effect on the CNS. The effect on the EEG during the waking phase, e.g. the effect on the visual evoked potential from our experiments, is in agreement with these results (latency increase in the beta-range around 3 hours in the acute phase).

The reduction in the degree of latency increase under steady-state conditions compared to acute conditions may indicate an adaptation of the CNS. This synchronising effect is valid for the colour and contrast channels with Alinidine and for the contrast channel with Clonidine.

In the acute phase, Clonidine and Alinidine differ clearly in metabolism and effects on the circulatory and central nervous systems. Since it is known that Alinidine is partly metabolised to Clonidine, the biphasic nature of the effect of Alinidine in the CNS may be thereby explained.

The maximal effects in the CNS are at about the same time as the psychophysical maxima (2-4 h.). The first peak of the Alinidine curve at 2 h. probably corresponds to the maximal effect in the CNS. The second, smaller one coincides at 4 h. with the maximal effect on the heart under acute conditions (day 1). A reduction in efficacy between 2 and 4 h. coincides with the half-life of the metabolism of the substance. The plasma ^{14}C-elimination also shows two peaks at 44 and 210 min.. Therefore we suggest that the Alinidine curve in the first few hours may show a summation with the Clonidine curve. This would explain the biphasic nature of the former curve.

Alinidine shows a reduction in its effect on the CNS under steady-state conditions as well. However the biphasic nature remains. The second peak is shifted from 4 to 7 h. and this initial phase is somewhat wider but still coincides with the peak effect on the circulatory system.

The form of the curves of the effects of Alinidine on the central nervous and circulatory systems shows a similarity especially in the blood pressure curve. The question as to whether the effect of Alinidine on the CNS is primary - i.e. a direct attenuation of the electrical activity - or secondary - an effect of the fall in blood pressure - can not as yet be decided at this stage in research. In the case of the effect of the drop in the blood pressure, this could cause a decrease in the oxygen supply to the cortex. Measurements of P_{O_2} profiles in the cortex in animal experiments (Johnson et al.<10>) could clarify the situation.

There is also a coincidence between the peak effects of Clonidine with the second peak in the acute and steady-state phases of Alinidine. There may also be a relation to the subjective effects which will be reported elsewhere. These are, however, typical for effects in the visual cortex. Since they coincide in time with the peak efficacy of Alinidine in the CNS, we postulate the visual cortex as one source of action of the substance in the brain.

Clonidine has a different effect. In the acute phase, a biphasic profile was not measured. This is also the case for the blood pressure curves. There is some similarity however. between 0.4 - 4.00 h and there is a significant effect on the CNS. This range is narrower (2-4 h.) under steady-state conditions. The amplitude is also decreased. As with Alinidine, we propose an adaptation of the central nervous system to the effects of Clonidine as an interpretation. Different effects of these drugs on the frequency ranges analysed might be an indication of the effects of the underlying mechanisms producing the evoked response in the beta- and theta-ranges. The fact that only weak effects on the CNS could be measured in the contrast and brightness channels of the visual system compared to the colour system, may possibly be due to the fact that the stability of the signals increases from colour to luminance and then to contrast conditions, i.e. contrast can be least affected. Colour is on the one hand the most diffcult channel to record from reliably, but is also the most sensitive channel to changes in the visual system. The differential effect measured in the studies according to activation and attenuation in the CNS may be a simple and effective way of characterizing the effects of drugs.

The evoked potential is ideal to show empirical correlations to other physiological and psychological parameters. The fact that the evoked potential shows an effect on one component in the beta-range of Clonidine and Alinidine with a latency of about 100 ms and on the other hand a close correlation to known metabolic and psychological parameters, indicates a high sensitivity of this technique. In the case of Alinidine, a two component theory (central and cardiovasular) could explain the effects on the visual and circulatory systems. We propose that the evoked potential may be more sensitive in evaluating the effect of substances active in the central nervous system than subjective perception. The drug effects in the visual cortex correlate also well with the effects in the EEG and psychometric measurements.

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UNE APPROCHE DES EFFETS DE PSYCHOSTIMULANTS SUR L'ACTIVITE ELECTRIQUE CEREBRALE CHEZ LE PRIMATE NON HUMAIN

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RESUME

Cette communication présente une approche des effets de psychostimulants sur l'activité électrique cérébrale du primate non humain, par l'utilisation d'une méthode mettant en oeuvre la Transformée rapide de Fourier. Trois substances psychostimulantes ont été étudiées au cours de deux expérimentations complémentaires. Deux d'entre elles sont des psychostimulants de référence : la caféine et le sulfate de d-amphétamine, la troisième est une molécule originale dotée de propriétés stimulantes et éveillantes particulièrement active.

Cette première approche a ainsi permis de mettre en évidence des propriétés tout à fait spécifiques de cette nouvelle molécule au niveau du spectre de densité de l'EEG, et de pouvoir la situer par rapport aux effets provoqués par deux autres stimulants classiques et obtenus dans les mêmes conditions expérimentales.

INTRODUCTION

Depuis plus de 25 ans des études relatives aux effets des substances psychotropes sur le système nerveux central en général et l'électroencéphalogramme en particulier ont été menées dans de nombreux pays. Le perfectionnement des techniques de traitement automatique du signal depuis ces dix dernières années a permis d'effectuer une avancée importante dans la connaissance des psychotropes essentiellement en ce qui concerne les tentatives de classification des molécules en fonction de leurs effets sur les différentes bandes de fréquences.

De très nombreux travaux ont été effectués : parmi les premières classifications de molécules psychoactives, celle de FINK en 1963 peut être citée (6).

Cependant peu de recherches font état d'une classification des psychostimulants et des données recueillies dans la littérature font souvent état de divergences dans les résultats obtenus (5) (16) (17).

Dans le cadre de l'amélioration de la valeur opérationnelle du combattant, notre laboratoire participe aux recherches relatives au contrôle pharmacologique des états de vigilance. La mise en évidence des propriétés de nouveaux psychostimulants fait appel aux techniques classiques d'électroencéphalographie et aux techniques plus récentes de traitement automatique du signal par l'étude des spectres de densité de puissance. Notre objectif est donc d'approfondir nos connaissances vis à vis des nouveaux psychostimulants par l'étude des modifications électroencéphalographiques engendrées par l'administration de ces molécules à une dose efficace, et par comparaison des effets observés avec ceux obtenus par l'administration de substances psychostimulantes de référence.

A cet effet deux expérimentations préliminaires ont été effectuées. Toutes deux utilisent le macaque rhésus comme modèle animal, en raison de sa proximité phylogénétique avec l'homme, ainsi que pour des raisons éthiques et légales (8).

La première expérimentation réalisée sur quatre sujets a pour but :

1. de valider la méthode de traitement du signal EEG mise en oeuvre par l'étude de l'homogénéité des spectres obtenus en situation témoin et leur reproductibilité
2. d'observer les effets de l'administration de psychostimulants sur le spectre EEG et de les comparer aux témoins
3. de définir, pour certaines molécules, une dose efficace, responsable du spectre spécifique observé.
4. d'établir une sorte de carte d'identité spectrale spécifique d'une molécule donnée et commune à tous les animaux enregistrés.

La deuxième expérimentation réalisée sur six sujets a pour but :

1. de vérifier les résultats obtenus à l'issue de la première expérimentation
2. d'approcher par l'électrophysiologie, la pharmacocinétique des molécules administrées.

Le plan adopté pour présenter ces travaux sera donc le suivant :

- 1° partie : exposé de la méthode utilisée
- 2° partie : principaux résultats obtenus
- 3° partie : discussion générale et conclusion.

I - METHODE

11 - PRINCIPE

Le principe de la méthode utilisée consiste, après mise en place chirurgicale d'électrodes chroniques, dans l'enregistrement des signaux électrocorticographiques recueillis chez le singe macaque rhésus, lors de l'administration de différentes substances psychotropes. Les données enregistrées sont alors comparées à celles obtenues lors de l'administration d'un placebo.

12 - ANIMAUX ET TECHNIQUE CHIRURGICALE

Quatre macaques rhésus mâles adultes sont utilisés au cours de la première expérimentation (S4, T7, A34 et A21). Six macaques rhésus mâles adultes sont utilisés au cours de la deuxième expérimentation (S4, T7, A34, U1, R3 et A46).

Ces animaux, dont le poids varie entre neuf et douze kilogrammes au cours des enregistrements, sont parfaitement adaptés aux conditions expérimentales et n'ont subi aucun traitement récent pouvant entraîner une interférence avec les différentes administrations.

Trois sujets sont communs aux deux expérimentations réalisées à un an d'intervalle, ce qui doit permettre des contrôles de reproductibilité des résultats pour les mêmes animaux dans les mêmes conditions expérimentales. Ces sept sujets ont subi une implantation d'électrodes chroniques, selon une technique standardisée (10). Les électrodes corticales superficielles, constituées de boules d'argent sont fixées au contact de la dure-mère, dans les régions frontales, pariétales et sub-occipitales. Elles sont paires et symétriques par rapport à la suture sagittale. L'ensemble de ces électrodes isolées, est soudé à un connecteur femelle solidarisé au crâne par un amarrage de fil d'acier et par une prothèse en résine acrylique (Texton).

13 - LOCAUX ET MATERIELS

L'électroencéphalogramme des animaux est enregistré en situation de contention dans des sièges dits "de contention" de conception originale permettant aux macaques rhésus d'adopter une posture voisine de la posture naturelle de repos (15). L'adaptation aux conditions d'expérience a été entreprise avant l'implantation et régulièrement entretenue. Les sujets sont enregistrés, par paire, et sont disposés côte à côte sur un portoir de façon à ce qu'ils puissent se voir et éventuellement se toucher. Cet ensemble est mis en place dans une cabine d'isolement insonorisée, ventilée et munie d'un éclairage permettant un contrôle par circuit vidéo du comportement des animaux.

Les enregistrements sont effectués de façon ininterrompue sur un support magnétique (Ampex PR 2230, FM, 7 pistes). A partir de ces enregistrements, il est procédé à une analyse spectrale mettant en oeuvre l'algorythme de la Transformée rapide de Fourier (FFT). L'appareil utilisé est le SPECTROVAR CS 2/4 (15). Les données analogiques stockées sur le support magnétique peuvent ensuite être retranscrites sur un support graphique (Polyraphe ECEM, 16 pistes).

Deux dérivations EEG sont enregistrées par sujet (dérivations pariéto-frontales), cependant pour des raisons techniques seul l'hémisphère gauche sera pris en compte pour l'analyse spectrale dans la deuxième expérimentation.

Enfin les données obtenues sont traitées par un logiciel défini en fonction du protocole envisagé. Les résultats sont interprétés statistiquement par l'utilisation d'un test non paramétrique utilisé par de nombreux auteurs (3), (18), et appliqué pour comparer les résultats obtenus fréquence par fréquence ou par bandes de fréquences.

14 - ADMINISTRATION DES MOLECULES

Quatre traitements ont été administrés :
- Placebo (sérum physiologique)
- Amphétamine (sulfate de d)
- Caféine
- CRL 40476 (2° expérimentation seulement)

L'amphétamine et la caféine ont été choisies comme psychostimulants de référence. Le CRL 40476, psychostimulant original de synthèse, est doté d'une action modulatrice (activatrice) spécifique des récepteurs adrénergiques alpha 1 post-synaptiques centraux accompagnée d'une augmentation de la vigilance et sans effets périphériques. Les propriétés de cette molécule ont été présentées au symposium relatif à l'amélioration biochimique de la performance, à LISBONNE en 1986 (13).

- Doses administrées :
  - . 0,25 et 0,50 $mg.kg^{-1}$ de sulfate de d-amphétamine
  - . 7,5 et 15 $mg.kg^{-1}$ de caféine
  - . 22,5 $mg.kg^{-1}$ de CRL 40476

Le choix des doses administrées est fonction des résultats recueillis dans la littérature et des observations réalisées au laboratoire.

Les doses de 0,25 $mg.kg^{-1}$ d'amphétamine et de 7,5 $mg.kg^{-1}$ de caféine sont apparues comme parfaitement stimulantes chez le macaque (9) (11).

Les doses de 0,50 $mg.kg^{-1}$ d'amphétamine et de 15 $mg.kg^{-1}$ de caféine sont en revanche supérieures à la dose seuil stimulante chez le macaque.

Quant à la dose de 22,5 $mg.kg^{-1}$ de CRL 40476 elle s'est avérée une dose efficace sur le plan des propriétés éveillantes mais peu ou faiblement active sur le plan agitant (13).

- Voie d'administration :
  - . sulfate de d-amphétamine) intra-
  - . caféine) musculaire
  - . CRL 40476 per os (sondage naso-oesophagien)

Les administrations placebo (solvant) sont effectuées par voie intra-musculaire ou orale en fonction de la voie d'administration utilisée pour la substance étudiée.
- Volume ingéré : 10 ml
- Volume injecté : 1 ml
- Solvant : gomme arabique ou sérum physiologique.
- Mode : administration répétée (deux ou trois jours consécutifs selon le protocole).
- Délai : l'administration de la molécule a lieu quinze minutes avant le début de l'enregistrement.

15 - PROTOCOLE

- Pour la 1ère expérimentation le protocole est le suivant :

. enregistrement de chaque paire pendant 1 heure (de 12 H 30 à 13 H 30) deux jours par semaine le mardi et le mercredi. Une semaine "d'enregistrement" est alternée avec une semaine "de repos" ; ce qui, vu le nombre de sujets, laisse 12 jours de repos entre deux enregistrements consécutifs.

. c'est ainsi que pour chaque sujet il a été obtenu 12 enregintrements :
- 4 enregistrements témoins
- 2 enregistrements par dose et par molécule.

- Pour la 2ème expérimentation le protocole est le suivant :

. enregistrement de chaque paire pendant 8 heures (de 9 H 00 à 17 H 00) trois jours par semaine (les mardi, mercredi et vendredi).
Chaque paire est enregistrée durant trois jours avec le même traitement, cela permet donc, pour chaque paire de sujets, d'alterner une semaine d'enregistrement avec deux semaines de repos.

. pour chaque sujet il a ainsi été obtenu 12 enregistrements ; soit chroniquement :
- 3 enregistrements témoin placebo
- 3 enregistrements Amphétamine (0,5 $mg.kg^{-1}$)
- 3 enregistrements Caféine (15 $mg.kg^{-1}$)
- 3 enregistrements CRL 40478 (22,5 $mg.kg^{-1}$)

16 - TRAITEMENT DU SIGNAL ET PRESENTATION DES RESULTATS

- En ce qui concerne l'appareil utilisé ; le Spectrovar C.S. 2/4* est constitué d'un micro ordinateur COMMODORE de type 8032 comportant une mémoire de 32 k-octets architecturée autour d'un microprocesseur INTEL 6502. Le double lecteur de disquette de 340 kilo-octets permet l'archivage des résultats ainsi qu'un post-traitement des données stockées en cours d'acquisitions. Le module de traitement du signal permet l'acquisition de signaux sur 2 mois. Ces signaux sont soumis à deux filtrages. Le premier est en fréquence, de type passe haut (0,15 Hz-6dB/oct) et le second est sur fiche anti-repliement. Les signaux sont échantillonnés à la fréquence de 128 HZ sur 8 bits.

Le traitement peut être effectué sur une plage de fréquence de 15-30 Hz. Le seuil d'acceptation est réglé pour un seuil de 75 %. Le pas d'analyse est de 10 secondes et le temps de traitement de 2,5 secondes. Il est utilisé une fenêtre de pondération dite "rectangulaire".

- A partir des enregistrements d'une heure (1ère expérimentation) il est réalisé des spectres moyens représentant une durée de 10 minutes.

- D'un enregistrement de 8 heures (2ème expérimentation) il est procédé à un moyennage des spectres pour obtenir un spectre moyen par heure.

Parallèlement les résultats obtenus sont présentés sous la forme de tableaux indiquant pour chaque fréquence (de 1 à 30 Hertz) et pour chaque spectre moyen (par 10 minutes pour la première expérimentation ou par une heure pour la seconde) :

. la puissance du signal, en microvolt au carré (2° expérimentation).

. Le pourcentage de la puissance du signal pour chaque fréquence par rapport aux autres fréquences.

Enfin il est indiqué le pic de fréquence maximum pour chaque spectre moyen.

Les spectres de densité de puissance sont obtenus pour chaque spectre moyen et pour l'ensemble des spectres moyens étudiés, sous forme "pseudo tri-dimensionnelle".

II - PRINCIPAUX RESULTATS OBTENUS

1 - PREMIERE EXPERIMENTATION

11 - Enregistrements Témoins

L'étude des tableaux de résultats et des spectres moyens par dix minutes qui en sont issus, permet de formuler les observations suivantes :

- chez un animal et lors d'une séance d'enregistrement d'une heure, les spectres moyens par 10 mn obtenus présentent des profils tout à fait semblables.
- Cette homogénéité des spectres, vérifiée statistiquement, est également retrouvée pour un même animal lors des différents enregistrements témoins effectués.
- En revanche la comparaison des spectres moyens inter-individuels fait apparaître une certaine hétérogénéité que l'on peut expliquer par exemple, par la localisation variable des électrodes d'enregistrement au niveau des aires pariéto-frontales.

