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19. ABSTRACT (Continue on reverse if necessary and identify by block number) This report describes the work accomplished on the University Research Initiative program entitled "Cognitive and Neural Bases of Skilled Performance." The activities of the neuromagnetism laboratory are described. These include a comparative study of electrical and magnetic P300 related to visual and auditory stimuli. The results results obtained using an odd-ball paradigm were inconclusive, but a new procedure was developed which uses all trials rather than trials on which only infrequent events lead to P300 responses. It is tentatively concluded that different source configurations underly P300s associated with different modalities, and possibly also different tasks within a modality. In the previous report we described a new method for analyzing spontaneous					
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brain activity in the alpha bandwidth. We extended this method to other bandwidths and conducted some of the first studies of the modulation of spontaneous brain activity, independent of the evoked response, during the performance of high-level cognitive tasks. Research based on this methodology is now being conducted under the aegis of a separate grant. In the course of this report period we conducted a study using the 14-channel neuromagnetometer at Bellevue Hospital. It was found that the increase in amplitude of the auditory N100 with ISI is not the same in the two hemispheres. The left hemisphere tends to display a monotonic increase in N100 amplitude with ISIs up to 16 sec, while the right hemisphere is not differentially affected by ISIs in excess of 4 sec. In a collaborative effort with the Los Alamos National Laboratory we found that different components of auditory evoked responses originate at different locations in the two hemispheres. Also, in a study of visual responses to equiluminance color stimuli we found the first evidence for separate sources for the cardinal directions in color space. In a study of visual spatial attention we found enhanced responses to stimuli located at positions on which attention was focussed. Unlike the early effect of attention observed in the auditory domain, this effect occurs about 200 msec after stimulation and the source appears to be near the boundary between the occipital and parietal areas. We could not find a differential effect of divided attention, which may therefore be fundamentally different from focussed spatial attention.

*no units: Electric response
200 msec after stim. (1977)*



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INTERIM SCIENTIFIC REPORT**Cognitive and Neural Bases of Skilled Performance:****A UNIVERSITY RESEARCH INITIATIVE**

by Lloyd Kaufman, Principal Investigator

New York University

Introduction

This report, which is submitted in accord with the requirements of Contract No. F49620-88-C-0131, between AFOSR and New York University, describes the scientific progress made up to the present time (May 1989) on this project, and provides a Forecast of activities to be completed during the remainder of this final year.

The original proposed project, which began in September, 1986, had four basic components. These included the improvement of university facilities to permit the conduct of advanced research that would be in the interest of the Department of Defense, the actual conduct of such research, the training of students and postdoctoral personnel to conduct the research, and the coordination of research and training efforts with Department of Defense laboratories which would be to the mutual benefit of the University and the DoD. Hence, this report describes our progress to date in the scientific areas.

One of the goals of this project was to enhance the instrumentation and technology involved in measuring and analyzing the brain's magnetic field so that it would become possible to study the pattern of brain activity involved in various aspects of human performance. A special emphasis was placed on the way in which workload affects the activity of the brain and, ipso facto, the performance of the human operator. An equally important goal was the design and conduct of meaningful substantive experiments concerning aspects of brain activity underlying processes such as attention and its deployment in various tasks. The Following section reviews our accomplishments in all of these areas over the term of the project.

Summary of URI Progress

The performance of a complex task, like piloting an aircraft or diagnosing the cause of a malfunction in a complex system, depends strongly upon cognitive skills. Our knowledge of the mechanisms of cognition (which includes attention, memory, learning, decision making and perception) is very limited, and this constrains our ability to assess and predict performances in complex tasks. The aim of our present URI program was to contribute to this basic knowledge by encouraging prominent researchers in these areas to find common foci so that their efforts mutually reinforce each other. One such focus that transcends the traditional boundaries of the individual disciplines comprising *cognitive science* is that of the role of the human brain.

Our understanding of the activity of the brain and how it relates to cognition and performance is sharply limited by the brain's complexity as well as by its inaccessibility. Any means for improving access to the brain's activity and for discovering the relation of this activity to cognition is bound to be of interest to a multidisciplinary group of

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researchers and their students.

Studies of the brain should clarify the nature of otherwise unobservable processes that underly performance. Without this, cognitive science is left with untestable theories of underlying mechanisms. The field abounds with examples of ongoing arguments. For example, does the machinery of the visual system involved in the perception of real objects play a role in the formation and processing of mental images? This question is of concern to many authors, but recent advances in the neurosciences are making it possible to arrive at an objective answer to the question. As to the relevance of the question, it is worth noting that evidence indicates that ability to "visualize" situations has an effect on objective measures of certain perceptual-motor tasks. Major steps are being made towards answering questions about factors underlying high-order cognitive processes. The URI program at NYU has been contributing to this program through its work on cognition, perception, and in neuromagnetism. The latter technology is providing a unique window into brain function. Before the full value of this new technology could be realized, however, substantial progress had to be made in the technology of functional brain imaging as well as in the development of new approaches to employing this technology in the study of brain and performance. As a result of nearly three years of work in the URI program, we are now ready to make meaningful steps forward. However, the progress has been so rapid that the outside observer is bound to be confused by the types of activities involved in paying the groundwork. This Interim Scientific Report is designed as a means by which a reviewer can become oriented within this new field, as well as a document describing at least the major landmarks that led to the present state of the field. At the present time we are able to deal effectively with issues of fundamental importance to cognitive psychology. Some of this work is being conducted under the aegis of another AFOSR-supported project, but this work had its origin in the now terminating URI program. For example, it is well known that words standing for imageable objects are more easily remembered than words standing for abstract concepts. Is this because the visual cortex (which occupies a major portion of the brain) has a role in certain types of memory? Again, the answers are now appearing, and some of these answers may well have useful implications for designing human-computer interfaces, for example.

New methods for the study of brain activity represent remarkable advances over those available just a few years ago. These include measuring brain activity in connection with single photon emission tomographic (SPECT) techniques involving materials with half-lives on the order of 2 minutes, which is an order of magnitude better than that for deoxyglucose - a widely used substance PET scan. While it is sometimes still necessary to average data over subjects to reveal the distribution of brain activity and how it varies with the nature of the cognitive task, this improved time-resolution is getting closer to what is needed for studying the variation in brain activity during the performance of a complex mental task. Also, despite earlier disappointments, increasingly sophisticated EEG techniques may be making it possible to examine how activity shifts from one area to another during different types of performances and when correct and incorrect decisions are being made (Gevins, et al., 1988). In addition, slow but steady progress is being made in the study of attention using the event related potential of the EEG. We do not have the time to go into these related new technologies here, but shall briefly describe the new methods being employed in the URI program at New York University.

The URI program at NYU has primarily focussed on the study of the brain's magnetic field as a means for enlarging our view of the types of brain activity underlying cognition. As planned, this has attracted an interdisciplinary group at NYU, and while other areas of research are being pursued by them, they have joined forces to attack problems of mutual interest.

The flow of ionic currents in the neurons of the brain gives rise to magnetic fields that can be detected outside the scalp. The main advantage in studying these fields, especially components of the field oriented radially with respect to the scalp, is that the intervening tissues are transparent to them, and they are largely undistorted by the changes in conductivity normally present within the skull. This makes it possible to locate sources with a precision and reliability of less than 3 mm in three dimensions. This claim is based on theory (cf. Williamson and Kaufman, 1987) and has recently received experimental verification in a study funded in part by the URI (Yamamoto, et al., 1988). During the course of the present program, considerable effort went into the development and refinement of the instrumentation (including superconducting sensors), installing and evaluating a magnetically shielded room, developing and procuring analytical hardware and software, and devising experimental procedures that are uniquely suited to this new technology. As a result, there have been many substantive research accomplishments.

The Neuromagnetism Laboratory (NML) at NYU contains a 5-channel system that measures the field at five places at once outside the scalp. This is the main instrument used in the URI program, and is the prototype of all such instruments manufactured in the United States. As we shall see later, a major effort was devoted toward procurement, development and evaluation of major facilities to make it possible to use such systems. This work involved the selection and evaluation of a magnetically shielded room (MSR), a gantry for maneuvering the dewar, and a system for precise measurement of positions of sensing coils relative to the scalp (PPI).

The NML also has access to a system composed of two 7-channel instruments which is located at the NYU Medical Center. The 5-channel system served as the model for the design and construction of these 7-channel systems. Although this twin 7-channel system was not funded by AFOSR, it was and is being used in some of the studies connected with the URI, and some of the expenses incurred in its operation were covered by the existing URI project.

One of the more recent of these studies using the 7-channel systems involved a direct comparison of how the two hemispheres respond to tone bursts. The two systems made it possible to monitor activity of both hemispheres at the same time. It was found in seven subjects that the response of the left hemisphere to tone bursts grows larger with the time interval between tone bursts, even when the interval becomes as long as 16 seconds. However, the right hemisphere has a shorter "memory" in that its response did not grow any further in amplitude when the interval became longer than 4 seconds. This functional asymmetry may be related to the fact that the left hemisphere is generally more involved with language than the right, and this ability to handle language must be tied to an ability to store strings of information for relatively long periods of time (Kaufman, et al., 1989a). The fact that this appears to occur so early in the system (at auditory cortex) is quite interesting, and we have already undertaken follow-up work on this phenomenon.

In still another use of the twin 7-channel systems, we developed a new method for analyzing multichannel neuromagnetic recordings of spontaneous brain activity that avoids specific assumptions concerning the nature of the source (Ilmoniemi, et al., 1988). The results of this work are consistent with a model in which there are different sources for each alpha spindle. In the context of other work involving alpha rhythms (Lopez da Silva, et al., 1976), it appears possible that activity of these sources can be modulated independently during the performance of specific cognitive tasks. We are currently extending work done on the covariance of MEG activity among sensing channels in an attempt to devise a method that would permit localization of sources of alpha activity as well as their differentiation from each other.

Very early in the URI program it was found that attending to one of two tones led to a relative enhancement of the response of the auditory cortex to that tone. While electrical recordings (cf. Hillyard, et al., 1973) showed that the N100 component of the auditory evoked potential are similarly enhanced by attention, the results of such studies led theorists to conclude that the effect was not on sources in auditory cortex *per se*, but on other non-specific sources contributing to the effect of the sensory stimulus (Näätänen and Picton, 1987). As a result of our work, it is now clear that sources located in the tonotopically organized portion of auditory cortex are also affected by selective attention. In our experiments this effect of attention seems to be symmetrical, i.e., it does not differ between the hemispheres. The effect of selective attention occurs during a dichotic listening task in which attention is paid to tones that are lateralized toward one side, and it also occurs when tones of different pitch are presented concurrently to both ears, with attention allocated to a particular pitch. Both conditions lead to the same effect (Curtis, et al., 1988). This suggests that the "place coding" of pitch, as exemplified by the tonotopic organization of the auditory cortex, may be functionally similar to the way in which visual spatial position is encoded at the levels of visual and parietal cortex, where similar effects of attention are encountered (see below).

We have extended this work to the area of visual spatial attention, and it now appears that selective attention to events in one position in space enhances responses to those events (as contrasted with events to which attention is not paid), but the effect of attention is on later components and the source or sources of these components appear to lie in or near the occipital-parietal boundary rather than within the primary projection area (Luber, et al., 1989), while the effects of auditory attention described above appear to arise in primary auditory cortex. This difference has interesting theoretical implications to which we shall refer later. It should also be noted that in our most recent work in this area, funded under another AFOSR project, it was found that the effect described above is due to focussed attention, and cannot be deployed to divided attention. That is, when the subject attends to two different stimuli at the same time, this is not reflected in the evoked field. Moreover, there isn't a differential effect when the subject attends more to one stimulus than another, but still attends in some degree to both. Hence, divided attention involves other mechanisms. More details will be given in other reports.

Work on the URI made it possible for us to conduct subsequent studies under sponsorship of another grant in which it was found that imageable words stronger effects on activity of the visual cortex than do abstract and relatively non-imageable words. This was true when words were presented as visible text (Kaufman, et al., 1989b) as well as when presented in the form of synthetic speech. In general, when subjects form images

of the objects the words stand for, the activity of the visual cortex is modulated. Just to demonstrate the ultimate fruitfulness of the URI program, we describe some of the work for which the URI laid the technical foundations.

