AD_____

COOPERATIVE AGREEMENT NUMBER: DAMD17-94-V-4036

TITLE: National Rehabilitation Hospital Assistive Technology Research Center

PRINCIPAL INVESTIGATOR: Richard M. Materson, M.D.

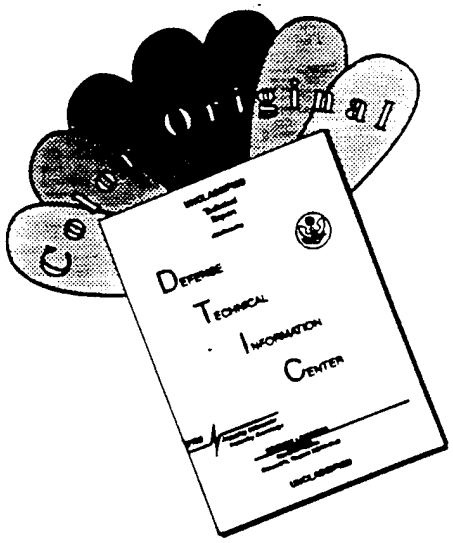
CONTRACTING ORGANIZATION: National Rehabilitation Hospital
Washington, DC 20010

REPORT DATE: October 1995

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISCLAIMER NOTICE



THIS DOCUMENT IS BEST QUALITY AVAILABLE. THE COPY FURNISHED TO DTIC CONTAINED A SIGNIFICANT NUMBER OF COLOR PAGES WHICH DO NOT REPRODUCE LEGIBLY ON BLACK AND WHITE MICROFICHE.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1995	Annual 30 Sep 94 - 29 Sep 95

4. TITLE AND SUBTITLE
National Rehabilitation Hospital Assistive Technology Research Center

5. FUNDING NUMBERS
DAMD17-94-V-4036

6. AUTHOR(S)
Richard S. Materson, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
National Rehabilitation Hospital
Washington, DC 20010

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

The Assistive Technology Research Center was established by the National Rehabilitation Hospital to facilitate transfer of technologies from aerospace and defense arenas to improve the lives of persons with disabilities. The Center's work has evolved in two general areas: a) Assistive Technology Transfer and b) Cognitive Studies. In year 1, the Center expanded its infrastructure to accommodate future research and carried out research projects as proposed. For the Assistive Technology section, complimentary work was conducted in areas of evaluation and innovative design, including further development and testing of exoskeletal systems made from lightweight, composite materials and the exploration of alternative manufacturing procedures. Preliminary work was conducted on the preliminary development of a portable evaluation system for use in telemedicine rehabilitation applications. Finally, preliminary analysis and review of the literature resulted in development of two research projects that will examine the efficacy of using virtual reality for assessment and educational purposes within the rehabilitation environment, including 1) Assessment of Unilateral Spatial Neglect in a Virtual Reality Environment and 2) Virtual Reality as a Tool for Family Education in Visuo-Spatial Neglect. In the Cognitive Studies Section, a number of preliminary, single-subject design studies were completed that allowed for evaluation of hypotheses and methodologies related to the application of the ANAM battery to treatment of mild head injury patients.

14. SUBJECT TERMS
Assistive Technology; Cognitive Performance; ANAM; Virtual Reality; Composite Materials

15. NUMBER OF PAGES
76

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

GENERAL INSTRUCTIONS FOR COMPLETING SF 298

The Report Documentation Page (RDP) is used in announcing and cataloging reports. It is important that this information be consistent with the rest of the report, particularly the cover and title page. Instructions for filling in each block of the form follow. It is important to ***stay within the lines*** to meet ***optical scanning requirements***.

Block 1. Agency Use Only *(Leave blank)*.

Block 2. Report Date. Full publication date including day, month, and year, if available (e.g. 1 Jan 88). Must cite at least the year.

Block 3. Type of Report and Dates Covered. State whether report is interim, final, etc. If applicable, enter inclusive report dates (e.g. 10 Jun 87 - 30 Jun 88).

Block 4. Title and Subtitle. A title is taken from the part of the report that provides the most meaningful and complete information. When a report is prepared in more than one volume, repeat the primary title, add volume number, and include subtitle for the specific volume. On classified documents enter the title classification in parentheses.

Block 5. Funding Numbers. To include contract and grant numbers; may include program element number(s), project number(s), task number(s), and work unit number(s). Use the following labels:

C	- Contract	**PR**	- Project
G	- Grant	**TA**	- Task
PE	- Program Element	**WU**	- Work Unit Accession No.

Block 6. Author(s). Name(s) of person(s) responsible for writing the report, performing the research, or credited with the content of the report. If editor or compiler, this should follow the name(s).

Block 7. Performing Organization Name(s) and Address(es). Self-explanatory.

Block 8. Performing Organization Report Number. Enter the unique alphanumeric report number(s) assigned by the organization performing the report.

Block 9. Sponsoring/Monitoring Agency Name(s) and Address(es). Self-explanatory.

Block 10. Sponsoring/Monitoring Agency Report Number. *(If known)*

Block 11. Supplementary Notes. Enter information not included elsewhere such as: Prepared in cooperation with...; Trans. of...; To be published in.... When a report is revised, include a statement whether the new report supersedes or supplements the older report.

Block 12a. Distribution/Availability Statement. Denotes public availability or limitations. Cite any availability to the public. Enter additional limitations or special markings in all capitals (e.g. NOFORN, REL, ITAR).

- **DOD** - See DoDD 5230.24, "Distribution Statements on Technical Documents."
- **DOE** - See authorities.
- **NASA** - See Handbook NHB 2200.2.
- **NTIS** - Leave blank.

Block 12b. Distribution Code.

- **DOD** - Leave blank.
- **DOE** - Enter DOE distribution categories from the Standard Distribution for Unclassified Scientific and Technical Reports.
- **NASA** - Leave blank.
- **NTIS** - Leave blank.

Block 13. Abstract. Include a brief *(Maximum 200 words)* factual summary of the most significant information contained in the report.

Block 14. Subject Terms. Keywords or phrases identifying major subjects in the report.

Block 15. Number of Pages. Enter the total number of pages.

Block 16. Price Code. Enter appropriate price code *(NTIS only)*.

Blocks 17. - 19. Security Classifications. Self-explanatory. Enter U.S. Security Classification in accordance with U.S. Security Regulations (i.e., UNCLASSIFIED). If form contains classified information, stamp classification on the top and bottom of the page.

Block 20. Limitation of Abstract. This block must be completed to assign a limitation to the abstract. Enter either UL (unlimited) or SAR (same as report). An entry in this block is necessary if the abstract is to be limited. If blank, the abstract is assumed to be unlimited.

*U.S.GPO:1993-0-358-779

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the US Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

__✓__ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

____ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Richard Matersons 10/30/95

PI - Signature Date

TABLE OF CONTENTS

NATIONAL REHABILITATION HOSPITAL

ASSISTIVE TECHNOLOGY RESEARCH CENTER

COOPERATIVE AGREEMENT DAMD17-94-V-4036

FIRST YEAR ANNUAL REPORT

A. INTRODUCTION

In this report, we provide status information on a number of projects that were begun and/or carried out by the National Rehabilitation Hospital (NRH) Assistive Technology Research Center (ATRC) in year one of the cooperative agreement. This document also contains revised plans for year two. These reports were provided to our designated project officer, Fred Hegge, PhD, in a meeting that took place September 22, 1995.

ATRC activities are directed by a senior management team comprising Richard Materson, MD, the principal investigator; William Peterson, MS, director of Assistive Technology Transfer actitivites; Joseph Bleiberg, PhD, director of Cognitive Studies activities; Jack Winters, PhD, director of Catholic University support for the ATRC; and Ruth Brannon, MSPH, administrative coordinator of ATRC activities. This group meets regularly to review progress on ATRC goals and objectives.

These goals and objectives were reviewed by the ATRC Advisory Group which met December 14th and 15th, 1994. (The report of this meeting is included in Appendix A.) As a result of Advisory Group recommendations and the input of Dr. Hegge, the ATRC concentrated in Year 1 on developing projects delineated in the original proposal and on establishing linkages with a number of government labs through telephone contact and visits to NRH.

The remainder of this report is devoted to activities of the two main components of the ATRC: a) the Assistive Technology Transfer program and b) the Cognitive Studies program.

B. ASSISTIVE TECHNOLOGY TRANSFER SECTION
Year 1 - Progress Report

Introduction

The Assistive Technology Transfer Project (ATTP) within the ATRC is responsible for identifying promising technologies within DOD, NASA, and federal labs which may have an impact on the rehabilitation field and for performing the necessary research to transfer that technology. During the first year, our initial objective was to establish an infrastructure capable of supporting grant activities and for doing sound research. In order to meet those objectives, the ATRC hired two additional engineers and subcontracted with The Catholic University of America (CUA) for additional staff and support. Equipment was purchased and space was reconfigured at both NRH and CUA to provide the necessary infrastructure. Projects were identified utilizing advanced materials, advanced fabrication techniques, virtual

reality, and "intelligent" expert systems. Five projects proposals have been written and submitted to the appropriate Internal Review Boards (IRBs) and two more are soon to follow. Progress on these and other ATTP projects is detailed below.

Infrastructure

The Assistive Technology/Rehabilitation Engineering (AT/RE) service areas were reconfigured to provide the necessary space for grant activities. In doing so, five staff members who work on a different grant were moved off site to a new location and AT/RE clinical staff were relocated to make room for ATRC staff and activities. The NRH Performance Diagnostic Lab (PDL), located in the AT/RE service area, was expanded to assist with ATRC projects and CUA dedicated two labs in the School of Engineering for grant purposes. These labs are in addition to the Biomechanics and Rehabilitation Design Lab already in place at CUA and accessible to ATRC staff.

Roughly $115,000 was spent on new equipment that was integrated into the PDL. This equipment included: an AMTI force platform (coupled to an existing force platform installed in the PDL) used to measure ground reaction forces during specific tasks; a miniature six-axis force transducer used as a portable sensing device to measure forces and moments simultaneously; LABView for Windows -- a data acquisition/analysis software package used by the ATRC for data acquisition and graphical display; and a virtual reality computer system consisting of a SGI Indigo2 computer with Extreme graphics, a head mounted display used to immerse an individual into a stereoscopic representation of a graphical "virtual" world, a right handed CyberGlove to allow the user to interact with their "virtual" world, and a Flock-of-Birds electrogoniometer system which allows the system to simultaneously track position and orientation of up to three receivers (i.e., head, hand and trunk). All of this equipment was installed, calibrated and integrated into the PDL for purposes of conducting research.

Three full-time staff were hired as part of the ATRC Technology Transfer Project: a Post-Doctoral Fellow, a Research Rehabilitation Engineer, and an Administrative Secretary. These three staff joined the Director of the Assistive Technology/Rehabilitation Engineering program, the Manager of the PDL, and two CUA professors to establish a core of expertise capable of conducting and overseeing the research projects. ATRC staff consulted with other allied health professionals, e.g., physicians, physical and occupational therapists, and psychologists, on various projects as needed. Also during the course of this past year, five college interns and two volunteers have assisted on ATRC Technology Transfer projects.

Status: Ongoing

Virtual Reality

In the original ATRC proposal, virtual reality (VR) technology was identified as a prime example of how technology developed by the military can be used in the private sector. The

first fully operational VR system was used as a flight simulator by the United States Air Force and has subsequently been used to simulate everything from tank battles to space shuttle missions. These applications have led to more sophisticated and affordable systems thus increasing the ability of the private sector to invest in VR technology to conduct research on its possible uses in other arenas. One such possibility is the use of VR as a tool for therapeutic intervention in rehabilitation.

The ATRC invested in a VR system which consists of: a Silicon Graphics Indigo2 computer with Extreme graphics; a head-mounted display (HMD) for stereoscopic vision and immersion of the user; an eighteen sensor glove (Cyberglove) for interacting with the virtual world; an electrogoniometer (Flock-of-Birds) which provides position and orientation data to the computer on whatever it is attached to (i.e., the head-mounted display, the instrumented glove, or even one's leg); and VR software (Sense8 World Tool Kit) for coordinating all aspects of a virtual environment.

ARTC first linked VR peripheral devices with the computer and became familiar with VR programming (using World Tool Kit) and methods of incorporating three dimensional objects into a virtual world. Several VR demonstrations were developed to give clinicians and others a better "feel" for what virtual reality is about and to stimulate thinking about possible therapeutic applications. As a result, several VR-based therapy routines were developed based upon therapist's input and used with specific patients. These routines include a virtual motorcycle ride, a virtual traffic intersection, a virtual soccer game, and a flip program that allows the user to pick up and flip virtual objects.

These therapeutic virtual worlds were generated with specific patients and tasks in mind. For example, the virtual motorcycle ride was used to entice a patient who had suffered a stroke into lifting his right arm (which therapists were having difficulty getting him to do). While steering the virtual motorcycle, the patient raised his right arm. Another example is a virtual soccer game. Here, the patient had a disorder which made it very difficult for her to move her legs (flexion/extension about the knee). The therapy goal was to entice the patient to move her legs to prevent further problems. A virtual soccer game was developed that allows the user to walk up to a virtual soccer ball and kick it. Since the therapist had control over the computer "gains" used to propel the soccer ball, the patient could kick the ball great distances with only subtle movement of her legs. It challenged the patient to see how far she could kick the ball, resulting in a noticeable increase in leg motion.

Another trial application involved the use of VR as a tool for architectural visualization of home-site modifications recommended by a clinical team for a particular patient who has multiple sclerosis and had purchased a two-story home sight unseen. The patient uses a wheelchair for ambulation and was not capable of accessing the second floor of the home without the recommended modifications. Measurements of the house were taken and a virtual representation of the house was generated. Proposed modifications were then added to the virtual house and the user was able to get a "feel" for what the second floor looked like and how the specific modifications would work once installed.

These are examples of VR applications that tested the system and allowed the ATRC staff to gain experience. A team of professionals consisting of engineers and clinicians was convened to look at the newly acquired technology and to make recommendations on its use. Team members include: Sujat Sukthankar, PhD; William Peterson, M.S.; Joe Bleiberg, PhD; Brendon Conroy, M.D.; Jack Spector, PhD; William Garmoe, PhD; Debra Rost, OT; Patty Pyatak, SLP; and Corrie Lathan, PhD. The team concluded that VR would be a useful tool in the evaluation of individuals with unilateral left hemispatial neglect since VR offers the following advantages over traditional methods of visuo-spatial neglect testing:

1. The ability to have total control over the stimulus field;
2. The ability to target stimuli within the patient's visual fields;
3. The ability to test in three dimensional environments;
4. The ability to suspend physical laws such as gravity; and
5. The ability to objectively measure performance outcomes.

As a result of the team's deliberations, two format research projects have been identified: 1) "Assessment of Unilateral Spatial Neglect in a Virtual Reality Environment;" and 2) "Virtual Reality as a Tool for Family Education in Visuo-Spatial Neglect."

Status: Ongoing, with major enhancements

Composite Leg Brace Project

The National Rehabilitation Hospital has been committed for some time to developing, testing, and commercializing a new generation of composite leg braces for persons with physical disabilities. The ATRC has committed some of its resources to continue these efforts. The following is a brief description and status report of brace tasks worked on during the past year:

Mechanical/Fatigue Testing of Clinically Tested Composite Ankle Joints

Two out of four composite ankle joints which were subjected to over 70 hours of clinical evaluation while being incorporated into a pair of Scott-Craig long leg training braces were reevaluated using dynamic fatigue and static load tests by SPARTA, Inc. Upon completion of the evaluation, it was determined that the structural integrity of the composite ankle joints was not compromised as a result of loads and stresses applied to them during clinical trials. As a result, the composite ankle joint design was judged to be successful and is currently a candidate for future marketing endeavors.