Quoiqu'il en soit ces premiers résultats mettent en évidence le caractère homogène et reproductible des spectres individuels obtenus et constituent ainsi un début de validation de la méthode de traitement du signal utilisé.

* Constructeur : Société ALVAR, 6bis rue du progrès 93100 MONTREUIL

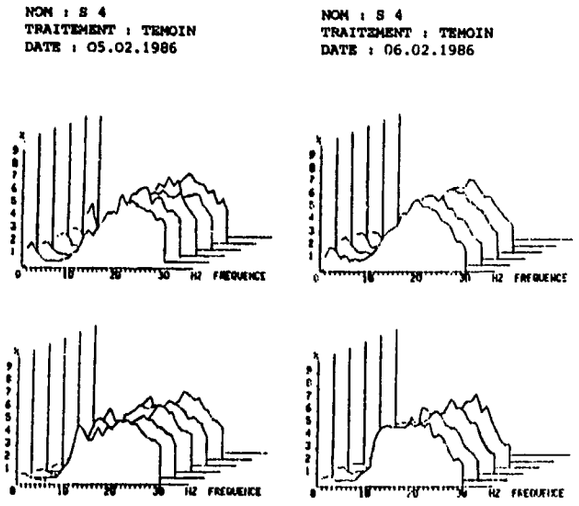


Figure n° 1

Exemple de reproductibilité de l'homogénéité des spectres de densité de puissance EEG (voir texte)

12 - Enregistrements après traitement par Caféine

Aucune différence significative n'a pu être mise en évidence en fonction de la dose de caféine administrée (7,5 ou 15 $mg.kg^{-1}$). Par ailleurs, il est observé un renforcement des puissances situées dans les basses fréquences, inférieures à 5 Hertz, et ceci chez tous les animaux enregistrés, même lorsqu'il existait déjà un fort taux de basses fréquences.

Enfin, il est à noter une diminution sensible de la puissance du spectre au niveau de la bande alpha (7 à 13 Hertz).

(cf. figure n° 2)

13 - Enregistrements après traitement par Amphétamine

L'administration de sulfate de d-amphétamine aux doses de 0,25 et 0,50 $mg.kg^{-1}$ n'entraîne pas de modifications fondamentales du spectre EEG en fonction de la dose administrée.

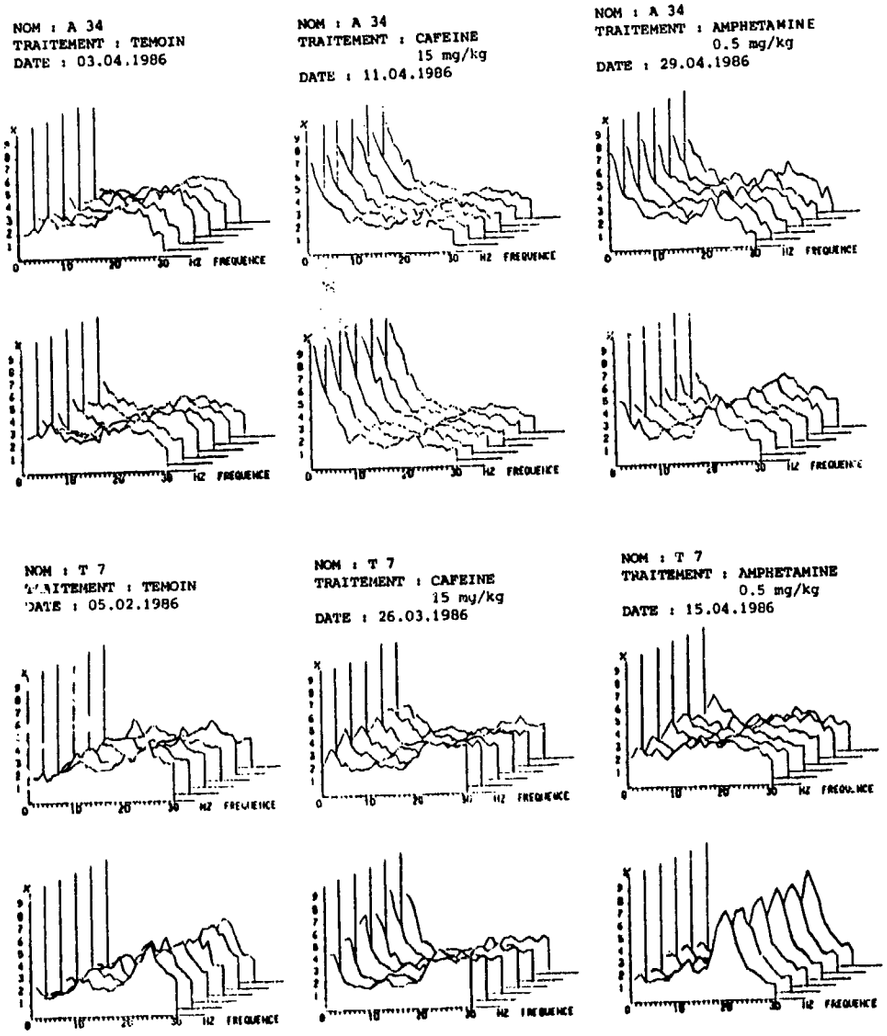
L'étude de l'allure des spectres permet de noter, par rapport aux spectres témoins une sorte de recentrage de la puissance spectrale autour de 20 Hz, alors que l'ensemble de la bande béta décroît assez nettement en puissance.

Cet aspect est plus net au niveau de l'hémisphère droit qu'au niveau de l'hémisphère gauche des sujets enregistrés.

(cf. figure n° 2)

14 - Discussion

A l'issue de cette première expérimentation il a été montré la possibilité d'obtenir pour un même animal, des spectres de densité de puissance fiables et reproductibles pendant l'heure suivant l'administration du placebo ou du traitement. Ces spectres qu'ils aient été obtenus après administration de placebo, de caféine, ou d'amphétamine sont spécifiques de l'animal enregistré et de la molécule administrée. Dans les conditions de l'expérience les différentes doses administrées n'ont pas permis de définir une dose seuil efficace sur le spectre de densité de puissance, pour les psychostimulants étudiés. Il n'a pas non plus été possible d'établir de façon rigoureuse, un ensemble de modifications spécifiques d'une molécule (ou carte d'identité spectrale) communes à tous les animaux traités ; ce fait pouvant s'expliquer par le nombre trop faible de sujets (quatre).



1er SPECTRE : SPECTRE MOYEN DES 10 PREMIERES MINUTES.
2ème SPECTRE : SPECTRE MOYEN DE LA 10° A LA 20° MINUTE.
3ème SPECTRE : SPECTRE MOYEN DE LA 20° A LA 30 ° MINUTE.
4ème SPECTRE : SPECTRE MOYEN DE LA 30° A LA 40° MINUTE.
5ème SPECTRE : SPECTRE MOYEN DE LA 40° A LA 50° MINUTE.
6ème SPECTRE : SPECTRE MOYEN DE LA 50° A LA 60° MINUTE.

Figure n° 2

Spectres de densité de puissance EEG
après administration de psychostimulants. (voir texte).

2 - DEUXIEME EXPERIMENTATION

Elle avait pour but :
1. de vérifier les résultats obtenus à l'issue de la première expérimentation.
2. de tenter de mettre en évidence la pharmacocinétique des molécules administrées.
3. d'étudier les effets de l'administration d'un psychostimulant original (le CRL 40476) sur le spectre de densité de puissance.

21 - Vérification des résultats obtenus à l'issue de la première expérimentation

21.1 - Au niveau des enregistrements témoins

La comparaison des spectres moyens d'une heure obtenus au cours d'une même expérimentation de 8 heures met en évidence une certaine hétérogénéité entre les spectres pour un même animal.

Le même résultat est retrouvé lors de la comparaison, pour un même animal, des spectres moyens obtenus lors d'une première journée témoin placebo avec ceux obtenus lors d'une deuxième journée témoin placebo et ceci dans l'ordre chronologique d'apparition (1er spectre moyen du 1er jour avec le 1er spectre moyen du 2ème jour, etc...).

En revanche, et cela a été retrouvé pour tous les animaux étudiés, la comparaison des moyennes globales de chaque journée témoin placebo, permet de mettre en évidence une forte homogénéité pour l'ensemble des spectres obtenus chez un même animal.

21.2 - Traitement par la caféine

Les observations effectuées lors de la première expérimentation semblent se confirmer. En effet, pour tous les animaux étudiés, (cf. figure n° 3) il apparaît dès la première heure une augmentation très nette des très basses fréquences (ondes delta 1 à 4 Hz) accompagnée d'une réduction des fréquences de la bande alpha (7 - 13 Hz). La puissance spectrale au niveau de la bande thêta est de façon générale légèrement diminuée ; de même au niveau de la bande bêta, il est très globalement observé une diminution de la puissance bien qu'un pic soit parfois remarqué au niveau de 20 Hertz.

Les modifications spectrales, précédemment décrites, sont à l'issue de l'étude d'un échantillon de spectres, reproductibles non seulement au cours des 8 spectres moyens d'une heure mais également au cours des différentes administrations de caféine, chez un même animal.

21.3 - Traitement par l'amphétamine (figure n° 3)

Les résultats obtenus lors du traitement par le sulfate de d-amphétamine permettent de définir certaines tendances générales quant aux modifications des puissances du spectre en fonction des fréquences. C'est ainsi que l'on a pu observer :
- au niveau de la bande delta : une augmentation de la puissance spectrale.
- au niveau de la bande thêta : les variations observées sont variables avec cependant une légère tendance à l'augmentation de puissance.
- au niveau de la bande alpha, il est noté une relative stabilité de la puissance spectrale évoluant pour certains sujets vers une augmentation.
- au niveau de la bande bêta, une nette diminution de la puissance spectrale est notée, particulièrement marquée au niveau bêta 2 (25 - 30 Hz).
  Toutefois il a été remarqué chez deux animaux des modifications spectrales différentes de celles précédemment exposées ; la puissance dans la bande delta diminue alors même que celle de la bande bêta augmente.

22 - Pharmacologie des molécules administrées

Il a été procédé à l'examen des spectres moyens d'une heure pour déceler d'éventuelles modifications ou l'évolution de l'allure générale des spectres au cours des huit heures d'enregistrement.

C'est ainsi que :
- Pour la caféine : aucune évolution marquée de l'allure du spectre n'a pu être observée au cours des huit heures d'enregistrement chez les animaux étudiés.
- Pour la d-amphétamine : il n'a pas non plus été possible d'observer par la seule étude de l'allure générale des spectres moyens d'une heure, une cinétique de la molécule administrée.

Les résultats obtenus ne sont pas entièrement en accord avec les données actuelles sur le métabolisme et la cinétique des deux molécules étudiées. En effet selon ANGGARD (1) et BAGOTT et DAVIS (2) la demi-vie de la d-amphétamine serait de l'ordre de 30 mn à 3 heures chez le rat et légèrement plus longue chez les autres animaux. Il apparaît ainsi nécessaire d'approfondir notre méthode d'étude de la cinétique des modifications spectrales, provoquées par l'administration de d-amphétamine, afin de tenter de corréler l'action centrale de ces molécules avec leur métabolisme.

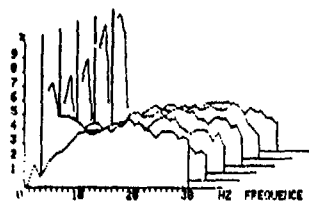
Par contre la caféine pouvant avoir une durée d'action assez longue (supérieure à 7 heures), la cinétique de cette molécule n'a pu être mise en évidence dans les conditions de l'expérience.

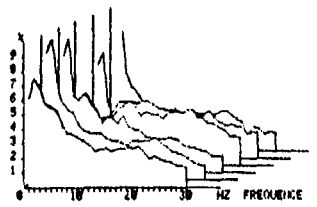
23 - Etude des effets de l'administration d'un nouveau psychostimulant

Après contrôle de l'homogénéité des spectres obtenus en situation témoin placebo, il a été administré une dose considérée comme efficace au niveau de l'effet éveillant, d'un psychostimulant original le CRL 40476 (13).

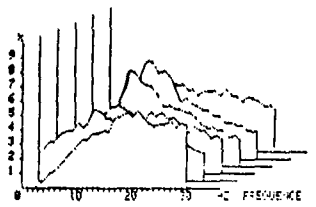
Les effets obtenus au niveau des spectres de densité de puissance sont univoques pour l'ensemble des traitements et des animaux enregistrés. Ils consistent en une augmentation importante de la puissance spectrale au niveau de la bande delta (2 à 4 hz) accompagnée le plus souvent d'une réduction de la puissance au niveau des ondes bêta, la puissance au niveau des ondes alpha restant stable. L'étude de la cinétique permet de mettre en évidence un effet moins marqué de cette molécule la première heure suivant l'administration, comparé aux heures suivantes. (cf. figure n° 3).

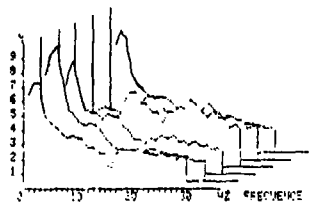
Sujet A34





Sujet U1

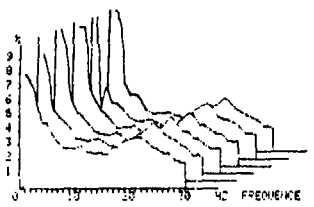


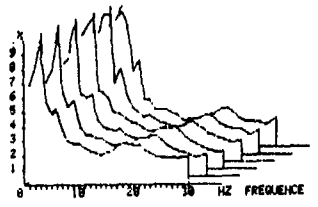


Placebo

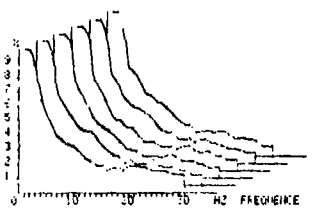
d-Amphétamine

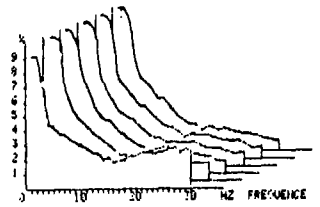
Sujet A34





Sujet U1





Caféine

CRL 40476

Figure n° 3

Spectres de densité de puissance obtenus après administration d'un placebo et de trois psychostimulants chez le macaque A34 (en haut) et le macaque U1 (en bas). (Enregistrements hémisphère gauche, dérivation pariéto-frontale).

III - DISCUSSION - CONCLUSION

L'ensemble des données obtenues à l'issue de cette étude préliminaire d'une approche des effets des psychostimulants sur l'activité électrique cérébrale chez le primate non humain, permet de formuler un certain nombre de résultats.

1. La grande homogénéité observée au niveau des spectres moyens calculés et obtenus sur la totalité de l'enregistrement en situation témoin placebo chez tous les animaux enregistrés, met en évidence, d'une part, le caractère reproductible des résultats lors d'une même situation expérimentale, et d'autre part, leur fiabilité, et valide ainsi la méthode utilisée.

2. Les modifications notées au niveau des spectres de densité de puissance lors de l'administration de certains psychostimulants chez le macaque rhésus aux doses indiquées, par rapport aux spectres enregistrés lors de l'administration d'un placebo, peuvent être résumées dans le tableau suivant :

	delta 1.5-3 Hz	thêta 3.5-6.5 hz	alpha 7-13 Hz	bêta 1 13.5-20 Hz	bêta 2 20.5-30 Hz
CAFEINE $15\ mg.kg^{-1}$	↑↑	↓	↓	≅ ↓	≅ ↓
D-AMPHETAMINE $0,5\ mg.kg^{-1}$	↑	↑ ⊖	↑	↓	↓↓
CRL 40476 $22.5\ mg.kg^{-1}$	↑↑	⊖	⊖	↓	↓

(↑ augmentation, ↓ diminution , ⊖ pas de changement, ≅ variable)

Variations caractéristiques des spectres de densité de puissances enregistrées en dérivation pariéto-frontale chez le macaque rhésus, après administration de différents psychostimulants

3. Ces données ont été obtenues à partir d'un échantillon de 240 enregistrements, témoins placebo et traitement par psychostimulants, chez sept sujets différents.
   En ce qui concerne la caféine, les résultats obtenus au cours de ces expérimentations chez le primate non humain, sont en accord avec ceux obtenus chez l'homme par POLLOCK et coll (14) ainsi que par BRUCE et coll (4) lors de l'administration per os de doses de caféine respectivement de 200 mg, 250 mg et 500 mg. Notamment il est retrouvé une diminution de la puissance spectrale dans les bandes de fréquence thêta et alpha. De même, la puissance globale spectrale est diminuée par rapport à la puissance globale enregistrée en situation témoin pour un même animal. En revanche ces auteurs n'ont pas noté d'augmentation des puissances dans la bande delta, alors que cette modification est caractéristique des enregistrements dont les résultats sont présentés dans cet exposé.
   En ce qui concerne le sulfate de d-amphétamine, bien que certains résultats soient divergents, il est possible de dégager un ensemble de modifications au niveau du spectre de densité de puissance semblables à celles retrouvées par de nombreux auteurs. C'est ainsi que l'on retrouve une diminution de la puissance spectrale au niveau de la bande bêta. Cette réduction au niveau des hautes fréquences a été retrouvée aussi bien chez le rat (5), le chat (16), le singe (12) que chez l'homme (7) (17).