The meaning of the term *modulated* requires some explanation. Our procedure is based on one that was first employed by Kaufman and Price (1967) and by Kaufman and Locker (1970). In these studies, after bandpassing the EEG, the average evoked response was computed and then subtracted from each epoch of the ongoing activity. This remaining ongoing activity is incoherent with the subtracted activity that is time-locked to the stimulus event. It was then squared (rectified) and then averaged. The resulting average is the normalized variance about the mean response within the bandwidth of interest. As such, it is a measure of the power within that bandwidth minus any contribution by the evoked response. Kaufman and Price found a significant modulation of very high frequency EEG activity, while Kaufman and Locker observed a long-term depression of activity within the usual EEG band of frequencies associated with stimulation. Pfurtschuller et al. (1977, 1988) studied the effect of squaring activity from within the alpha band (without first removing activity that was time-locked to the stimulus) and found a systematic depression of alpha activity similar to that observed by Kaufman and Locker. These authors described the phenomenon as "event related desynchronization." In any event, we have found that alpha activity apparently originating in visual cortex is inhibited during the formation of mental images, during mental rotation, etc. Furthermore, the duration of this modulation is commensurate with reaction time needed to complete the mental task. By contrast, evoked responses do not show similar differences in duration. Also, the effect is present in the beta band as well. Thus, beta does not replace alpha, but it too is inhibited during a mental task. In addition, the distribution of the alpha activity differs from that of the beta activity across the scalp, thus suggesting at least partly different source configurations. This is also true of the distributions of the residual alpha and beta activity during their inhibition while subjects engage in mental tasks like forming images. Finally, strong asymmetries in these distributions demonstrate for the first time that they are not due to differences in skull thickness or other extraneous electrical features of the brain, but are inherent in brain anatomy or function or both.

Our most recent results were obtained in experiments where subjects were instructed either to form an image of the object represented by a visualizable word, or to find a word that rhymes with the presented word. As soon as either task was done, the subject pressed a key. The band limited MEG was then averaged relative to the time of the response rather than relative to the time of presentation of the stimulus, and the variance computed around the average that was time-locked to the response. A truly remarkable effect was discovered. The power in the alpha band originating in visual cortex exhibited a dramatic dip prior to the reaction and for some time afterwards when the subject followed the instruction to form a mental image, while the power in the MEG from the same place showed a dramatic rise when the subject sought a rhyming word. This suggested that the auditory cortex might be involved during mental rhyming, while visual cortex is involved in mental imagery.

Results of this type encouraged us to determine whether activity of other portions of the brain e.g., the speech areas, can be modulated by language-related tasks. In a particularly exciting experiment that is still underway we found that when subjects search memory to determine if a particular acoustic stimulus was or was not one of a set of

previously heard acoustic stimuli, spontaneous activity of the temporal lobe is inhibited. The maximum amount of relative inhibition of the spontaneous activity (in the alpha band) appears to be located over the temporal lobe, near the position of the lateral sulcus, although mapping is not yet complete. If confirmed, this would place the cortical tissue affected by searching acoustical memory in or near the auditory cortex. Another tantalizing finding in two subjects is that this effect is lateralized. There is no modulation of spontaneous activity during search of acoustic memory over the right hemisphere, but there is a profound modulation over the left. Again, this requires additional study to determine how general the effect is in the population, and also to determine if it is connected in any way with the asymmetry found in the effect of ISI on the amplitude of the magnetic N100 component. Obviously, these studies must be extended to cover other frequency bands of the MEG.

This result is analogous to what we had already observed in studies of visual memory search. In fact, the visual memory search research led to our effort to extend the same paradigm to the auditory domain.

In a series of visual experiments, subjects were presented with different memory tasks. In one task they were simply required to respond by pressing a button when a stimulus was presented. In second version they were required to respond by pressing one of two buttons, one if the stimulus was one of a set of forms seen previously, and the other if it was not. This led to a longer reaction time, and also a commensurately longer period during which activity of visual cortex was suppressed. Thus, when subjects engage in a prolonged and active search of memory for forms, visual cortex is involved, even though the forms are present for only a brief period of time. The time-course of the effect of visual cortex may be as long as 2 seconds, and this is nearly the same as the time it takes for the subject to react by pressing a button to signify whether or not he had seen the form previously. The effect on visual cortex continues throughout the process of searching visual memory - which suggests that visual cortex plays a role in processing mental images (Kaufman, et al, 1989c).

In another current experiment we are varying the size of the memory set of visual forms so that the subject has to remember if the probe was or was not identical to only one previously seen form, whether it was one of two previously seen forms, or if it was one of three previously seen forms. We are finding a monotonic increase in reaction time, as in the classic Sternberg paradigm. We are attempting to discover if the duration of the inhibition of spontaneous activity in the alpha band increases as well. However, this effect clearly engages the visual cortex. Therefore, we now have evidence that the performance of various cognitive tasks engages different parts of the brain, and the particular regions involved depend upon the modality to which stimuli were presented, even though the stimuli are not present when the task is actually being performed. Furthermore, we have preliminary evidence that instructions to engage in the formation of a mental image prompted by a spoken word also results in changes in activity of visual cortex.

Virtually all of the work described above belongs properly in the domain of cognition and much of it is being conducted with funds from another grant. None of it would have been possible without the work on the URI, the history of which is given below. However, the URI program that is about to end was strongly interdisciplinary in nature, and also involved work that belongs more properly in sensory processes than in

cognition. For example, some of our work involved the field of color vision. In this field most of our knowledge is based on psychophysics and on physiological studies of the eye and of the pathways leading to the brain. Relatively little is known of the central cortical mechanisms involved in color vision. However the three cardinal directions of color space can be independently adapted. That is, the two chrominance channels (red-green and blue-yellow), as well as the luminance channel (white-black) exhibit selective elevations of thresholds after a period of adaptation to stimuli selected from along these directions in color space (Krauskopf, Williams, and Heeley, 1982). This leads to the inference that these three directions are represented by different populations of cells within the central visual system. However, the evidence from single unit electrophysiology is inconclusive. The method of neuromagnetism is being used to investigate this possibility in human subjects.

Colors with luminances equal to their white backgrounds (as determined by flicker photometry) are being flickered on a screen and the brain's response to these colors is being compared with its response to increments and decrements in luminance. Thus far it appears that the sources activated shortly after changes in chrominance are the same as those activated by changes in luminance, but different sources at different places appear to become active later on, thus suggesting a divergence of the chrominance and luminance pathways at higher levels of the visual system. In a report to be presented at the International Conference on Biomagnetism (Krauskopf, et al., 1989), we have found that at least two different sources are activated by these different stimuli, which is consistent with the hypothesis that the cardinal directions of space are represented by divergent pathways within the visual cortex). We expect this work to be completed at the end of the current URI, and do not plan to continue it if a new award is made.

While much of the work accomplished under the aegis of the current URI was centered on our unique capability in neuromagnetism, substantial progress was made in tangentially related areas. Some of this work affected our neuromagnetic studies of cognitive processes, while other work clearly did not. Psychological studies of effects of imageability on verbal memory provide good examples of the related work. Extensive work on memory for fragmented pictures and on perceptual learning was conducted by Professor Snodgrass, and while it did not have an immediate impact on studies of the activity of the brain, although it may well have such an impact in the future. Even so, this work was an important component of the URI, and we were recently delighted to learn that this important work will receive separate support under another AFOSR grant.

Another important component of the URI was the extensive theoretical work on the dimensional structure of knowledge conducted by Professor Falmagne and his students, as described in various progress reports. Preprints and reprints describing this work are appended to this report.

In addition to the broad range of work in all of these areas, the current URI had an important training component and, consistent with this, attempted to provide for interaction with Air Force laboratories. We shall not comment on any of this here, as it lies outside the purview of an interim *scientific* report.

Early Experimental Studies

Auditory Attention

During the previous reporting periods of this project we completed a major study of selective auditory attention which was fully described in previous reports. The first publication derived from this work appeared during the current period (Curtis, et al., 1988). In this study we employed a dichotic listening paradigm in which subjects attended to strings of tone bursts presented to one ear while ignoring similar bursts of different (more than an octave away in pitch) that were presented to the other ear. The significance of this paradigm for theories of attention is traced by Treisman (1964; 1967; 1969) with a typical opposing view presented by Deutsch and Deutsch (1963). (Also see Broadbent, 1957; 1958; and Cherry, 1953.) Responses evoked by both the ignored and attended signals contain components corresponding to the N100 component of the auditory event related potential (ERP). It was found that the N100m (the magnetic counterpart to the N100 of the ERP) varied in amplitude with attention, i.e., its amplitude was greater if attention was being paid to the stimulus. A similar effect was studied in detail by Hillyard and his colleagues with electrical recordings (Hillyard, et al., 1973; 1983; 1984; 1985). The latter papers dealt largely with the effect of attention on the amplitude of the N100 component of the ERP. We went further than this in that we dealt with the problem of locating the source of the observed N100m, and computed the strength of the equivalent current dipole source. Thus, it was found that the equivalent current dipole source of the observed field of N100m was located in or near auditory cortex in the lateral sulcus. This demonstrated that activity of auditory cortex is modulated by attention. This conclusion should be contrasted with the previously widespread and prevailing view that the effect of selective attention on N100 could well be due to the summation of endogenous activity of sources distant from auditory cortex with that of exogenous activity of a source or sources in auditory cortex (see Naatanen and Picton, 1987 for a review). In view of the fact that 30 - 50% changes in source strength (current dipole moment) was attributable to attention, and that the changes in ERP amplitudes are not larger than this, we must conclude that the modulation of auditory cortical activity plays a major role in the effect of attention on N100 of the ERP. Essentially the same results were found for conditions in which the subject's attention was allocated to stimuli that different in apparent direction (lateralization) or when the stimuli were presented to one ear and attention was allocated on the basis of a difference in pitch. No significant hemispheric conditions were observed. Despite this, there remains the possibility that other non-auditory cortex sources may contribute to the effect of attention on N100.

Although our data support a strong contribution of sources in auditory cortex to attention-related variations in N100, this does not rule out possible roles for other sources. In a spherical model radial current dipole sources make no contribution to the external magnetic field. Therefore, sources that are oriented radially with respect to the local contours of the overlying skull may be expected to make little contribution to the neuromagnetic field associated with N100m. However, these same "quasi-radial" sources would contribute strongly to the electrical N100.

One of the stronger bits of evidence that such magnetically weak or silent sources may actually be present is that by Hari, et al. (1982). These investigators found that the amplitude of the electrical N100 increased monotonically with ISI up to ISIs as great as

16 seconds. This effect is quite striking, and it is reminiscent of the psychological refractory period studied by Karlin and Kestenbaum (1968). However, the amplitude of N100m increased with ISIs only up to 8 seconds. It was concluded that additional and magnetically silent sources contributed to N100, and these were responsible for the increase in amplitude with ISI longer than 8 seconds. These sources were presumed to be radial in orientation, and not necessarily located in auditory cortex.

ISI and N100

In the course of our work on this project we noted that Hari, et al. measured the field associated with N100m over only one hemisphere, while the vertex electrode used to detect N100 was sensitive to activity in both hemispheres. It was postulated that asymmetrical variations in amplitude of N100 with ISI between the hemispheres could account for the discrepancy between the electrical and magnetic recordings. This would be an interesting finding in itself, but it would essentially trivialize the notion that a magnetically silent source had contributed to N100, since the hemisphere not being observed would indeed be silent, but only accidentally and not essentially.

As a follow-up to this early observation, we explored the possibility that variation in amplitude of N100m with ISI is asymmetrical, in that the sources of this component in each hemisphere show different effects of ISI. Inasmuch as one of us (L. Kaufman) was in Norway attending a NATO conference in March of 1987, it was possible to travel to Helsinki and conduct a pilot study in collaboration with R. Hari, the senior author of the paper that first described the difference between the electrical and magnetic responses as ISI is varied. (It should be noted that no travel expenses were charged to this project.) Using the same instruments and experimental paradigm as that employed in the original study by Hari, et al., it was found that the two hemispheres do indeed show different effects of ISI. Owing to the short time available for this study, it was not possible to obtain enough data so that we could evaluate the magnitude of the asymmetry and determine if it was sufficient to account for the discrepancy between the electrical and magnetic recordings. This has now been completed in a study at NYU, and its results will be recounted below.

Early P300 Studies

In another study early in the project we joined forces with E. Donchin and his colleagues from the University of Illinois in an attempt to replicate our original studies of the P300 phenomenon (Okada, et al., 1982a). The significance of P300 for cognitive processes related to workload is made clear by McCarthy and Donchin (1981) and by Isreal, et al. (1980), for example. The main reason for attempting a replication is that controversy surrounds the interpretation we gave to our original data, namely, that the hippocampal formation is the most likely source of P300. We set out to replicate the McCarthy and Donchin study using the PEARL system from the University of Illinois, together with their software, in acquiring and analyzing the data. Owing to a high level of ambient magnetic noise at low frequencies, a very large number of trials was needed to obtain enough data for detecting P300m. Therefore, we did not completely replicate McCarthy and Donchin, but we did complete a set of visual odd-ball trials and were able to map the extracranial magnetic field associated with P300. This map confirmed our earlier study in that the equivalent current dipole source was located in or near the

hippocampal formation. Since the completion of that experiment, a magnetically shielded room and improved instruments (funded by the DOD-University Research Initiative Program at NYU) were installed in the Neuromagnetism Laboratory and we began to acquire P300m data. This work, which was done in collaboration with E. Donchin, did not live up to its early promise, since subjects proved to be unstable over time.