Clinical Trial of Composite Knee Joints

Newly developed composite knee joints have been incorporated into a pair of Scott-Craig long leg training braces typically worn by paraplegics learning to ambulate. The knee joints were bonded to aluminum uprights using a non-reversible epoxy bonding agent. The purpose

of the clinical trials is to determine whether or not the composite knee joints can withstand the stresses applied to them in a structured clinical environment. The goal is to subject the braces to a minimum 50 hours of clinical trials during which various ambulatory and functional tasks will be realized including swing through gait; sit to stand transitions; ambulating up and down steps; standing from a prone position; ambulating up and down a ramp; and falling.

To date, the knee joints have been subjected to 43.75 hours clinical trials including: 8,850 feet ambulated using swing through gait; 257 sit to stand transitions; 42 steps ambulated; 17 floor to stand transitions; 235 feed ambulating up and down a ramp; and 37 practice falls. Upon completion of these trials, the composite knee joints will be removed from the training braces and returned to SPARTA for another battery of dynamic fatigue and static loading tests to determined whether structural integrity of the joints has been compromised due to clinical use. Clinical trials are expected to be completed by the end of November 1995 and mechanical tests completed by January 1996. Based upon results from the clinical trials and mechanical tests, a determination will be made about the future marketability of this design.

Reversible Bonding Agent

The composite joints designed for this project (ankle and knee joints) all incorporate 1/4 by 5/8 inch "pockets" used to couple the joints with uprights. In order to make this a modular system, it is necessary to identify a bonding agent capable of being reversed thus allowing an orthotist to dismantle a brace and rebuild it whenever necessary. NRH has contracted with SPARTA, Inc. to assist in the identification of a reversible bonding agent capable of withstanding the stresses of daily use.

To date, four agents have been identified and tested as possible candidates. All four candidates have failed. A fifth candidate has recently been developed by a chemist from Locktite. Tests on this agent are expected to begin sometime during the month of November 1995. If successful, it will be identified as the reversible bonding agent of choice for this project. However, if it fails, further research will continue and will probably include engineers and chemists from various Department of Energy labs since representatives from these labs have expressed an interest in working with the ATRC on these and other issues.

Injection Molding Process for Composite Ankle Joints

As mentioned above, a composite ankle joint has been developed and successfully tested both mechanically and clinically. However, the cost of manufacturing this joint is prohibitive in today's market. Preliminary test results indicate that an injection modeling process for manufacturing composite ankle joints can be accomplished and still stay within acceptable safety margins. Using this type of manufacturing process would reduce manufacturing costs dramatically thus making the NRH Composite Ankle Joints more affordable. Therefore, NRH has contracted with SPARTA to develop and test an injection molding process for manufacturing composite ankle joints. Results are expected by April 1996. If successful,

the newly designed ankle joints will be subjected to the same mechanical tests and clinical trials as their predecessor to ensure their structural integrity and safe use.

Postformable Composite Upright

An important component when making an entirely composite bracing system is the development of a composite upright that is both postformable and strong. Orthotists routinely postform uprights to make them biofidelic and cosmetically appealing. Composite materials inherently are not good candidates for postforming and therefore present a problem with respect to traditional methods of assembly by orthotists. Because of this, efforts have been made to overcome these challenges but have proved fruitless thus far.

Becker Orthopedic, Inc. has been successful in developing a postformable composite upright prototype and NRH has contracted with this company to manufacture ten feet of this material using a 1/4 by 5/8 inch rectangular geometry so that we may test its postformability and mechanical integrity. The rectangular geometry is necessary in order to integrate the upright with the composite knee and ankle joints already designed which incorporate 1/4 by 5/8 inch "pockets" for coupling the upright to the joint. Delivery of the upright material is expected in November 1995 and testing will begin immediately by both SPARTA and NRH to determine if it is an appropriate candidate for inclusion into our composite long leg bracing system. Results are expected by February 1996.

Brace Instrumentation Project

When NRH and SPARTA began its research and development of a fully composite long leg bracing system, it quickly became evident that the industry lacked information on the actual loads (axial, bending, and torsional) subjected to a brace during normal ambulatory and functional tasks. As a result, design criteria for bracing components has typically been determined by using reverse engineering techniques of existing components (i.e., stainless steel ankle joints and knee joints) and not on actual loads. Depending upon components tested, the information revealed may very well lead to over design. Conversely, there is also the possibility that the component tested may be under designed, and catastrophic failure of future brace components could occur. Thus, there exists a need for a quantitative study to determine the overall mechanical loads on individual long leg brace system components. In Year 1, the ATRC recognized the importance of such a study and developed a proposal to determine these loads.
Status: Ongoing

Materials and Orthotics Projects

One of the key areas of innovation in DOD and NASA labs has been in advanced and smart materials. The ATRC is interested in identifying appropriate materials, fabrication techniques, and design methodologies that can have the impact on the rehabilitation field and performing the appropriate research necessary to transfer the technologies into the private

sector. This involves developing or obtaining prototypes, then utilizing our resources to evaluate and refine these prototypes with the ultimate aim of producing deliverable products. This deliverable can take one of two forms: i) the transfer of a process (e.g., a published technique that can be replicated with manuals and some type of support infrastructure); or ii) the delivery of a device into the marketplace.

In general terms, two interrelated classes of projects can be identified: i) projects focussing on innovative materials and fabrication methodology; and ii) projects that develop and evaluate innovative orthoses. Often the latter can serve as testbeds for the former. The ATRC has identified three projects that are related to this materials/orthoses thrust. These projects complement the Composite Leg Brace Project which also has a strong materials/design (and evaluation) component.

Innovative Fabrication/Design Methodologies for Orthoses

During the first year, our initial objective was to enhance our internal knowledge and expertise of advanced materials and fabrication techniques. As part of this effort, the ATRC staff identified postformable thermoplastic composites as a priority area, particularly the fabrication of thin, strong, mildly postformable shells. We were able to identify several techniques for fabricating these shells. Our subsequent objective was to select several innovative fabrication approaches that we felt had significant potential for transfer into the rehabilitation sector and to develop in-house capabilities for materials fabrication, prototype design and evaluation.

In carrying out these objectives, staff visited a local (and NRH affiliated) othortics and prosthetics (O&P) company, NASCOTT, to learn about current O&P practices. Trips were made to NASA Langley to learn about their manufacturing and postforming techniques for composite materials. Federal labs throughout the country were contacted and discussions followed about potential collaborative efforts in the materials field.

NASA was very helpful and directed us towards two fabrication techniques/tools which we evaluated for potential ATRC projects: 1) a Silicon Thermal Expansion Molding (STEM) process; and 2) a Toroid (Induction) Bonding Gun. The STEM showed tremendous potential for fabricating thermoplastic composite shells, and the Toroid Bonding Gun demonstrated potential for postforming those shells to make them more biofidelic.

An advantage of the STEM approach is that it is reasonably cost-effective and could, in principle, be utilized within a conventional orthotics shop. There are three basic components to this process: an outer aluminum mold, an inner silicon rubber core, and the thermoplastic matrix and fibers that are sandwiched between the outer and inner molds. Upon heating, the silicon rubber expands considerably more than the aluminum, and the thermoplastic melts and "wets" the fibers while under high pressure. The result is a high-quality thermoplastic composite shell. For NASA's high-temperature applications, the pressures can be remarkably high. By adding small silica beads when making the silicon rubber mold, the

degree of expansion (for a given temperature) can be controlled. By additionally considering the free volume at room temperature and the melting temperature of the thermoplastic through mathematical analysis, one can estimate the appropriate conditions for obtaining a desired range of pressures that will allow for a smooth composite to be formed without exploding the external aluminum mold. Several aluminum molds have been machined. By adding clay of specified thickness and then pouring a silicon-silica mix into the cavity, we are able to make matching internal molds with a prespecified free volume. To date, we have manufactured shells that have the shape of truncated cones of a diameter range that includes that of the upper arm of a typical adult. By varying the type of thermoplastic matrix material and the fiber weave, shells with different mechanical properties are possible.

Another promising technology, the Toroid Bonding Gun, is capable of joining composites, plastics, metals, and combinations thereof through induction bonding and is capable of heating extremely small and specific areas without affecting the surround. This makes the tool a likely candidate for locally postforming composite materials and for attaching/detaching bonds. In year 2, we plan to purchase the Toroid Bonding Gun to investigate its use in orthotics.

Posture-Assist (Anti-Gravity) Shoulder-Arm Orthoses

Several years ago, the Rehabilitation Engineering Research Center (RERC) on Rehabilitation Robotics in Delaware[1] identified a significant need for an orthotic device that helps hold up one's arm while extended perpendicular to the body. Such a device can benefit a wide array of people including those with muscular dystrophy, multiple sclerosis, brachial plexus injuries, and those who work in jobs requiring them to hold their arms out perpendicular to their body for long periods of time. The RERC developed a prototype "anti-gravity" device that could attach to a chair or wheelchair. This passive device uses a complex array of springs within parallelogram structures to counterbalance the weight of the arm. In 1994, CUA students fabricated a newer design that mounted to a backpack frame. Both of these past prototype designs are fairly bulky and attach to a large base.

Using these conceptual frameworks, the ATRC focused on designing a study to fabricate and then evaluate a low-profile, streamlined system that is miniaturized and conformed such that it can fit with relative ease under most clothing. The device will use four parallelogram links, with the most proximal link mounted reasonably close to the origin of the clavicle and the most distal link coupled to the forearm, such that there are three degrees-of-freedom in the horizontal and vertical planes. The device will be partly mounted to the body using postformable composite shells described above.

---

[1]Funded by the National Institute on Disability and Rehabilitation Research (NIDRR).

Leg-Powered Shoulder-Assist Orthoses

Body-powered upper-limb prostheses, designed primarily during the 1940s, have proved to be a remarkably robust technology with low rates of abandonment versus "higher-tech" powered prostheses. At the foundation of this technology is the use of Bowden cables to transmit power and information (force, length, velocity) from one region of the body to another. This concept has also been used to design a leg-controlled feeder that, for a limited population of users, appears to be quite effective. The success of these technologies appears related to the intimate contact between the device and the person which allows the part to essentially become an extension of the body, not unlike a tennis racquet or hockey stick in the hands of an experienced player. This phenomena has been coined Extended Physiological Proprioception (EPP). Given the effectiveness and simplicity of this class of technology and its ability to be combined with artificial muscles, the ATRC designed a project to investigate its use with hemiplegic stroke patients who, while seated, could utilize the uninvolved leg to help move or stabilize the involved arm. This could be useful for therapy and for performing range of motion exercises.

The primary purpose of this project is to develop a prototype to test the EPP concept for new applications. The focus is on a shoulder-assist orthoses in which the shoulder with three degrees-of-freedom and the elbow with one degree-of-freedom are mapped to corresponding contralateral leg motions with three degrees-of-freedom. The design includes a shoulder-arm orthoses (including a scapular component that will move with the underlying scapular), a leg orthoses, Bowden cables, and a chair.

Status: Ongoing with major enhancements

Intelligent Rehab Assistant

Remarkable advances in telecommunication and computer technologies are gradually transforming society. Sensors are now smaller and often cheaper and wireless systems are now commonplace. DOD has invested heavily in these technologies. An area that is attracting considerable private and public investment is that of "tele-assistants." Some of these systems are intended for home use and others as assistants to specific types of professionals. Their impact on health care delivery, both in the private sector and within the DOD and VA medical infrastructure, is unknown. Yet in this era of health reform, it seems likely that the impact may be significant, perhaps profound. We know that assistive technology, when used appropriately, has enhanced the quality of life, independence, and quality of care of many persons with disabilities.

The purpose of this project is to develop portable, "intelligent," user-friendly evaluation tools that can be used to quantitatively assess a patient's neuromotor (and perhaps neurocognitive and biomechanical function using an appropriate battery of tests. Evaluation would be based upon synthesis of: multiple channels of objective sensor-based information; multiple tasks within a test battery; and standard clinical assessment measures.

The primary thrust during this first year has been on system development: creating an efficient and robust calibration procedure and an aggressive, near-real-time data analysis scheme.

Conceptual Framework of a Rehab Assistant

Our approach has been guided in part by NASA's Principal-Investigator-in-a-Box/Automated Support System for Expert Tele-Science ([PI]/ASSET) technology. This interactive portable computer assistant has a strong artificial intelligence base that has been used to assist astronauts in performing human movement research studies on the space shuttle. The system consists of a set of modules that serve to provide near-real-time data synthesis using: i) LabView (National Instruments) for data collection; ii) NASA's CLIPS as the expert inference engine; and iii) Apple's HyperCard as a front-end interface. Part of our first-year plan included interacting with Dr. Nick Groleau of NASA AMES to obtain the [PI]/ASSET technology and to utilize it in our development process.

Portable Sensor Technologies

Three portable sensor technologies were identified during the initial development stages of the Intelligent Rehab Assistant that are of interest. These sensors measure: electromyographic (EMG) activity using up to 15 electrode/preamp units (Motion Control, Inc.); force using a miniature six-axis force transducer (Assurance Technologies, Inc.); and motion using a Flock-of-Birds electrogoniometer system which simultaneously tracks position and orientation of up to three receivers (Ascention Technologies, Inc.). measurement system called Flock of Birds (Ascension Technology, Inc). Each involves sampling multiple channels of information over time. Our focus during Year 1 has been on EMG and force signal collection/analysis.

Data Acquisition, Filtering and Storage

LabView, a graphical, object-oriented, software package from National Instruments is being used for data acquisition, filtering, and storage and also for preliminary development of front-end user interfaces. LabView is a sophisticated package that requires significant development time. It allows natural human interfaces such as buttons, knobs, displays and the like. At the top level are more general menu-oriented interfaces that help guide the user through the experimental protocol. Below this are the specific user interfaces for each task, including user inputs (e.g., sampling rates, data storage locations) and the display selected results.

Expert Inference Engine

Fuzzy-CLIPS is an expert system package that allows both crisp and fuzzy rules to be formulated and can receive both crisp and fuzzy data. The strength of this package rests in its ability to synthesize a variety of types and forms of information in making decisions. The

outcomes of this process are summary observations and suggestions for the user. The ATRC has investigated the feasibility of developing a robust, task-independent synergy engine that uses fuzzy inference to aggressively search for muscle and force synergies both within a task and across a battery, prioritizes the information, and reports the most notable findings. We have also considered specific rules that can be used for trouble-shooting.

Calibration

One of the key initial areas of focus has been on efficient calibration so that all signals are scaled to an estimate of maximal level. The desire was to have a calibration system that can work at any site, thus allowing the system to be portable. Calibration of EMG (n=15) and force (n=6) was deemed to be of highest priority. One concern, from both practical and theoretical perspectives, was how to scale EMGs placed over muscles that are part of the shoulder girdle and torso. After considering several alternatives, our approach has been to develop a device that can mount to a door, is easily adjustable, houses the force transducer, and then couples at the other end to the hand or to a skin surface such as the upper arm via appropriate attachments. The subject then imparts a voluntary "maximum" force on the device, in specified directions and with different body configurations. Through correlation and fuzzy inference, our objective is to minimize the number of tests that need to be performed to adequately calibrate the system with a bias towards using hand-grip interface tasks. As a byproduct, this is innovative research on human postural coordination and large-scale muscle synergy, capable of being published on its own merit.

Status: Ongoing

Year 1 Presentations

1. Peterson, W.A., Brannon, R., Dang, T., Morris, K., Scott, K., The Use of Non-Metallic Composite Materials for Development of Lightweight Bracing Components. Poster session at the Advanced Technology Applications for Combat Casualty Care II Conference. Silver Spring, MD. May, 1995.

Plans for Year 2

Virtual Reality Projects

Project 1

"Assessment of Unilateral Spatial Neglect in a Virtual Reality Environment"

This proposed study is intended to assess elements of unilateral spatial neglect in a virtual reality environment. Two different elements of visual neglect will be investigated: 1) overt attention to hemispace on a bisection task; and 2) covertly-assessed attention to hemispace

implicit in performance on a block stacking task. Performance on each of these two tasks will be assessed under three conditions: 1) high salience in the affected field where information presented to the affected side of extrapersonal space will be highlighted in such a way as to attract as much of a patient's attentional resources as possible; 2) low salience in the intact field where information presented to the unaffected extrapersonal space will be degraded or distorted with the intent to drive the patient's attention to the otherwise affected hemifield; and 3) an unenhanced condition where unaltered stimuli will be presented to both the affected and intact extrapersonal fields.