4. Les deux doses administrées pour chaque molécule de référence, lors de la première expérimentation n'ont pas permis de dégager la dose seuil entraînant les modifications spectrales observées. Des travaux seront à poursuivre dans ce sens, notamment pour essayer de comparer la dose seuil des effets électrophysiologiques et la dose seuil des effets comportementaux caractéristiques des psychostimulants.

5. La recherche de la pharmacocinétique des effets électrophysiologiques des molécules administrées n'a permis que d'entrevoir la possibilité d'une telle étude par l'obtention de résultats partiels qui dans l'état actuel des travaux entrepris n'ont pu être mis en évidence que pour l'administration de CRL 40476. Des études plus fines en début de traitement (par exemple étude des spectres moyens de 10 mn pendant la 1ère heure après administration de la molécule) ou des études plus prolongées (au delà de la 8ème heure) devront être envisagées dans l'avenir.

6. L'étude des effets du CRL 40476 sur l'activité électrique cérébrale du macaque a permis de mettre en évidence des modifications de la puissance spectrale tout à fait spécifiques de cette molécule et reproductibles à la fois chez le même animal mais aussi chez tous les animaux enregistrés.
   L'allure générale du spectre de densité de puissance ainsi obtenu apparaît comme relativement proche du spectre obtenu lors de l'administration de caféine, notamment en ce qui concerne les modifications observées au niveau de la bande delta (forte augmentation de la puissance spectrale) et au niveau de la bande bêta (diminution de la puissance spectrale). De plus, la puissance globale du spectre est diminuée dans une proportion de 50 % par rapport à la puissance enregistrée chez les sujets témoins, proportion identique à celle retrouvée lors de l'administration de caféine.

En conclusion,

Les résultats des travaux qui viennent d'être exposés ont permis d'effectuer chez le macaque rhésus, une approche des effets de psychostimulants sur l'activité électrique cérébrale, par l'utilisation d'une methode mettant en oeuvre la Transformée rapide de Fourier. Trois substances psychostimulantes ont été étudiées au cours de deux expérimentations complémentaires : deux d'entre elles sont des psychostimulants de référence : la caféine et le sulfate de d-amphétamine, la troisième est une molécule originale dotée de propriétés stimulantes et éveillantes particulièrement puissantes. Cette première approche a ainsi permis de mettre en évidence les propriétés tout à fait spécifiques de cette nouvelle molécule au niveau du spectre de densité spectrale de puissance du EEG du primate non humain, et de pouvoir la situer par rapport aux effets provoqués par deux autres stimulants classiques et obtenus dans les mêmes conditions expérimentales.

Il apparaît ainsi nécessaire de poursuivre les travaux entrepris afin de :
1. confirmer les résultats par l'obtention de données supplémentaires recueillies à partir d'autres sujets.
2. reprendre la détermination de la dose seuil au niveau des effets électrophysiologiques.
3. affiner l'étude de la cinétique des molécules, notamment au cours de la 1ère heure d'enregistrement, et après la 8 ème heure.
4. étendre l'étude des effets électroencéphalographiques à d'autres stimulants, puis éventuellement à d'autres psychotropes.

R E F E R E N C E :

1 - ANGGARD E.
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DISCUSSION

BERRY, US: You indicated that the new compound, CRL-40476 is useful in stimulating vigilance. Could you compare it and d-amphetamine in regard to side effects?

LAGARDE, FR: The purpose of this work was to determine the very original properties of this new psycho-stimulant agent against two other conventional stimulants; viz., caffeine and d-amphetamine. (The drug d-amphetamine is still given to aircrew in France; and, of course, it has well-known side effects.) The new drug was studied in our laboratory in the non-human primate, the rhesus monkey. At the dosage indicated — 25 mg/kg — there were no side effects in the performance of the animal nor in its vegetative parameters; viz., in blood pressure and heart rate. The main effect of the drug was that it kept the animal awake, though not as a stimulant. This effect would give the impression that the drug is not comprised of an amphetamine-like type of molecule. It's an action which is quite specific — as based on other studies in apes and rats — in that it appears to work on post-synaptic brain centres at that level of dosage. Of course, at a higher dosage it would probably have a doping effect.

SPONTANEOUS CEREBRAL ELECTRICAL ACTIVITY DURING PROLONGED HYPOGLYCEMIA: a Quantitative Study in Humans

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SUMMARY

The authors stress the importance of neuroglycopenia secondary to hypoglycemia as a possible cause or contributing factor in aircraft accidents. A study was designed to investigate the neurophysiological correlations of neuroglycopenia. The generation of spontaneous cerebral electrical activity in healthy young adults is quantified in a computer-assisted study, with subjects placed under fixed hypoglycemic conditions.

INTRODUCTION

The term 'hypoglycemia', which literally means low blood sugar, must be distinguished from 'neuroglycopenia', a condition which refers to the symptomatology produced by a lack of glucose in neurons. In fact, hypoglycemia may or may not be associated with neuroglycopenia symptoms (1) depending on the following factors: initial blood glucose concentration; the rate of decreasing glucose levels; individual response. The evaluation of tissue damage due to neuroglycopenia is not only important in patients suffering from organic hypoglycemia and in the large number of insulin-dependent diabetics, but also in Aviation Medicine. In this field, the hypoglycemic disorders having particular significance are those which occur after a meal. These are frequently referred to as: functional, postprandial, alimentary or reactive hypoglycemia (2). Clinical manifestations of hypoglycemia can be divided into those attributable to the sympathochromaffin response and those resulting from the low intraneuronal glucose level. Owing to the marked variability among individuals with regard to behavioral responses and neurophysiological alterations, it is impossible to set a blood glucose threshold below which the term 'true hypoglycemia' may be applied. A number of authors recommend that a venous blood glucose value below 50 mg/dl (2.7 mmol/l) during an oral glucose tolerance test be sufficient to make a diagnosis of postprandial hypoglycemia (3). An extensive study on the prevalence of postprandial hypoglycemia has been conducted by Farris on 4,928 male subjects in the U.S. Army (4). Values below 50 mg/dl were encountered in 8.4% of this test population. Other authors have stressed the frequent finding of low blood sugar levels among normal asymptomatic subjects, reporting the prevalence to be as high as 48% in this group (5,6). In consideration of the high prevalence of low blood glucose values among asymptomatic normals, a working definition of hypoglycemia as glucose levels below 45 mg/dl (2.2 mmol/l) has been proposed (7).

Glucose is an optional energy source in many tissues that are capable of utilizing alternative types of substances to satisfy their metabolic needs. However, the central nervous system (CNS) uses glucose as its sole fuel, since under physiologic conditions other substrates are either imperviable to the blood-brain barrier or present in the bloodstream in insufficient amounts for adequate uptake by neurons (8). Glucose is metabolized along the oxidative pathway to near completion, as evidenced by the respiratory quotient of brain tissue which approaches 1.

Although it has been known for over 25 years that reduced blood sugar negatively affects tolerance to the +GZ type gravitational forces experienced in flight (9), little attention has been devoted to this problem. Reduced G tolerance resulting from hypoglycemia has been implicated in the causation of fatal aircraft accidents (10,11). In a study conducted on Canadian Air Force pilots, Powell and coworkers (12) found subnormal glucose levels in 55% of the survivors of incidents involving loss of consciousness. More recently, experimental evidence has shown that episodes of mild hypoglycemia are capable of provoking subtantial cerebral dysfunction (13,14,15,16), potentially sufficient to jeopardize flight activities. From studies of this type emerge results indicating that signs of neuroglycopenia are already evident at glucose levels of 55 mg/dl (3 mmol/l), although wide variation exists among individuals.

SPONTANEOUS CEREBRAL ELECTRICAL ACTIVITY

Ever since the advent of clinical electroencephalography (EEG), the measurement of alterations in spontaneous electrical activity of the cerebral cortex, as recorded from scalp electrodes, has been used to assess CNS function during the metabolic disturbance

caused by hypoglycemia (17). Many experiments focusing on acute hypoglycemia have been conducted on psychotic patients treated with shock-doses of insulin (Sakel's therapy) (18). The first signs of spontaneous cerebral electrical activity involvement are a reduction in alpha rhythm frequency, an increased sensitivity to hyperventilation with a tendancy to generate delta waves (19). In some individuals significant changes in EEG activity appear at 50 mg% blood glucose, whereas others show unaltered tracings until 30-35 mg% (20). Davis (1943) reported EEG changes in young students who had blood glucose levels of 53-83 mg% (21). These effects were most evident in those subjects having slower baseline tracings and to a lesser degree in subjects with higher frequency basal rhythms and lower voltage. In a recent (1985) investigation by Harrad and coworkers (22), a quantitative method was employed to reveal significant EEG slowing with a shift of rapid alpha to slow alpha waves and an increase in the amplitude of delta and theta waves.

Experimental models in cats (23) and rats (24) have demonstrated electrical silence at blood sugar levels around 25 mg%. The pattern of EEG alterations, however, varies considerably during the course of hypoglycemia. Alterations which predominate are generalized, synchronous, bilateral, paroxysmal, in the form of slow monorhythmic bursts or irregular slow waves, spikes or polyspikes (25).

Of particular interest is the relationship between hypoglycemia and epilepsy. The hypoglycemic state is capable of revealing and amplifying the EEG abnormalities in epileptic foci (26). The convulsions due to hypoglycemia are associated with concomitant low O_2 and glucose utilization, in contrast to convulsions provoked by analeptic drugs and electroshock treatments which increase cerebral blood flow and consumption of oxygen and glucose (27). Pretreating immature rats with glucose reduces mortality during clinically induced epileptic seizures and has a protective effect on subsequent brain development (28). The neurological consequences of epilepsy in the adult animal, however, have been correlated to certain systemic effects of the convulsions themselves (acidosis, hypotension, hypoxia) (29). Alterations found in hypoxia are similar to those present in hypoglycemia (30); breathing 100% O_2 is also reported to correct the EEG abnormalities produced by moderate hypoglycemia. Severe hypoglycemia is associated with a concomitant decrease in O_2 consumption (18,31,32,33, 34).

In many respects, hypoglycemia and hyperventilation (cerebral hypoxia due to hypocapnia) act synergistically in the production of EEG abnormalities (21,31,34).

The aim of our study was to establish whether the hypoglycemic state, kept constant at 40 mg% (biochemically), could be responsible for EEG alterations objectively quantifiable as signs of neuroglycopenia.

MATERIALS AND METHODS

Subjects: Eight normal subjects (7 male, 1 female) ages ranging from 26 to 30 years (av = 28 $\pm$ 2) participated in the study after informed consent was obtained. No subject reported a family history of diabetes mellitus or neurologic disorders. Each subject underwent routine EEG to rule out the presence of anomalies prior to admission to the study. All routine tracings presented at least 40% alpha activity. The study protocol started at 9:00 AM, after subjects had fasted overnight and had eight hours of restful sleep, and it lasted until early afternoon.

EEG

EEG signals were recorded from silver-silver chloride electrodes applied according to the international 10/20 system in positions F3, C3, F4, C4, P3, O1, P4, O2 using collodion technique. Interelectrode impedance was maintained at approximately 5 Kohm. EEG activity was recorded from four bipolar longitudinal leads (F3-C3, F4-C4, P3-O1, P4-O2). The test was conducted in a shielded room, using an OTE 18 neurograph (HFF25 Hz, TC 0.3 sec., notch filter on, 50 uV/cm). Ambient temperature was kept comfortable to avoid excessive perspiration on the part of subjects, who were tested in the supine position. EEG's were recorded in euglycemic conditions (78 $\pm$ 2.3 mg%) and at a fixed level of hypoglycemia of approximately 40 mg%. Recordings were performed: a) for three minutes with subjects' eyes closed; b) three minutes with eyes open and gaze fixed ahead, so as to reduce eye movements to a minimum; c) one minute with intermittent light stimulation at 5, 10, 15 and 20 Hz (flash of 1 Joule); d) three minutes during hyperventilation with eyes closed. Baseline electrical activities and those obtained under various physical stimuli (hyperventilation and intermittent light stimulation) were thus studied according to the standard paradigm for routine EEG examinations.

GLUCOSE CLAMP TECHNIQUE

A constant intravenous infusion of human insulin (0.83 mU/Kg/min) was administered to each subject. Blood glucose levels gradually decreased and were maintained at 43 $\pm$ 3 mg/dl by the Glucose Clamp Technique (36) which utilizes an artificial pancreas (Biostator-Miles). The pre-established glucose concentration was reached after about 90 minutes of infusion. The glucose required to maintain this constant level of hypoglycemia was 0.79 $\pm$ 0.07 mg/Kg/min and plasma concentration of insulin was 39.6 uU/ml. EEG recordings were performed after about 90 minutes of stable hypoglycemia.

PROCESSING OF DATA

Analog signals recorded on magnetic tape in PCM (OTE AJWA Recorder, 0-80 Hz range) were transferred to an A/D convertor and fed into an HP1000 computer as amplitude values of the original signals, sampled in 2 second epochs at 64 samples per second. Fast Fourier Transform (FFT) was applied to signal values thus stored. For each subject under each of the experimental conditions and from each recording channel, the power spectra of the original signals were obtained. Data processing was carried out on a one-minute artifact-free portion of the signal for both eyes-closed and eyes-open conditions; 30 seconds of intermittent light stimulation at 5, 10, 15 and 20 Hz and on the last minute of the hyperventilation tracing. For the statistical evaluation of results, the following bands were considered: delta (2-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta 1 (13-20 Hz), and beta 2 (20-32 Hz). Activity below 2 Hz was excluded to avoid signals deriving from slow ocular movements. The following spectral descriptors were used: absolute power of each band; relative percentage of each band (100% being the activity between 2 and 32 Hz); mean (barycentric) frequency of each band; dominant frequency of the alpha band; peak value of the alpha band.

The final spectrum was obtained by averaging all spectra from each subject under each experimental condition and for each channel.

Statistical evaluation was performed using the paired Student's t test.

RESULTS

COMPARISON BETWEEN EUGLYCEMIC AND HYPOGLYCEMIC CONDITIONS

With subjects' eyes closed (Tab.1): In hypoglycemia, delta tended to increase in all leads; the mean frequency and the dominant frequency of the alpha band were reduced over all (Fig.1), with statistical significance in the frontal regions ($p<0.05$).

With eyes open (Tab.2): The dominant frequency and the mean frequency of the alpha band were reduced significantly ($p<0.05$) in the frontal leads.

During intermittent light stimulation (Fig.2,3): In hypoglycemia, a significant increase in the relative percentage of theta activity was noted in all leads at 10, 15 and 20 Hz ($p<0.05$ or less) with a concomitant decrease in the relative percentage of alpha ($p<0.05$ or less on all channels at 15 Hz; $p<0.05$ on occipital leads at 10 and 20 Hz).

During hyperventilation: The following results were observed in hypoglycemia:
- increase in the relative percentage of theta activity ($p<0.05$ in the left occipital lead) and beta 1 ($p<0.05$ in frontal leads); concomitant reduction in the relative percentage of alpha ($p<0.05$ or less in frontal leads);
- significant decrease in the mean frequency of alpha in all leads ($p<0.05$ or less);
- decrease in the dominant frequency ($p<0.05$ in frontal leads) and peak value of the alpha band in all leads.

Selective effect of hyperventilation under each metabolic condition (eyes closed + hyperventilation versus eyes closed)
In euglycemia: As expected, hyperventilation increased absolute power and relative percentage of the delta band with statistically significant differences on frontal leads ($p<0.05$); it decreased the mean frequency of the delta band (in frontal leads $p<0.05$) and the beta 1 band ($p<0.05$ in occipital leads) (data not shown).

In hypoglycemia (Tab.3): No significant modification in the absolute power of alpha rhythm; whereas an increase was found in alpha mean frequency ($p<0.05$ in occipital leads) and alpha dominant frequency ($p<0.05$ in occipital leads); the absolute power of the beta 1 band also increased ($p<0.05$) in frontal leads.

DISCUSSION

Many of the modifications in spectral parameters encountered during episodes of hypoglycemia are to be found in the alpha band: reduced absolute power, mean and dominant frequencies and a decreased peak value of the dominant frequency; most evident in frontal leads. Figure 4 shows the compressed spectral analysis of a single subject in euglycemia and hypoglycemia under different testing conditions. Previous experiences reported in the literature have long emphasized the slowing of the dominant alpha rhythm at blood sugar levels below 50 mg% (37). The appearance of theta and delta rhythms with more severe hypoglycemia has also been demonstrated (25), initially prevailing in the fronto-temporal regions symmetrically before becoming generalized (38).

When the level of hypoglycemia is kept constant at 40 mg%, results point to a partial loss of CNS electrical autorhythmicity with a certain degree of regional selectivity. The greater sensitivity of the frontal areas to hypoglycemia may be correlated to clinical observations of depressed higher level integrative processes induced by low blood sugar (14).