In the experiment referred to here, we used a standard odd-ball paradigm in which subjects had to keep count of infrequently occurring events presented in via either the visual or auditory modalities. In the earlier trials we did indeed see P300m responses of substantial amplitude, and the data suggested that the location of the source was dependent upon the modality. However, in order to fully map the field so that we could compute statistically significant dipole fits, the 5-channel neuromagnetometer had to be move to a very large number of different locations, and many replications were needed at each of these locations. Since we were essentially discarding 80% of the trials (where no odd-ball was presented), this was an extraordinarily inefficient experiment. Furthermore, owing to the long period of exposure to the same conditions, subjects habituated to the paradigm and the P300m became very unstable. In an attempt to rescue the data we made use of several time-consuming procedures. These included rescaling each P300m using each electrical P300, under the assumption that its changes would be correlated with changes in P300m. To make a long and sad story short, none of this satisfied us, and we had to conclude that the experiment was inconclusive.

We were reluctant to abandon this important endeavor, so Dr. Donchin met with Drs. Kaufman and Curtis, who were working together on this project. We decided to employ a new paradigm that had recently been developed in Dr. Donchin's laboratory, since it was capable of allowing us to obtain P300 responses on each trial, permitting the use of all of the data and not merely the odd-ball trials. This will be described below under **Current Work**, but we should say now that we are indeed collecting extremely robust P300m data and are already in a position tentatively to conclude that there are different sources of P300m, depending upon *both* the nature of the task and the modality involved.

Localization of Sources of Long-Latency Auditory Evoked Magnetic Fields

A considerable amount of technical work was also completed in the report period. Among these are studies pertaining to source localization.

Neuromagnetic studies of Pelizzone et al. (1984, 1985) in our laboratory demonstrated that the neural source of the N100m transient component to a 1-kHz tone burst was laterally displaced in the subject's head by about 1 cm posterior to the region that responds to steady-state stimulation at the same frequency. This showed that individual active regions of auditory cortex may be resolved, suggesting the possibility that spatial separation of the sources of other transient components may also be established. To determine to what degree this may be attained, one of us (S.J. Williamson) collaborated with the neuromagnetic group at Los Alamos National Laboratory to carry out systematic measurements with a single-sensor SQUID system of the responses to long tone bursts. This was the first quantitative analysis to determine the positions for the equivalent current dipole sources for all four long-latency components (P50m, N100m, P200m, and the steady field). All sources were found at positions indicating they lie near or in

auditory cortex, consistent with published results for N100m and P200m. This has now been confirmed in an independent study by Papanicolaou et al. (1989).

A strong effect of stimulus frequency was found for the position of the source of P50m, but remarkably there were no consistent trends to the direction of the source's shift with stimulus frequency. This finding would appear to demonstrate important individual differences for the functional map of human auditory cortex. The P200m source is generally weaker than that of N100m and in some subjects may overlap the early portion of the steady field. The position of the source of the steady field could not be distinguished from that of N100m. There was, however, a clear separation of the sources of P50m and P200m from N100m. These results have been published in a report by Arthur et al. (1987).

Early Technical Work

Improved Dewar Gantry

Magnetically Shielded Room

Performance of our 5-sensor neuromagnetometer system (Williamson et al. 1984) was dramatically improved with the installation of a magnetically shielded room (MSR), whose purchase was made possible with the URI grant. Our experience with unshielded measurements showed that below about 3 Hz, environmental noise rises above the intrinsic sensor noise and shows an approximately inverse power-law dependence on frequency. This is a spectral region of particular interest for studies of higher levels of brain function, such as the P300 signal (Okada et al. 1982). Magnetic shielding offers a solution to this problem, as first demonstrated by Cohen et al. (1970) when recording magnetocardiograms in a multi-layer chamber at the Francis Bitter National Magnet Laboratory at M.I.T. While that shield was constructed with a shape approximating that of a sphere, recently constructed shields (Mager 1981; Kelhä et al. 1982) show that adequate performance can be obtained with a cubic or rectangular shape and four or five shells of magnetic shielding. Such a geometry is particularly advantageous because it provides greater usable interior space for a given exterior size. Eddy-current shielding has also been used to some advantage with rooms fabricated from thick aluminum plate (Zimmerman, 1977), but the effectiveness of this shielding is markedly reduced below a few hertz frequency, where the environmental noise is often most severe.

During the summer of 1987 a two-shell MSR was installed in our laboratory at the Washington Square Center of New York University. It was erected in room 925, on the 9th floor of Meyer Hall of Physics. This MSR was prefabricated by Vacuumschmelze GmbH of West Germany, and the parts were assembled on site under the supervision of the company's personnel. The interior has floor dimensions of 3 m × 4 m and a height of 2.4 m. As such it is comparable to, or exceeds in size, conventional rf-shielded rooms and Faraday shields commonly used in EEG research. Such a generous space is important for subject comfort and safety, and to make it convenient for the experimenter to assemble visual displays.

Our MSR consists of an inner shield of mu-metalTM mounted on 8-mm thick aluminum plate that serves as an eddy-current magnetic and radio-frequency shield. It has a conventional stretch-wall covering over interior and exterior for protection and attractive

appearance. The inner wall montage is supported on the outside by a stiff aluminum framework of 15-cm thickness, and the outer surface of the framework is covered by a second mu-metal shield and stretch-wall partitions. A single door, balanced on heavy-duty ball bearings, provides magnetic continuity for the two layers of magnetic shielding. The door is secured by a wheel-type of locking mechanism that can be opened from either the inside or outside.

The strength of the MSR frame is sufficient that when a 300 kg weight is attached to the center of the ceiling, the sag is less than 0.3 mm. This makes it possible for the ceiling to support a pair of aluminum rails used to suspend a gantry for supporting the 5-sensor system. Furthermore, the stiff framework supports the gantries for the pair of CryoSQUID sensors (developed with support from a DOD-University Research Instrumentation Grant from the Air Force Office of Scientific Research). The vertical support for each gantry is bolted to the corners farthest from the door. With this arrangement of overhead gantry and two side-reaching gantries, the three dewars (holding a total of 7 sensors) can be positioned independently over three different areas of the subject's head.

Air circulation for the inside of the MSR is supplied by a duct fed directly by the laboratory building supply. Helium gas slowly vented by the boiling liquid helium in the 5-sensor dewar is conducted by tygon tubing to the outside to avoid any possible build-up. Vents high on the front wall permit free-flow of air in any event. Access ports are provided for air circulation, a projection video display, and filtered electrical leads.

The attenuation provided by this MSR was evaluated by R.T. Johnson and J.R. Marsden by placing an electromagnet about 5 m or more from the wall of the room with its axis vertical. A SQUID magnetometer positioned at the center of the room detected the interior field strength when fields of various frequencies were applied. After a 60-Hz shaking field was applied, the steady earth's field is attenuated by a factor of 10^3 . However, shielding is less effective for very low-frequency fields as is usual with such materials, being only about 30 db. The effect of eddy-current shielding becomes apparent above about 10^{-1} Hz, and the attenuation rises to a value of about 10^4 at 10^2 Hz with a tendency toward saturation at higher frequencies. The shielding is not quite as effective as for MSRs having three¹⁷ or more¹⁵ separated layers of magnetic shielding, but the present room is considerably less expensive and has greater interior space. Furthermore, when second-order gradiometers are used as detection coils in the room, the noise spectrum is similar to that of the more expensive MSRs.

The improvement in noise level provided by the MSR is indicated by data obtained for the noise spectrum. The field spectral density was measured by J. Shang and B. Schwartz of our laboratory with the center detection coil of our 5-sensor system placed near the center of the room and oriented vertically. This sensor, has a second-order gradiometer as its detection coil, with a baseline between adjacent coils of 4 cm. In the absence of the MSR the low-frequency ambient noise first became apparent over the intrinsic sensor noise at a frequency of 25 Hz (Williamson et al. 1984), increasing steadily with decreasing frequency. With the MSR it becomes apparent at the considerably lower frequency of about 0.8 Hz (Buchanan et al. 1987). This spectrum may be compared with the performance of our 5-sensor system when reference signals from three other SQUID sensors in the dewar are appropriately amplified and subtracted from each of the signals. These three have magnetometer detection coils that are oriented to monitor three orthogonal components of the ambient field. With such "electronic

balancing" of the signal we were able in our unshielded environment to reduce the onset of the ambient noise in the spectrum to about 3 Hz (Williamson et al. 1984). Thus, the MSR performs better than the method of electronic balancing that we had previously relied on. To determine where neural sources lie within the head it is necessary to measure accurately the position and orientation of each field sensor with respect to landmarks on the subject's scalp. Traditionally the dewar containing the sensor was placed in the desired location, and the position of its tail with respect to convenient landmarks was measured across the scalp. But this procedure has inherent inaccuracies, due principally to the irregular shape of the head. One advance was to align the patient's head within a reference framework, and to move the dewar accurately with respect to this framework. The "Scanner" device developed in our laboratory (Williamson et al. 1984) is an example of such a setup where the dewar is held in a carriage that moves so that the dewar's axis always points toward the center of the patient's head. This has an advantage when the head is modeled as a sphere for computing source locations, for the field component provided by the sensors is exactly the radial component. Another procedure is to use a computer-controlled mechanized gantry that moves the dewar to a pre-determined position and orientation in space (Vrba et al. 1984). Recently we installed a commercial device for purposes of evaluation. Provided that the device performs properly, we shall make an effort to obtain funds to purchase it, so that it may remain in our laboratory.

The new gantry is based on a different principle which permits the operator to move the dewar by hand to the desired location. Independent movement is provided along two orthogonal horizontal directions and the vertical direction, with rotation allowed about the vertical axis and the horizontal axis where the gantry supports the dewar. Friction holds the dewar in place when the operator releases it, and a secure lock is provided by compressed gas brakes that secure all these degrees of freedom. The dewar can also be rotated about its own axis to set orientation of the individual sensors at a desired angle. The exact position and orientation of the dewar relative to the subject's head is indicated by a system known as the "Probe Position Indicator", purchased with funds from a DOD-University Research Initiative awarded by AFOSR.

"Rainbow" - A Device for Quantifying Positions in a Magnetic Resonance Image

The positions of field measurements about a subject's head are indicated in a coordinate system that we call the "head-based coordinates." It is defined with respect to the periauricular points and nasion, which are the reference positions on which the EEG 10-20 electrode system is also based. One ultimate goal of the neuromagnetism program in our laboratory is to establish a three-dimensional functional image of the brain, in which regions of neural activity are shown in relationship to anatomical features. As a first step in this direction, we developed a system to define the same head-based coordinate system for magnetic resonance images (MRIs). A plexiglass framework called "Rainbow" was devised to embrace the subject's head when the MRI is recorded. Features on Rainbow are rendered as a series of bright spots on the MRI, so that by use of a 3D digitizer (such as the Probe Position Indicator) any position on the MRI can be related quantitatively to the head-based coordinate system.

Thus by digitizing one MRI slice after another, a 3D rendition of the subject's head can - in principle - be developed. In the future such a display could be shown on a solids

rendering system such as the Hewlett Packard Model 9000/350SRX workstation. For the moment, graphics facilities in our laboratory permit any 2D slice to be illustrated in line drawing format.

One application of 3D images will be to compare the orientation of the equivalent current dipole model representing neural activity with the local cortical topology. In this way it will be possible to determine whether the current lies perpendicular to the cortical surface or parallel. It would be the former if pyramidal cells or dendrites of other cells having preferred vertical orientations are responsible for the field, and the latter if directed projections from one area of cortex to another are responsible. Thus, important information concerning the underlying physiology can be deduced. Algorithms for digitizing the MRI scans and exploiting information provided by Halo have been developed by Ms. Gladys Klemic, a graduate student.

Profile: Software to Depict a Current Dipole in the Head

A graphics program christened "Profile" has been developed by Mr. Lian Tao, a graduate student, to relate the locations of deduced neural activity in the brain to external features of a subject's head. Profile displays on a terminal screen, or plots on an X-Y digital recorder, the three orthogonal profiles of a subject's head. The data are obtained by use of a 3D digitizer or the Probe Position Indicator system. The user chooses the side of the head to be displayed in the sagittal cross section, as well as whether the transverse cross section is to be depicted from below or above, and whether the coronal cross section is seen from in front or in back. On each cross-section is shown the position and orientation of the dipole (or dipoles) that are deduced from field measurements to account for a measured field pattern. A vector depicts the dipole, and its length denotes the current dipole moment. A rectangle centered on the position indicates the uncertainty in the location of the dipole. The sagittal profile can also be distorted slightly to insure that the subject cannot be identified.