Four groups of subjects will be used for this project: 1) fifteen adult patients with clinical evidence of unilateral left hemispatial neglect; 2) fifteen normal adults demographically matched to group 1; 3) ten adults who have undergone right temporal lobectomy for seizure control leaving them with residual left visual field losses and/or evidence of residual unilateral left hemispatial neglect; and 4) ten normal adults demographically matched with group 3.

The study is intended to address the following questions:

1) Can unilateral visual neglect be adequately assessed in a virtual reality environment?

2) Can tasks designed to take advantage of the VR environment better assess qualities of unilateral visual neglect than do current procedures?

3) Can the effects of unilateral visual neglect be exacerbated or attenuated by manipulating certain stimulus qualities within the VR environment?

4) Are those elements unilateral visual neglect assessed and manipulated within the VR environment more apparent on overt or covert tasks of hemispatial attention?

Project 2

"Virtual Reality as a Tool for Family Education in Visuo-Spatial Neglect"

Neglect is defined as a failure to respond, report, or orient to meaningful stimuli presented on the side contralateral to a lesion. The complex nature of this neuro-psychological pathology makes its treatment and management very difficult. While there are several theories to explain the neglect phenomenon, there is a dearth of objective educational tools to help one understand its functional implications.

Rehabilitation of neglect patients includes helping them to learn compensatory behaviors to overcome shortcomings brought on by their stroke. Educating family members is also a crucial component of the rehabilitation process since family members are often required to

assist the individual with daily tasks. Currently there are no standard methods for family education other than video-tapes and pamphlets on the phenomenon of neglect. While educational video-tapes and text-based materials do help raise family member awareness, they are non-interactive and therefore non-participatory. The immersive, interactive nature of VR provides us with a powerful option for family education and could augment or even enhance existing methods for family member education. Therefore, a research proposal is being developed to study the effects on family members from an immersive educational experience that emulates a person's visual field cut thus possibly enhancing their perception and appreciation of the neglect phenomenon. The overall objectives of this study will be to:

1. Develop a VR based family education tool for visual neglect; and

2. Evaluate the efficacy of a VR based educational tool for increasing family member awareness of implications on patient performance.

The first phase of this study involves the development a VR based tool to help quantify the visual field cut in patients with neglect. In order to do so, the visual field will be separated into individual grid locations. The patient will be presented with a screen with random numbers (0-9) flashing at various grid locations in a pseudo-random manner. The patient will be asked to indicate the number that flashes on the screen within a predetermined amount of time and his or her responses will be recorded. Data recorded will be used to define the individual's visual field cut and will be stored in an ASCII file for future reference.

The second phase involves the development of software to incorporate results from the visual field cut (explained above) with virtual simulations and to use the visual field mapping as a means to "mask" what an individual can see when exposed to virtual simulations. The result of overlaying an opaque visual mask onto virtual simulations should hopefully allow us to simulate an individual's visual field cut and to share that visual deficit with family members. The following virtual simulations are currently being considered for this study:

1. A virtual lap tray with assorted foods/objects at various locations on the tray from which the individual will be asked to verbally respond to questions regarding the trays content;

2. Sorting of dishes and hardware in a virtual kitchen scene; and

3. Pushing and returning a virtual shopping cart to a grocery store, including a street crossing.

Family members of person's with left sided neglect will be divided into two groups. Both groups will receive a predefined intensive training session about left sided neglect and how the resultant visual field cut can affect the individual's ability to dress themselves, to

properly lock their wheelchair, to independently feed themselves, to properly shave their face, etc. This training session will likely last a couple of hours. One group will also be exposed to a virtual representation of their family member's visual field cut during certain tasks as described above. All family members will then be questioned about their educational experiences to determine if the VR based educational tool increased their awareness about the affects of neglect and how that awareness may have helped them to better cope with their loved one's loss.

Proposed New VR Project

Balance Testing Project

VR has been used in the past to help individuals overcome their fear of heights. We can find nothing, however, in the literature on using VR in balance studies. We feel this could be an exciting area of research. The Performance Diagnostic Lab, as part of the ATRC, is currently equipped with a Vicon Motion Analysis System, two AMTI force platforms, a flock-of-birds (FOB) electrogoniometer system, and a VR workstation. A new data acquisition workstation is proposed in this year's budget which would be interfaced with a data acquisition card to collect data from both AMTI force platforms thus creating a balance assessment system. A proposal will be developed to hopefully provide insights into how the bodies balance mechanism reacts to visual stimuli.

Composite Brace Project

The ATRC will continue its efforts to develop a fully composite long leg bracing system. As stated earlier, the following tasks are ongoing.

- Clinical trial of composite knee joints
- Development of an injection molding process for composite ankle joints
- Development of a postformable composite upright
- Development of a composite footplate and stirrup

Brace Instrumentation Project

The objective of the brace instrumentation study is to determine the overall mechanical loads on individual long leg brace system components. The goal of this study is to obtain a quantitative understanding of the overall mechanical loading of the Scott-Craig long-leg brace during various ambulatory and functional tasks and to address the issue of over design which may result in excessive safety margins and increased weight and bulk. The absolute loads placed on the braces will be measured by using conventional, foil-type strain gages. Strain gages are electrical resistors which have been designed to be bonded to the surface of a solid object and undergo a change in resistance when a strain is produced in the direction of its sensing grids. Up to 70 gages will be used to measure the medial-lateral (M/L) and anterior-posterior (A/P) bending moments at specific areas on the brace, and axial loading and torque

about the long axes of brace uprights. Two force platforms imbedded into the Performance Diagnostic Lab floor will be used to provide researchers with additional quantitative information about the ground reaction forces generated during each task.

Information gathered from the strain gages and force platforms will assist researchers in determining the absolute loads on each brace during six ambulatory tasks: (i) swing through gait, (ii) sit to stand, (iii) ambulating up and down steps, (iv) standing from a prone position, (v) ambulating up and down a ramp, and (vi) falling. A total of 10 to 12 pair of braces will be instrumented with strain gages and tested under this proposal. Users will be asked to perform as many of the six predetermined tasks as possible under the careful scrutiny of a physical therapist. Results from this study will help the orthotic industry with the design of future components and will assist the ATRC in the future design and development of nonmetallic composite bracing components.

Materials and Orthotics Projects

Ongoing Orthoses Projects

Posture-Assist (Anti-Gravity) Shoulder-Arm Orthoses

A working prototype of this device with miniature joints and thin shells is expected before the end of 1996. Because of this, prioritization of a target population (e.g., adult or child size) is needed. A human subjects protocol will be submitted this Fall with initial evaluation of human subjects occurring during the Winter and Spring. Based on the results of this pilot study and informal feedback from users, it is expected that some design alterations will be required. During the Summer of 1996, a more controlled study will be performed that will include a standard laboratory-based functional evaluation.

Leg-Powered Shoulder-Assist Orthoses

The prototype Leg-Powered Shoulder-Assist Orthoses is expected to be completed during December 1995 and tested via the existing human subjects protocol for normals. Based on the results of this first study, the project will either be given a green light to continue with a focus on the hemiplegic stroke population, or stopped. In the latter case the findings will be published and the device will still be available as a testbed for other projects. In the former case, the next phase of testing will focus on several types of tasks: general postural stability of arm positions, range-of-motion, and simple ADLs.

Innovative Materials/Fabrication/Design Methodologies

Silicon Thermal Expansion Molding (STEM)

The STEM project is now felt to be at an engineering stage that will result in production of strong, light-weight, moderately postformable shells that is needed for research projects. Each new "run" requires fabrication workup followed by heating and cooling in an oven, a process that takes much of one day but requires only the occasional focus of the researcher. We will systematically continue this project until we have shell end-products that best meet our needs. This project is expected to be completed about midway through Year 2. We then need to evaluate the process for possible transfer, starting with feedback from NASCOTT.

Vacuum Forming

During Year 1, several vacuum forming and draping approaches were identified as candidate fabrication methods worth investigating. NASCOTT, for instance, already uses vacuum draping for certain (non-composite) applications. The necessary materials for higher temperature (thermoplastic composite) vacuum forming was purchased in Year 1 and we expect to establish in-house capabilities in this area during Year 2. This will require only a moderate investment of time and resources.

Toroid Bonding Gun

The Toroid Bonding Gun technology is to be purchased during Year 2. This technology allows for fast, very localized, selective internal heating of an appropriately planned application. This will be evaluated for possible applications which we feel could profoundly impact the orthotics field. Two such ideas are: 1) reversible bonding for modular orthoses (e.g., composite-metal, composite-composite surfaces coated with a thermoplastic adhesive with an embedded susceptor); and 2) selective "on-the-fly" hardening of drapable, form-fitting orthotic shells while on the person.

"Smart" Materials

There is a strong desire to pursue the area of "smart" materials -- materials with intrinsic electrical-mechanical-thermal coupling that allows them to function as either an actuator or a sensor. There are two classes of intriguing applications. The first class of materials are low-frequency "shape memory" materials that could function as static orthoses which are pre-designed to slowly (below rates sensed by muscle spindles) change conformation, triggered simply by body temperature. This could be used, for instance, for management of contractures. The second class of materials are thin, higher-frequency materials that have been used to annihilation vibrations in DOD applications such as a helicopter fuselage. These materials could possibly be used for management of tremor and other forms of oscillation due to neuromotor impairment.

Intelligent Rehab Assistant

There are two areas of consideration for this project. First, there is the need to develop an effective, deliverable Rehab Assistant system that can become an integral part of rehabilitation service delivery. Second, there is the need to use and evaluate the Rehab Assistant as it evolves focusing on key strategic projects which capitalize on our expertise, interests, and resources.

During Year 2 we plan to continue with our development of the expert inference engine, with a focus on determining appropriate crisp and fuzzy rules, and on information synthesis. Our focus is on condensing multi-channel sensor data into a set of prioritized English phrases. In this way, the user need not be bothered by an overwhelming array of sensor data, but will instated receive a synthesized summary consisting of priorities, observations or suggestions.

Currently our front-end interface uses LabView which is adequate for research studies but not ideal for a general-purpose Rehab Assistant. We desire to put into place a more general front-end user interface that includes an interactive authoring tool. Plans are under way to evaluate "On Call Companion" from Method Factory to determine whether or not we could use its authoring package for our purposes.

C. COGNITIVE STUDIES SECTION
Year 1 - Progress Report

Introduction

The original proposal contained statements of Year 1 and Year 2 overall objectives, specific hypotheses, and technical objectives. Below, text from the original proposal is in bold, followed by a status report.

Overall Objective 1: **"There should be extensive involvement of DOD scientists in the NRH-based projects to ensure collaboration, communication, and coordination across activities."**

Status: Achieved and ongoing

Commander Dennis Reeves, USN, is one of the three co-principal investigators for the ATRC Cognitive Studies Section (ATRC-CSS). He has been a collaborator and co-author of the two peer-reviewed papers already published, the one paper in preparation, and the two major presentations given at the August, 1995 American Psychological Association (APA) Annual Conference. Dr. Reeves has participated in all major decisions, including personnel selection. He also participated in the project's Advisory Board meeting, held on August 12, 1995, in which progress to date was reviewed and the Year 2 plan developed.

Overall Objective 2: **"NRH-based projects should be designed to have an open data structure to DOD scientists."**

Status: Planning process led to re-design; new design to be implemented in Year 2

The Advisory Board meeting of August 12, 1995 explicitly addressed the issue of how to make our data available to DOD scientists. The outcome of this discussion is reflected in the new Year 2 project "Computerized Library of ANAM Reference Cases."

Specific Hypothesis 1: **"Our previous six-subject finding that variability of sustained performance is a sensitive index of mild brain injury will be replicated using a large sample."** Specific Hypothesis 2: **"Our previous six-subject finding that control subjects, between Trials 7 and 12 on Day 2, develop a stable and efficient performance level, while mild brain injured subjects continue to show initial inefficient and unstable performance levels even by Trial 44 on Day 4, will be replicated."**

Status: Ongoing

The above hypotheses were based upon a preliminary analysis of data we had collected prior to the start of the ATRC-CSS. Formal analysis of those data was performed as part of Year 1 of the ATRC-CSS by a statistician consultant, Mark Czarnolewski, Ph.D. The data analysis showed that all ANAM summary scores (reaction time, throughput, and variability) were able to identify mild brain injury, even at more than one year post injury. However, reaction time and throughput were more effective than were the variability data in differentiating the six mild brain injured from the six matched controls. A paper based on this study is nearly completed and is to be submitted to the Journal of Clinical and Experimental Neuropsychology by November 1, 1995. The Year 2 proposed project "Long-Term Stability and Variability of ANAM Performance in Brain Injured and Control Subjects" includes an extended replication of this study.

Specific Hypothesis 3: **"Our previous single-subject finding that reduced variability of sustained performance is a sensitive index of stimulant drug response will be replicated with group data."** Specific Hypothesis 4: **"D-amphetamine and similar stimulants are cognitive enhancing agents for persons suffering persisting cognitive impairment secondary to mild brain injury."**

Status: Ongoing

We have completed seven single-subject triple-placebo-crossovers. Each study has included at least eight days of testing per subject (two days each of baseline, placebo, Drug 1, and Drug 2), and one subject was run through a second complete triple-crossover to pilot test an alternative methodology. The results do not support Specific Hypothesis 3: reaction time and throughput data are more effective than variability data in demonstrating positive medication effects. The results do support Specific Hypothesis 4: two of the seven subjects showed

ANAM enhancement on medication. These early data also suggest that while methylphenidate and d-amphetamine are similar drugs, patients can show positive response to one but not the other drug, and one of our "responders" actually showed a positive response to one drug and a negative response to the other.

The across-day baseline levels of performance, within each subject and before ingestion of the drug/placebo capsule, showed unexpectedly high variability, calling into serious question whether stable baseline performance levels had been achieved. This was despite giving subjects at least two days of ANAM practice in the baseline period. The reason only two out of seven subjects showed drug responses may have been that positive findings were masked by the high across-day variability.

The Year 2 proposal is to continue the single-subject drug trials while at the same time using the drug trials as a setting for exploring methodologies to address the across-day variability issue. One procedure already in pilot testing is to obtain baseline scores each day, then use that day's baseline for the calculation of that day's drug effects. This technique is promising. We will perform the next eight drug studies using it, then assess whether it corrects for the problems with the original procedure and does not introduce new problems.

The above described across-day variability also raises questions about the amount of across-day variability that is "normal." Part of the study "Long-Term Stability and Variability of ANAM Performance in Brain Injured and Control Subjects" includes administering the identical testing procedures of the drug trials (eight days of 5 hours per day, with washout days, etc.) to 12 healthy control subjects who will receive no drug. While this is quite labor intensive and costly, it is essential for determining whether the variability reflects "noise" in our methodology or is a symptom of brain injury.

Specific Hypothesis 5: **"Stimulant drugs are not cognitive enhancing agents in well-rested control subjects during sustained performances of less than six hours."**

Status: Not started; not included in Year 2 proposal

Specific Hypothesis 6: **"The cognitive evoked potentials of stimulant drug responders will show less variability in the drug than in the non-drug condition, essentially replicating the single-case study described previously (Starbuck et al., 1994)."**

Status: Ongoing, with major enhancements

At the time the original proposal was prepared, cognitive P-300's were the best psychophysiological measure readily available to us. In February of 1995, one of our collaborators, Victoria Starbuck, Ph.D., of the Neurology Department, Georgetown University School of Medicine, made FMRI studies available to the present project. We have completed a placebo-crossover d-amphetamine study using FMRI and the results are excellent. The results also are consistent with our prior P-300 ERP study. We therefore

have amended the Year 2 plan to replace P-300 with FMRI and have incorporated Dr. Starbuck and Dr. Robert Platenberg (Chair of Radiology at Georgetown) as co-investigators. The Curriculum Vitae (CV) for Drs. Platenberg and Starbuck are in Appendix B.