Under euglycemic conditions, hyperventilation with the subject's eyes closed was shown to be associated with certain 'slowings', a finding which is well documented in the literature, especially in young adults. Conversely, the same effect was not evident when similar conditions (eyes-closed+hyperventilation) were tested in hypoglycemia. In fact, there was an increase in alpha mean and dominant rhythms and relative percentage of the beta band. Hence our data do not confirm a synergistic effect between hypoglyce-

CLOSED EYES

P_3-C_3

		DELTA		THETA		ALPHA		BETA 1		BETA 2	
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EU	94.13	13.52	120.7	24.6	571.4	282.3	72.21	16.39	54.77	14.86
	HY	107.8	24.47	125	31.5	298.56	83.3	69.75	12.97	55.89	10.91
SACC.	EU	14.04	3.76	16.65	2.17	49.87	8.48	10.14	1.94	8.05	2.14
	HY	18.83	4.78	20.06	3.54	91.31	8.24	10.44	1.38	9.12	2.84
MEAN F.	EU	2.59	0.03	5.73	0.1	* 10.04	0.21	15.91	0.13	24.34	0.27
	HY	2.57	0.03	5.84	0.11	* 9.79	0.16	15.94	0.13	24.45	0.17
PEAK F.	EU					* 10.57	0.38				
	HY					* 9.57	0.41				
PEAK V.	EU					353.3	186.81				
	HY					178.4	58.04				

		DELTA		THETA		ALPHA		BETA 1		BETA 2
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EU	76.7	10.2	93.7	19.28	329.3	1064	70.67	23.82	47.85	17.31
	HY	73.6	17.7	97.2	24.8	195.6	73.2	57.96	16.39	49.68	23.60
SACC.	EU	16.38	2.81	16.9	1.72	66.8	7.64	11.66	2.89	10.20	298
	HY	13.78	3.51	21.12	3.15	37.92	6.91	12.39	1.81	10.76	294
MEAN F.	EU	2.58	0.03	5.69	0.06	* 10.13	0.21	15.91	0.13	24.8	0.28
	HY	2.58	0.02	5.8	0.1	* 9.85	0.15	16.03	0.11	24.7	0.19
PEAK F.	EU					* 10.36	0.47				
	HY					* 9.58	0.32				
PEAK V.	EU					191.7	61.49				
	HY					111.5	33.48				

P_3-O_1

		DELTA		THETA		ALPHA		BETA 1		BETA 2
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EU	70.76	23.6	116.1	34.7	927.3	352.4	80.82	26.11	46.93	16.83
	HY	92.01	37.3	138.4	49.8	889.6	391.3	112.7	45.27	63.89	24.82
SACC.	EU	9.39	2.96	13.39	2.8	61	8.26	9.97	2.69	6.37	2.03
	HY	8.18	1.37	13.12	1.9	60.45	5.95	10.82	3.18	6.29	2.65
MEAN F.	EU	2.65	0.01	5.92	0.1	10.05	0.21	16.11	0.28	23.76	0.31
	HY	2.60	0.04	5.99	0.09	9.84	0.18	16.06	0.18	23.85	0.31
PEAK F.	EU					10.21	0.34				
	HY					10.07	0.23				
PEAK V.	EU					607	266.14				
	HY					401.40	278.5				

P_4-O_2

		DELTA		THETA		ALPHA		BETA 1		BETA 2
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EU	90.41	17.17	136.2	37.7	1095	368.8	98.18	34.16	54.22	19.34
	HY	111.17	24.1	166.4	43	10 57	396.4	127.2	49.4	69.9	27.117
SACC.	EU	7.72	1.86	11.74	1.81	65.63	5.75	9.02	2.34	5.05	1.62
	HY	12.6	5.93	13.40	2.06	60.12	8.33	8.78	2.69	5.07	2.21
MEAN F.	EU	2.66	0.02	5.88	0.08	10.07	0.21	16.04	0.13	23.8	0.32
	HY	2.67	0.04	5.84	0.16	9.82	0.19	16.06	0.14	24	0.30
PEAK F.	EU					10.29	0.18				
	HY					9.93	0.25				
PEAK V.	EU					776	315.6				
	HY					722	291.5				

Table 1. Comparison between euglycemia (EU) and hypoglycemia (HY) during the eyes closed recording. * = $p < 0.05$

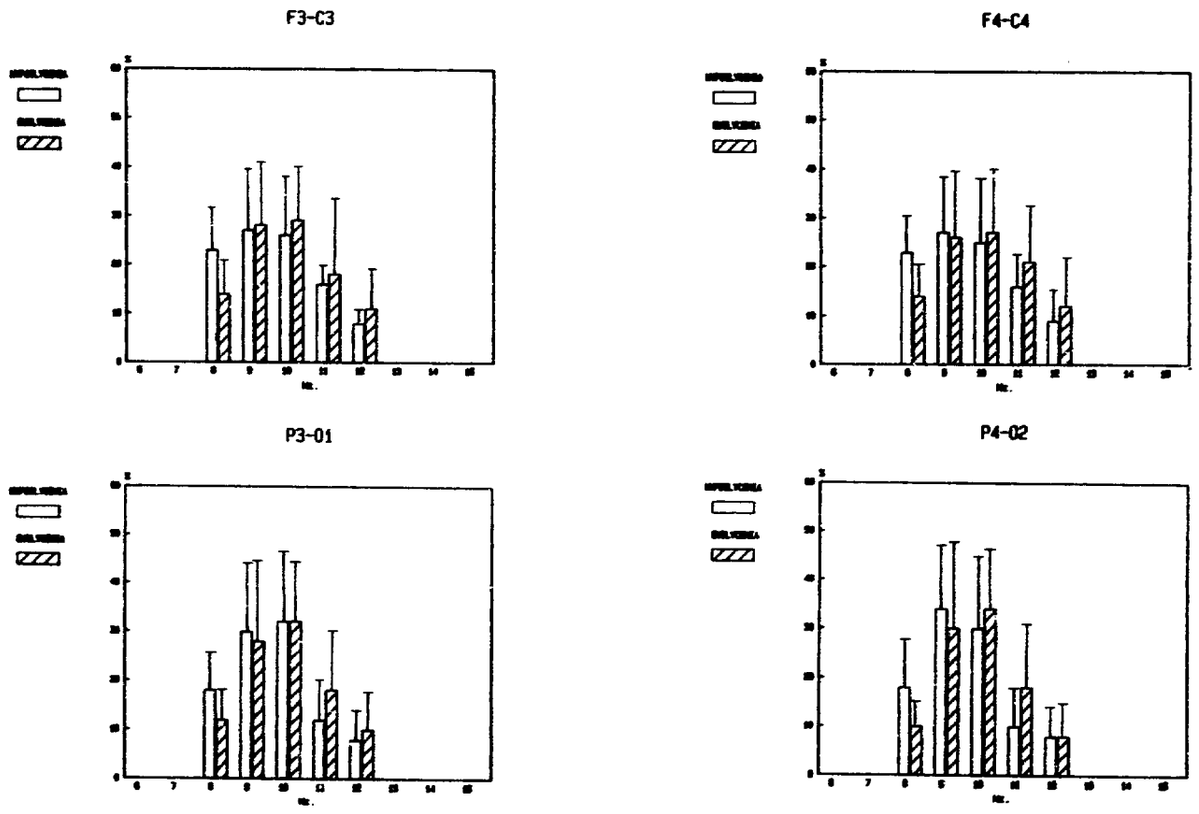


Figure 1. Relative activity of each 1-Hz band within the alpha rhythm under the two metabolic conditions during the eyes closed recording. Data are reported as Mean ± S.D.

OPEN EYES

F_3-C_3

		DELTA		THETA		ALPHA		BETA 1		BETA 2
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EU	188.2	53.9	121.9	36.1	92.9	18.4	57.9	11.9	59	13.03
	HY	262.3	88.5	143.8	31.5	111.3	20.3	66	17.20	65.4	18.5
BACI	EU	33.9	5.6	23.9	2.53	19.4	3.6	11.04	1.57	11.6	3.37
	HY	35.17	6.02	22.1	2.29	21.0	4.4	10.9	1.47	10.8	1.90
MEAN F	EU	2.56	0.03	5.51	0.12	* 10.23	0.15	14.11	0.14	24.8	0.16
	HY	2.57	0.03	5.46	0.11	* 9.88	0.14	14.07	0.11	24.9	0.05
PEAK F	EU					* 10.6	0.41				
	HY					* 9.8	0.51				
PEAK V	EU					36.6	9.2				
	HY					43.3	9.5				

F_4-C_4

		DELTA		THETA		ALPHA		BETA 1		BETA 2
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EU	170.4	71.9	107.5	36.88	114.8	31.7	56.7	17.1	53	15.7
	HY	212.8	119.9	134	50	96.29	19.7	53.6	17.4	51.3	13.3
BACI	EU	33.7	6.9	20.13	1.46	24	5.22	10.6	1.6	11.4	3.2
	HY	38.3	6.9	21.33	2.54	18.4	2.9	10.7	2.7	10.6	2.87
MEAN F	EU	2.54	0.03	5.52	0.11	* 10.4	0.12	16.02	0.14	24.8	0.15
	HY	3	0.02	5.42	0.11	* 10.1	0.10	15.9	0.07	25.2	0.16
PEAK F	EU					* 11	0.4				
	HY					* 9.6	0.6				
PEAK V	EU					55.1	19.6				
	HY					33.7	7.9				

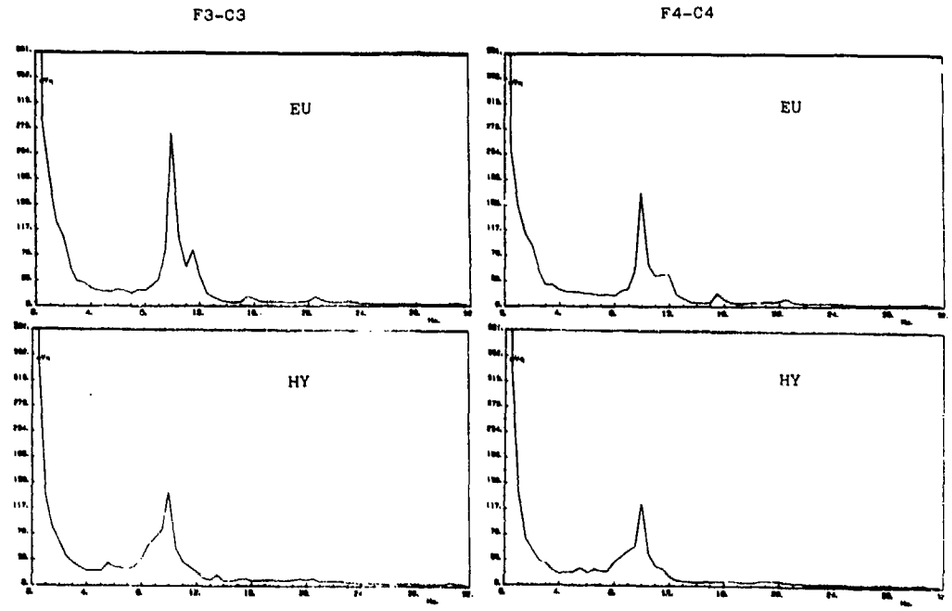
P_3-O_1

		DELTA		THETA		ALPHA		BETA 1		BETA 2
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EU	51.4	15.6	52.5	7.83	80.09	91.9	33.07	7.5	24.8	11.4
	HY	83.1	31.1	70.2	17.29	209.5	83.5	47.23	10.7	27.2	10.67
BACI	EU	21.7	4.84	23.5	2.8	31.4	3.9	13.9	1.38	9.4	2.08
	HY	18.8	3.39	18.48	2.9	41.7	7.2	13.2	2.01	7.5	1.54
MEAN F	EU	2.6	0.01	5.68	0.06	10.3	0.15	15.76	0.14	24.5	0.21
	HY	2.6	0.02	5.67	0.09	10.13	0.18	15.77	0.18	24.3	0.13
PEAK F	EU					10.6	0.5				
	HY					10.2	0.57				
PEAK V	EU					38	10.3				
	HY					103.8	45.3				

P_4-O_2

		DELTA		THETA		ALPHA		BETA 1		BETA 2
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EU	89.9	41.5	62.4	11.8	126.6	44.9	30.3	11.78	33.4	13.9
	HY	99.9	40.0	81.3	22.3	214.1	70.3	57.9	17.66	33.5	12.2
BACI	EU	23.1	5.9	20.98	4.89	32.4	4.9	14.3	1.61	9.5	2.16
	HY	18.6	3.8	18.18	2.62	40.7	5.5	13.6	1.66	8.8	2.13
MEAN F	EU	2.6	0.06	5.63	0.08	10.5	0.15	15.75	0.15	24.6	0.24
	HY	2.6	0.07	5.63	0.08	10.3	0.2	15.78	0.22	24.3	0.24
PEAK F	EU					11.07	0.39				
	HY					10.96	0.5				
PEAK V	EU					47.7	16.7				
	HY					103.8	34				

Table 2. Comparison between euglycemia (EU) and hypoglycemia (HY) during the open eyes recording. * = $p < 0.05$



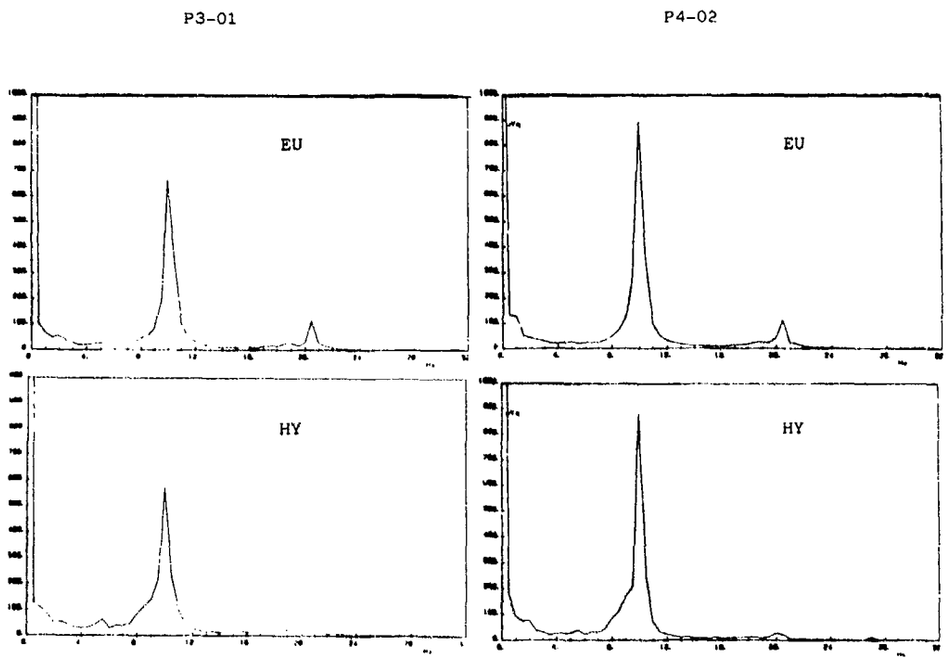


Figure 2. Averaged power spectra in euglycemia (EU) and hypoglycemia (HY) during intermittent light stimulation (10 Hz).

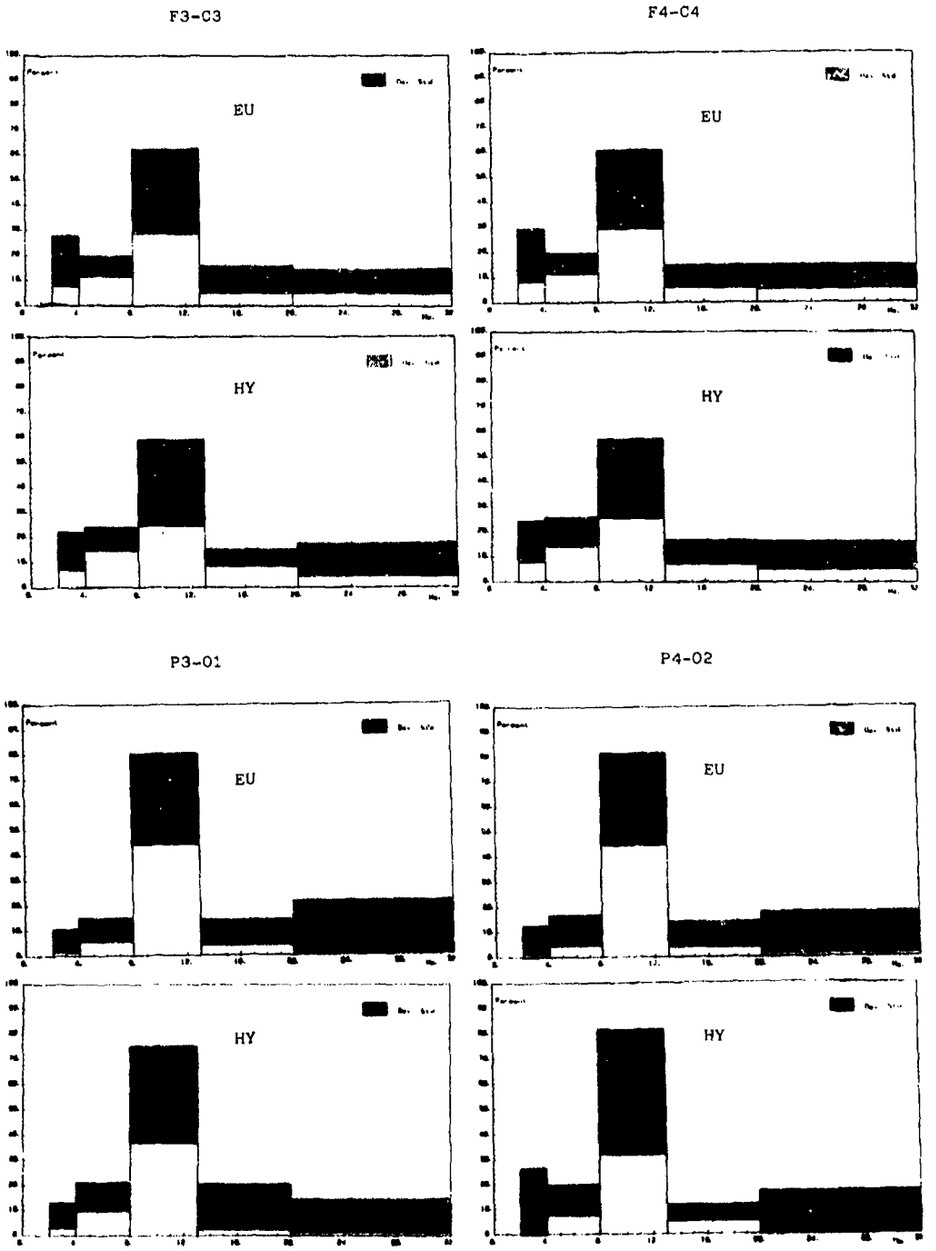


Figure 3. Percentages of activity within the frequency bands (2-4; 4-8; 8-13; 13-20; 20-32 Hz) during intermittent light stimulation in euglycemia (EU) and hypoglycemia (HY). Photic stimulation = 10 Hz. Data are mean ± S.D.