Method for Locating a Small Magnetic Object

During the course of this program we were presented with an opportunity to investigate the feasibility of using SQUID systems to locate a small magnetic object within the human body. While such an object would be modeled as a magnetic dipole, not a current dipole, we concluded that similar techniques could be applied in mapping the field pattern and using them to deduce where the object lies. Success in using such a procedure for a magnetic dipole would give additional confidence for using analogous procedures of localization for current dipoles. Furthermore, having a technology for detecting objects too small to be imaged by x-rays may have a variety of important applications.

The object of interest was a piece of a thin acupuncture needle lodged under the right scapula of a young male adult. It was estimated to be about 5 mm in length and only 0.2 mm in diameter. The needle could not be found in surgical procedures accompanied by studies of 30 standard X-ray images. To locate it, we mapped the magnetic field component normal to a plane lying above the object, using a standard SQUID neuromagnetometer. Assuming that the needle could be modelled as a magnetic dipole, we were able to infer its lateral position, depth, orientation, and magnetic moment. With this

information, directed CT scans, high-resolution X-ray films, and the subsequent surgical removal of the needle proved that it could be located in the body with an accuracy of better than three millimeters. The principle limit on this accuracy is in specifying the location of the object relative to reference positions on the overlying skin. In this instance, different placements of the patient's right arm caused the skin to be displaced relative to the rib cage. Therefore, to achieve accurate localization the patient had to assume a given position for both the neuromagnetic studies and surgical procedure. This work was done in collaboration with Risto J. Ilmoniemi, Ph.D., Harold Weinberg, M.D., and Arthur D. Boyd, M.D.

To map the magnetic field pattern over the back, our patient lay prone on a firm bed, which was supported by rollers. During a scan, the bed was smoothly moved under the magnetometer, while its position was monitored by the voltage from a linear potentiometer attached to the bed. Each linear scan was performed three or more times to assure reliability; upon completion of a set of scans, the bed was displaced laterally by 2 cm and another set of scans was recorded. A pointer mounted on the dewar holder enabled us to reference positions across the plane of measurement to positions on the posterior torso. The only significant source of noise was a slow variation of the ambient field, which produces a drift of the baseline. The first depended upon identifying the positions of the positive and negative field extrema, as well as determining the values of the field at these extrema. We developed a procedure whereby this information is sufficient to determine the three position coordinates of the dipole, the two angles specifying its orientation, and the moment specifying its strength. We developed a set of curves that enables these parameters to be determined without recourse to a computer. A second method was based on using a computer routine to determine the least-squares fit to the field pattern. The deduced positions of the dipole determined by the two methods agreed to better than 3 mm, with the least-squares method being the more accurate because it more effectively averages over imprecisions in the data.

Several verification tests were carried out with a 15-mm length of an acupuncture needle mounted on the subject bed, so that its position and orientation could be directly measured, confirmed the accuracy of this analysis. In fact, it was found that instrumental noise caused an error of only 0.8 mm in position. The position indicated by the magnetic analysis was used to determine where CT scans should be made, in an attempt to confirm the presence of the needle. Transverse scans through the thorax were obtained through the predicted location at 3-mm displacements longitudinally. A small (1-2 picture elements) high-density feature was evident in a single scan within the intercostal space between the fifth and sixth ribs, at the predicted depth and lateral position. Based on this information, a surgical procedure was scheduled. On the morning of the procedure, magnetic scanning was repeated with the subject prone and right arm raised above the head, mimicking the position to be assumed during surgery so that the deduced position could most accurately be related to marks placed on the skin. Subsequently, a high-resolution X-ray film was obtained for a frontal cross section of the upper right thorax, and it showed the needle curved at the lateral position indicated by the magnetic analysis. CT scans taken through and near the magnetically deduced position again confirmed the presence of the needle at the predicted depth. A surgical procedure was conducted with the incision made directly above the position indicated by the magnetic and X-ray studies. As soon as the depth of the incision was about 25 mm, the needle was observed in a

curved configuration within the intercostal space between the fifth and sixth ribs, and it was removed. A paper describing this study has appeared in the IEEE Transactions of Biomedical Engineering (Ilmoniemi et al. 1988).

A New Method for Calibrating Multisensor SQUID Systems

Increasing interest in determining the strength of neural sources as well as their positions in the shortest possible time has drawn attention to the need for fixed arrays of sensors and for a method to accurately calibrate the individual sensors. Very accurate calibration is not of prime interest when an array is moved from one place to another sequentially to determine a field pattern, because generally the array is rotated from one measurement to the next in a quasi-random manner so that the effect of calibration inaccuracies tends to average toward zero. However, high accuracy becomes important when the array monitors the field pattern at a set of fixed positions over the scalp. We have developed a technique with a relative accuracy of about 2% for calibrating individual sensors in a neuromagnetic probe, whose detection coils have the popular geometry of a second-order gradiometer. This procedure was described in a paper that appeared in the IEEE Transactions of Biomedical Engineering (Costa Ribeiro et al. 1988).

It is quite simple to place a small calibration coil under the dewar, feed an ac current through its windings, and move the coil so that the sensor's output is maximized, thereby indicating the coil is centered on the axis of a given detection coil. However, the magnitude of the sensor's output is very sensitive to the distance between the calibration coil and detection coil, and this distance in general is not known to within the required fraction of a millimeter to achieve 1% accuracy. In practice the result has an accuracy of perhaps only 10%. A variation of this procedure relies on placing the coil in succession at a number of precisely determined locations sufficiently far from the probe that the field of the coil at the sensors is accurately dipolar. From the recorded outputs of all sensors for each coil location, high accuracy may be obtained when the calibration factors are determined by a least-squares fit (Ilmoniemi et al. 1988).

We have successfully applied another method for calibrating second-order gradiometers that relies precisely on the fact that such coils are relatively insensitive to a uniform field. The procedure is to use a large, square field coil whose sides (2.64 m length) are roughly two orders of magnitude greater than the baseline of the detection coil. A large *calibration coil* is placed so that the detection An ac current at 20 Hz is provided by a function generator, and the corresponding output of the SQUID electronics was amplified, bandpass filtered, and monitored by a digital voltmeter. This output is proportional to the difference between the field at the center coil and end coil of the detection coil, a number that is easily calculable from the known dimensions of the calibration coil and detection coil. Of particular importance is the fact that the net flux in the detection coil is insensitive to its exact position with respect to the calibration coil: moving one upward or downward by 4 cm produces only a 1% change in the value of the calibration factor. This is the desired feature of the large-coil technique.

The calibration factor determined in this way is accurate only to the extent that the detection coil's field balance (match of the area-turns ratio of all the coils of the gradiometer) is sufficiently high. The field imbalance can be determined by applying a uniform field and measuring the resulting output voltage of the sensor. For this purpose, a

reasonably uniform field can be produced with a set of four coaxial, square coils of side 2.64 m (Meritt et al. 1983). The number of turns of wire in the four coils was originally 59,25,25,59. These field coils were positioned with an accuracy of better than 2 mm in an attempt to achieve sufficient field uniformity. Precise measurements of the resulting axial field profile (in the vertical direction) were made by differential methods with a fluxgate magnetometer to verify the quality of uniformity. They showed that the steel reinforcing rods in the concrete floor of the laboratory enhanced the field produced by the lowest coil and shifted the field center upwards from the geometrical center of the coil set. This effect could be countered by removing two turns of wire from the lowest coil.

To measure the effect of field imbalance in the windings of the detection coil, a 20-Hz current was passed through the uniform-field coil, and the corresponding ac output voltage of each SQUID system was noted with a digital voltmeter. Correcting for the small (about 3.5%) nonuniformity of the field yielded the field imbalance factor for each detection coil, which was on the order of 10^{-5} . Taking this into account for the measurements with the calibration coil yielded the calibration factor for the sensor. This is typically about 1.2×10^{-7} tesla/volt for the sensors in our 5-sensor probe (Freddy). The value of the calibration factor for each coil could be determined reproducibly with an accuracy of 2%. In comparing calibration factors across coils we found a 10% spread in their values, which may be attributed to differences in the construction of the SQUID systems.

A Method of Verification

Another way to measure the field imbalance correction, which at the same time verifies the value for the field calibration factor, is to measure the change in the output when the calibration coil is moved axially up or down by a known distance. If the displacement is small it is enough to consider the field profile only up to the fourth-order term. When displacing the calibration coil in our system by 4 cm the output voltage changes by only 1%, in agreement with the theory.

Single-Position Calibration

Another advantage of using a single large external coil for calibration is the possibility of doing it rapidly for all the sensors in an array. In fact it is not necessary to place each detection coil at the center and coaxially aligned with the calibration coil. The field produced by a large square calibration coil can be computed for the position of each turn of each detection coil. The theory for this was developed. Although this calibration procedure is comparatively insensitive to the vertical position of the calibration coil, it is nevertheless sensitive to other parameters such as the size of that coil: a 1% change in the length of the sides of the calibration coil affects the calibration by 3%. On the other hand, an error in the angular orientation by 1 deg affects the calibration by only 0.16%. Another advantage of this single-position calibration, beyond its rapidity, is the possibility of using it to determine the exact angular position of the array relative to a fixed laboratory frame of reference (the calibration coil) during an experiment where the array is tipped in order to be positioned over the source. The calibration factors can be determined prior to such a measurement, with the array upright, by passing a known current through the calibration coil.

Analytical and Theoretical Work

Sources of Error in Determining the Location of a Neural Source

The early success of neuromagnetism motivated the development of magnetic sensing systems to measure the magnetic field near the scalp at several positions simultaneously. Probes with 4, 5, and 7 sensors are presently in use (Ilmoniemi 1984; Williamson et al. 1984; Romani 1985). In addition to greatly reducing the time required to record a field pattern, these multi-sensor systems make it possible to determine the position, strength, and orientation of a localized neural current source with a *single-position measurement*, that is, without having to move the probe from one place to another. A particular advantage of this is the possibility of following subtle shifts of activity between adjacent neural populations in studies such as those recording responses evoked by visual patterns of differing content.

The effects of calibration error and magnetic noise on the accuracy of locating an equivalent current dipole source in the human brain were investigated by computer analysis for 5- and 7-sensor probes and for a pair of 7-sensor probes. The importance of using a large array, with sensors strategically placed, is illustrated by an analysis for case when the probe is placed at a field extremum. Then a noise level of 5% of peak detected signal produced uncertainties of about 20% in source strength and depth for a 5-sensor probe. These are reduced to 8% when the array is increased to a pair of 7-sensor probes, and uncertainties of about 15 mm in lateral position with the 5-sensor probe are reduced to 1 mm for the pair of 7-sensor probes.

The head was modeled as a uniform sphere or a set of concentric spherical shells of differing conductivity, representing regions such as the brain, skull, and dermis. The source was modeled as a current dipole, which is described by five parameters: its position (x, y, z) , orientation ψ of its moment in the plane tangential to the radius passing through its location, and the value Q of this moment. The five field values obtained from a single-position measurement with a 5-sensor probe are sufficient to determine these five parameters, provided that the probe is not centered on certain symmetry lines or points, such as directly over the dipole (Hämäläinen et al. 1985; Ilmoniemi 1985). Indeed, if additional information is available to fix the orientation of the source, a four-sensor system may serve for locating a dipole (Vyedensky et al. 1988). However, we might expect that locating a dipole with a 4- or 5-sensor system is very sensitive to calibration errors since the parameters are not overdetermined by the data. The computations were made for successively larger arrays of sensors presently in use: a 5-sensor probe with 4 outer coils equally spaced about a central coil; a 7-sensor probe with 6 outer coils equally spaced about a central coil; and a pair of 7-sensor probes (hereafter called a 14-sensor system). The probe in these computations was placed directly over a position on the scalp where the normal component of the field is maximum, which is useful for achieving good accuracy in determining the depth and strength of a current dipole. The five-sensor probe we considered has a set of five detection coils (Freddy), each being a second-order gradiometer with a coil radius $a = 0.75$ cm and baseline $b = 4.0$ cm between adjacent coils. The coils are arranged in the pattern of a cross, so that the centers of the pickup coils (lowest coil of the gradiometer) of the four outer coils are 2.0 cm from the axis of symmetry. The seven-sensor probe is identical to the 5-sensor probe

except that it has two additional outer sensors, thus forming a hexagonal array about the center coil. The fourteen-sensor probe consists of two 7-sensor probes, positioned at each field extremum with identical orientations.