Appendix C shows the P-300 ERP's and FMRI's. The P-300 data was just published in a peer reviewed journal, and the FMRI data has been accepted for presentation at two upcoming peer reviewed conferences, one for neuropsychologists and the other for neuroradiologists. Appendix C includes copies of these presentations.

Technical Objective Years 1-2: **"Our technical objective is to create a database to permit defining the psychometric properties of ANAM, including its concurrent validity, construct validity, and relation to demographic and subject variables such as age, gender, intelligence, and education."**

Status: Ongoing

The Year 2 project "Computerized Library of ANAM Reference Cases" proposes to assemble a searchable database of the complete raw data for each of the subjects we (and Drs. Reeves, Kane, and Spector) study. These subjects are well characterized demographically and psychometrically, and thus can be used by other investigators as control or reference cases. Moreover, making the raw data available, rather than summary scores of our choosing, provides the maximum possible "open" data access. In the spirit of Overall Objective 2, Dr. Reeves will be active in the design of the database to ensure that it is maximally useful for military as well as civilian scientists.

Year 1 Products/Publications/Presentations

1. Starbuck, Platenberg, Bleiberg, et al. Working Memory: A case study of signal enhancement with d-amphetamine treatment following head injury. Accepted for presentation (verbal acceptance received), International Neuropsychological Society Annual Meeting, February 14, 1996.

2. Bleiberg and Reeves. Issues in assessing psychopharmacologic enhancement of performance. Invited pre-conference workshop, Brain Injury Association Annual Conference, December 3, 1995.

3. Starbuck, Platenberg, Bleiberg, et al. FMRI: A case study of d-amphetamine mediated signal enhancement during working memory tests. Accepted for presentation at Eastern Neuroradiological Society Annual Meeting, October 7, 1995.

4. Starbuck, Bleiberg, and Kay (1995). D-amphetamine-mediated enhancement of the P300 ERP: A placebo-crossover double-blind case study.

Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 8, pp. 189-192.

5. Reeves, Kane, and Bleiberg (1995). Overview of computerized neuropsychological assessment with Emphasis on the DOD approach. Day-long ANAM Category A CEU workshop at the American Psychological Society Annual Meeting.

6. The above workshop received such high ratings that APA invited us to repeat it at next year's conference in August, 1996, in Toronto. (We accepted).

7. Bleiberg, J., Nadler, J., Reeves, D., Garmoe, W., Cederquist, J., Lux, W., and Kane, R. (1994). Inconsistency as a marker of mild head injury. Presented at the Annual Meeting of the International Neuropsychology Society.

8. Bleiberg, J., Reeves, D., and Garmoe, W. (1994). Enhancing performance via pharmacologic intervention. Presented at the International Rehabilitation Medicine Association VIIth Super Course.

Year 2 Plan

Study 1: Psychopharmacologic Enhancement of Performance Following Brain Injury

This is a continuation of the ongoing Year 1 project. The only changes are:

1. Accelerated pace of data collection to complete 20 additional single-subject triple-crossover studies.

2. Use of the first eight of the above studies to pilot-test a new methodology of using within-day baselines, and operationalizing drug effects as deviations from such baselines.

3. Addition of psychopharmacologist/psychiatrist consultant, Michael Egan, M.D., to assist with interpretation of drug effects and mechanisms of action (see Appendix B for CV)

4. Replacement of P300 ERP with FMRI as the psychophysiological measure and inclusion of Drs. Starbuck and Platenberg as co-investigators (see Appendix B for CV's)

5. Appendix D contains a description of the FMRI procedures and Dr. Starbuck's protocol for cognitive activation

Study 2: Long-Term Stability and Variability of ANAM Performance in Brain Injured and Control Subjects

This is a combination of several substudies to examine stability and variability of ANAM performance in persons with brain injury and in healthy controls.

Substudy 1: Performance of healthy control subjects on the NRH single-subject triple-placebo-crossover procedure

The purpose of this study is to identify "normal" patterns of within-day and across-day variability in ANAM performance. The procedure will be to administer the identical testing procedure used in the single-subject drug trials to twelve healthy control subjects (no medications will be involved). Data analysis will consist of inspection of descriptive statistics and graphs to determine if healthy controls show the expected patterns of either stable performance or mostly stable performance with occasional steps of improvement. If this proves to be the case, then the results would be widely disseminated so that other researchers would know that ANAM stability in healthy controls may not apply to ANAM performance in brain dysfunctional populations. Should the data show high variability in healthy controls, it would suggest that ANAM, or our procedure for using ANAM, was "noisy" and in need of modification before being applied to pharmaceutical trials.

Substudy 2: Test-retest reference levels of ANAM performance in healthy controls from two age strata

This study will provide reference levels of several dimensions of ANAM performance for two age ranges. The ANAM performance dimensions are: initial performance level, learning curve over five same-day ANAM administrations, and repeat performance one month later. Ancillary measures to provide some concurrent validity will consist of 45 minutes of standardized psychometrics (Trails A&B, Consonant Trigrams, WAIS-R Information subtest, and the NART). The procedure will be for subjects to receive five consecutive ANAM administrations over a 1.25 hour period, then receive .75 hour of psychometrics, which then will be repeated four to five weeks later. The age strata will be late adolescence and middle age. No compensation to subjects is planned.

Adolescents will be 60 16-18 year-olds from the football squad of Gonzaga High School (invitation already obtained). Subjects with a history of concussion will be included in the study, but will be excluded from any norms or reference ranges derived from the study. Subjects will be tested during the pre-season. In addition, should any of the subjects become concussed after testing, we will be notified by the head coach and will repeat the five ANAM trials at weekly intervals to map the natural history of ANAM performance during concussion recovery. The reason for inclusion of subjects with prior history of concussion is to compare them to non-concussed peers. During Year 2 we also will seek access to study female 16-18 year-olds, and this would become a study during Year 3. The decision to use male subjects in Year 2 was based on our making two inquiries, one to a female soccer team

and the other to a male football team, and receiving an invitation from the latter and a rejection from the former.)

Middle-aged subjects will be 30 high functioning, healthy 50-60 year-olds, balanced for gender. Materials and procedures will be identical to those described above.

Data analysis will consist of comparing the two samples on all measures to determine any age-related effects, conducting correlational analysis between ANAM scores and psychometrics to explore concurrent validity, calculating test-retest reliability coefficients for all measures, and producing summary statistics to serve as preliminary normative reference points, to include means, standard deviations, medians, deciles, and ranges.

Substudy 3: Exploration of core deficits secondary to concussion

As already noted, we have analyzed pilot data for 6 mildly brain-injured and 6 closely matched healthy controls. The data show that the control group quickly achieved stable performance early in Day 1, but then showed an additional and substantial step of improvement late in Day 2. The brain-injured group did not show this second step of improvement even by Day 4, and rather showed erratic performance around a stable mean. These pilot data suggest that the brain-injured group may have an underlying deficit in the capacity to achieve performance "efficiencies" on repetitive tasks. This is a finding that has not been reported in the literature, and the presently proposed study, in Year 2, is an extended replication to determine if the finding is robust and reproducible. If replication is successful, then in Years 3 and 4 the study would broaden focus to identify co-variates and assess interventions.

NRH recently started offering a comprehensive clinical assessment and treatment program for concussion patients. This program provides an ideal setting for Substudy 3: it is a source of subjects, subjects receive standardized medical and neuropsychological evaluations from personnel who also are part of the research team, specialized diagnostic procedures are available (eg. sleep lab, EEG, MRI), and a full range of treatments is offered (eg. medication, speech therapy, psychotherapy, physical therapy). There are two Year 2 goals: to replicate the pilot study using a sample size of 15 concussion patients and 15 control subjects, and, to integrate a research infrastructure (objective measures, coding system for variables of interest, and a database so clinical data can be captured for research, etc.) into the clinical program.

The replication study uses identical procedures and materials as the pilot study. Sample size is increased to 15 per group to permit increased statistical power. Subjects who show deficits will be considered for medication trials (Study 1).

Project 1: Computerized Library of ANAM Reference Cases

Studies 1 and 2 will produce data useful to other investigators. For example, the NRH subjects can be used as control subjects in other studies, producing large cost savings. Project 1 focuses on making these data readily available, in maximally useful form, to selected DOD and civilian investigators. Once developed and tested, the methodology used to disseminate the NRH data then will be used to integrate and disseminate data sets from other investigators (Drs. Reeves, Kane, and Spector have agreed to contribute the data sets from their past and future ANAM studies). The end result will be a centralized, searchable source of ANAM data derived from reliable sources.

Specifications of the data "library" are that: cases be searchable by demographic, psychometric, and diagnostic variables; that summary data (alphanumeric and graphic) for each reference case be routinely available; that the entire raw data set be available to contributing participants; that "information only" levels of access be available to the broader neuropsychological community; and, that participants be able to access the system electronically.

APPENDIX A

ADVISORY COMMITTEE MEETING

SUMMARY

Assistive Technology Research Center

Advisory Committee Meeting

December 15 and 16

MEETING SUMMARY

ATTENDEES

Lee Rivers
Joseph Lane
Dennis Reeves
John Goldschmidt
Ray L. Gilbert
Barbara DeLateur
Lynn Gerber
Michael Hopmeier
Fred Hegge
Richard Materson
William Peterson
Joseph Bleiberg
Jack Winters
Ruth Brannon
Jimmy Abbas
Gerben DeJong
Deborah Wilkerson
Heidi Hicks

Wednesday, December 14

The meeting was opened by Mr. Edward Eckenhoff, President and CEO of the National Rehabilitation Hospital. Mr. Eckenhoff's remarks were followed by introduction of the Committee members, the Army representative, Dr. Fred Hegge, and description of the ATRC objectives and role of the Advisory Committee.

Dr. Materson presented ATRC goals,

- Improving the lives of persons with physical disabilities by identifying promising technologies from military and other settings that can be adapted for this use

- Increasing military awareness of the efficacy of rehabilitation technology and its application in military and related government settings

and he outlined four specific objectives of the Center, including:

- Identification of technologies originally developed for military an/or space applications that hold promise in addressing the medical, rehabilitation, and community support needs of people with disabilities

- Conducting research on ways in which technology can be modified or adapted for use in meeting the needs of people with disabilities

- Evaluating the effectiveness of technologies transferred from military settings, using both quantitative and qualitative methods

- Disseminating the results of efforts to promote effective technology transfer through publications, presentations, and other methods.

Dr. Winters expounded on the objectives by painting a verbal picture of future uses of assistive technology, including:

- Customized, light-weight, fiber-reinforced moderately postformable thermoplastics that are fabricated within one-half hour of patient arrival via CAD/CAD technology

- Small, light-weight biologically-inspired actuators powered by small, ultra-high-energy-density batteries

- Quantitative evaluations, routinely performed at home, with information automatically collected and transmitted to selected remote sites.

- Routine televisits, complete with direct visual contact between the user and appropriate provider(s)

Major Recommendations

A number of perspectives were represented by the members of the committee. These perspectives contributed to a rich discussion about the niche that could be occupied by the ATRC. Summarized below are the principle recommendations-by topic of discussion:

Identification of ATRC Target Audience: There was clear consensus that the target audience for ATRC outputs are persons with disabilities. The driving force behind this project is Mr. Eckenhoff's desire to do something to improve the lives of persons with disabilities. Thus, the foremost criteria by which to evaluate projects is the determination of how a project will ultimately benefit the person with a disability.

Identification of Specific Projects: It was the consensus of the group that NRH should initially concentrate its efforts on project ideas that are of interest to NRH. Two such projects were spelled out in detail in the proposal; namely, the Cognitive Evaluation Studies and the Composite Leg Brace Project. Others have not yet been fully developed; namely, the Virtual Reality projects, the portable evaluation projects, and expansion of composite materials projects.

This recommendation reflected a concern that the funding level and time frame of the overall project do not allow for an indepth or sophisticated process of identifying other

technologies that may be of use to persons with disabilities. The Committee agreed that one important criteria for selecting areas of concentration was the determination of how close a concept is to a critical or core mission that already exists at NRH.

Dr. DeLateur offered a test for assessing potential projects: a) is it new, b) is it true, and c) does it matter.
Mr. Rivers added the need to assess the probability of successful completion within the funding time frame.

Role of the Advisory Committee: There was agreement that the Committee can be of most help in identifying resources to assist with expansion of existing projects. Committee members urged the project team to identify specific needs for information and/or consultation and to take responsibility for linking with appropriate members for assistance. Mr. Hopmeier in particular urged the research team to identify specific ways that Committee members can be of assistance. A number of linkages were identified; for instance, Mr. Rivers offered the information of the National Technology Transfer Center. In addition, Committee members encouraged the ATRC to leverage the current funding into additional funding as research leads to expansion of ideas. Dr. Goldschmidt spoke, for example, about funding opportunities through the Veterans Administration.

Academic Linkages: Several members, specifically Drs. DeLateur and Gerber, spoke to the needs to root ATRC activities in an academic framework, especially in tieing activities to conceptual/theoretical models. This recommendation was made particularly in reference to the leg brace project, when Dr. Gerber spoke to the need of identifying standards of performance and calculating reaction force parameters. Dr. DeLateur also raised definition related to restraining force and to aspects of anatomic knee sheering.

Linkages to the Rehabilitation Community: Another theme of discussion was the importance of the ATRC linking with the rehabilitation community. Joe Lane spoke to this point in asking the ATRC to define its role vis-a-vis the NIDRR-funded Rehabilitation Engineering Centers. There was agreement that the ATRC should work collaboratively with the RRECs and other centers conducting technology transfer efforts that might benefit persons with disabilities.

Commercialization. The Committee recommended that the ATRC concentrate more on developing technologies that may be of use to persons with disabilities rather than on commercialization of products. It was the general view that the ATRC would not focus on commercialization efforts. This opinion was not universal, however, as Mr Gilbert, in particular, stressed the importance of commercialization as the means by which technologies get to the people who can benefit from them. He recommended using ATRC funds to leverage the commercialization of technologies developed or assessed by the ATRC. Mr. Gilbert's perspective is that the "real driver (in technology transfer) is the market place." Mr. Lane also challenged the ATRC team to determine where on the continuum of technology development, ranging from technology invention to assessment to commercialization, the Center will be positioned.

Future Directions

1. Develop full proposals on the following topics:

   a. Virtual reality applications in the treatment and education of persons with physical disabilities

   b. Use of portable evaluation systems for diagnosing/evaluating rehabilitation functional levels outside the rehabilitation facility

   c. Expansion of the composite materials project (leg brace) to develop additional exoskeletal applications for persons with disabilities.

2. Create a center of expertise in rehabilitation technology transfer that benefits persons with disabilities, fits the mission of the National Rehabilitation Hospital, and provides opportunities for a bi-directional flow of information that can benefit the U.S. military, NASA, and NRH.

3. Create linkages with the technology community, through the Advisory Committee mechanism, that will allow the ATRC to leverage its funding to provide maximum benefit to its target audiences.

The Committee's overall advice was summed up by Dr. Gerber, who said, "Keep It Simple, Get a Product, and Show How It Relates to the Audience."