EYES CLOSED(EC)/HYPERVENTILATION (HY)

F_3-C_3

		DELTA		THETA		ALPHA		BETA 1		BETA 2	
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EC	102.7	24.6	125.8	31.5	298.5	83.3	* 69.7	12.9	55.8	18.99
	HY	113.1	25.6	150.8	36	394.5	72.6	* 106.7	23	84.2	38.3
SACI	EC	10.85	4.76	20.08	5.56	61.3	8.2	10.66	1.36	9.12	2.8
	HY	15.44	2.15	20.89	5.1	38.5	6.4	14.2	2.16	11.6	3.91
MEAN F	EC	2.57	0.03			9.79	0.16	15.96	0.13	24.6	0.17
	HY	2.59	0.02			9.98	0.19	15.98	0.14	24.6	0.19
PEAK F	EC					9.57	0.41				
	HY					9.43	0.49				
PEAK V	EC					170	58				
	HY					150	49.5				

		DELTA		THETA		ALPHA		BETA 1		BETA 2	
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EC	92.01	17.7	138.4	49.7	849	391	112.3	45.2	65.8	34
	HY	97.96	35.2	165.8	47.1	875	457	114.1	42.2	71.3	37.2
SACI	EC	5.10	1.37	13.12	1.95	61.65	5.95	10.82	3.18	6.29	2.6
	HY	8.81	1.53	14.20	1.92	58.7	5.56	11.34	2.75	6.87	2.69
MEAN F	EC					* 9.73	0.18	16.06	0.18	23.8	0.31
	HY					* 9.94	0.18	15.9	0.19	24	0.16
PEAK F	EC					* 10.07	0.25				
	HY					* 10.29	0.26				
PEAK V	EC					60.	270				
	HY					595	370				

P_4-C_4

		DELTA		THETA		ALPHA		BETA 1		BETA 2	
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EC	73.6	17.7	97.2	26.8	293.6	73.2	* 57.96	16.5	49.6	10
	HY	120	39	142.3	45.1	278	70.6	* 89.6	27.1	75.7	34
SACI	EC	12.78	3.51	21.12	3.11	37.9	6.91	10.89	1.81	10.7	2.3
	HY	16.9	3.41	28.18	3.2	35.7	5.2	14.2	2.27	12.8	4.07
MEAN F	EC	2.58	0.01	5.80	0.10	9.85	0.15	16.03	0.11	24.7	0.19
	HY	2.60	0.02	5.79	0.13	9.98	0.17	16	0.13	24.7	0.2
PEAK F	EC					10.21	0.32				
	HY					9.86	0.34				
PEAK V	EC					111.5	23.6				
	HY					95.1	31.8				

P_4-O_2

		DELTA		THETA		ALPHA		BETA		BETA 2	
		MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
POWER	EC	111.77	24.13	166.4	43.9	1023.95	396	127.2	47.4	69.9	17
	HY	119.2	39.5	165.01	64.3	868	301	117.7	47.1	73.3	42
SACI	EC	12.60	5.97	13.4	2.08	83.1	8.33	8.78	2.49	5.97	2.2
	HY	8.01	1.07	13.07	1.99	63.87	5.44	9.33	2.87	5.6	2.7
MEAN F	EC					* 9.77	0.19	16.08	0.14	24	0.1
	HY					* 9.91	0.21	15.9	0.16	23.8	0.19
PEAK F	EC					* 9.93	0.25				
	HY					* 10.29	0.24				
PEAK V	EC					727	291				
	HY					570	232				

Table 3. Comparison between eyes closed recording (EC) and eyes closed plus hyperventilation (HY) in hypoglycemia. * = $p < 0.05$

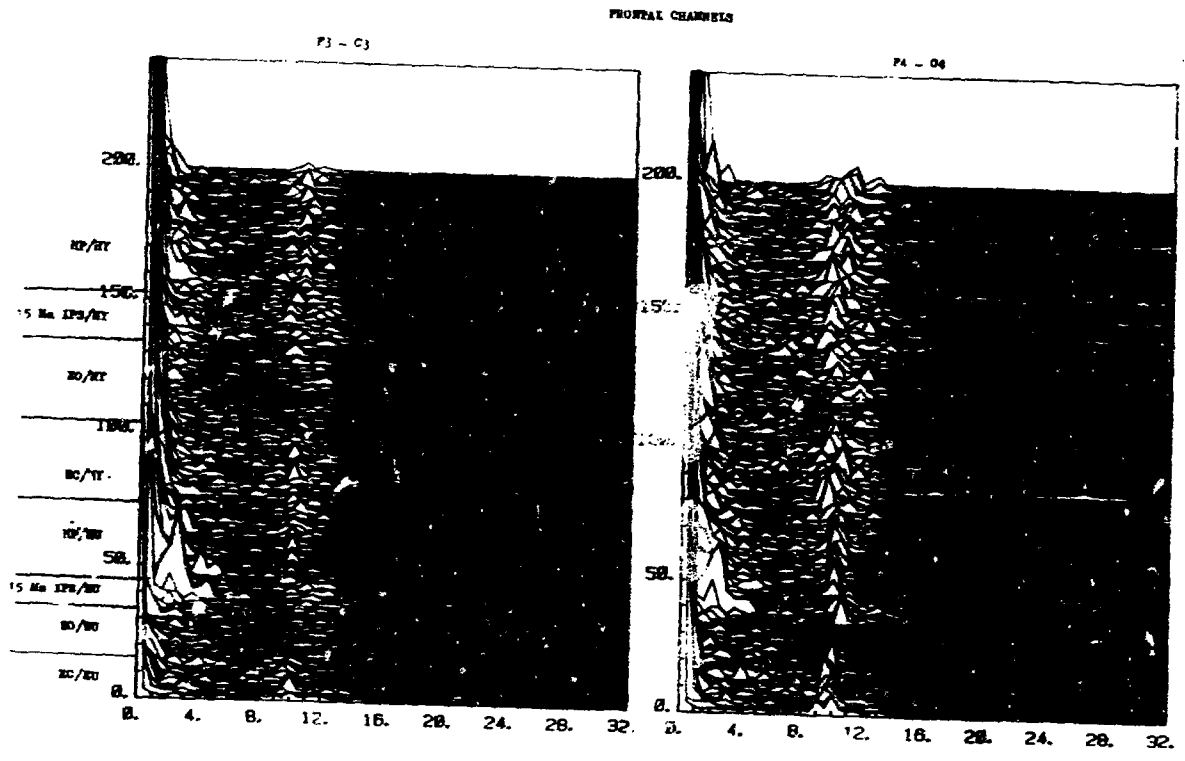


Figure 4. Compressed spectral array (Fourier) of a single subject under different testing conditions. EC= eyes closed; EO = eyes open; IPS = Intermittent photic stimulation; HP = hyperventilation. EU= euglycemia; HY = hypoglycemia

mia-induced alterations in baseline EEG and hyperventilation when blood sugar is constantly maintained at 40 mg% levels. In fact, hypoglycemia and cerebral hypoxia induce different neurochemical modifications. Hypoxia is thought to act by depleting energy reserves in a diffuse, rather homogeneous manner; the structural and metabolic changes which take place with severe hypoglycemia having a more regional distribution (39,40).

Using positron emission tomography, Duara and coworkers (1983) (41) observed various regional cerebral metabolic levels for glucose under normal conditions, particularly high in the frontal areas.

By and large, cerebral blood flow is known to be linked to oxidative metabolism in the brain (42). Progressive hypoglycemia is accompanied by a slow increase in cerebral blood flow both in the experimental animal and man (43). In an experimental model in which the effects of acute hypoglycemia were investigated in the rat, the response to PCO_2 in the cerebral circulation remained intact (increase in blood flow), whereas a certain degree of autoregulation was lost in response to gradual variations in arterial blood pressure (44).

Although precise data regarding cerebrovascular modifications in the course of prolonged hypoglycemia in man are lacking in the literature, one may speculate that local homeostatic factors, such as PO_2 and PCO_2, come into play during episodes of hypoglycemia with superimposed hyperventilation.

In conclusion, our study demonstrates that the most subtle EEG sign of hypoglycemia (i.e., the slowing of the alpha rhythm) is well evident at 40 mg% blood sugar with frontal preponderance. Moreover, under our experimental conditions, hyperventilation does not act synergistically with hypoglycemia as regards EEG alterations. The former, on the contrary, seems in some way to counteract the slowing of the alpha rhythm caused by low blood sugar alone.

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Relation between VEP and visual function in lesions of the optic nerve and visual pathway

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INTRODUCTION

Several authors have claimed that visual evoked potential (VEP) abnormality is not closely related to sensory visual loss in patients with multiple sclerosis (17,15). However, all of their studies assessed sensory visual loss entirely in terms of Snellen visual acuity. Recent findings indicate the possibility that this lack of correlation between VEPs and sensory data might be due, at least in part, to the inability of Snellen's test to detect the full range of visual losses associated with visual pathway dysfunction.

Before discussing abnormalities of pattern VEPs in patients with demyelinating diseases we should first review the reasons why Snellen acuity provides only an incomplete test of visual function loss.

CONTRAST SENSITIVITY LOSS IN VISUAL DISORDERS

In everyday life, perhaps the most important aspect of vision is the ability to see and recognize objects. This ability is commonly assessed by procedures such as the Snellen test in which the patient reads smaller and smaller letters. The smaller the letters that can be accurately recognized, the better the patient's spatial vision is conventionally assumed to be. This assumption seems to be intuitively obvious, so that a 20/20 Snellen score has become a household word for clear and acute vision.

Recently, however, it has grown clear that some patients retain a normal ability to see small objects while their ability to see larger objects is degraded. The claims of such a patient that his vision was weak or "washed out" in an eye with 20/20 acuity might once have been difficult to attribute to organic pathology since the symptoms are quite different from those associated with refractive disorders of vision. Recent neurophysiological and psychophysical studies, however, allow such a complaint to be accepted as having a possible organic basis. One way of measuring visual sensitivity to contrast is to use a sinewave grating as test target (29). This stimulus has the advantage that visual sensitivity to fine detail can clearly be distinguished from visual sensitivity to intermediate and coarse detail.

Figure 1 shows the variation of light intensity across a sinewave grating, and also illustrates the definition of grating "contrast".

One "cycle" of a grating consists of a bright bar plus the adjacent dark bar, and the width of a cycle is called the "period", usually expressed in terms of the angle subtended at the eye (in degrees). The reciprocal of the period is called the grating's "spatial frequency," usually expressed in cycles per degree of visual angle. Thus a narrow-barred grating has a high spatial frequency, and a wide-barred grating has a low spatial frequency.

The test procedure is to find the lowest contrast for which the patient can just tell that the screen contains a grating rather than being uniformly blank. This "grating threshold contrast" is measured for gratings of several spatial frequencies. A plot of grating contrast threshold versus grating spatial frequency is called a "contrast sensitivity function," the term "modulation transfer function" having fallen from favour.

The normal contrast sensitivity function is illustrated in Fig. 12 (dotted line labelled SHARP). This curve describes how the contrast required to see a grating progressively increases as the grating's bar width is decreased (i.e. as spatial frequency is increased). Eventually, at the limit of resolution, even a grating of 100% contrast cannot be distinguished from a homogeneous field of the same mean luminance. The spatial frequency at which the curve cuts the abscissa is defined as the grating resolution. The effect of moderate blur is to reduce sensitivity to high spatial frequencies, while comparatively sparing sensitivity to low spatial frequencies (see "difference" curve).

The clinical use of sinewave gratings was introduced by Bodis-Wollner in 1972 (3). He found that visual pathway disorder could produce an effect on sensitivity that was quite different from refractive error (i.e. blur). A patient with a cortical lesion was insensitive to intermediate spatial frequencies, while sensitivity to high spatial frequencies (i.e. visual acuity) was spared. Sinewave gratings have since been used to measure visual losses in several disorders including multiple sclerosis, where they can reveal visual loss that is hidden to the Snellen test. Regan, Silver and Murray (27) described four classes of visual loss in multiple sclerosis.
These are: (1) Approximately similar loss for all spatial frequencies (Fig. 3B); (2) reduced sensitivity for high spatial frequencies only (Fig. 3C); (3) reduced sensitivity for low and intermediate spatial frequencies (Fig. 3D); (4) reduced sensitivity for intermediate spatial frequencies only (Fig. 3E). Classes 3 and 4 are not detected by the Snellen test. Classes 1 and 2 are detected by the Snellen test, but are confounded. Classes 1, 2 and 4 have been reported by several authors (4, 20, 27, 30). Fig. 4 gives two examples of Class (4), i.e. reduced sensitivity to intermediate spatial frequencies, sparing both high and low frequencies.

In some patients with MS, contrast sensitivity loss depends on the orientation of the test grating (20,21,28). This finding implicates cortical neurons, since orientation-specific neurons are not found peripheral to primary cortex in primates. This conclusion is further supported by the finding that VEPs elicited by gratings show orientation-specific delays in patients with MS (6). However, cortical dysfunction is not the only possible reason for contrast sensitivity loss. Low-frequency contrast sensitivity is lost while visual acuity is spared in glaucoma and ocular hypertension (2,24) a finding that has been attributed to dysfunction in retinal ganglion cell dendrites.

Fig. 3 brings out two further points. We have already seen that the right-hand side of the normal contrast sensitivity curve is rather steep (Fig. 2). Suppose, for explanatory purposes, that is vertical. Now we suppose that the contrast of the visual world is reduced (e.g. by early cataract). As a result, low-contrast objects might disappear altogether: On a foggy day, for example, a large apartment block might be invisible. But, as illustrated in Fig. 3A, grating acuity would be comparatively unaffected (completely unaffected in our exaggerated example).

The final point, brought out in Fig. 3F, is that monocular diplopia can produce a misleading "notch" in the contrast sensitivity function. Some subjects experience transient monocular diplopia after a period of monocular occlusion, so that the test procedure itself can create the "notch" loss (20). Other subjects experience narrow--angle (e.g. 2 min. arc) monocular diplopia that has an optical rather than a neural cause (7,19), and this form of monocular diplopia gives a particularly sharp "notch" in the contrast sensitivity functions especially when there is slight refractive error (1). The proposed explanation for the notch is that there is partial cancellation between the two displaced retinal images (20). This cancellation occurs at the spatial frequency for which a grating half-cycle corresponds to the diplopia angle between the two displaced images. For example, optically--caused diplopia with 2 min. arc diplopia displacement will cause a "notch" in the contrast sensitivity function centred on a spatial frequency of 15 cycles/deg. However, although monocular diplopia may be responsible for some of the sharp "notch" losses of behavioral and VEP contrast sensitivity curves reported in the literature, it does not explain the broader intermediate--frequency loss seen in patients with multiple sclerosis (Figs. 3E and 4), nor can it account for contrast sensitivity loss that is different is different parts of the visual field (14,20), nor does it explain cases where flicker and pattern sensitivities are differently affected (5,20,21), or cases where contrast sensitivity loss is temporally as well as spatially tuned (20,21).