Effect of Calibration Errors

Certain detection coil positions play more important roles than others in determining the values of various dipole parameters obtained from a least-squares fit to the data. To illustrate this we computed the consequence of a calibration error in any one of the sensors. Nonlinearity in the relationship between field values and best-fitting parameters was evident, because identical positive and negative increments generally changed each parameter in opposite directions but by different amounts. We took the larger change to characterize the corresponding uncertainty in the best-fitting value. Our computations show that an error as small as 1% in any sensor causes the dipole to rotate and shift by ~5 mm in the coordinate z longitudinal to the direction of the dipole. If the errant sensor lies off the axis passing through the extrema of the field pattern, the shift is due to breaking of mirror symmetry about this line.

The lateral position x is influenced most strongly by errors in the center sensor and the one farthest from the dipole. The center field in comparison with fields at the outer sensors fixes the depth of the dipole and therefore how far it lies from the probe. Longitudinal position z is also influenced more strongly by coils lying farther from the dipole. The orientation ψ of the dipole's moment is related to this, being most sensitive to error in the farthest sensor, with all of the others being much less important. The deduced depth d of the dipole is most sensitive to a calibration error for the center sensor. This is because its signal in comparison with those of the outer sensors determines the scale length of the pattern: a stronger signal decreases the length scale, thus implying a shallower dipole, and *vice versa*. The strength Q of the dipole is also most sensitive to the field indicated by the center sensor. While Q is directly related to the field at the extremum it is also affected by the depth of the dipole: to produce a given maximum field, the deduced Q must increase with increasing depth.

Similar computations have been carried out for 7-sensor and 14-sensor probes. The effects of calibration errors for the center sensor, sensors nearest the dipole, or sensors farthest from the dipole are similar, but the magnitude of the maximum shift of a dipole parameter is generally reduced. Part of this advantage comes from the effect of diluting the importance of any one sensor when the total number of sensors is increased, and in the case of the 14-sensor probe part comes the broader expanse of the field pattern that is sampled. One exception to the improvement in accuracy with increasing number of sensors is determination of the parameters Q and d with the 5-sensor and 7-sensor probes. This is because the center sensor has dominant importance for these parameters in comparison with any of the outer sensors, so a calibration error for the center sensor produces virtually the same change in Q and d for both the 5-sensor and 7-sensor probes. To emphasize this point, there is a dramatic improvement in the precision for Q and d when the second 7-sensor probe is positioned over the other field extremum to produce a 14-sensor system. Determining the locations of the two extrema fixes the length scale of the pattern more firmly than the ratio of central to outer fields of any one extrema, thus reducing the importance of both center sensors.

From these trends we conclude that the scalar properties (strength Q and depth d) have values that are most sensitive to calibration errors in the central sensor, whereas the vector properties (longitudinal and transverse position, as well as orientation) are most sensitive to the coils placed farthest from the source. We emphasize that these trends apply when the probes are placed directly over the field extrema, so as to monitor the strongest fields. There is no implication in this choice of position that it is optimal for determining the full set of dipole parameters; indeed, the optimal position and orientation of the probe will depend on the parameter of interest and on the depth of the dipole.

Influence of Noise on Locating a Source

The preceding discussion of calibration errors has a straightforward extension to the effect of field noise on the uncertainty in the best-fitting values of the dipole parameters. For simplicity we assume that the noise in the various sensors is uncorrelated and of the same rms value. To generalize the discussion, it is convenient to express the rms field noise in any sensor in terms of the field at the positive extremum. Thus, when the same normalized noise amplitude is applied to an outer coil, which has a lower signal level, the actual signal-to-noise ratio for that coil is worse than for the center coil. The results for the 5-sensor, 7-sensor, and 14-sensor probes are shown in Table I. On going from 5 to 7 sensors, there is substantial improvement in reducing the uncertainties for some parameters (x , z , ψ), while there is very little benefit for others (Q and d). The most dramatic improvement is obtained on going from the 7-sensor to 14-sensor probe, where all the uncertainties are diminished. The reason is evident: On going from 5 to 7 sensors the additional outer detection coils enhance the probe's ability to resolve asymmetry in the field pattern, and this better establishes the position (x, z) and orientation ψ of the source with respect to a field extremum. A similar improvement is seen on going from 7 sensors to 14 sensors, but there is also a marked improvement in determining Q and d . The latter benefit was gained because placing a second probe over the second field extremum accurately fixes the distance between the extrema of the pattern, thereby more accurately determining d . Then the average of the field values accurately fixes Q . In addition, determining the general location of both extrema limits the uncertainty in the dipole's orientation ψ . This was said in a different way by Ahonen et al. (1986) who noted that the accuracy of a dipole fit is enhanced for an array of sensors if the lateral spacing between their detection coils is increased, even if the dipole lies at a relatively shallow depth. Cuffin (1986) has also considered the effect of noise on dipole localization for several types of measurements, and although the position of the probe in his calculations does not coincide with ours there is general agreement between his results and ours for the uncertainty in strength, orientation, and depth of the dipole source.

It may be concluded that the 5-sensor probe with a 10% noise level produces rather poor results: the source strength is known to only about 40%, its orientation to only 60° , and the lateral position to only 2 cm. Decreasing the noise to 5% provides substantial improvements, with uncertainties that are comparable to much of the data being reported in the literature with a single sensor being used for sequential measurements at some 30 or more positions.

The main advantage in adding two more sensors to produce a 7-sensor probe is in improving the uncertainty in position and orientation of the dipole. For a comparable

TABLE I

Magnitude of the uncertainties in best-fitting current-dipole parameters for various levels of field noise in the sensors. Noise is expressed as a percentage of the dipole's field at a field extremum. The dipole is located at a depth of 2 cm beneath the surface of a uniform conducting sphere of radius 9 cm.

PROBE (%)	NOISE (%)	$\delta Q/Q$ (%)	$\delta d/d$ (%)	δx (mm)	δz (mm)	$\delta \psi$ (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

noise level, these uncertainties are reduced by a factor of 2 - 3. A further reduction of ~3 is achieved in the uncertainties for *all* parameters by going to a 14-sensor probe. Here the results are comparable to what might be considered state-of-the-art, where Q and d are known to about 10%, transverse position to 1-2 mm, and orientation to 10° . Clearly, a 5% noise level with a 14-sensor probe would represent a substantial advance on this. High precision of this type is advantageous when searching for subtle changes in position or orientation of a confined neural population under study. These small uncertainties are comparable to the practical limits imposed by variability of many types of biomagnetic activity and by errors attendant to positioning a probe over the scalp.

Relationships Between Physiology and Perception

We have considered how the functional aspects of neural activity in auditory cortex revealed by magnetic studies may relate to human perception or performance. The possibility of establishing such relationships is based on earlier studies of activity in visual cortex, where research in our laboratory showed that simple reaction time varies with

stimulus parameters in the same way as the neuromagnetic latency for observing maximum field strength. This correspondence was established for the latency of steady-state responses to contrast-reversing grating patterns, where latency was found to increase with (1) increasing spatial frequency (Williamson et al. 1978), (2) decreasing contrast (Okada et al. 1982b) and (3) decreasing luminance (Okada et al., unpublished). We investigated a different aspect of neural activity in auditory cortex, taking advantage of the fact that neuromagnetic theory shows how quantitative measures of neural activity may be determined, both in source strengths and source position in three-dimensional space. Our earlier studies of auditory responses combined with recent findings in other laboratories is a fertile basis for developing such relationships.

In 1982 studies by Romani et al. (1982a,b) demonstrated the existence of at least one tone map across human auditory cortex. The stimulus was a tone whose amplitude was sine-wave modulated at nearly 100%, and the magnetic response at the modulation frequency was mapped over the temporal and parietal areas of the head. Measurements of the total strength of the equivalent current dipole accounting for the observed field pattern showed that source strength is independent of tone frequency for a given subject. Also, for two subjects studied, strength was also independent of subject. From the current dipole moment of the source, the minimum number of cells responding to a given tone was estimated to be some 10^4 . Thus a sizeable population is responsible for the observed magnetic field. The spatial extent of such a population cannot be inferred from the data (Okada, 1985), but a population of 10^4 neurons could be highly localized since some 10^5 neurons are found under each square millimeter of cortical surface. It is unlikely that the population is so widely distributed as to be spread over an area with linear dimensions as great as a centimeter in each direction, for the entire tonotopic sequence extends over a track having a length on the order of 3 cm.

Recently, Pantew et al. (1988) reported neuromagnetic evidence for a tonotopic sequence for the N100m component of the transient response to a tone burst. The general locus of activity agrees quite well with the trend observed in the steady-state response, with responses to tones of higher frequency lying deeper beneath the scalp. Thus both the N100m and steady-state response (the latter having an apparent latency of about 50 ms) are tonotopically organized. There is evidence these maps do not coincide, for careful measurements by Pelizzone et al. (1984) for the magnetic field patterns of N100m and steady-state response evoked by 1 kHz tones show that the two sources lie at the same depth but the steady-state response lies 1 cm more posterior than the transient.

Hoke et al. (1988) have recently reported evidence for an amplitopic map for the N100m component, and the trajectory of this sequence across cortex is approximately at right angles to that of the tonotopic sequence, with activity shifting toward shallower depth and anteriorly with increasing stimulus intensity. Here as well as for the tonotopic sequence, there is a logarithmic representation, with cumulative distance across the cortex between one region of activity to another being proportional to the logarithm of the sound intensity. Each 10 dB increase in sound intensity produces a shift of about 0.3 cm across cortex.

The tonotopic and amplitopic functional maps have an interesting relationship to psychophysical studies of perception, and the two measures taken together provide an important physiological implication. To see this consider the fact that the just-noticeable tone difference for pitch discrimination at low levels of intensity is roughly proportional

to frequency. This holds for frequencies down to about 1 kHz for studies with frequency-modulated tones (Shower and Biddulph, 1931) and down to about 500 Hz for successively presented tone bursts (Wier et al., 1977). These and other psychophysical data are discussed by Scharf and Buus (1986) in the *Handbook of Perception and Human Performance* (K.R. Boff, L. Kaufman, and J.P. Thomas, 1986). The just-noticeable tone difference at a frequency f for tone bursts corresponds to a frequency shift of about $1 \times 10^{-3} f$. The tonotopic map reported by Romani et al. (1982b) indicates that a relative frequency shift of $\Delta f/f$ corresponds to displacement of activity across cortex by $\Delta D = 0.58(\Delta f/f)$ cm. Therefore the just-noticeable tone difference at low sound intensities represents a fixed shift of activity across cortex of about $6 \mu\text{m}$. This is a remarkably short distance. It is much less than typical 'minicolumn' of Montcastle (1979), which is about $50 \mu\text{m}$ in diameter as determined by Nissl stain, and is even much less than the size of a single pyramidal cell, as gauged by the extent of dendritic arborization. Yet the population of cells responding to the stimulus is on the order of 10^4 neurons.

It appears therefore that a perceptually different tone is not distinguished by a discrete shift of all activity from one region of cortex to another (perhaps adjacent) one, as would be the case were it to shift from, say, one minicolumn to another. Instead the distance by which activity shifts is much smaller than the linear extent of the responding population. If tone discrimination is associated with activity giving rise to either the P50m or N100m transient components, the process may well depend on small shift in the position of the maximum of activity that is distributed along the cortex. It seems unlikely that the physiological processes underlying pitch discrimination are to be found at subcortical auditory nuclei, where tonotopic maps are also found, because these maps show more convergence (shorter total length of the tonotopic sequence) than at cochlea or cortex (Clopton et al. 1974).

The fact that very small displacements of activity across cortex may correspond to perceptual differences has been revealed previously in electrophysiological studies of activity in auditory cortex of the mustached bat, *Pteronotus parnellii parnellii*. Suga and Horikawa (1986) found that the just-noticeable range difference for determining the distance of a target at mid-range is about 1.3 cm, and this corresponds to a shift across cortex of about $6 \mu\text{m}$. Thus, fine-grain sensitivity is found for a variety of function sequences, in both primates and non-primates.

We may also consider psychophysical implications of the other dimension across auditory cortex - the amplitopic map. Our analysis of the data of Pantew et al. (1988) indicates that there is a shift of approximately 0.3 cm across cortex for each 10 dB increase in sound intensity. For a small relative change $\Delta I/I$ of intensity the corresponding displacement would be: $\Delta D = 0.13 \Delta I/I$ cm. The data of Rabinowitz et al. (1976) and Jesteadt, Wier, and Green (1977) for just-noticeable differences in intensity show that discrimination improves with increasing intensity, from $\Delta I/I = 12 \times 10^{-2}$ at a sensation level of 40 dB to 5×10^{-2} at a sensation level of 80 dB. Accepting for the sake of illustration an intermediate value of 7×10^{-2} leads to the conclusion that the just-noticeable difference in sound level corresponds to a displacement of activity across cortex of about $100 \mu\text{m}$. This is considerably greater than the minimum displacement along the tonotopic sequence corresponding to the just-noticeable tone difference. We may infer that if such discrimination is carried out by regions of cortex monitored magnetically, the neural circuits responsible for amplitude discrimination differ from those for

tone differences. Indeed, the minimum required shift along the amplitopic sequence to account for the just-noticeable loudness difference is sufficiently large as to admit the notion that activity is displaced from one set of minicolumns to another. Since an area of cortex of 0.1 mm^2 is sufficient to account for activity of 10^4 , it is not inconceivable that the active region for a given intensity is $100 \mu\text{u}$ along the amplitopic sequence and $1,000 \mu\text{u}$ at right angles to it. There is, however, no direct evidence that the active area is indeed so small or that it extends only $100 \mu\text{u}$ along the sequence. These considerations have been submitted for publication as part of a book chapter (Williamson and Kaufman 1988).