ADVISORY COMMITTEE MEMBERS

Felix Zajac, Ph.D.
Director, Rehabilitation R&D (153)
VA Medical Center
3801 Miranda Avenue
Palo, Alto, CA 94304
(415) 493-5000 Ext. 4297

Lee Rivers, Executive Director
National Technology Transfer Center
316 Washington Avenue
Wheeling, WV 26003
(304) 243-2455

Richard Foulds, Ph.D.
Director of Applied Science and Engineering
University of Delaware
Alfred I. duPont Institute
P.O. Box 269
Wilmington, DE 19899
(302) 651-6830

Joy Hammel, Ph.D., O.T.R.
Assistant Professor
Program in Occupational Therapy
Shenandoah University
333 West Cork Street, 5th Floor
Winchester, VA 22601
(703) 665-5561

Ray L. Gilbert, Manager
Technology Transfer Division
NASA Headquarters
300 E Street, S.W., Code CU
Washington, D.C. 20546
(202) 358-0703

Leonard Ault, Deputy Director
Technology Transfer Division
NASA Headquarters
300 E Street, S.W., Code CU
Washington, D.C. 20546
(202) 358-0721

Joseph Lane, Associate Director
Center for Assistive Technology
School of Health Related Professions
University of Buffalo
515 Kimball Tower
Buffalo, NY 14214
(716) 829-3141

Doris Rouse, Ph.D.
Director, Center for Technology
Applications
Research Triangle Institute
P.O. Box 12194
Research Triangle Park, N.C. 27709
(919) 541-6976

Dennis Reeves, Ph.D.
13448 Samantha Avenue
San Indiego, CA 92129
(619) 538-4569

Dr. Frederick W. Hegge
Director, DIR - OMPAT
Division of Neuropsychiatry Research
Walter Reed
Washington, D.C. 20037
(301) 427-5210

Barbara DeLateur, M.D.
Good Samaritan Professional Office Bldg.
Suite 406
5601 Loch Raven Boulevard
Baltimore, MD 21239
(410) 532-4717

John Goldschmidt, M.D.
Director of Rehabilitation, Research &
Development Services
Department of Veterans Affairs
Mail Stop 117A
810 Vermont Avenue, N.W.
Washington, D.C. 20420
(202) 535-7278

Lynn Gerber, M.D.
Chief of Rehabilitation Medicine Dept.
National Institute of Health - Bldg. 10
Room 6S 235
9000 Rockville Pike
Bethesda, MD 20892-1604
(301) 496-4300

Michael Hopmeier
Sundrup Technology, Inc.
308 West D Avenue, Building 260
Eglin AFB, Florida 32542
(904) 698-2001

APPENDIX B

COGNITIVE STUDIES

NEW CURRICULUM VITAE

GEORGETOWN UNIVERSITY MEDICAL CENTER

Department of Neurology

CURRICULUM VITAE

Victoria N. Starbuck, Ph.D.
August, 1995

Education:

Post-Doctoral Fellowship in Clinical Psychology at George Washington University, 1994 - Present.
Ph.D. in Experimental Psychology - Neuropsychology from Georgetown University, 1993.
B.A. in Psychology received in 1983 from Bennington College.

Employment:

1984-1986: U.S. Army Research Institute for the Behavioral Sciences, Alexandria Virginia. Graduate level intern.
1986-Present: Psychometrist and Administrative Assistant for Law Enforcement Assessment Center.
1987-1989: Georgetown University Medical School, Department of Pharmacology. Laboratory Technician.
1989-1993: Georgetown University Hospital, Department of Neurology. Psychometrist. Supervisor: Dr. Gary Kay
1993-Present: Instructor of Neuropsychology in the Department of Neurology at Georgetown University Hospital, Washington, D.C.

Papers and Abstracts:

The Role of Sleep Apnea Induced Hypoxia on Cognitive Performance. (June, 1990) Kay, G., Starbuck, V., Heritage, L., Anderson, D., Yeh, R., Potolicchio, S. U.S. Army Natick Research, Development and Engineering Center, Contract No. DAAK60-89

Clauw, D.J., Morris, S., Starbuck, V., Epstein, S., & Kay, G. Neuropsychological Function in the Eosinophilia Myalgia Syndrome. Arthritis Rheum 1993; 36(9S):A101.

Kay, G., Morris, S., & Starbuck, V. Age and education based norms control for the effects of occupation on pilot test performance, 13th Annual Conference of the National Academy of Neuropsychology, Phoenix, AZ, October, 1993. Abstract published in The Clinical Neuropsychologist.

3800 Reservoir Road NW Washington DC 20007-2197
202 687-8525 202 784-2261 *fax*

Starbuck, V.N., Kay, G.G., Robinson, D.N. The N400 in Recovery from Aphasia. (Abstract) The Clinical Neuropsychologist. Vol. 7, pg. 354. July, 1993.

Yan, J., Starbuck, V.N., Potolicchio, S., Kerasidis, H., Kay, G., Clauw, D. Neurophysiological and Cognitive Changes in Patients with Eosinophilia Myalgia Syndrome. Poster Presented at the 45th Annual Meeting of the American Academy of Neurology, New York City, May 1993.

Starbuck, V.N., Kay, G.G., Robinson, D.N. (August 1993). The N400 in Recovery from Aphasia. Paper presented at the meeting of the American Psychological Association, Toronto, Canada.

Starbuck, V.N. Electrophysiological Attributes of Recovery from Aphasia. Grand Rounds, Washington D.C. Veterans Association Hospital. November, 1993.

Starbuck, V.N., Bleiberg, J., Potolicchio, S.J., & Kay, G.G. (1994). Dexedrine Mediated Enhancement of the P300 ERP in Recovery from Brain Injury. Paper presented at the Seventh World Congress of the International Rehabilitation Medicine Association, Washington, D.C.

Clauw, D.J. Kay, G., Potolicchio, S., & Starbuck, V. Abnormal Auditory Evoked Potentials in Fibromyalgia. Arthritis Rheum 1994; 37(62):R29.

Clauw, D.J. Morris, S., Starbuck, V., Blank, C., & Kay, G. Impairment in Cognitive Function in Individuals with Fibromyalgia. Arthritis Rheum 1994; 37(6S):R29.

Levy, L., Starbuck, V., Kay, G., Lin, C., Ariz, C., Kattah, J., Cohan, S., Potolicchio, S., Schellinger, D., LeBihan, D. (1995). Functional Magnetic Resonance Imaging of Memory in Transient Global Amnesia. Paper presented at the XV Symposium of Neuroradiologicum. Japan, 1994.

Starbuck, V.N., Bleiberg, J., Potolicchio, S., & Kay, G.G. (1994). Dexedrine Mediated Enhancement of the P300 ERP in Recovery from Brain Injury. Paper presented at the Seventh World Congress of the International Rehabilitation Medicine Association, Washington, D.C.

Starbuck, V.N., Levy, L.M., Kay, G.G., Eberle, C., Donohue, B., Lin, C. (1995). Functional MRI of Memory: Encoding and Recognition. APA Blue Ribbon Award Winning Paper, Division 40 presentation at the American Psychological Association Annual Convention, New York.

Kay, Gary & Starbuck, V. Computer Applications in Neuropsychology. In M. Maruish & E. Berg (Ed.) Advances in Neuropsychological Assessment, Lawrence Earlbaum Publisher, New York, In Press.

Levy, L., Starbuck, V., Kay, G., Lin, C., Kattah, J., Martuza, R., Potolicchio, S., Makariou, I., Schellinger, D. (1995). Functional MRI of Memory: Activation patterns with encoding and recognition in normal and impaired memory. Published Proceedings of the American Society of Neuroradiology. Chicago, April 23-27, 1995. pp. 94.

Levy, L., Starbuck, V., Kay, G., Lin, C., Ariz, C., Kattah, J., Cohan, S., Potolicchio, S., Schulein, D., & LeBihan, D. (1995). Functional MRI of Memory in Transient Global Amnesia. Poster Presented at Roengentgen Society 95th Annual Meeting, Washington, D.C., April 30-May 5. Published Proceedings, pp. 212.

Levy, L., Starbuck, V., Kay, G., Lin, C., Ariz, C., Kattah, J., Cohan, S., Potolicchio, S., Schellinger, D., LeBihan, D. (1995). Functional Magnetic Resonance Imaging of Memory in Transient Global Amnesia. In press. Neuroradiology.

Starbuck, V.N., Bleiberg, J., & Kay, G.G. (1995). D-Amphetamine Mediated Enhancement of the P300 ERP: A Placebo-Crossover Double-Blind Case Study. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, Vol. 8, Number 3.

Workshops & Presentations:

Adams, Ken, Kay, Gary, & Starbuck, V.N. Computerized Neuropsychological Evaluation. Workshop presentation. Academy of Neuropsychology, 1989 Annual Convention, Washington, D.C.

Starbuck, V.N. The N400 in Recovery from Aphasia. Grand Rounds, Department of Neurology, Georgetown University School of Medicine. Washington, D.C. May, 1993.

Starbuck, V.N. fMRI of Memory and Language: Clinical Applications. Grand Rounds, Departments of Neurology and Neurosurgery, Georgetown University School of Medicine. Washington, D.C. February, 1995.

Poster Presentations:

Abernathy, M., Wieneke, J., Ramos, M., Call, D., Ekdom, B., Starbuck, V., Kay, G. Transcranial Doppler: Intracranial Blood Flow Velocities in Headache-Free Migraineurs and Non-Headache Prone Volunteers. Poster Presented at the Annual Meeting of the American Academy of Neurology, 1989.

Potolicchio S.J., Kay, G., Starbuck, V., and Caputy, A. Simultaneous EEG Topographical Mapping and Neuropsychometric Testing in Temporal Lobe Epilepsy. Poster presented at the Annual Meeting of American Academy of Neurology, 1989.

Kerasidis, H., Starbuck, V.N., Kay, G.G., Potolicchio, S.J., Jr. Cognitive Event-related Potentials in Temporal Lobe Epileptics. Poster presented at the 44th Annual Meeting of the American Academy of Neurology, San Diego, CA. May, 1992.

Kay, G.G., Morris, S., & Starbuck, S. (1993). Age and Education Based Norms Control for the Effects of Occupation on Pilot Test Performance. Poster Presented at the 1993 National Academy of Neuropsychology meeting. Phoenix, AZ.

Yan, J., Starbuck, V.N., Potolicchio, S., Kerasidis, H., Kay, G., Clauw, D. Neurophysiological and Cognitive Changes in Patients with Eosinophilia Myalgia Syndrome. Poster Presented at the 45th Annual Meeting of the American Academy of Neurology, New York City, May 1993.

Platenberg, C., Starbuck, V.N., Kay, G., Lin, C., Rajan, S., Potolicchio, S., Schellinger, D. (1994). The Right Hemispheric Localization of Broca's Speech Area in a Right Handed Individual by fMRI and WADA Testing. Poster presented at the 30th Annual Meeting of the American Journal of Neuroradiology.

Kay, G., Starbuck, V., Levy, L. Functional MRI in Transient Global Amnesia: A Case Study. Poster presented at the 23rd Annual Meeting of the International Neuropsychological Society, Seattle, Washington February, 1995.

Levy, L.M., Starbuck, V.N., Kay, G.G., Lin, C., Kattah, J., Martuza, R., Potolicchio, S. Makariou, I., & Schellinger, D. (1995). Functional MRI of Memory Activation Patterns with Encoding and Recognition in Normal and Impaired Memory. Poster presented at the 30th Annual Meeting of the American Journal of Neuroradiology.

Platenberg, R.C., Starbuck, V.N., Kay, G.G., Lin, C.S., Rajan, S.S., Potolicchio, S.J., and Schellinger, D. (1995). Unusual Right Hemisphere Localization of Broca's area in a Right Handed Patient by Functional MRI and WADA. Poster presented at the 33rd Annual Meeting of the American Society of Neuroradiology, Chicago, IL.

Professional Organizations:

American Psychological Association: Associate Member
National Academy of Neuropsychology: Associate Member

Doctoral Dissertation:

The N400 in Recovery from Aphasia. Georgetown University: Washington, D.C. 1993.

ROBERT CRAIG PLATENBERG, M.D.
28 June 1995

PII Redacted

[redacted]

WORK: Georgetown University
Medical Center
3800 Reservoir Road, NW
Washington, D.C. 20007

[redacted]

LICENSURE:	Massachusetts	License # 70404
	District of Columbia	License # 19675
	Maryland	License # D43405
	Virginia	License # 0101051960
	DEA	License # BP3226594

CERTIFICATION: Board Certified - American Board of Radiology

EDUCATION:

Post Graduate Training

Fellowship in Neuroradiology
TUFTS, New England Medical Center
Boston, MA 1987-1989

Radiology Residency
Wilford Hall USAF Medical Center
Lackland AFB, TX 1984-1987

Flexible Internship
Malcolm Grow USAF Medical Center
Washington, DC 1981-1982

Medical Education and Degree

Georgetown University School of Medicine
Washington, D.C. 1977-1981
Pass in Pass/Fail System
MD Degree

Undergraduate Education

USAF Academy
Colorado Springs, Colorado 80840
3.45/4.0 GPA BS Degree Life Sci
Captain of Fencing Team
Competed in 1977 NCAA for Fencing

PROFESSIONAL EXPERIENCE

November, 1993 to present	Georgetown University Assistant Professor, Neuroradiology Director Neuro MRI
June, 1992 to November, 1993	Physician, Neuroradiology Drs. Groover, Christie & Merritt, P.C. 4930 Del Ray Avenue Bethesda, Maryland 20814
August, 1989 to June, 1992	Chief of Neuroradiology Wilford Hall USAF Medical Center Lackland AFB, TX
June 1982 to June 1984	Two years as a Primary Care physician at Malcolm Grow USAF Medical Center, between internship and residency. Saw outpatient general medicine and orthopedics, supervised eight physician's assistants. Past Advanced Cardiac Life Support Instructor and Past Advanced Trauma Life Support Instructor

HONORS AND AWARDS

Most valuable fencer USAF 1977
Air Force Commendation medal for Primary Care work at Malcolm Grow USAF Medical Center
Meritorious Service Medal for Neuroradiology at WHMC

SOCIETY MEMBERSHIP

Diplomat of National Boards
Radiological Society of North America
Senior Member American Society of Neuroradiology

SCHOLARSHIP & RESEARCH

Publications

Vertebrodiastasis Experimental Lengthening of the Juvenile Goat Spine. Stefko, R.M., Cain, J.E.Jr., Lauerman, W.C., Brann, C., Platenberg, R.C., Pyka, R. Spine. 18(12):1616-20, Sep 15 1993.

Pathomechanical Analysis of Thoracolumbar Burst Fracture Reduction, A Calf Spine Model. Cain,J.E., DeJong,J.T., Dinenberg,A.S., Stefko,R.M., Platenberg,R.C., Lauerman,W.C., Spine 18(12): 1647-54, Sep 15 1993.

Clinical Significance of Hind Brain Herniation and deformity as shown on MRI in Patients with the Chiari II Malformation; Wolpert SM, Scott RM, Platenberg RC, Runge WM. AJNR 9:1075

Moya-Moya Disease in Patients with Down's Syndrome; Outwater EK, Platenberg RC, Wolpert SM, AJNR 10: 523

GdDPTA Usage in :MRI: Klucznik RP, Platenberg RC, Wolpert SM, Runge VR. Applied Radiology Nov-Dec 1989.

Exhibits

MRI with histopathologic correlation in a naturally occurring primate model of disk degeneration; Platenberg RC, Hubbard GB, Ehler WT, Hixson CJ, Klucznik RP, Lauerman WC, Cain, JE. American Society of Neuroradiology 29th Annual Meeting, Washington, DC June 1991.

Posters

Unusual Right Hemispheric Localization of Broca's Area in a Right Handed Patient by Functional MRI and WADA; Platenberg RC, Starbuck VN, Kay GG, Lin CS, Rajan SS, Potolicchio SJ, Schellinger D, American Society of Neuroradiology 33rd Annual Meeting, Chicago, Illinois March 1995.

The MRI of Pseudolaminar Necrosis; Platenberg RC, Davis BT, Makariou EV, Schellinger, D. American Society of Neuroradiology 33rd Annual Meeting, Chicago, Illinois, March 1995.

Scientific Presentations

Anatomic Analysis of the Spinal Perithecal Epidural Space and Patterns of Disease Propagation within this Space. Schellinger D, Levy LM, Davis BT, Platenberg RC, American Society of Neuroradiology 33rd Annual Meeting, Chicago Illinois, March 1995.