So far we have discussed the sinewave grating test only. For regular clinical use the grating test for contrast sensitivity has a number of disadvantages including: (1) It is a detection test rather than, like the Snellen test, being a recognitions test. Therefore it can underestimate visual loss is amblyopia and multiple sclerosis; (2) grating contrast sensitivity loss commonly depends on grating orientation in multiple sclerosis and parkinson's disease, so that a grating test can miss visual loss unless repeated at several orientations; (3) Unfamiliarity; (4) Several of the tests are expensive.

A low-contrast chart test was designed to overcome these disadvantages, and to allow patients to be tested on a regular basis in the office or clinic. The test is as follows: (1) First Snellen acuity is measured in the usual way by means of a conventional high-contrast letter chart; (2) Then a similar measurement is performed using a low-contrast letter chart that resembles the conventional Snellen chart except that contrast is about 7% rather than 96%. The two readings are marked on a nonogram chart that immediately indicates whether contrast sensitivity is abnormal, and whether there is any retinal or neuro-ophthalmological component of visual loss hidden to the Snellen test. This quick test gives similar clinical information to the sinewave grating test (22), and picks up hidden visual loss in multiple sclerosis, Parkinson's disease, early diabetic retinopathy, ocular hypertension and glaucoma (20,21,22,24).[1]

VEP DELAY, VISUAL ACUITY AND VISUAL CONTRAST SENSITIVITY

The widely accepted protocol of Halliday et al (12,13) for VEP testing in patients with MS uses large checks of about 50 minutes of arc in side length. This large check size corresponds to a low fundamental spatial frequency of 0.4 cycles per degree.

In this study, we tested the idea that patients with a loss of visual contrast sensitivity to low spatial frequencies, sparing Snellen acuity, would show reduced VEP amplitude for large checks but not for small checks. Conversely, patients with reduced Snellen acuity and selective sensitivity loss to intermediate or high spatial frequencies would show no loss of VEP amplitude to large checks, but VEP amplitude for small checks would be attenuated.

We tested these predictions by recording pattern VEPs and Snellen acuity and attempting to link these data by measuring contrast sensitivity curves using sinewave grating stimuli.

Methods

Pattern VEPs were recorded using conventional methods. Large checks subtended 45 minutes of arc in side length and occupied a field subtending 7° (vertical x 9° and were viewed from 135 cm. Small checks subtended 11 minutes of arc in side length and occupied a field subtending 3.5° (vertical x 4.5° when viewed from 270 cm. Viewing was central and monocular. The unused eye was occluded. Visual evoked potentials were recorded between an electrode on the inion and an electrode placed anteriorly along the midline one third of the distance between the inion and nasion. An electrode on the midline one

[1] A commercial version of the low contrast charts is available from Paragon Services, P. O. Box 113, Lower Sackville, Nova Scotia, B4C 2S8, Canada.

third of the distance between the inion and nasion posterior to the nasion was grounded. The VEP latency was measured to the first positive peak, and amplitude was measured from the baseline to this peak.

Thirteen patients were tested. All had experienced one or more episodes of retrobulbar neuritis. Five had conditions diagnosed as definite MS, according to the criteria of Schumacher et al. Their mean age was 37 years (range, 24 to 52 years). Control data were obtained from ten subjects with no ophthalmologic or neurologic symptoms or signs, and a mean age of 31 years (range, 17 to 53 years). All subjects had corrected acuities of 6/7.5 or better.

Results

Figure 5A and B illustrates a dissociation between VEP findings and Snellen acuity: the right eye's acuity was lower than the left eye's (OS6/45; OD, 6/6), but VEPs to large checks were approximately similar in amplitude and latency in both eyes. The left eye's latency was 112 ms, and the right eye's was 108ms, both well within the normal limit of 126ms. This apparent conflict was reconciled by the contrast sensitivity curve shown in Fig. 5B. The left and right eyes had similar contrast sensitivities at low spatial frequencies, consistent with the VEP data, but the right eye had reduced contrast sensitivity at high spatial frequencies, consistent with decreased Snellen acuity. Small-check VEPs were also consistent with the contrast sensitivity curve, amplitude for the left eye being greater than for the right eye. Latency for small checks was 134ms for the right eye, beyond the normal limit of 131 ms, while the left eye's latency was 125ms. The latency difference between VEPs to large and small checks was 125ms. The latency difference between VEPs to large and small checks was 25ms for the right eye, well outside the normal limit of 12ms, while the difference was 13ms for the left eye. Again, this was consistent with the pattern of loss shown by the contrast sensitivity curve. In some patients contrast sensitivity was depressed over the whole range of spatial frequencies. Fig. 5C and D illustrate such a case. As expected, both small-check and large-check VEPs were attenuated in the affected eye.

In one patient visual acuity was little affected (OS, 6/7.5; OD, 6/6-2), but contrast sensitivity in the left eye was more depressed at lower spatial frequencies than at high spatial frequencies. Consistent with these sensory changes, VEP amplitude for small checks was only a little depressed in the left eye, but large-check VEP waveforms were quite different in the two eyes, the left eye's waveform being aberrant.

Comment

Two possible reasons for the reported dissociation between Snellen acuity loss and VEP abnormality in patients with MS are as follows: (1) Snellen acuity expresses a patient's ability to see fine detail (i.e., high spatial frequencies), whereas clinical VEP techniques commonly involve stimulating the eye with large checks of about 50 minutes of arc in side length (whose fundamental spatial frequency is 0.4 cycles per degree), thus assessing visual responses to coarse detail; (2) visual acuity is a measure of visual sensitivity, whereas VEP abnormality is commonly expressed in terms of delay, i.e., the transmission time of visual signals along the visual pathway. In principle, sensitivity and response delay could be affected more or less independently by MS. For example, there is evidence that temporal aspects of visual perception can be abnormal in parts of the visual field where visual sensitivity is unaffected; visual perception has been reported to be delayed and double-flash resolution to be degraded in parts of the visual field where perimetric acuity is normal.(25,26)

VEP DELAY IS A NONSPECIFIC INDICATOR OF VISUAL PATHWAY DISORDER, BUT VEP FATIGUE MAY HAVE IMPROVED SPECIFICITY FOR DEMYELINATING DISEASE

Introduction

Halliday et al. (12,13) found that large-check pattern VEPs are delayed in many patients with multiple sclerosis, and the pattern VEP test has since been widely used as an aid to differential diagnosis. The VEP test has, however, an important drawback. As pointed out by Halliday et al. (13) abnormal pattern VEPs are not specific to multiple sclerosis: many different diseases have been found to cause delayed or otherwise abnormal VEPs. Here we describe preliminary experiments whose aim was to improve the specificity of VEP tests.

Our rationale was as follows. Animal studies have shown that some demyelinated axons fatigue rapidly and are unable to conduct at high firing rates (8,9,10). Furthermore, visual fatigue can be experimentally induced in patients with multiple sclerosis (11), and is sometimes reported as a clinical symptom. We reasoned that, if the conventional pattern VEP test could be combined with a test for visual fatigue, the new test might be more specific for multiple sclerosis than the conventional VEP delay test.

Methods

Pattern stimulation was conventional. A TV stimulator (Nicolet model 1005) was viewed monocularly from 114 cm. The unstimulated eye was occluded. The checkered pattern subtended 9.7° (horizontal) x 7.6°, and the side length of the black and white checks was 45 min arc. The luminance of the bright squares was 2.7ft lamberts (9.3 cd/m^2), and the contrast of the checkerboard pattern alone was close to 100%. Subjects fixated a cross at the centre of the field. The checkerboard pattern reversed 1.9 times per second. Each reversal triggered an averaging computer whose sweep time was 300 ms. A total of 200 sweeps was summed for each trace. The amplifier bandpass was 1 to 30 HZ.

In the first experiment the checkerboard field was superimposed on a bright, rectangular area subtending 10.8° (horizontal) x 8.7° that reduced the pattern contrast to 60%. First, a monocular pattern VEP was recorded with the superimposed light steady. Then a VEP was recorded with a superimposed light flickering, but of the same mean luminance. The flicker waveform was white noise, low-pass filtered with a corner frequency of 0.9 HZ. Note that the only difference between these two stimulus conditions was that the superimposed homogeneously-illuminated area was steady in one case and flickering in the other.

In the second experiment, the fatiguing stimulus was a moving pattern, rather than a flickering, homogeneous rectangular area. First, as in Experiment 1, a monocular pattern VEP was recorded with the superimposed rectangle of homogeneous light steady. Then, by using a special-purpose electronic circuit, the superimposed rectangle of light was transformed without any change in mean luminance from a homogeneously-illuminated area to an area of checks subtending 50 min arc side length. This area of checks was oscillated from side to side horizontally by a white noise waveform that was low-pass filtered with a corner frequency of 0.1 Hz (RMS amplitude about 60 min arc), and at the same time oscillated vertically with a different noise waveform of similar bandpass and amplitude. Consequently, the superimposed pattern was in two-dimensional, pseudo-random motion. A pattern VEP was recorded under these conditions.

Results and Discussion

Of 10 multiple sclerosis patients with delayed VEPs, seven showed abnormal attenuation when the pattern-reversal stimulus was accompanied by flicker and seven showed abnormal attenuation when moving checks were superimposed on the pattern stimulus. In total 9/10 were abnormal on one or other fatigue test. One patient showed abnormal latency changes only. The one patient who showed no fatigue was the only one who had no history of clinical visual signs or symptoms.

Of 10 patients with glaucoma, four had delayed VEPs, and of 10 patients with Parkinson's disease, two had delayed VEPs. None showed fatigue. Of 10 patients with ocular hypertension, four had delayed VEPs. Two of these four patients showed fatigue to flicker. One patient with undelayed VEPs showed VEP fatigue to flicker. It is not altogether surprising that four patients with ocular hypertension had delayed VEPs even though clinical perimetry (Goldmann and Octopus) detected no neuro-ophthalmological involvement, since it is known that a substantial proportion of patients with ocular hypertension with no clinical field defects have abnormal contrast sensitivity in the peripheral visual field (14,17,18,25).

We conclude that not all VEP delays are the same. Fatigue tests can distinguish between disease that produce otherwise-similar VEP delays; none of 20 patients with glaucoma and Parkinson's disease showed fatigue, compared with the 90% of multiple sclerosis patients whose VEPs fatigued. We suggest that the standard VEP diagnostic test could be made more specific for multiple sclerosis by adding a fatigue measurement. Complete specificity is not achieved, however, because fatigue tests do not distinguish between multiple sclerosis and ocular hypertension. Perhaps the fatigue tests reveal the presence of neurons in the visual pathway that are functioning with a reduced safety factor. Presumably, functional integrity would be reduced by partial demyelination in multiple sclerosis and by persistently elevated interocular pressure in ocular hypertension while, in our glaucoma patients, neurons were either unaffected or completely non-functional.

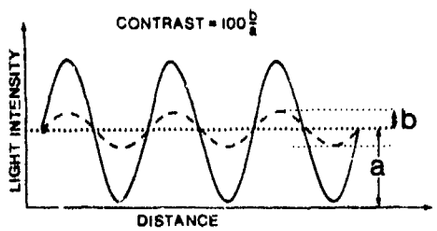


Figure 1

The variation of light intensity across a sinewave grating of almost 100% contrast (continuous line) and across a sinewave grating of 20% contrast (dashed line). Note that the mean intensity (dotted line) is the same for both gratings, independently of contrast. Percent contrast is defined as $[100(I_{max}-I_{min})/(I_{max}+I_{min})]$, where I_{max} is the maximum and I_{min} the minimum intensity. The contrast equals (100b)/a in the figure.

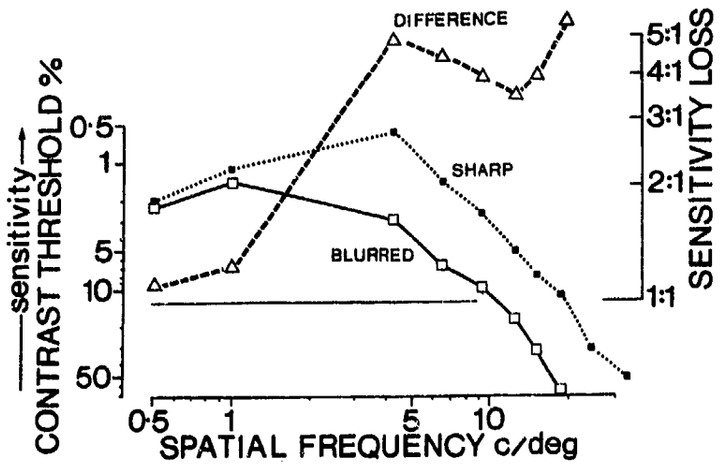


Figure 2

The normal contrast sensitivity function (dotted line) and the effect of refractive blur of 1 diopter (continuous line). The "difference" curve was obtained by subtracting the "sharp" and "blurred" curves, and shows the ratio of sensitivities before and after blurring (right-hand ordinates). Mean of 19 eyes. From D. Regan, R. Silver and T. J. Murray (1977), "Visual acuity and contrast sensitivity in multiple sclerosis: Hidden visual loss," Brain, 100, 563-579.

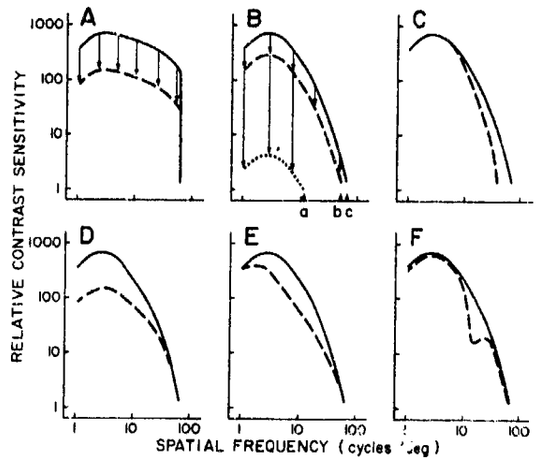


Figure 3

NORMAL AND ABNORMAL CONTRAST SENSITIVITY FUNCTIONS Panel A is a reductio ad absurdem to show that, because of the steep slope of the normal curve (here exaggerated to vertical), a moderate uniform loss of contrast sensitivity has comparatively little effect on visual acuity. B--a normal curve (continuous line), moderate (dashed line) and severe (dotted line) uniform loss of contrast sensitivity. C--selective high-frequency loss. D--Selective intermediate-frequency loss. F--sharp "notch" caused by monocular double vision.

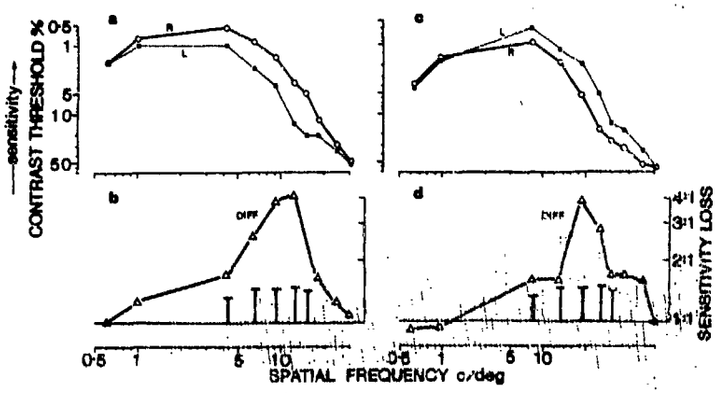
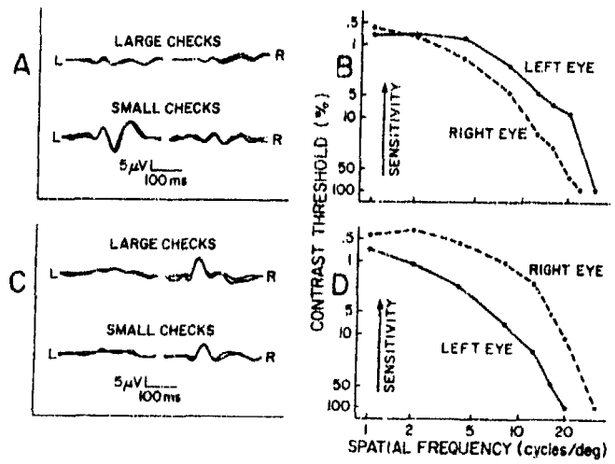


Figure 4

SELECTIVE CONTRAST SENSITIVITY LOSS FOR INTERMEDIATE SPATIAL FREQUENCIES. A--Contrast sensitivity for a sinewave test grating versus spatial frequency for the right (R) and left (L) eyes of a patient with multiple sclerosis. Panel B shows the difference between the two eyes (Diff). The heavy T-shaped bars show standard deviations for this ratio, calculated for 29 control subjects. Panels C and D are for a second patient. From D. Regan, R. Silver and T. J. Murray (1977), "Visual acuity and contrast sensitivity in multiple sclerosis: Hidden Visual Loss," Brain, 100, 563-579.

Figure 5

CONTRAST SENSITIVITY AND PATTERN VEPs IN A PATIENT SUSPECTED OF MULTIPLE SCLEROSIS the left-hand panel shows that the left and right eyes had similar contrast sensitivities for gratings of low spatial frequency, but the right eye's sensitivity was depressed at high spatial frequencies. The right-hand panel shows VEPs to large-check (45 min. arc) and small-check (11 min. arc) patterns. From D. Neima and D. Regan (1984), "Pattern visual evoked potentials and spatial vision in retrobulbar neuritis and multiple sclerosis," Archiv. Neurol. 41, 198-201.