Current Work

This section will bring the report up-to-date with respect to just completed or nearly completed research projects supported or partly supported by the current URI project.

Visual Spatial Attention

Work on visual attention was initiated under the aegis of the URI program and it is being continued with the support of AFOSR under a different grant. However, since the project was initiated under the URI, we report on it here as well as in the report on the other project, where it will be dealt with in more detail.

This project is the vehicle for a doctoral dissertation by Bruce Luber. The committee members are L. Kaufman, S.J. Williamson and G. Sperling. It deals with the fact that evoked responses to stimuli lying in different visual directions are affected by whether or not attention is paid to them (Eason et al., 1969). It was found that the series of positive and negative peaks of the VEP resulting from stimulation from one side of fixation (the side on which attention is focussed) are enhanced relative to those resulting from stimulation of the unattended side. Hillyard and Magun (1986) suggest that these effects are due to a gating mechanism, possibly acting at a sub-cortical level. This view is consistent with an early filter such as that postulated by a Treisman-like theory. Harter and Aine (1984) suggest that the enhancement is not due to changes in the geniculo-striate pathway, but in the tecto-pulvinar-parietal pathway.

Luber generates his stimuli with an Amiga 1000 computer linked to an Electrohome video projector which projects images into a magnetically shielded room. The images are reflected by mirrors to the eyes of a subject seated on a kneeling stool so that the back of the subject's head can be positioned under a dewar. The projected stimulus is, at the eye of the subject, composed of a 1 deg per side square containing 1 black and 1 white vertical bar or 4 black and white vertical bars. The "fat" bars are presented with a probability of 0.8 and the "thin" bars with a probability of 0.2. Both fat and thin stimuli are presented for 33 msec and the ISI varies from 850 to 1350 msec. They are presented as two independent sequences with fat and thin bars concurrently presented 5 deg to left and right of fixation. Subject's attention is directed to either the right or left stimulus and magnetic fields are recorded during a session. Mapping the resulting fields revealed that the side toward which attention is focussed evoked magnetic responses that were larger in amplitude than those on the other side. Furthermore, the responses to both the attended and unattended stimuli were essentially identical until about 240 msec after stimulation. After that time, the later components of the response to the attended stimulus were significantly greater in amplitude than those to the unattended stimulus. Furthermore, the location of the equivalent current dipole source of these relatively enhanced responses was not in primary visual cortex, but appeared to be located in the vicinity of the occipital-parietal boundary. Hence, the results are not comparable to those reported earlier for auditory attention, where early components with source or sources in primary auditory cortex were affected by attention. Rather, the later and non-primary visual areas were involved in this experiment on focussed attention. Since subsequent work, conducted under the aegis of another AFOSR project, showed that even this effect dissipated under conditions of selective attention, it appears that we will have to look to other regions of the brain for the sites involved in this process.

Hemispheric Asymmetry and the Auditory Response

As mentioned in the introduction to this report, Kaufman and R. Hari did some preliminary work in Helsinki which suggested that the amplitude of the N100m component of the auditory evoked field may well increase in amplitude at different rates in the two hemispheres. This could provide a simple explanation of the fact that ISI increases result in an enhancement of amplitude of the electrical N100 recorded at Cz, when the ISI gets as long as 16 sec, but the amplitude of N100m does not increase beyond an ISI of 4 sec. The reason is simply that the recordings were made over the right hemisphere, while the recordings made at Cz were affected by both left and right hemispheres. In an experiment completed by L. Kaufman, B. Butensky and S.J. Williamson we found that the amplitude of N100m changes with ISI up to 16 sec in about the same manner as that of N100 at Cz, provided that N100m is recorded over the left hemisphere. However, recording it over the right hemisphere results in satiation of the ISI effect after 4 sec. This was done with 7 subjects. It suggests the the "memory" of the left temporal lobe is longer than that of the right, and this may well have something to do with language function. A paper (Kaufman, Butensky and Williamson, 1989) was submitted and accepted after peer review for presentation at the International Biomagnetism Conference in 1989. It should be noted that this paper raises some problems for those who propose magnetically silent sources as contributors to the endogenous N100 and its changes in amplitude with attention. Also, the hemispheric asymmetry we have definitively established may well be related to the echoic storage process that is probably related to the handling of language. This is a subject for further research.

Chrominance Channels

Professor John Krauskopf, Dr. David Travis (Post-doc partly supported by URI) and Ms. Gladys Klemic (graduate student supported by URI) have concentrated on the role of "higher order mechanisms" in color vision. The first stage of receptor mechanisms are now fairly well understood, and research by Krauskopf and his colleagues in the psychophysical domain (Krauskopf, Williams and Heeley, 1982) and the physiological domain (Derrington, Krauskopf and Lennie, 1984) has helped to clarify the nature of the second stage opponent mechanisms. It is clear that the parvocellular lateral geniculate layers consists of two major types of center-surround chromatically opponent units. Lennie, Sclar, and Krauskopf (1985) applied the same electrophysiological methods to cortical units as were used to study lateral geniculate units, and found cells tuned to respond best to isoluminant stimuli in many different directions around the color circle. Detailed analysis of psychophysical habituation experiments and results of experiments on the discrimination of threshold changes in color also point to the existence of higher order mechanisms tuned to many different directions in color space (Krauskopf, Williams, Mandler, and Brown, 1986).

Dr. Krauskopf has been continuing to study these higher order mechanisms using psychophysical and physiological procedures. In the past year he has made use of the 5-channel system at the Neuromagnetism Laboratory at NYU where he and his students have been using isoluminant chromatic stimuli to determine if it is possible to detect spatially separated regions in visual cortex that are tuned to respond to the different directions in color space. Thus far, microelectrode studies have not clarified this issue. In this preliminary work isoluminant red and green stimuli are presented alternately. Also,

increments and decrements in luminance of white patches on a neutral background are similarly alternated. The chromatic stimuli, which are matched by means of heterochromatic photometry to their neutral backgrounds, evoked rather robust neuromagnetic fields. Mapping these fields in the occipital region showed activity of apparently common sources for both the chromatic stimuli and for the luminosity stimuli. However, with more extensive mapping it appears that spatially distinct sources may be activated by changes in luminosity as compared to changes in chromaticity. This separation of function is not apparent in early components of the evoked response, but is apparent in later components with sources outside the primary visual areas - especially for sources of responses to changes along the red-green axis. While blue-yellow pairs of stimuli have also been used, insufficient data have been collected to allow statements about their sources.

The foregoing work required the generation of isoluminant stimuli using a video projector to form the images of the stimuli on a screen inside a shielded room. This was not a trivial exercise. The general approach was to use time varying stimuli in which the chromatic content was varied so that they exhibit either a purely luminance variation or purely chromatic variations in different directions within an isoluminant plane. The goal was to find regions of the cortex that respond strongly to stimuli varying in different directions in color space. Although the data to date are meager, it is clear that stimulus production was successful, and that it is indeed possible to obtain responses and locate the sources of these responses.

P300 Studies

As indicated earlier, we found a paradigm that finally seems to work. Donchin and his colleagues have been presenting letters, e.g., and the cross-bar, or at the bottom of the letter. The top indicates that the next letter to be seen would most likely (80% of the time) be an H. The middle dot indicates that there is a 50:50 chance it would be an H or an S. The bottom dot indicates that the next letter would most likely (80%) be an S. We adopted this procedure, and also added an auditory condition in which a tone is presented along with one of higher pitch, the same pitch or a lower pitch, to indicate that the next tone would have either a high, low, or intermediate probability of being the same as the preceding main tone. We have already conducted reaction time studies to show that, insofar as RT is concerned, the acoustic and visual stimuli are effectively equivalent.

We may divide a stimulus sequence into the preparatory stimulus and the target stimulus. In the case of MEG recording, both the preparatory and the target stimuli lead to a subsequent P300m. These P300ms were recorded over the temporal areas. However, the P300m associated with the preparatory stimulus was quite strong in amplitude at some locations within this region, while the P300m associated with the target stimulus has a different scalp distribution. Therefore, it appears as though anticipation results in a P300m having a source that differs from that of the P300m resulting from resolution. Furthermore, although the auditory stimuli also led to quite clear P300m phenomena, these too differ in scalp distribution from that of the visual P300m. All of this requires repeated trials among many subjects, but it does appear as though P300 is not a unitary phenomenon, and that its source depends upon the nature of the task as well as upon modality. We hope to deal with this problem further if our application for a new URI grant is approved. However, we predict that the basic findings alluded to above will

result in a peer-reviewed publication before the end of the present project.

Forecast

In the remaining few months of this URI project we plan to complete the chrominance and P300 experiments and prepare papers for publication. In addition we also shall complete the preparation of a paper on the ISI effect and still another paper on focussed and divided visual attention. Owing to the great length of this report, we did not describe the extensive work already covered on correlation methods and the "alphon" hypothesis in the previous Interim Scientific Report. This work shall also be completed and a second paper submitted for publication.

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BRAIN ACTIVITY RELATED TO SPATIAL VISUAL ATTENTION

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INTRODUCTION

Effects on evoked potentials of attending to sensory stimuli have been known for twenty years. For example, Eason, et al. (1969) showed that responses to stimuli placed at positions in visual space to which a subject paid attention were enhanced as compared to responses to stimuli placed at positions that were ignored. Effects of attention to directions in visual space are particularly interesting, as there is an isomorphic mapping of that space onto the visual cortex, and this makes it possible to examine how this type of attention may modulate the activity of specific regions of the brain.

METHODS

A visual stimulus containing either 2 or 4 bars within a square field 1 deg on a side was presented in random sequence above the horizontal meridian either 5 deg to the left or to the right of a central fixation point. The 4-bar pattern had a 10% probability of occurrence, with the 2-bar pattern occurring on 90% of the presentations. All bar patterns were presented for 34 msec with a random ISI of 1100 msec mean and 250 msec SD. The subject was instructed to maintain fixation on a small cross while attending to either the right or left field. Subjects depressed a button whenever the 4-bar pattern appeared in the field to which attention was being paid.

RESULTS

Both the attended and ignored stimuli evoked neuronal activity whose magnetic fields could be detected over the occipital and parietal regions of the scalp. Typical responses to the attended and ignored stimuli are shown in Figure 1. There is a strong resemblance between the field patterns and response strengths until about 200 msec after the onset of the stimulus. Between 200 and 360 msec the response strength to the attended stimulus is enhanced relative to the response to the ignored stimulus. Measurements of this sort were made at approximately 120 different locations about the scalp. Isofield contour maps were constructed. These demonstrate that the early components (up to about 200 msec) could be accounted for by equivalent current dipoles located in the visual areas.

Figure 1. Time courses of averaged responses for attended visual stimuli (solid line) and unattended (dashed line), obtained over the occipital area of the scalp. Stimulus onset is at 0.0 seconds.