Transient Mutism after Medulloblastoma Removal - Significance of Vermial Lobule Size, Platenberg RC, Neff SR, Wolpert SM, American Society of Neuroradiology 27th Annual Meeting, Orlando FL, March 1989.

SCHOLARSHIP & RESEARCH

Scientific Presentations (Continued)

MR of Cerebellar Vermial Hypoplasia- Anderson ML, Wolpert SM, Platenberg RC. American Society of Neuroradiology 27th Annual Meeting, Orlando FL, March 1989.

SPGR Imaging in Children; Klucznik RP, Platenberg RC, American Society of Neuroradiology 29th Annual Meeting. Washington DC June 1991.

Posterior Sacroiliac Fixation using a Sacropedicular Targeting Device -Anatomic Study, Cain JE, Miller MD, Lauerman WC, Platenberg RC, Wilson MR, Littlefield WG. American Society of Orthopedics National Residents Meeting, March 1991.

Prepared Lectures:
One hour, dual slide projected professional lectures on topics in Neuroradiology.

Neuroanatomy for Radiologists
Basic MRI I: Nuclear Magnetism
Basic MRI II: Signal Generation
MRI Scan Parameters
Signa Specifics
The MRI of Hemorrhage
Vascular Malformations
White Matter Diseases
The Failed Back Syndrome
Temporal bone Imaging
Blood Outside of Blood Vessels - Trauma
The Radiology of Maxillofacial Trauma
Fast Spin Echo MRI
New Fast MRI Techniques
Functional MRI
Imaging of the Paranasal Sinuses
Cervical Spine Trauma
Comparative Brain Morphology

Guest Lectures/Presentations

-Seminar 1985: Thombolytic Therapy in Acute Arterial Occlusion
-Seminar 1986: Thallium 201 Myocardial Imaging and the Rotating Slant Hole Collimator
-Lecture, November 1984: Basic Chest Radiology for Nurse Anesthetists, Wilford Hall USAF Medical Center
-Lecture, March 1987: Basic Preoperative Chest Film Interpretation for Nurse Anesthetists, Wilford Hall USAF Medical Center
-Lecture August 1989, and August 1990, The Radiology of Maxillofacial Trauma presented at the San Antonio Maxillofacial Trauma Symposium

-Lecture April 1993 Fast Spin Echo MRI, Wilford Hall Residency and Brook Army Residency Program San Antonio, Texas
-Lecture April 1994 Imaging of the Paranasal Sinuses, New Fast MRI Techniques, Wilford Hall and BAMC radiology residency programs.
-Lecture March 1995, Functional MRI and The Failed Back Syndrome Wilford Hall radiology residency program.

SMRT 4th Annual Meeting Lecture, The Failed Back Syndrome and Routine Spine Imaging Washington D.C., Hilton March 1995.

SCHOLARSHIP & RESEARCH(Teaching)

Medical Student Teaching

Tufts, New England Medical Center 1987-1989 - Quarterly instruction in Neuroradiology.

Wilford Hall Medical Center 1989 - 1992; Medical Student Rotation on Neuroradiology Service from various institutions.

Georgetown University 1994 - present; Medical Student Rotations on Neuroradiology service.

Resident Teaching

Tufts, NEMC 1987-1989 Radiology and Neurology Resident teaching; Grand Rounds

Wilford Hall Medical; Center 1989 - 1992; Numerous Case Conferences. Organized and lectured in Didactic Month of Neuroradiology Noon Lectures 1990, 1991, 1992.

Georgetown University Noon Lectures on Neuroradiology topics listed above November 1994 to present. Resident case conferences.

Other Conferences

Tufts NEMC 1987-1989

Monthly Neurology-Neurosurgery Grand rounds
Weekly Neurosurgical Conferences
Weekly Pediatric Neurology Conference
Monthly Orthopedic Conference

Wilford Hall Medical Center 1989 - July 1992

Monthly Neuroradiology Neuropathology Conference
Quarterly Endocrine Conference
Monthly Neurology/Pediatric Neuroradiology Conference (Intermittent)
Yearly Quality Assurance/Risk Management Evaluation
Correlating Brain tumor histopathology and neuroradiologic findings
Assessing Complications of Myelography

SCHOLARSHIP & RESEARCH(Continued)

Georgetown University School of Medicine

Weekly Combined Epilepsy Conference
Weekly Head and Neck Surgery Conference
Monthly Craniofacial Surgery Conference
Bi-monthly Spine Oncology Conference
Bi-monthly Neuropathology-neuroradiology case Conference
Monthly Spine Grand Rounds

Research

Assisted in study of Post-basilar Artery Reanastomosis in a Baboon
Assisted in Liposome Transfer of Methotrexate Across the Blood Brain Barrier in Rats with Gliomas

Active Research Areas
Functional MRI Research of Posterior Fossa Motor Activity
functional MRI of Vestibular activation
Functional MRI Research of Cognition and Attention
Auditory and visual PASAT testing in normal and ADHD
Location and Identity working memory testing-same
MRI Spectroscopy of epilepsy Patients
Diffusion in stroke and epilepsy

COMMITTEES

Georgetown University
Director of Neuroradiology MRI Georgetown University
Quality Assurance Program Director Neuro MRI- GUMC
Pediatric MRI Sedation Committee- GUMC
Evaluation coordinator for medical student neuroradiology rotation

Wilford Hall Medical Center
Pediatric Oncology Cancer Conference Committees - WHMC Neurosurgery Tumor Board - WHMC

Quality Assurance Evaluator and Monitor for Government MRI Contract #F41636-88-D0001-WHMC

Technical Team Member for Evaluation of MRI Technologist Services for Wilford Hall Medical Center

Wrote options for and accomplished 95% and 100% blueprint approval for:

1) GE Signa 1.5 Tesla MRI at WHMC DACA 87-89-D-0010
2) 2-GE 9800 HTD CT scanners - WHMC DLA 120-89-R-0733
3) 2-Phillips Poly AU, DVI Angio Rooms - WHMC

Wrote contract for
2 OEC Diasonic C-Arm Fluoroscopy units WHMC

Project Monitor for:
Mobile Technology Incorporate Government Contract #F41800-88-0-001 for Mobile MRI and Technical Services, WHMC

WORKS IN PROGRESS

fMRI of Broca's Area in a Right Handed Individual

The MRI of Pseudolaminar Necrosis

fMRI of Attention Using a Modified PASAT Test

CURRICULUM VITAE

Michael F. Egan
National Institute of Mental Health
NIMH Neuroscience Research Center at St. Elizabeths
2700 M. L. King Jr. Ave, S.E.
Washington, D.C. 20032

DATE OF BIRTH:	January 2, 1958
PLACE OF BIRTH:	Washington, D.C.
CITIZENSHIP:	U.S.
AGE:	37
ADDRESS	Apt 205, 2101 N St, N.W., Washington, D.C 20037
TELEPHONE :	Home: 202-457-1715
	Office: 202-373-6223
MARITAL STATUS:	Married

Education and Employment History

College: University of Virginia, B.A. with Honors in Philosophy, Member:Biology Honor Society, Charlottesville, Va. 1975-1979.

Medical School: University of Maryland School of Medicine, Baltimore, Md. 1979-1983.

Internship: Community Medicine, University of Colorado Health Science Center and Affiliated Hospitals, Denver, Colorado. 1983-1984.

Residency: University of Colorado Health Science Center, in Psychiatry. 1984-1987

Chief Resident: Denver General Hospital 6/87-12/87, Denver, Colorado.

Fellowship: National Institute of Mental Health, Neuropsychiatry Branch NIMH Neuroscience Research Center at St. Elizabeths Hospital, Washington, D.C.
12/87-7/88: Ward Administrator
7/88-7/89: Medical Staff Fellow
7/89- 5/95: Senior Staff Fellow
7/91-7/93 Attending Physician

Medical Director: NIMH Neuroscience Research Center at St. Elizabeths. 2/94-current

Acting Branch Chief, Clinical Research Services Branch, NIMH. 6/95-current

Board Certification

Certified by American Board of Psychiatry and Neurology, April, 1989.

Licensure

Colorado Board of Medical Examiners
Virginia State Board Of Medicine
California Board of Consumer Affairs
Maryland Board of Physician Quality Assurance

Professional Societies

American Psychiatric Association
Washington Psychiatric Society
American Association for the Advancement of Science
Associate Member, American College of Neuropsychopharmacology
Society for Neuroscience

Awards and Honors

Outstanding Summer Intern, NIH Summer Intern Program, 1978
B.A. with Honors in Philosophy, University of Virginia, 1979.
Residents Golden Apple Teaching Award in Psychiatry. University of Colorado School of Medicine, 1987.

Research Support

CRADA Agreement with Neuromedica, Inc. 1995-1998
Title: Therapeutic and diagnostic research using a novel carrier system for the delivery of compounds to the brain.
Support: $90,000/year x 3 years

Additional Professional Activities

Committees

Chairman, Subcommittee on Quality and Appropriateness of Medical Care and Support Services, NIMH Neuropsychiatric Research Hospital at St. Elizabeths. 1989-1991.
Member, Quality of Care Committee, NIMH Neuropsychiatric Research Hospital at St. Elizabeths, 1988-1991.
Chairman, Committe on Training and Education, NIMH Neuropsychiatric Research Center at St Elizabeths, 1989-1991.
Member, Medical Board, NIMH Neuropsychiatric Reasearch Hospital at St Elizabeths. 1989-1991
Chairman, Medical Board, NIMH Neuropsychiatric Reasearch Hospital at St Elizabeths. 1994-current

Teaching Experience

1) Instructor, third year medical student course in psychiatric diagnosis and phenomenology, University of Colorado Health Science Center, 1986-1987.
2) Lecturer, PGYII (Psychiatry) course on biological psychiatry, George Washington University Medical School, 1989-current.
3) Instructor, seminar in psychopharmacology, PGYII, George Washington University Medical School, 1991-current.

Other Professional Activities

Consultant to Northern Virginia Psychiatric Group, Fairfax, VA, 1989-1994.
Consultant, Chesnut Lodge Hospital, Rockville, MD, 1993-1994.
Consultant, Dominion Hospital, Fairfax, VA, 1994-current
Consultant, National Rehabilitation Hospital, Washington, D.C. 1994-current
Private Practice Research Associate, Neuropsychiatric Services, Falls Church, VA 1994-current
Senior Research Associate, Washington Clinical Research Center, Falls Church, VA 1994-current

Ad Hoc Reviewer, Biological Psychiatry, 1990-1991.
Ad Hoc Reviewer, Psychiatry Research, 1994.

Publications

1)Corash L, Spielberg D, Bartsocas C, Borer D, **Egan M**, et al. Reduced chronic hemolysis during high dose vitamin E administration in Mediterranian-type G-6-PD deficiency. NEJM 303(8); 416-420, 1980.

2)Kirch DG, Palmer M, **Egan M**, Freedman R. Electrophysiological interactions between haloperidol and reduced haloperidol and dopamine, norepinephrine, and phencyclidine in rat brain. Neuropharmacology 24(5); 375-379, 1985.

3)Wyatt RJ, Alexander R, **Egan M**, Kirch DG. Schizophrenia: just the facts. Schizophrenia Research 1; 3-18, 1988.

4) Bell J, Bickford-Wimer PC, de la Garza R, **Egan M**, Freedman R. Increased central noradrenergic activity during benzodiazepine withdrawal: an electrophysiologicalstudy. Neuropharmacology 27(11):1187-90, 1988.

5) Bickford-Wimer P, Nagamoto H, Johnson S, Adler L, **Egan M**, Rose M, and Freedman R. Auditory sensory gating in hippocampal neurons: A model system in the rat. Biol Psychiatry 27;183-192, 1989.

6) Gold J, **Egan MF**, Goldberg T, Kirch D, Daniel D, Bigelow L, Wyatt RJ. Tardive Dyskinesia: Neuropsychological, CT, and symptomatic findings. Biol Psychiatry 30:587-599, 1991.

7) Khot V, **Egan MF**, Hyde T, Wyatt RJ. Neuroleptics and Classical Tardive Dyskinesia. in Drug-Induced Movement Disorders, ed. A.E. Lang, Futura Press, 5; 121-166, 1992.

8) **Egan MF**, Karoum, **FK**, Wyatt RJ. Effects of acute and chronic clozapine and haloperidol administration on 3MT accumulation in rat prefrontal cortex, nucleus accumbens, and striatum. Eur J Pharmacol 199; 191-199, 1991.

9) **Egan MF**, Hyde TM, Tirschwell DL, Kleinman JE, Weinberger DR. Laterality of appendicular tardive dyskinesia in chronic schizophrenia. Biol Psychiatry, 31; 1098-1109, 1992.

10) **Egan MF**, Hyde TH, Albers GW, Elkashef A, Alexander RC, Reeve A, Blum A, Saenz RE, Wyatt RJ. Treatment of tardive dyskinesia with vitamin E. Am J Psychiatry, 149; 773-777, 1992.

11) Karoum F, **Egan MF**. Dopamine release and metabolism in the rat frontal cortex, nucleus accumbens, and striatum: a comparison of acute clozapine and haloperidol. Brit J Pharmacology 105; 703-707, 1992.

12) Chrapusta S, Karoum F, **Egan MF**, RJ Wyatt. Gamma-Butyrolactone-sensitive and -insensitive dopamine release, and their relationship to dopamine metabolism in three rat brain regions. Eur J Pharmacol, 222;129-135, 1992.

13) Karoum FK, Chrapusta S, **Egan MF**, The application of combined gas chromatography mass spectrometry to the analysis of central and peripheral biogenic amines: some new observations. in Methods in Biogenic Amines Research eds. Parvez S, Nagatsu T, Nagatsu I, Parvez H. 2nd edition, Elsevier Press NY, NY, 1992.

14) El-Mallakh R, **Egan MF**, Wyatt RJ. Creatine phosphate and enolase: intracellular enzymes serving as markers of central nervous system damage in neuropsychiatric disorders. Psychiatry, 55;392-402, 1992.

15) Gupta S, **Egan MF**, Hyde TH. An unusual presentation of tardive dyskinesia with prominent involvement of the pectoral musculature. Biol Psychiatry 33;291-292, 1993.

16) **Egan MF**, El-Mallakh RS, Suddath RL, Lohr JB, Bracha HS, Wyatt RJ. Cerebrospinal fluid and serum levels of neuron-specific enolase in patients with chronic schizophrenia. Psychiatry Research, 43; 187-195, 1992.

17) **Egan MF**, Abi Dargham A, Kirch DG, Wyatt RJ. Serum creatine phosphokinase in patients with tardive dyskinesia. Brit J Psychiatry, 162;551-553, 1993.

18) Karoum FK, Chrapusta S, **Egan MF**, Wyatt RJ. Three-methoxytyramine is the major metabolite of dopamine in the rat prefrontal cortex: reassessment of the effects of neuroleptics on dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a simple two pool model. J Neurochem 63(3): 972-979, 1994.

19) **Egan MF**, Duncan CC, Suddath, RJ, Mirsky A, Wyatt RJ. Information processing abnormalities correlate with structural brain alterations and and clinical features in patients with chronic schizophrenia. Schizophrenia Research, 11:259-271, 1994.

20) Wyatt RJ, Kirch DG, **Egan MF**. Schizophrenia: biochemical, endocrine, and immunological studies. in Comprehensive Textbook of Psychiatry eds. Kaplan HI, and Sadock BJ, 6th edition, Williams and Wilkens Baltimore, MD, pp927-942, 1995.

21) Chrapusta SJ, Karoum F, **Egan MF**, Wyatt RJ. Haloperidol and clozapine increase intraneruonal dopamine metabolism but not gammma-butyrolactone-resistant dopamine release in rat prefrontal cortex, nucleus accumbens and striatum. Eur J Pharmacology 233:135-142, 1993.

22) Karoum FK, Chrapusta S, **Egan MF**, Wyatt RJ. Absence of 6-hydroxydopamine in the rat brain after stimulants and other dopaminergic agents: a mass-fragmentographic study. J Neurochem, 61:1369-1375, 1993.