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CORRELATION BETWEEN EEG ABNORMAL ACTIVITY AND AIRCRAFT ACCIDENTS. A LONG TERM OBSERVATION

by

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SUMMARY

During 1975-76, 64 student pilots of the Hellenic Airforce Air Academy were studied with EEGraphic protocol including activation procedures. In 13 of them, abnormal encephalographic activity was observed. During their 10-year flying career as fighter pilots, six pilots with abnormal EEGs were involved in 10 aircraft accidents due to pilot error, while only 3 pilots of the 51 with normal EEG were involved in 4 accidents due to pilot error.

INTRODUCTION

- Electroencephalograms (EEGs) have been used since World War Two as a useful auxiliary tool for the selection and evaluation of pilots.

- From 1940 to 1943, Forbs, Gibbs, Davis, Adrian, Williams and Thorner studied a large number of candidate pilots and aircrew EEGs and assessed the frequency, the potential height, the presence or absence and the distribution of paroxysmal discharges.

- Later, Buchtal and Lennox (1951-52) of the Danish Airforce, Pickold (1955-57), Gastant (1960), Roboulet and Soussen (1958), Lafontain and Laplane (1963) of the French Airforce, Von Wulffien of the Danish Airforce, Carlo-Serra (1959) of the Italian Aeronautic Academy, supplied a lot of information on the correlation of EEG bradyrythmic manifestations and pilots flying performance.

- Sam Jacobsen (1957) studied EEG in pilots during simulated regular flights and during flights under stress and collected remarkable data on EEG activity during flight.

Johnson (1962) described the disregulatory role of helicopter flyers. John Scott (1964) in Canada, O'Connor in England, William King and Liski (1974) in the USA and Oberholz et al (1975) in West Germany stressed the value of EEG in selection and evaluation of flying personnel.

METHOD

- Subjects. During 1975-1976, a total of 64 student pilots of the Hellenic Airforce Air Academy participated in this study. All were male and their ages ranged from 18 to 22, with an average age of 21 years.

As candidates for the Air Academy all of them had been subjected to a detailed clinical and laboratory examination as well as neuropsychiatric and psychological evaluation (MMPI, Wesler, etc), within the standard selection procedure. An EEG was not part of the neuropsychiatric evaluation, because of the large number of candidates (3500 applicants for 100 posts).

All students who participated in this study had similar socioeconomic and educational backgrounds. None of them had a personal or family history of neuropsychiatric disease.

- Apparatus and procedure: A 16-pen EEGraphic infection monitor (Elema Sonader) was used with 10-20 application system of the electrodes. Electroencephalographic study consisted in:

a. Wakefulness EEG

b. Sleep EEG (drug induced, Nembutal caps 100mg)

c. EEG after sleep deprivation for 26-32 hours

Cooperation of the student pilots was very good.

All EEGs were evaluated separately by three neurologists with rich experience in EEG reading, and were classified in two groups: A and B.
In group A were classified EEGs with one of the following patterns:

a. Totally normal EEGs

b. EEGs with rare mild theta slow waves bilaterally without accentuation and without any change during hyperventilation or after sleep deprivation.

c. Sleep EEG with expected patterns of diffuse slow activity, vertex waves, and sleep spindles.

In group B were classified EEGs with one or both of the following abnormal findings:

a. Wakefulness EEG showing mild to moderate sharp or sharp form slow activity with hemispheric preponderance and with or without intensification after activating procedures (hyperventilation, photic stimulation, sleep deprivation).

b. Sleep EEG showing clean sharp discharges with hemispheric preponderance.

All 64 student-pilots graduated successfully as fighter pilots and for ten years were flying F-104, Mirage F-1C, and F-4. They all had their regular annual check-up in our Aeromedical Center and none had any major health problem.
During the 10 year period, 9 of the 64 pilots studied were involved in 14 aircraft accidents due to pilot error, none of them fatal.

- Results. Of the 64 student pilots, 51 had EEGs that were classified in group A (normal or variations of normal) while 13 had EEGs with abnormal findings and were classified in group B as follows:

7 showed abnormal EEG activity during wakefulness

2 showed abnormal patterns after sleep deprivation

1 had abnormal EEG activity during drug induced sleep

3 showed abnormal patterns after both sleep deprivations and drug induced sleep

- Comparison of the two groups regarding involvement in aircraft accidents.

Of the 51 pilots of group A, 3 (5.9 percent) were involved in 4 aircraft accidents due to pilot error. Of the 13 pilots of group B, 6 (46 percent) were involved in 10 aircraft accidents due to pilot error (see table).

- Comparing the two groups, we observe that the percentage of pilots involved in aircraft accidents is 7.8 times higher in group B. What is more significant is the involvement of group B pilots in multiple accidents (six pilots involved in 10 accidents) in comparison to group A pilots (three involved in 4 accidents).

- From the above observations it seems likely that detailed EEGraphic monitoring of aircrew may have prognostic value for flight safety. Similar correlation between abnormal EEGs and increased aircraft accidents was made by Lennox and Buchtal (1951-1955) who observed Danish pilots for 9 years and found a threefold increase in fatal aircraft accidents due to pilot error in those with "abnormal" EEGs.

- In 1962, Ades Hanlou studied U.S. Navy pilots and found that those with abnormal EEG findings were clearly involved in more accidents due to pilot error.

- Sam Jacobsen reports that all Norwegian pilots with bradyrythmic abnormalities in their EEGs were involved in their career in at least one accident due to pilot error.

- In 1974, William, King and Liski evaluated with EEG 713 U.S. pilots for space missions. 90 pilots had abnormal EEG findings, 33 percent of them (30 pilots) were involved in one major aircraft accident in an 8-year period.

- With the aforementioned data one is confronted with the question, whether or not EEGraphic study of pilots should play a more decisive role both in initial selection and in medical evaluation of the flying status of pilots.

- In the Hellenic Airforce, all first year student pilots are screened for EEG abnormalities. In case EEGs repeatedly show spike-wave complexes or focal spikes in otherwise healthy student pilots, they are disqualified without further investigation. In case we observe other EEG bradyrythmic abnormalities in EEGs of student pilots, we apply the following additional investigation protocol:

a. EEGs with activation procedures (sleep deprivation, pressure of carotids, drug induced sleep, and application of rhino-pharyngeal electrodes.

b. Detailed neuropsychiatric evaluation.

c. Brain CT scan.

d. Detailed cardiological evaluation.

e. Investigation of Carbohydrate intolerance.

- If EEG bradyrythmic abnormalities after the activation procedures take a sharp form or are intensified, then we disqualify the student pilot. If there is no change, the student pilot continues his training and is reexamined after one year.

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DETECTION OF LATENT EPILEPSY IN AIRCREW CANDIDATES.

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SUMMARY

Epilepsy is a common medical disorder, with a prevalence of 0.5%-0.8%, and is the commonest cause of accidents due to medical incapacity in drivers.

Although imperfect, the Electroencephalograph(E.E.G.) is useful in the detection of a latent predisposition to epilepsy, and is recommended as an obligatory part of the initial medical examination of candidates for military aircrew.

Epilepsy is the commonest medical disorder likely to cause sudden, unheralded total incapacity. In certain occupations, for example professional drivers or pilots, the occurrence of an epileptic seizure would almost inevitably lead to an accident with risk of loss of life and material loss.

In a study of 1605 non-fatal accidents[1] reported to the police in which a medical disorder affecting the driver was considered to be the cause, 38% were due to a witnessed epileptic seizure, and a further 23% were caused by a sudden loss of consciousness of uncertain aetiology. An associated follow-up study of this latter group revealed that a large proportion were subsequently diagnosed as suffering from epilepsy. Insulin dependant diabetes mellitus(17%), all heart disorders(10%), and stroke(8%) were other important related medical disorders.

Raffle[2] studied all incidents involving London Transport drivers from 1953 to 1977 in which a medical condition was considered to be the cause of the incident. During this period he identified 127 incidents, in 59 of which an accident occurred. Acute ischaemic heart disease(34) was the commonest cause of an incident, followed by epilepsy(24), loss of consciousness of uncertain awtiology(14), syncope(21), transient cerebral ischaemic attack(6), hypoglycaemia(5), stroke(4). However when he looked at those incidents which caused an accident, when it is reasonable to assume a more rapid, possibly unheralded, onset and more severe incapacity, out of a total of 59, epilepsy was the commonest disorder(17), followed by loss of consciousness of uncertain aetiology(10), a combined total of 27(46%). Other conditions were syncope(12), acute ischaemic heart disease(8).

Lennox-Buchtal et. al.[3] studied the correlation of Eletroencephalographic (E.E.G.) findings with the crash rate of military pilots of the Royal Danish Air Force. Where the crash was attributed to pilot error, those with an E.E.G. abnormality, especially paroxysmal changes, were three times more common than those with no E.E.G. abnormality. It has been demonstrated that those with petit mal epilepsy show a significant deterioration in performance during sub-clinical spike-wave E.E.G. paroxysms[4,5,6,7] and it is possible that the occurrence of similar covert brain events could cause a momentary alteration of conscicusness which, although undetectable by an observer, could be a serious handicap in the performance of an exacting motor task such as driving, or piloting a high performance aircraft.

Quoting a U.S.A.F. Inspection and Safety Centre Report of inflight incapacitation(1963-1970) King and Liske[8] reported that syncope was most common(11), followed by epileptic seizures(6) and coronary heart disease(4). Rayman[9] reported on U.S.A.F. pilots flying with a medical waiver who were involved in an accident. Between 1962-1970 47 such accidents were identified and in 33 of these a medical disorder was considered a contributory factor. Most common were refractive errors of the eye, but next most common were disturbances of consciousness. Rayman also reported five cases of a witnessed epileptic seizure in U.S.A.F. pilots which occurred during flight.[10]

It is clear from these studies that epilepsy, or other causes of sudden loss of consciousness, is a common medical cause of an accident.

The incidence of epilepsy(including first seizures) in the young adult population has been found to be 30-50 per 100,000 per annum[11,12] with an increased incidence in childhood and old age. However in a defined population over a longer period those predisposed retain a predisposition, and therefore the cummulative incidence more accurately reflects the population at risk. This would be nearer the prevalence rate of epilepsy(0.5%-0.8%)[20].

If it is agreed that epilepsy is the commonest medical disorder leading to an accident or sudden loss of control, and that it is a relatively common disorder, by what means can those with a predisposition be detected? Unfortunately there is no infallible investigation, but certain symptoms indicate an increased risk in an individual. These include seizures after the age of five, or a past hsitory of penetrating or severe head injury, cerebral abscess, intracranial haemorrhage or haematoma, sub-arachnoid haemorrhage or craniotomy.

Although the E.E.G. can identify some persons with abnormal paroxysmal brain dysfunction identical to that found in those suffering from epilepsy, it is not an efficient method of identifying all those with a latent predisposition. In known epileptics only 50% of those with major tonic/clonic generalised epilepsy show spike-wave paroxysmal acitivity on an interictal record, whereas 70% of primary generalised epilepsy and 85% of classical petit mal epilepsy show these changes on the interictal record. The large number of false negatives means that the E.E.G. cannot exclude the possibility of a predisposition, and it must be accepted that a number of these will not show an abnormality on a screen E.E.G. However when paroxysmal spike-wave activity is seen it must be assumed that in that individual there is a disturbance of brain function similar to that found in those with

epilepsy, and that that individual must be predisposed, to some unknown degree to epilepsy.

There have been a number of studies of E.E.G. in healthy young adults who were usually recruits for military aircrew[13,14,15,16]. In the one study in which intermittent photic stimulation was omitted in 60% the prevalence of spike-wave paroxysms was 0.12%[13]. However in those studies where photic stimulation was included there is a uniformity of 0.4% to 0.6%[14,15,16]. Over the last ten years in the Royal Air Force(1976-1986) 3837 consecutive E.E.G. recordings have yielded a total of 30 with spike-wave paroxysms(0.78%, Table 1). These figures are identical to the prevalence of epilepsy in the general population.

There is a very strong clinical correlation between epilepsy and generalised or focal spike-wave paroxysms on E.E.G. A small number of persons who are known to show spike-wave paroxysms never have a seizure, but the precise number is unknown. Spike-wave paroxysms correlate with clinical seizures in those suffering from epilepsy, many of whom show similar E.E.G. paroxysms in the interictal periods.

A number of studies have attempted to assess the incidence of seizures by follow-up of subjects who show spike-wave paroxysms on E.E.G. but who have had no history of seizures[8,13,17,18,19] Table 2. These studies have all been hampered by small numbers and incomplete follow-up, and our experience in the Royal Air Force is similar. However, of these studies an accumulated incidence of 2-5% was found in five studies, with only one study showing no seizures[17]. These figures are likely to be the minimum incidence, and are significantly higher than the general population. There is no means by which we can distinguish those who will suffer a seizure, but it seems reasonable to assume that there is an increased risk of seizure in all who show these paroxysmal changes, and that the various physical stresses of flying may precipitate a seizure in a predisposed individual.

For this reason it is recommended that an awake E.E.G., with photic stimulation, should be included as part of the initial medical examination for all military aircrew, and if focal or generalised spike-wave paroxysms are seen that person should be considered at risk for epilepsy and assessed unfit for aircrew.

TABLE 1

PREVALENCE OF SPIKE-WAVE ON E.E.G.
HEALTHY AIR FORCE RECRUITS

	No.	%
Le Tourneau (US Navy)	36/28658	0.12
Oberholz et.al.(German AF)	3/1239	0.4
Bennett (1967 USAF)	8/1332	0.6
Richter (1971 USAF)	14/2947	0.5
R A.F.	30/3837	0.78

TABLE 2

CUMULATIVE INCIDENCE OF SEIZURES
IN FORMERLY HEALTHY SUBJECTS WITH E.E.G. SPIKE-WAVE

		%
King & Liske (1974)	1-30	3.33
Everett & Akhavi (1982)	0-14	0
Le Tourneau (1973)	1-31	3.26
Robin et.al.	1-20	5.00
Zivan & Marsan (1968)	1-47	2.12
R.A.F.	1-30	3.33

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DISCUSSION

KRIEBEL, GE: Dr. Merry pointed out the importance of photic stimulation. I would like to ask why you don't use it? Is it because you are just looking for jet pilots? During the past year, we had 5 helicopter pilots who had trouble with a stroboscopic effect that was induced by the rotor blades.

STAVROPOULOS, GR: (Reply indecipherable)

HICKMAN, US: Because of sensitivity, the EEG is not very effective in ruling out the possibility of epilepsy. When you perform EEGs, what is your threshold of abnormality for a pilot applicant? Do you use the Mayo Grade, or do you use some other categorization in order to not have such terrible non-specificity?

MERRY, UK: I don't use the Mayo Grade strictly, although my criteria are very similar to that grading. We don't grade them numerically; but I try to be specific only in the occurrence of spikes in the paroxysmal events, because this seems to correlate much more closely with the predisposition to epilepsy. The problem with non-specific paroxysmal discharges in the EEG is that they don't correlate so well with predisposition to epilepsy, although they are found in a proportion of the epileptic population. They are also found in quite a high proportion of normal people who never have a seizure, such as migraine sufferers; and, in particular, the age group -- 18 years — that we are looking at, whose central nervous systems are often not that mature electrophysiologically. Anyway, one sees quite a high proportion of paroxysmal features in "young" EEGs, so I regard as abnormal only those that show spikewave discharges, either focal or generalized. Everything else, apart from using activation methods to see if it does bring them up -- sometimes it does -- would be passed as normal. Whether or not we should be doing this is open to suggestions, but at the moment, we do pass everyone else for flight training.

ABRAHAM, UK: Could I ask both speakers whether they used one or two periods of hyperventilation in their activation procedure? If you use the second one, you are more likely to elicit abnormalities with very little extra difficulty; you just get a few more minutes of recording.

MERRY, UK: No, we only do one period of hyperventilation.

STAVROPOULOS, GR: We also only use one period.

OFFENLOCH, GE: When we did studies on meditating subjects, we were quite astonished to see a high proportion of paroxysmal activity. We did not know whether it was a pathological or a pathophysiological variant, so we asked leading authorities in the EEG field in Germany, and we came to the conclusion that we should regard it as a physiological variant. Have you the case history of the special pilot student who showed spike and wave activity in one of your slides? What happened to him later on; perhaps, he was young and the activity stabilized?

MERRY, UK: That was a candidate for pilot training who had spike and wave activity on photic stimulation. At rest, he had a non-specific paroxysmal tendency. My follow up on these people is very difficult and incomplete. They often leave and are not very pleased with my having taken them away from flight training. I have written to them, but they seldom reply. Some of them stay on in the Royal Air Force in "ground" branches. Of that group, I know of no other disturbance of consciousness or a seizure, apart from the one I mentioned. We do find those non-specific paroxysmal events in a reasonably high proportion of young people. Of course, one of the problems of our own making is that we take the EEG when the person is very tired having been up all night doing various activities. As soon as they sit down in the EEG chair, they either fall asleep or become drowsy, which, I feel, is quite a good activating measure if you want to look specifically for spike and wave discharges. However, when you are looking at slow wave changes and other activities, then it is very difficult to interpret them.