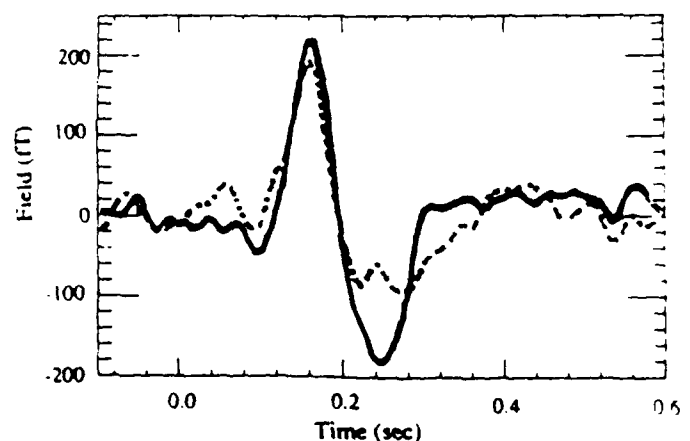
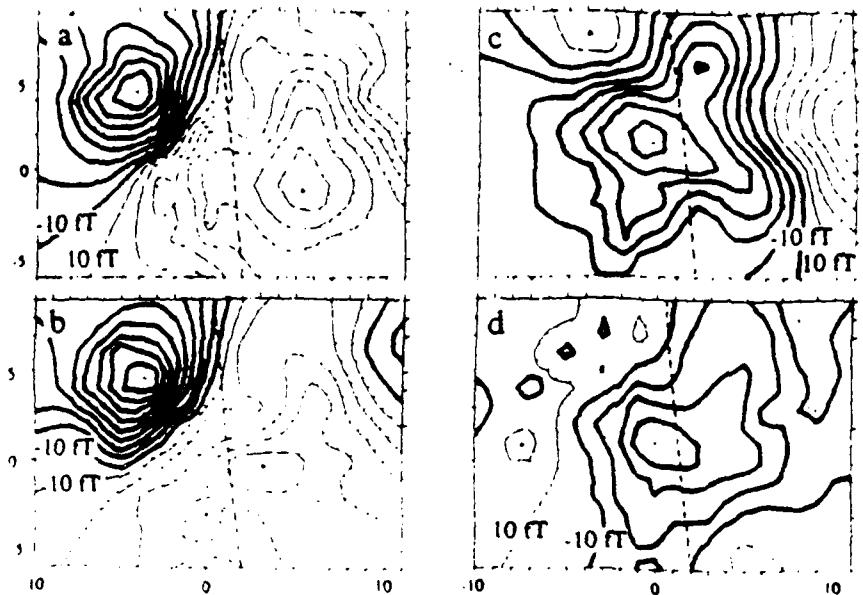


Figure 2. a) Isofield contour maps over occipital area for: 150 ms component when (a) attended and (b) ignored; 244 ms component when (c) attended and (d) ignored. The origin of each projection is approximately on the midline (dashed line) of the scalp about 2 cm above the inion. Isofield contours are drawn with 20 fT increments, and distances are in cm.



These dipole sources for various components differ in location and orientation, but are consistently the same whether or not attention was being paid to the stimulus. Figures 2a,b illustrate this in an azimuthal equal-distance projection centered at the origin of the axes on the map. In this figure, the midpoint between periauricular positions of the head is taken as the center of a sphere; and distances from the origin along any great circle are indicated by the same distances from the origin across the flat map. Later than about 200 msec latency there is a component that is much stronger when the stimulus is attended (Figures 2c,d). The isofield contour map demonstrates that the source of this component is several centimeters away from the sources of the earlier components, and may well be located in or near the occipital-parietal boundary.

Unlike results obtained using a similar paradigm in the auditory domain (Curtis, Kaufman and Williamson, 1988), where early components with sources in the primary auditory cortex reveal strong effects of attention, these results suggest that the visual attentional "filter" may be located at a later stage. This is consistent with results of single unit recordings obtained on macaque monkeys by Moran and Desimone (1985). However, the results of this study are inconsistent with those obtained by Van Voorhis et al. (1977) who found enhanced early components of visual evoked potentials obtained by averaging over subjects and using higher levels of stimulus luminance. We suggest that the effect of this parameter requires further investigation.

ACKNOWLEDGEMENTS

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DISTRIBUTED SEQUENTIAL ACTIVITY OF THE HUMAN BRAIN DETECTED MAGNETICALLY BY CryoSQUIDs

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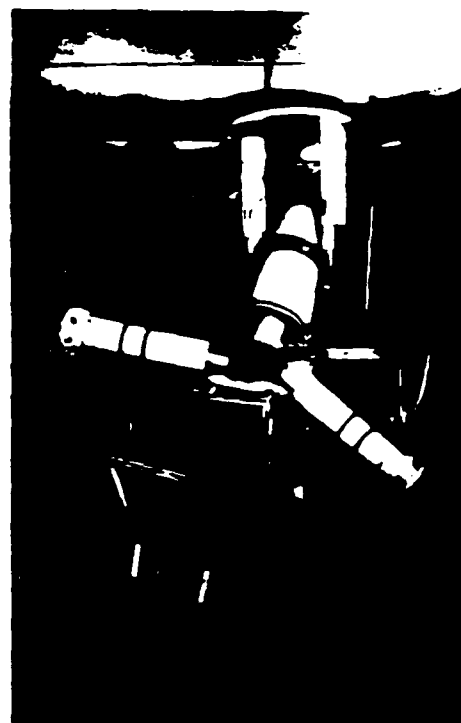
INTRODUCTION

Conventional SQUID-based magnetic sensors use liquid helium to maintain a low-temperature environment for the superconducting components. These systems require refilling approximately every three days and limit the angle by which the dewar may be tipped from the vertical. The recent development of a system based on helium gas refrigeration for cooling SQUID sensors eliminates these limitations (Buchanan, Paulson, and Williamson, 1988). Cooling is achieved by a three-stage configuration in which a two-stage Gifford-McMahon (GM) cycle establishes a stage at 15 K and a Joule-Thomson (JT) cycle maintains the final stage at 4 K for the SQUID and detection coil (Buchanan, Paulson, Klemic, and Williamson, 1989). This minimizes mechanical vibrations of the kind that may be introduced by a mechanical linkage as used for a Sterling cycle cryocooler (Zimmerman and Radebaugh, 1978), so that the sensor can be operated in any orientation including upside down (Figure 1). Residual vibrations from the movement of the displacer in the GM cooler introduce magnetic noise. But since it is time-locked to the motion, a simple computer can be used to register a template and subtract this from the data in real time, removing all detectible noise of refrigerator origin. We shall report the performance of the two CryoSQUIDs installed at the Neuromagnetism Laboratory at NYU and the application of this system to studies where the sequence of activity from different regions of the human brain is of particular interest.

OPERATION

Both the GM and JT cycles operate from a common feed pressure of 2.3 MPa provided by a commercial compressor. The return at 0.6 MPa from the GM cooler is fed directly to this compressor but the lower level return of 0.1 MPa from the JT cooler is first enhanced to 0.6 MPa by a second compressor. Cooling from room

Figure 1. Two CryoSQUIDs (small dewars on the left and right) and a five-sensory system (larger dewar supported from the ceiling) positioned about a subject in a magnetically shielded room. Each CryoSQUID is supported by an individual tripod gantry permitting horizontal and vertical adjustment as well as positioning in any orientation. Flexible tubing provides high-pressure helium supply and low-pressure return for the refrigerators. Black fins at the top of the dewars are essential to dissipate heat convectively during the initial cool-down, but attain a temperature of only a few degrees above room temperature in operation.



AN EFFECT OF HEMISPHERIC FUNCTIONAL DIFFERENCE ON THE N100 COMPONENT OF THE AUDITORY EVOKED POTENTIAL

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INTRODUCTION

According to Hari et al. (1982), the N100 component of auditory evoked potentials (AEP) recorded between a central lead (Cz) and mastoid reference exhibits a monotonic increase in amplitude with increases in interstimulus interval (ISI) up to 16 seconds. However, the corresponding N100m component of the auditory evoked field (AEF) occurring at the same time and measured over the right hemisphere increased in amplitude with ISI up to only 4 sec. They suggested that sources contribute to the N100 that are essentially invisible to magnetic recording of N100m. We wish to point out that the Cz electrode can be affected by cortical sources of N100 in *both* hemispheres, so if functional activity differs in auditory cortex of the two hemispheres it is conceivable that the "magnetically invisible" source is actually located in the hemisphere whose activity was not measured by their magnetic field sensor. Indeed, we found that the magnetic response of the left hemisphere for each of six subjects varies in the same way as Cz for increasing ISI, whether the response strength increases monotonically or (as in one subject) decreases at very long ISI. The ISI dependence of the left hemisphere response can account for virtually all of the change in amplitude of Cz with ISI. We conclude that the ISI data presented by Hari et al. can be explained without postulating a contribution by magnetically silent sources to the electrical N100.

METHODS

The observers were six paid volunteers (five males and one female), aged 19 to 28 years, with normal hearing. Stimuli were similar to those used by Hari et al.: 1000 Hz square-wave short tone bursts, 20 msec in duration and approximately 60 dB above the observer's threshold for normal hearing, with ISIs of 1, 2, 4, 8, and 16 sec. The stimuli were generated by an Amiga 1000 computer and delivered binaurally to the observer via plastic earphones. Each experimental session consisted of nine blocks of stimulus presentations: one block of 100 presentations for each of the 1, 2, and 4 sec ISI-levels, two blocks of 50 presentations for the 8 sec ISI-level, and four blocks of 25 presentations for the 16 sec ISI-level. A rest period of about 2 min separated the blocks, with a longer rest period about half-way through the session. The blocks were presented in a different random order for each observer, and the order was reversed during a second session for four of the observers. They were asked to pay attention to the tones by counting them.

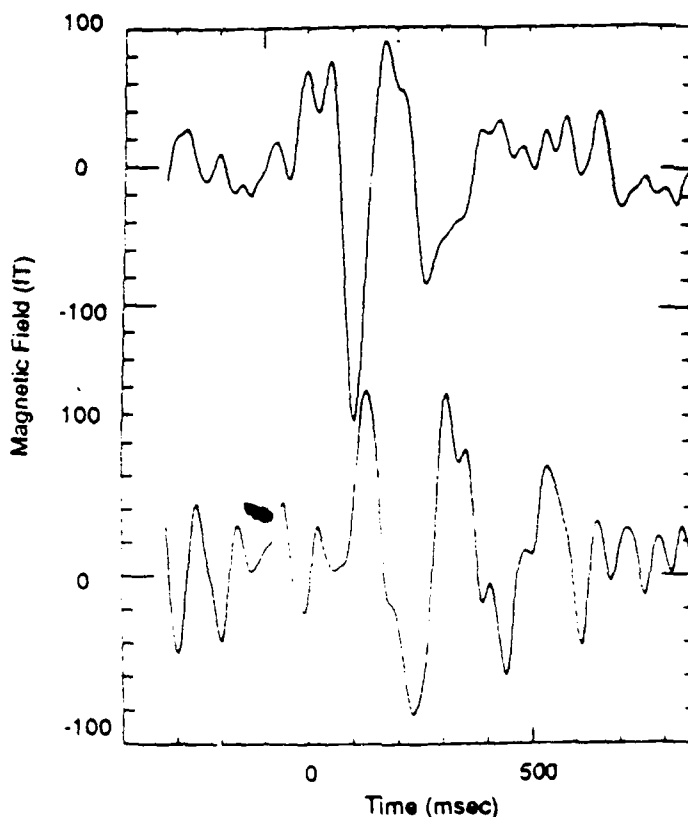
The positions over parietal regions of the head at which the amplitude of N100m was at its maximum value were determined prior to the formal experiment for each observer, using a 5-channel neuromagnetometer. This placement ensures that the observed neuronal activity arises from auditory cortex (Yamamoto et al. 1988). The position of the tail section of the dewar housing the sensors was marked on a tight-fitting swimming cap and preserved for subsequent measurement. The formal experiments in which both EEG and MEG recordings were obtained simultaneously were conducted at the Center for Neuromagnetism located at Bellevue Hospital in the NYU Medical Center. The electrical recordings were made between Fz, Cz, and Pz and a reference electrode attached to the right mastoid, within the bandwidth of 0.1 to 60 Hz. Two 7-channel neuromagnetometers (Biomagnetic Technologies, inc., San Diego) were used to record the MEG simultaneously from right and left hemispheres near the field extrema indicated on the swim cap, within the bandwidth from 1.0 to 50 Hz. The MEG and EEG data were separately averaged in the conventional manner, with the time of the onset of the tone burst serving as the temporal reference for all response latencies. Both MEG and

temperature is achieved after 20 hours simply by starting the compressors. The JT stage of the device is provided with a reservoir (30 cm³) to accumulate liquid helium. This reservoir serves both as a large thermal mass to stabilize the temperature of the SQUID and as a thermal reservoir. Movement of the displacer of the GM stage and gas in the tubing produces acoustic noise which has proven impossible to eliminate. When this noise must be eliminated the system can be operated in an "intermittent" mode in which the GM cycle is shut down and the JT flow is reduced, with the residual evaporation of helium in the reservoir providing steady cooling. If neuromagnetic studies are carried out over a period of 2 - 6 minutes, followed by a similar time of renewed refrigeration the procedure can be extended for several hours. The whole operation is computer controlled. In the "one-shot" mode there is 20 minutes of operation before all the helium is evaporated. This system has most recently been in continuous operation for two months without failure, other than stoppages due to human error.

APPLICATION

To illustrate the application of this system Figure 2 shows averaged neuronal activity obtained with the two CryoSQUIDs when a subject responds to a visual cue by pressing a switch. One sensor was placed over the right occipital area to record activity of visual cortex while the other was placed over the left Rolandic fissure to record motor and somatosensory activity related to finger performance. This shows the first strong peak of somato-motor activity occurring about 50 ms following the 120-ms component of activity in visual area. Identification of these sources was established by detailed mapping of the field pattern with the five-sensor system.