23) **Egan MF**, Hyde TH, Kleinman JE, Wyatt RJ. Neuroleptic-induced vacuous chewing movements in rodents: incidence and effects of long-term increases in haloperidol dose. Psychopharmacology, 117:74-81, 1995.

24) **Egan MF**. Evidence against the depolarization inactivation hypothesis of antipsychotic activity: implications for the dopamine hypothesis of schizophrenia. J Neural Transm (submitted), 1995.

25) **Egan MF**, Hyde TM, Elkashef A, Wyatt RJ. Response to letter re: treatment of tardive dyskinesia with vitamin E. Am J Psychiatry, 150(6):992-993, 1993.

26) **Egan MF**, Hyde TH, Hurd Y, Weinberger DR, Kleinman JE, Wyatt RJ. Alterations in dopamine receptor and neuropeptide gene expression in striatonigral and striatopallidal neurons in rats with vacuous chewing movements induced by chronic treatment with haloperidol. Synapse, 18:178-189, 1994.

27) **Egan MF**, Wing L, Li R, Kirch DG, Wyatt RJ. Effects of chronic cocaine treatment in the rat: long-term reduction in frontal cortical serotonin. Biol Psychiatry, 36(9): 637-640, 1994.

28) **Egan MF**, Chrapusta SJ, Karoum F, Wyatt RJ Dopamine release mediated by impulse flow through the medial forebrain bundle is not altered in the striatum and nucleus accumbens following chronic haloperidol treatment. Neuropsychopharmacology (in press) 1995.

29) Elkashef AM, **Egan MF**, Frank JA, Hyde TM, Lewis BK, Issa F, Wyatt RJ. Basal ganglia iron content in tardive dyskinesia. Biological Psychiatry, 35:16-21 1993.

30) Hyde TM, **Egan MF**, Wing LL, Wyatt RJ, Weinberger DR, Kleinman JE. Persistent catalepsy predicts the development of dyskinesias in rats treated with chronic injections of haloperidol decanoate. Psychopharmacology 118:142-149, 1995.

31) Karoum F, **Egan MF**, Wyatt RJ. Long term effects of repeated cocaine exposure on the dynamic of dopamine release and metabolism in the rat brain: confirmation of persistent reduction in dopamine metabolism in the hypothalamus and frontal cortex. Eur J Pharmacol. 254, 127-132, 1994.

32) Knable MB, Hyde TM, **Egan MF**, Tosauali M., Wyatt RJ, Kleinman, JE, Weinberger DR. Quantitative autoradiography of striatal dopamine D1, D2, and reuptake sites in rats with vacuous chewing movements. Brain Res 646:217-222, 1994.

33) **Egan MF**,Ferguson J, Hyde TH. Behavioral effects of chronic naloxone administration in rodents treated with very long term haloperidol. Brain Res Bull (in press), 1995.

34) **Egan MF**, Ferguson J, Hyde TH. Effects of habituation of assessment on vacuous chewing movements in rats treated with long term haloperidol decanoate. Pharmacol. Biochem, Behav (in press) 1995.

35) Chrapusta SJ, **Egan MF**, Karoum F, Wyatt RJ. Regional effects of general anesthetics on dopamine release in the rat brain: a 3-methoxytyramine study. Brain Res (in press), 1995.

36) Chrapusta SJ, **Egan MF**, Masserano JM, Wyatt RJ. Dopamine release in the rat cerebellum and hippocampus: a tissue 3-methoxytyramine study. Brain Research, 655:271-275, 1994.

37) Hyde TH, **Egan MF**, Kleinman JE. Diurnal variation in severity of tardive dyskinesia. Schizo Research (in press), 1995.

38) Lipska BK, Chrapusta S, **Egan MF**, Weinbrger DR. Neonatal excitotoxic ventral hippocampal damage alters dopamine response to mild chronic stress and haloperidol treatment. Synapse , 20:125-130, 1995.

39) Daniel DG, Randolph C, Jaskiw G, Handel S, Abi-Dargham A, **Egan MF**, Elkashef A, Liboff S, Linnoila M. Coadministration of fluvoxamine increases serum concentrations of haloperidol. J Clin Psychiat. (in press) 1995.

40) Daniel DG, Smith N, Hyde TM, **Egan MF**. Case report: tardive dyskinesia associated with risperidone. Am J Psychiatry (in press), 1995.

41) Chrapusta SJ, **Egan MF**, Wyatt RJ. Chronic haloperidol changes relationship between nigral and striatal dopamine release and metabolism in the intact rat. J. Neurochem (submitted), 1995.

42) Gold J, Rehkemper G, Egan MF. Neuropsychology of tardive dyskinesia and schizophrenia. in Szymanski S, Kane J, Casey D. (eds) New Research on the Course and Treatment of Tardive Dyskinesia. APA Press, Washington D.C. (in press), 1995.

Selected Abstracts

1) Wyatt RJ, **Egan MF**, Karoum FK, Masserano JM, Chrapusta S, and Hitri A. A biochemical comparison of long-term cocaine administration and schizophrenia. Abstract International Congress on Schizophrenia Research. 1993.

2) Wing LL, Elkashef A, Kirch DG, **Egan MF**, Hyde TM, Wyatt RJ, Kulaga H. CD5+ B Lymphocytes and the effects of continuous haloperidol decanoate and coenzyme-Q10: an animal model of immunological anomalies in schizophrenia. Abstract International Congress on Schizophrenia Research. 1993.

4) Chrapusta SJ, **Egan MF**, Karoum F, Wyatt RJ. Effects of anaesthetic agents on regional dopamine release in the rat brain: a 3-methoxytyramine study. Abstract, Society for Neuroscience, 1993

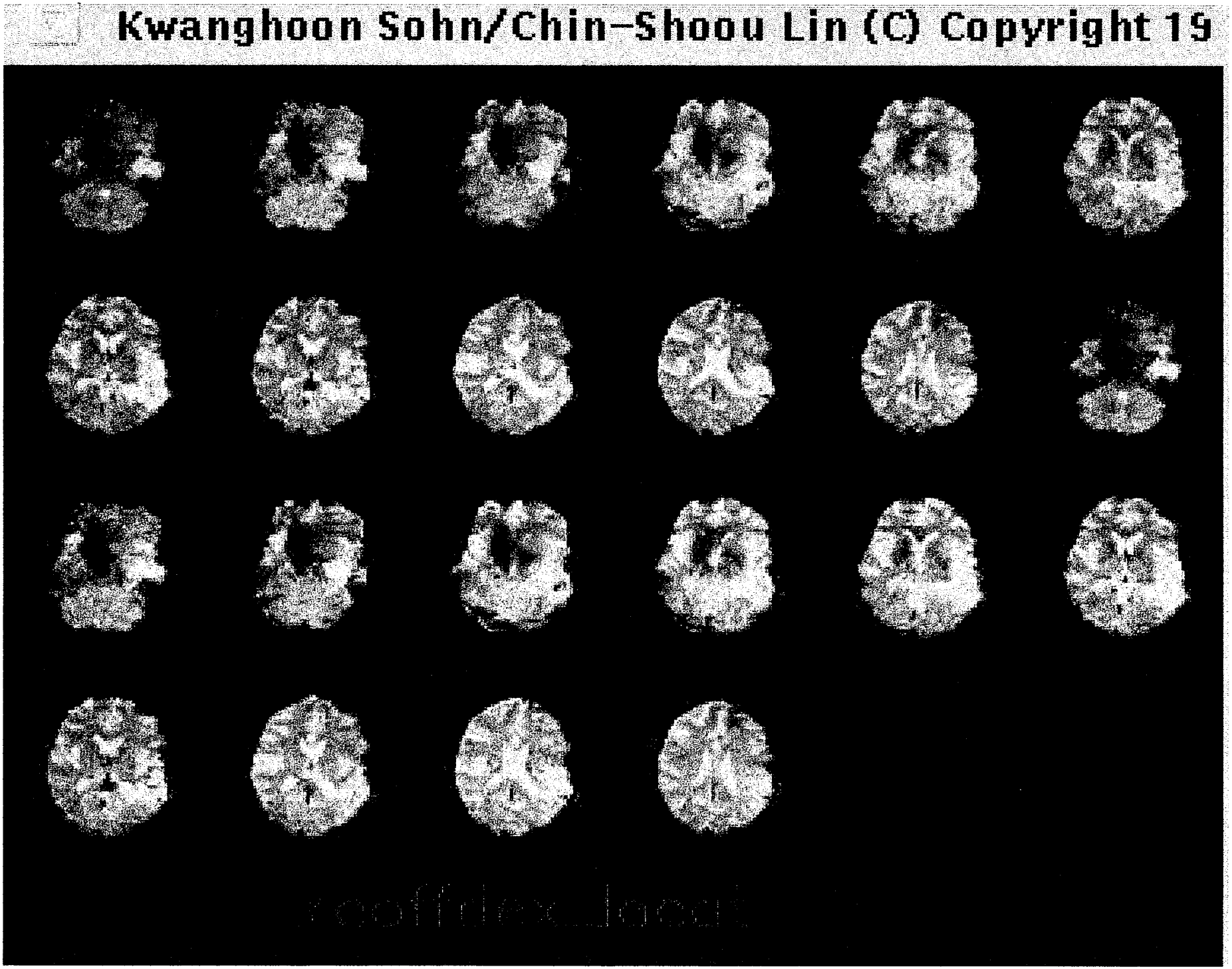
5) **Egan MF**, Chrapusta SJ, Karoum FK, Wyatt RJ. Evidence against the depolarization block hypothesis of the mechanism of action of antipsychotic drugs: effects of tetrodotoxin infusion inot the median forebrain bundle after acute and chronic dopamine release. Schiz Res 9:218, 1993

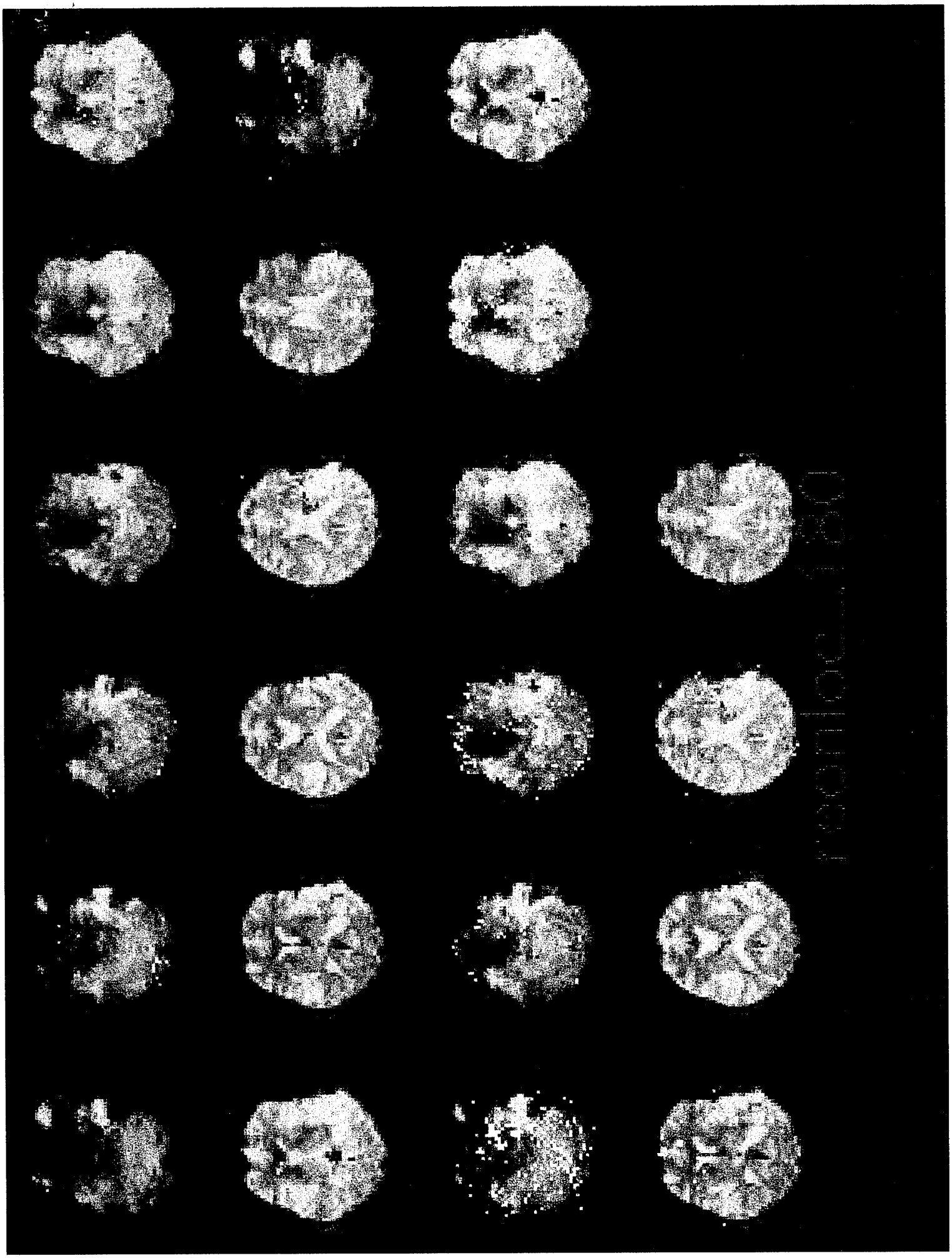
6) Egan MF, Bachus SE, Hyde TM,. Ferguson JN, Wyatt RJ, Kleinman JE. Effects of D1 antagonist SCH23390 on vacuous chewing movements and striatal neuropeptide mRNA following long term haloperidol decanoate. Abstract, Society for Neuroscience, 513.12, 1994

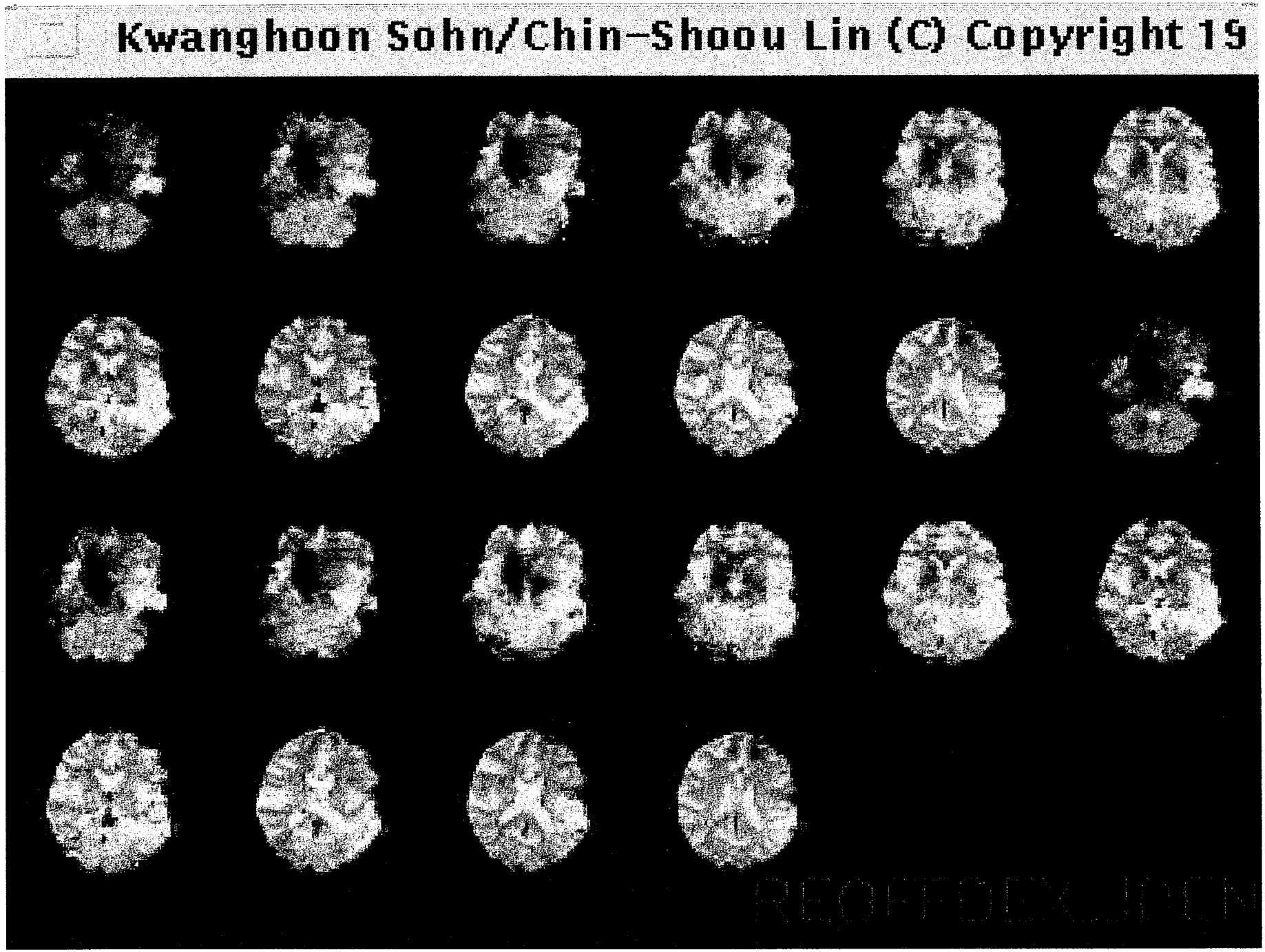
7) Ferguson JN, Egan MF, Bachus SE, Hyde TM, Wyatt RJ, Kleinman JE. Reduced striatonigral activity related to vacuous chewing movements induced by acute haloperidol treatment: a possible model for dystonia. Abstract, Society for Neuroscience, 513.13, 1994