THE AUDITORY EVOKED RESPONSE IN MILITARY PILOTS

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SUMMARY

This study relates to the effect of G forces, through an aerobatic flight profile without G suit protection, upon twenty military pilots with varying flight experience. The auditory evoked response during rest showed significant differences in Wave V and also in the I-V interval. Immediately following the flight, differences were observed in Wave III. These results suggest the importance which this electrophysiological method may have on measuring accumulated fatigue. Immediate fatigue implies complex mathematical problems presently under study.Simultaneously, hemorheologic, hormonal and biochemical studies have been conducted for a better understanding of the physiological effects of fatigue. Though it is recognised that the test population is relatively small (20 pilots), an expanded study is underway in order to compile more conclusive data.

INTRODUCTION

Four years ago, some theoretical concepts were stated about the pathology caused by whole-body vibration stress (2,5,7,14).Follow-on studies demonstrated compatible clinical otoneurologic and behavioral disturbances (5,6,8,15).

The study of the Brainstem Evoked Potentials (BAEP) showed changes in relation to the control population (5,16). However, the variability of the responses was too large, and an evaluation and interpretation of significant components was difficult and inaccurate (16). Besides, variability of BAEP of the controls presented similar problems (5). This difficulty was overcome when dealing with taxonomic distances (4). Using clustering algorithms and multivariate analisys it was possible to accurately discriminate occupational exposure to whole-body vibration of subjects from the control population (3,17).

Moreover, four pilots were tested before and after a ground attack mission of 25 minutes duration, and significant differences were found during rest, between pilots with more than 2000 hours of operational flight and pilots with less than 2000 hours (10). The mission flight also induced changes of the I-V interval. In one pilot, the difference was 640 ms. The vibration exposure was found to be the major factor responsible for this changes. Von Gierke (31) had argued on the importance of G forces in this results. From these discussions, an attempt was made to comfirm the results in a larger population of military pilots in order to comfirm the existence of delays in the neurosensorial waves of the auditory responses before and after flight. This paper describes and discusses the ensuing results.

MATERIAL AND METHODS

The BAEPs were recorded from 20 pilots aged between 19 and 40 years (Table I): five pilots with more than 1500 hours four of them belonging to the aerobatic team "ASAS DE PORTUGAL" (G1), six young pilots with less than 500 hours (G2), and nine student-pilots with less than 150 hours (G3).

G1		G2		G3	
QY	Age	QY	Age	QY	Age
3	40	1	26	7	21
4	39	2	22	10	21
5	34	8	25	12	22
6	33	9	25	14	21
11	26	13	23	15	22
		17	25	16	24
				18	19
				19	24
				20	21

Table I - Ages of pilots

All of them had been submited to a previous annual medical examination with emphasis on the absence of any kind of otoneurological abnormality. The recordings were carried out while asleep and fasting after a weekend without alcohol consumption. Prior to the registry of BAEP, they were submitted to a physical examination, including blood pressure, ECG, and blood and urine samples for hemorrheologic, biochemical and hormonal studies. The following day, they were successively submited to an identical flight of similar succession of aerobatic maneuvers: tonneau, looping, immelman and lazy eight, always over 1500 feet of altitude, at accelerations from -1 to 5 G. The plane was an unpressurized T37; aircrew did not used G suits and they occupied the right seat as passengers. All subjects knew previously all of the maneuvers of the flight profile. When the plane landed, each pilot was taken to the examination room. The procedures used the day before were repeated less than 5 minutes after landing. BAEP registry was carried out in a non-sound proof and non-electrically shielded room. The noise levels and electrical pattern of the chosen room were evaluated by two specialists and considered as satisfatory. Tests of BAEP were previously performed in four males 18, 23, 40, and 47 years old, respectively, in laboratory conditions, and in the room used in the field study. A Madsen ERA 2250 was used with the standard equipment.

BAEP registry conditions were as follows:

. analysis time	10 ms
. sweep rate	20 pps
. lower frequency	150 Hz
. higher frequency	2000 Hz

A "Click" of 100 μs, that was ipsilateral and of alternating polarity was used. The action current was recorded from the vertex and mastoid with tin cup AgCl electrodes, using EEG current gel. The positive elecrotode was on the vertex, the reference electrode on the ipsilateral mastoid and the ground electrode on the contralateral mastoid. The conditions were exactly the same for all the recording procedures. Attempts were made to identify BAEP Waves I, II, III, IV and V in each record (Fig. 1), and the latencies of each Wave and the interpeacks I-III, III-V and I-V were measured. Special attention was given to the presence of additional components (26).

The mean values and standard deviations for the different latencies and interpeaks were calculated for each pilot group (1,9,20,25). To test for the significance of the differences among the three groups, the ANOVA method (29) was applied to search for variations on main effects: 2 way interactions (group and rest-stress, right-left ear and group, right-left ear and rest-stress), and 3 way interactions (group, rest-stress, right-left ear). To discriminate between the clusters, numerical taxonomic methods were used, namely, clustering algorithms and principal components analysis (19, 28,29,30). The software packages used in this study were the SPSS and NTSYS as implemented in ICL computer system of the Centro de Cálculo Científico, Instituto Gulbenkian de Ciência. The software conversion was achieved by one of the authors.

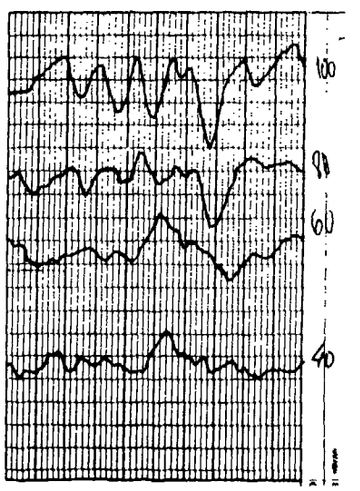

FIG 1 - The auditory evoked response in pilot 2 at rest.

The column ion exchange cromatography method was used in the study of total cathecolamines and 5-hydroxy-indolacetic acid.

RESULTS

The statistical values and tendencies of total cathecolamines and 5-hydroxy-indolacetic acid are presented in Table II

	G1	G2	G3	F
Cathecolamines	↘	↘	↗	S 0.01$ G 0.851 2 0.574
5-HIDROXY-INDOLACETIC ACID	-----	-----	-----	S ----- G ----- 2 -----

Table II - Changes in cathecolamines and 5-hydroxy-indolacetic acid under aviation stress.

The cathecolamines values are not statistically significant. The flight induced a decreasing tendency in G1 and G2, but a tendency to increase was observed in G3. 5-hydroxy-indolacetic acid was not found in any of samples.

The values of the latencies and interpeacks taken in the laboratory, and repeated in the room used in this study, were quite similar (P 0.01).

Changes and interactions of the values among the groups, both ears at rest, and after aviation stress, are presented in tables III and IV.

	F	Sign.
Wave I	2.215	0.122
Wave II	0.322	0.999
Wave III	6.680	0.003
Wave V	7.772	0.001
Int. I-III	1.760	0.178
Int. III-V	2.212	0.115
Int. I-V	4.133	0.020

Table III: The auditory evoked responses at rest

	F	Sign.
Wave I	0.912	0.999
Wave II	0.044	0.999
Wave III	6.374	0.013
Wave V	0.422	0.999
Int. I-III	2.692	0.102
Int. III-V	1.263	0.264
Int. I-V	0.037	0.999

Table IV - Aviation stress-induced changes auditory evoked responses

Waves I and II did not present significant differences between the ears, no variation was found among the groups, and the values were not influenced by flight stress.

Wave III presented significant differences among the groups and between both ears, and was influenced by flight.

Wave V was significantly different among the groups and the ears, but was independent of this kind of aviation stress.

The interval I-III does not present any significant difference as induced by any source of variation.

The interval I-V presented a significant difference among the groups, but was not altered by aviation stress nor did it show any difference between the ears.

In all of study, the 2-way and 3-way interactions were not statistically significant.

No additional components were observed (26). One G1 pilot, one G2 pilot and two G3 students-pilot showed important delays in all of the waves. The delays had the same magnitude in each of these pilots. They were otoneurologicaly reevaluated by means of impedancimetry and the new examination revealed Eustachian tube dysfunction. The differences among the Waves, I-II, II-III, III-IV, and IV-V, and the interpeaks I-III, III-V and I-V were statistically determined.

In a manner similar to that conducted in two previous papers (4,17), following standardization by variables of the taxonomic matrix, the taxonomic distance, DT, was used as a coefficient of dissimilarity between two OTUs (observation taxonomic units).

Since DE2 is the Euclidean distance between two OTUs squared, the taxonomic distance is defined as:

$$DT = \sqrt{\frac{DE2}{n}}$$

Where n is the number of pairs of variables observed in the two OTUs. Subsequently, the groups or "clusters" of the more similar OTUs was defined by the UPGMA method (unweighted pair-group method using arithmetic averages). The cophenetic correlation obtained for the analysis group Model I involving 8 variables, 4 for each ear, I-II, IV-V, I-III and I-V intervals, was 0.74. Based on the phenogram,it was noted the presence of 3 broad groups: one consisting of 3 pilots from group G1 and 1 from group G2 (4.6,11 and 8), another consisting of 3 pilots from group G3 and 1 pilot from G1 (10,14,18 and 3) and another consisting of 5 pilots from G3 and 3 pilots from G2 (7,15,16,19,20 and 9,13,17), (Fig.2).

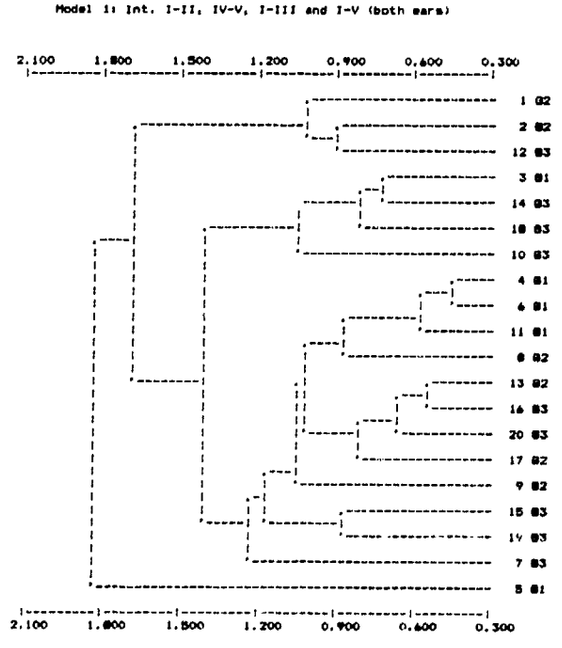

Figure 2. Phenogram 1

The cophenetic correlation obtained for the analysis group Model II involving the intervals II-III, IV-V, I-III and I-V in both ears, was 0.78. Based on the phenogram, it was noted that there were 3 broad groups: one consisting of 3 pilots from group G1 and 1 from G2 (4,6,11, and 17), another consisting of 3 from G3 and 1 from G1 (10,14,20 and 3) and another consisting of 2 from G2 and 2 from G3 (8,13 and 16,18). Pilot 5 from (G1), and student-pilots 15 and 19 from G3 were too distant from all the groups to be relevant (Fig. 3). The first small cluster we observe in both phenograms consisting of 2 pilots from G2 (1 and 2) and 1 from G3 (12), distant from the other groups, is a very interesting feature.

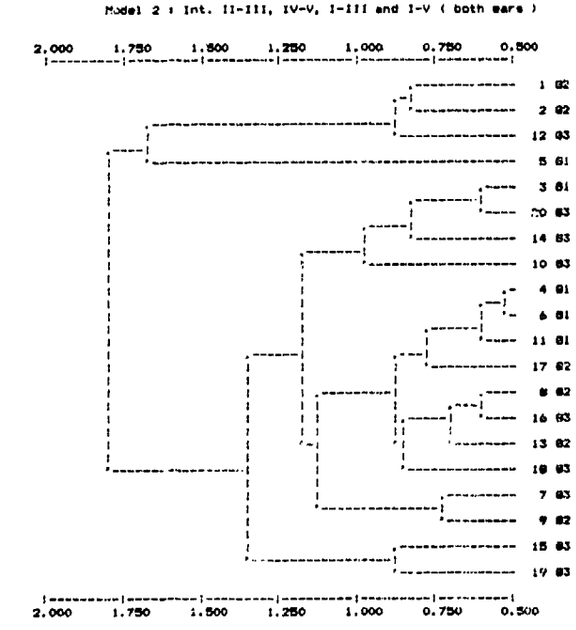

Figure 3. Phenogram 2

Pilot 5 (G1) died 17 months later in a T37 crash when performing an aerobatic maneuver.

Pilot 1 (G2) is grounded in definitely with neurophysiological problems.

Student-pilots 7 and 14 (G3) were eliminated from pilot training.

Pilot 12 (G3) died 19 months later in a car accident. He was the driver, and his colleagues informed that he had had numerous similar previous accidents.

DISCUSSION

The procedures to minimize the error factors in this field study led to apparently very interesting results.

The conditions for the stress flight, the unpressurised cabin, the absence of G-suits,and the procedures avoiding any possible exogenous or endogenous causes of emotional stress were satisfatorily achieved.

The influence of stress hormones modulating synaptic neuropeptide release was neutralized. The catheccolamine values were not significant. The student pilots group showed a discrete increasing tendency of levels while having knowledge of all the flight profile they would support but the values are not statistically significant.

Wave V is an important parameter when analysing the so called accumulated aviation fatigue. It was also influenced by the ear conditions. The interval I-V, which is independent of ear conditions, is the best parameter to evaluate quantitatively the accumulated fatigue.
These results confirm the previous observations that were made in four pilots (10).

The flight stimulus used seemed to be a small stress. Even in this conformity, the Wave III is the most important parameter to evaluate the immediate aviation fatigue.

The clusters displayed in the phenogram appear to be a very important factor in discriminating between the different pilot populations. It is natural to find pilots from G2 and from G3 with less than 500 and 150 hours of flight experience, respectively, to share a common and larger cluster with close taxonomic distances. Pilot 3 from G1 was the AFB commander with a very small flight activity. The subsequent death of the two pilots, with such large distances from all of the groups as evidenced in the phenograms, could be a dramatic warning about the importance of BAEP in decisions concerning flight status. Pilot 5, G1, had more than 2500 hours as a T37 instructor and as a member of the aerobatic team.

Another relevant figure was the incapacity of three students to successfully complete the flight training. An interesting feature in both phenograms is the positions of two pilots both from G2 together with 3 from G1 demonstrating perhaps some kind of precocious aging or may be simply, some normal borderline values. Considering the large individual variation, and the absence of previous BAEP data about these pilots, it may be urgent to routinely implement the registry of BAEP for all of the young volunteers for military pilot training. Other professions must be also considered. The best evaluation of accumulated fatigue must be throught individual follow up of BAEP studies.

BAEP was first described in 1970 (12). The major applications of this non-invasive method are: in audiology for differentiating the various types of hearing loss and measuring thresholds, and in neurological practice, for detecting even minor lesions in the upper part of the brain-stem (21).

The large variability of BAEP registry in normal subjects is a very important obstacle in analysing borderline values (21,23). Cluster analysis of evoked potentials was the method proposed by Schwartz et al. (27). In 1984, Reinis et al.(24) also applied cluster analysis to the study of visual cortical evoked responses dealing with Euclidian distances. In 1984, our group presented a paper applying cluster algorithms but with the exception that it dealt with taxonomic distances with promissory results. Reinis et al. pointed out that this method could be a useful tool in the analysis and classification of a large number of evoked responses. The final statement of these authors, "... furthermore, such clustering may eventually reveal some of the physiological mechanisms ...", is an interesting predictive assumption. In 1985, Palminha et al. (22) and, in 1986, Marvão et al. (18) using taxonomic distances, established some new concepts about neonatal myelinization steps, behavioral changes occurring at the age of 9 months, and predicting major difficulties which must be overcome in newborns suffering from different kinds of delivery stresses.

The waves and interpeaks that were found in this study and which changed with aviation fatigue, were the same ones observed in vibration stress and in numerous different hypoxic situations. The speculations made 4 years ago about the whole-body vibration stress, the systemic Raynaud - like phenomena and the consequent hypoxia are still a good model for our research program in aviation fatigue (2). The hemorrehologic parameters found in this study confirm this hypothesis.

There are numerous common features in different kinds of stress. The study of physical training and of the aging procces will provide important clues for the understanding of pathophysiology of fatigue.

The successful application of cluster algorithms and multivariate analysis to the study of BAEP in a larger population may permit, the establishment of new selection standards with which tc evaluate accumulated fatigue and to define mission profiles,to measure residual capacities, and even to confirm incapacity for flight duty or other demanding activities.

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14. Abstract

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The papers addressed a variety of topics including: (a) the computer-aided imaging of background and evoked brain electrical activity, (b) the new technique of magnetoencephalography, (c) the functional significance of P300, CNV, and EEG events as indices of behaviour, (d) the use of physiological measures for indexing in-flight and simulator mission effectiveness; and (e) the effects of acceleration, drugs and diseases on CNS activity.

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