Figure 2. a) Average of 100 responses to appearance of a change in luminance of a circle presented in the lower left quadrant of the visual field. b) Corresponding average of somatosensory activity recorded from over the Rolandic fissure of the left hemisphere.



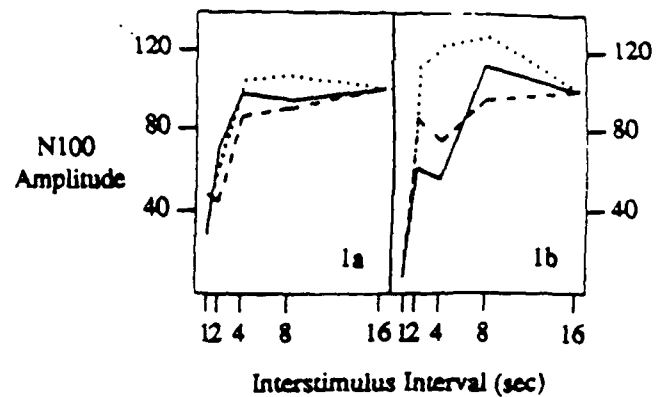
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Figure 1. a) Amplitude of the N100 component for various ISIs, detected electrically over the vertex (Cz, solid line) as well as magnetically over the right hemisphere (RH, dotted line) and left hemisphere (LH, dashed line). b) Amplitude variations for a second subject showing common behavior for all three measures.



EEG data were then digitally filtered between 3 and 30 Hz for comparison. The average of the N100m amplitude across all ISI-levels for each magnetic sensor was calculated, and the sensor yielding the maximum response for each dewar was used in data analysis. The amplitude values for individual subjects were normalized with respect to the amplitude at the 16 sec. ISI level.

RESULTS

The variation with ISI of the average N100 amplitude obtained at Cz and the N100m amplitude obtained from right (RH) and left (LH) auditory cortex is illustrated in Figure 1. The subject characterized in Figure 1a displays trends similar to those reported by Hari et al. with Cz increasing nearly monotonically with ISI but with RH reaching a steady value above an ISI of about 4 sec. However, it is clear that LH displays a trend that is similar to that of Cz. Figure 1b shows a different behavior of RH for a second subject, where there is a decrease in amplitude for the longest ISI. Yet even in this case LH and Cz display similar trends. These data, as well as results for four other subjects suggest that the ISI dependence of Cz may be due primarily to activity in the left hemisphere, although for two of them the trend for LH and RH coincide. The data are sufficient to confirm the hypothesis that asymmetric effects of ISI on the two hemispheres are sufficient to account for the effect of ISI on the electric N100 recorded at Cz. A claim that magnetically silent sources contribute to N100 can no longer be made without other evidence.

ACKNOWLEDGEMENTS

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NEUROMAGNETIC MEASUREMENTS OF VISUAL RESPONSES TO CHROMATICITY AND LUMINANCE

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INTRODUCTION

Psychophysical studies have demonstrated that there are three cardinal directions in color space which may be habituated independently (Krauskopf et al., 1982). Two are chromaticity directions which we call "red-green" and "blue-yellow", and the third is the achromatic direction for luminance. After viewing modulations along one chromaticity axis, detection thresholds for that direction increased, but thresholds for modulations along the other chromaticity axis or luminance axis were unaffected. Similarly, after exposure to luminance variations detection thresholds for luminance stimuli increased but those for either chromaticity direction did not. This implies that there are separate mechanisms in the brain for these specific colors. However electrophysiological experiments have not clearly identified these separate pathways. Cells in the lateral geniculate nucleus (LGN) signal for chromaticity and luminance simultaneously, though at different spatial frequencies (Derrington et al. 1984, see also DeValois 1975 for review of earlier results). Recent work on the striate cortex (Lennie et al., in preparation) shows that there is no clear separation of color and luminance, even in the "blob" and "interblob" regions of layers II/III, although contrary conclusions were reached by Livingstone and Hubel (1984). Furthermore the habituation effects observed psychophysically do not occur at the LGN (Derrington, 1984) or the cortex (Lennie et al.)

Recent anatomical studies have revealed a multiplicity of retinotopic cortical areas (VanEssen, 1985) and it has been suggested that they serve some distinct purposes. Indeed, Zeki (1973) has proposed a special role for area V4 in the process of color. Magnetic methods are capable of locating regions of activity on the scale of cortical maps, therefore the present study was undertaken. We have used a 5-channel SQUID system with second-order gradiometer detection coils, in a magnetically shielded room, to seek evidence of separate sources of response to chromaticity and luminance stimuli.

METHODS

Two classes of stimuli were generated by a personal computer that drives a TV projection system. The images were projected into the magnetically shielded room and onto the back of a translucent screen. One class of stimuli was maximally modulated along the red-green color axis, and the other was maximally modulated along the luminance axis. In both cases the stimulus was a circle of 0.5 deg diameter presented in the lower-left visual field against a white surround. The red and green stimuli were equiluminant with the white surround as determined by flicker photometry for each subject. The luminance (black-white) stimuli were against the same white surround. Red, green, black, and white stimuli were presented in random order, each for a duration of 400 ms with an inter-stimulus interval of 600 ms. The magnetic field was measured at 60-65 positions over the occipital and parietal areas of the head.

RESULTS

Red and green responses were averaged together (*rg*) and so were black and white responses (*bw*). At least four temporal components of the neuronal response were detected for both classes of stimuli. This differs from EEG studies (Paulus et al., 1987) that reported an early negative component (87 ms) only for color stimuli and a later positive component (110 ms) for luminance stimuli. The

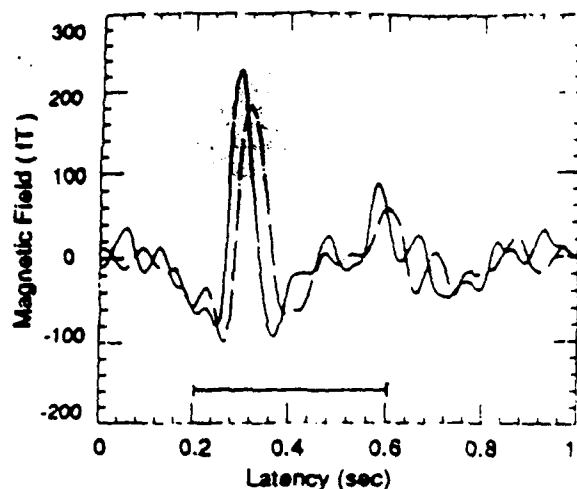


Figure 1. Average of 90 responses to *bw* (solid line) and *rg* (dashed line) stimuli. Bar at the bottom indicates the stimulus duration.

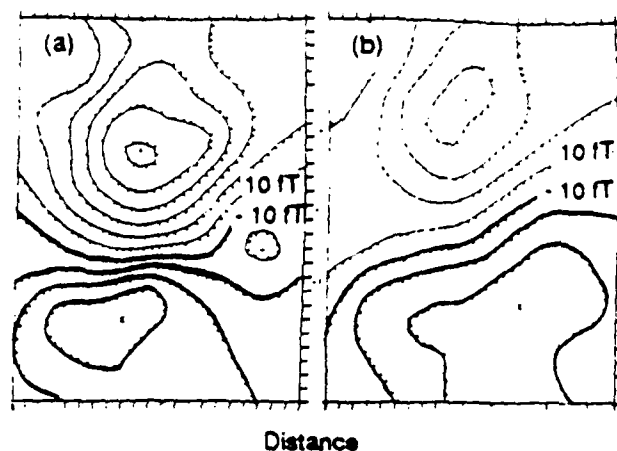


Figure 2. Isofield contour plot over occipital scalp showing the field pattern of cortical activity in response to (a) *bw* and (b) *rg* stimuli. Contours are in 20 fT steps, and distance intervals between ticks along axes are 5 mm.

latencies of *rg* responses in our study were consistently longer than *bw* response, typically by 10 - 20 ms, but this was found to be related to the amplitude of modulation along the *bw* axis. The latencies became comparable when the luminance change is reduced to just discernable levels.

Preliminary analysis of the data shows that for one subject all components show no significant difference in locations of neuronal activity between *rg* and *bw* responses. For a second subject the first two components also showed no difference but the later components, at 160 ms and 390 ms for *bw* and 180 ms and 410 ms for *rg*, showed a difference in location, with the *rg* source lying deeper.

ACKNOWLEDGEMENTS

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METHOD FOR LOCATING SOURCES OF HUMAN ALPHA ACTIVITY

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INTRODUCTION

Alpha activity is commonly defined as electrical fluctuations between 8 and 13 Hz that can be detected electrically on the occipital scalp and are attenuated by visual stimuli. While projections from brain stem play a role in its generation, evidence for the cortical origin of these electrical signals has been obtained from studies of potentials at various depths within the cortex of animals. Lopes da Silva and van Leeuwen (1978) suggest that alpha sources originate in different epicenters from which activity spreads across cortex in several directions. Previous magnetic studies on humans of the covariance between the EEG and magnetic recordings with a single sensor suggest that many sources are near or in the visual cortex (Carelli et al., 1983). Studies with a four-sensor system (Vvedensky, Ilmoniemi, and Kajola, 1986) indicate that there are time series of the rhythm lasting for typically 1 sec during which the oscillation period is constant. We call these time series *spindles*, whether or not occurring in the sleeping state. Ilmoniemi, Williamson, and Hostetler (1988) using a 14-sensor system found that the magnetic field pattern during a spindle appears relatively stable, indicating that its source is a specific configuration of neurons. Moreover, an analysis of the time-invariant spatial pattern based on a 14-dimensional signal space indicates it is possible to distinguish between most of the sources of the observed spindles. In other words, the human alpha rhythm represented by the spindles is generated by a large number, or possibly a continuum, of different source configurations. The purpose of the present study is to determine the location in the human brain where these spindles originate.

METHODS

Two dewars, each containing seven dc-SQUID sensors (Biomagnetic Technologies, inc.) were positioned over the left and right occipital areas to record activity. The detection coils were second-order gradiometers with 1.5-cm diameter and 3.7-cm baseline, and the sensor noise level was about 20 fT/ $\sqrt{\text{Hz}}$ for all channels. Calibration of the individual sensors was obtained with a relative accuracy of better than 1%. With the subject prone and alert, recordings within the bandwidth 0.5 - 50 Hz were made for 16-sec epochs of spontaneous activity with eyes closed. The total level of instrument and subject noise was determined with eyes open. Data were digitally filtered in the bandwidth 8-13 Hz and a computer routine was used to locate those time-series where the rms amplitude significantly exceeds the noise level.

A spindle was defined by a time series where the period between zero-crossings is stable for several cycles, and field polarities at the two dewars are opposite. To further improve the signal-to-noise ratio, the mean amplitude of a spindle was obtained from elements of the covariance matrix computed across the time-series of the spindle. The set of 14 mean values values for a spindle was used to determine the location of its source when represented by a current dipole. Positions of individual sensors relative to a head-based cartesian coordinate system, indexed to the periauricular points and nasion, was determined by the "Probe Position Indicator" method (Buchanan, Paulson, and Williamson, 1987). This procedure when used with the conventional procedure for recording the 100-ms component of an auditory evoked response provides 3-mm accuracy in determining the location of a current dipole in a conducting sphere, model head, and human auditory cortex (Yamamoto, Williamson, Kaufman, Nicholson, and Llinás, 1988). Less accuracy is expected in the present study since

only 14 measurement positions are recorded. Nevertheless, when the field extrema of a spindle lie within the montage of 14 sensors, or very close by, the position of its source in three-dimensions can be determined with reasonable accuracy as shown by Costa Ribeiro, Williamson, and Kaufman (1988).

RESULTS

Surveys of several subjects verify that field extrema of individual spindles are generally found over left and right hemispheres, approximately 3 - 10 cm above the inion and displaced 2 - 8 cm to either side. With dewars centered about 5 cm above the inion, displaced 7 cm to opposite sides of the midline, a series of spindles could be recorded whose field extrema in left and right hemispheres were within the recording montage or estimated to be within 4 cm of its boundary. The location of each spindle source was deduced using a sphere model for the posterior region of the head, with the center of the sphere being determined by the best-fitting radius of curvature of the scalp. The deduced locations of the sources lie in the occipital lobe within several centimeters of the midline. The estimated accuracy in locating the position of the individual current dipoles is generally 1 - 2 cm. The orientations of the current dipoles lie within about 30 deg of the midline. If intracellular cortical is directed perpendicular to the cortical lamina, as expected for post-synaptic activity of pyramidal cells, this implies that neuronal excitation is confined to the calcarine fissure, and in some cases a portion of the longitudinal fissure. The details of these findings for hundreds of spindles, as well as intercomparison across subjects will be reported. The results are consistent with spindles arising from neuronal activity near or within visual cortex.

ACKNOWLEDGEMENTS

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