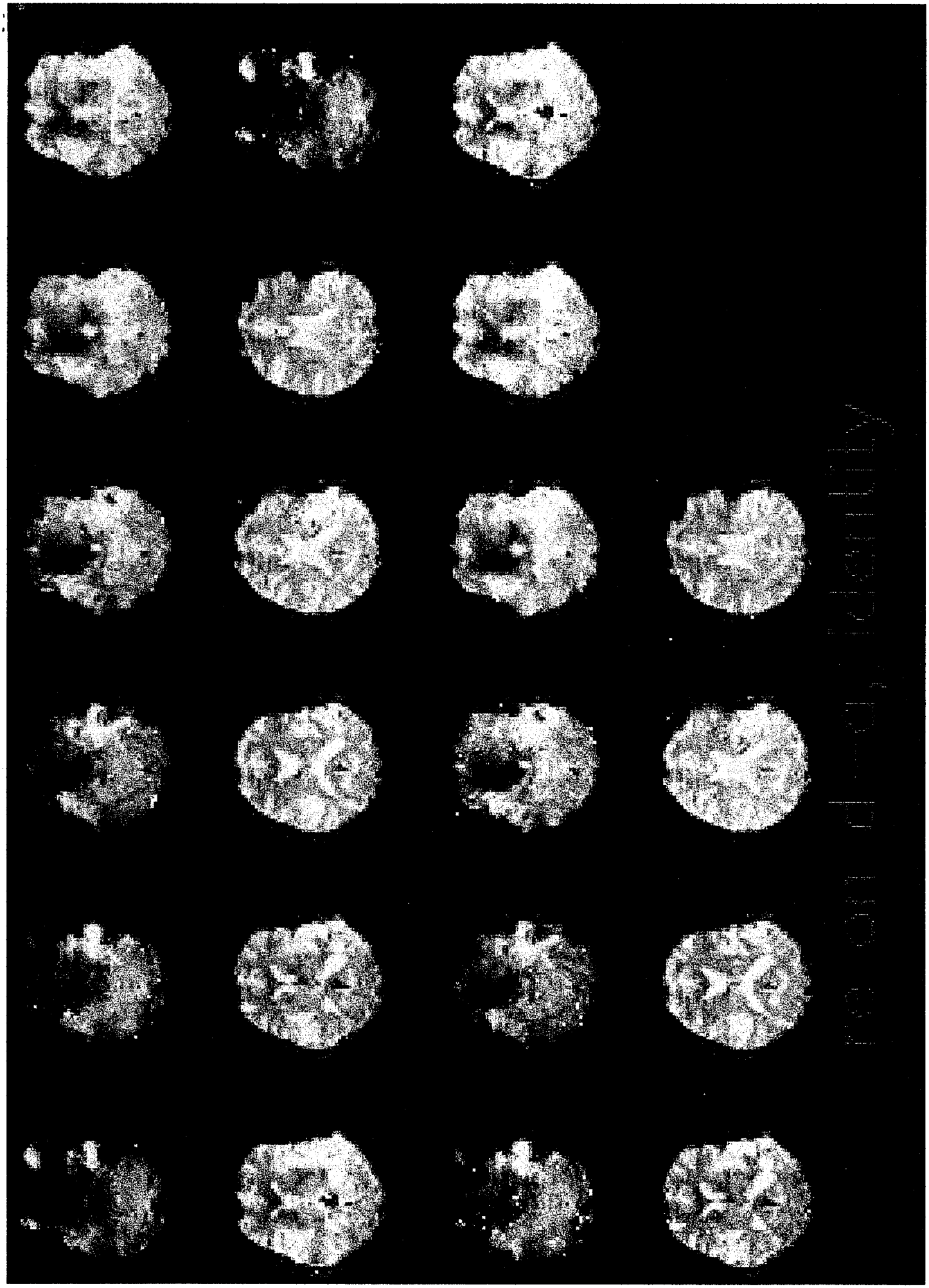
APPENDIX C

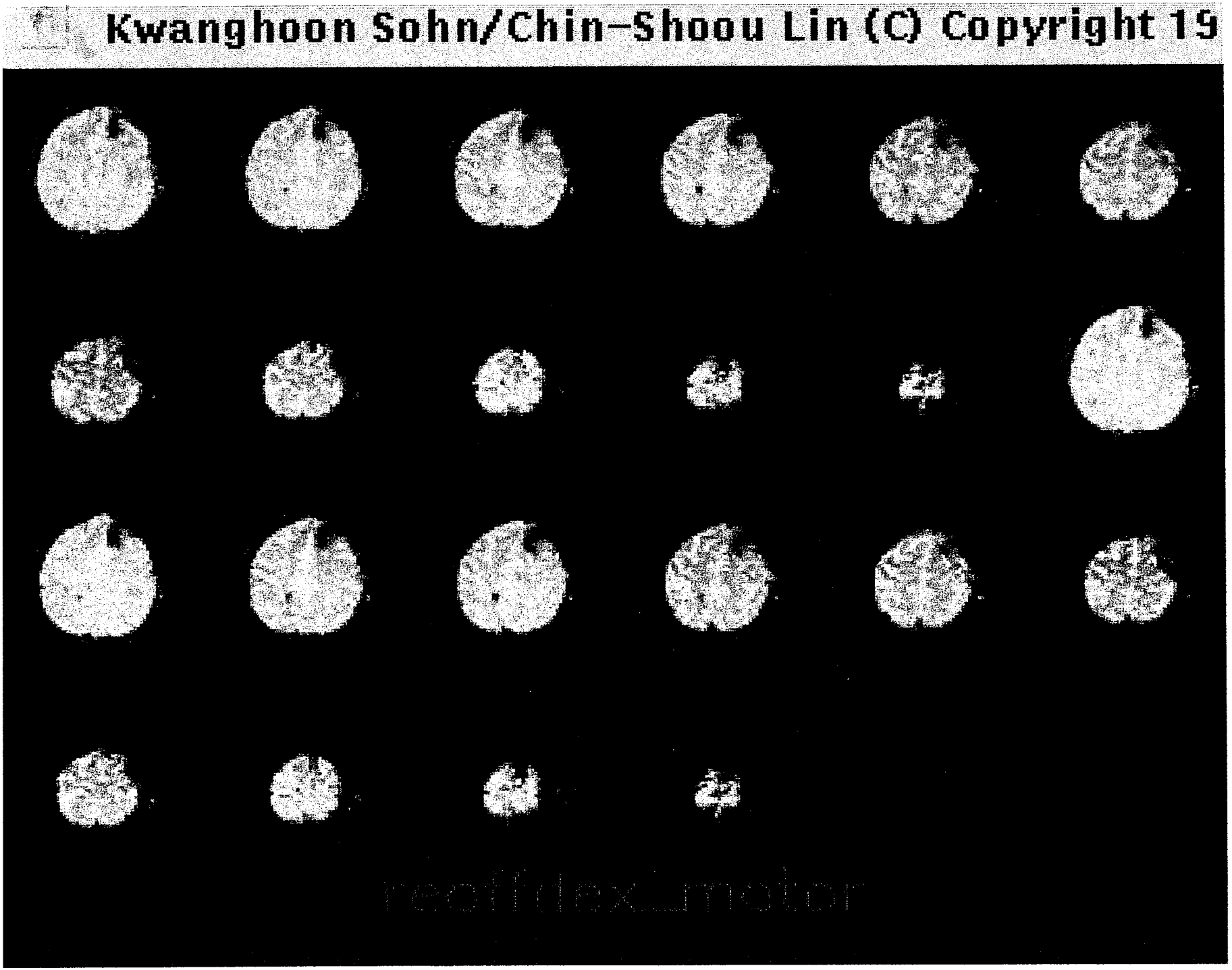
P-300 ERPs AND FMRIs

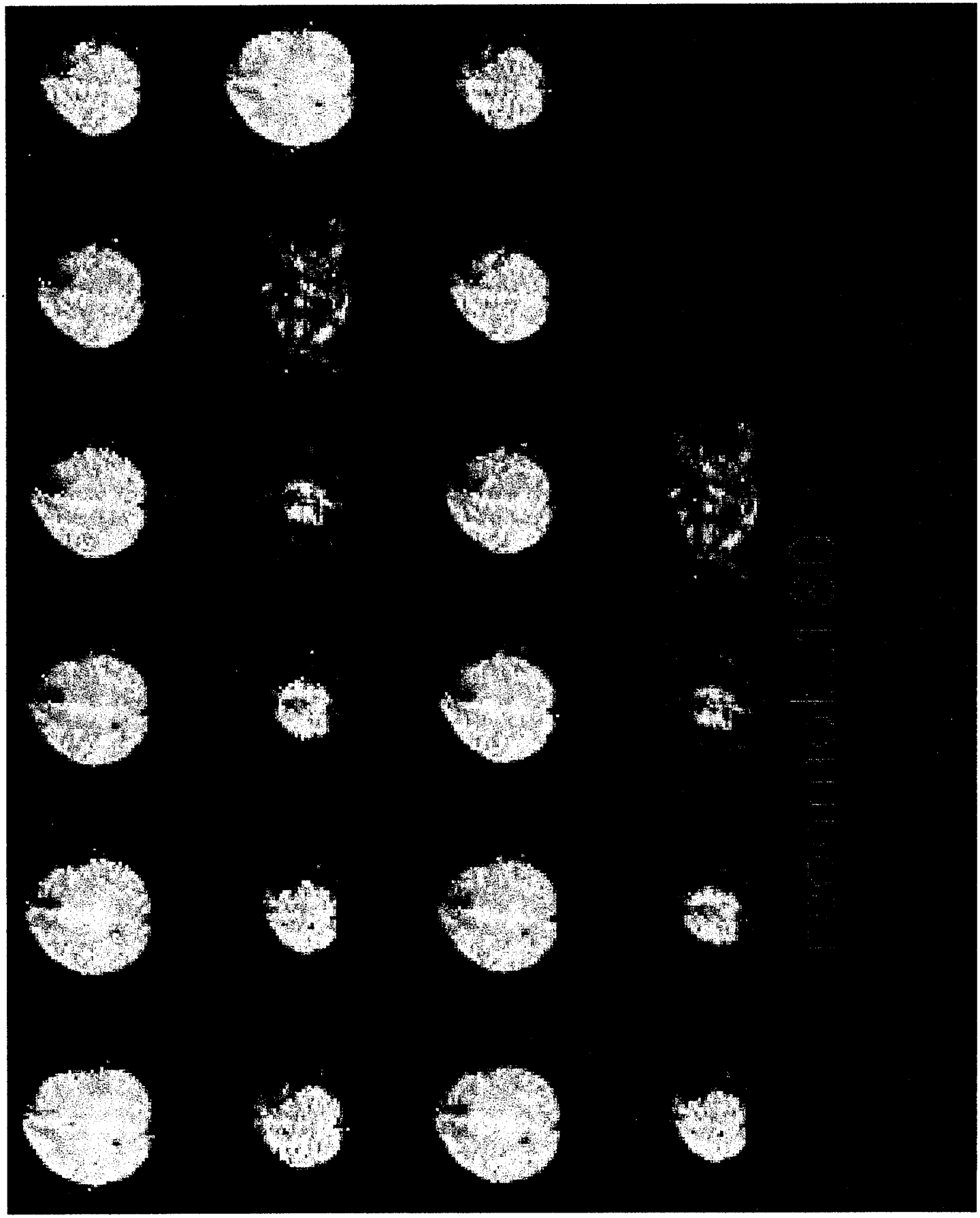

Kwanghoon Sohn/Chin-Shoou Lin (C) Copyright 19




Kwanghoon Sohn/Chin-Shoou Lin (C) Copyright 19




Kwanghoon Sohn/Chin-Shoou Lin (C) Copyright 19
reflex_motor



Neuropsychiatry, Neuropsychology, and Behavioral Neurology
Vol. 8, No. 3, pp. 189–192

D-Amphetamine-Mediated Enhancement of the P300 ERP: A Placebo-Crossover Double-Blind Case Study

Victoria N. Starbuck, Ph.D., *Joseph Bleiberg, Ph.D., and Gary G. Kay, Ph.D.

*Department of Neurology, Georgetown University Medical School, and *Department of Psychology, National Rehabilitation Hospital, Washington, D.C., U.S.A.*

Summary: A double-blind placebo-crossover study using D-amphetamine in a head-injured subject indicated improved cognitive performance and improved P300 results in the D-amphetamine condition. Cognitive improvement consisted of selective enhancement of divided attention and response inhibition. P300 ERP improvement consisted of substantially increased amplitude and a simultaneous decrease in P300 variability. There was also evidence of topographic redistribution of the P300 ERP. **Key Words:** Event-related potentials—Head injury—P300—Cognition—D-Amphetamine. **NNBN 8:189–192, 1995**

The current research was conducted to replicate and extend the findings of Bleiberg et al. (1), who reported a double-blind placebo-crossover case study of a brain-injured patient who showed improved cognitive performance on D-amphetamine. The improvement was evident both as an enhancement of overall performance levels and as a reduction in variability of performance. We subsequently replicated this study with the same subject (R.E.), but with the addition of P300 event-related potential (ERP) measurement. This method allowed us to examine the electrophysiological attributes of attentional mechanisms on and off D-amphetamine and to see whether the findings of the original study were replicable after a 6-month interval. In addition, R.E. was administered the CogScreen (2) computerized cognitive test battery to evaluate performance changes with drug treatment. The CogScreen subtests were selected to match those administered as part of the ANAM battery given in the previous study.

METHODS

R.E.'s history and current complaints were unchanged from those reported by Bleiberg et al. (1), except that the subject was 6 months older. The behavioral paradigm used to elicit the P300 was the "oddball paradigm," in which the subject listens to high- and low-pitched tones and is asked to count the number of infrequently occurring tones (3). The ratio of frequent to infrequent tones was 4:1. The P300 component is the waveform generated by the averaged evoked responses to the infrequent tones. This component occurs only in response to the items for which the person has been instructed to pay attention, regardless of the physical characteristics of the stimulus. As a result, the P300 has proved useful in investigating selective attention.

R.E. was assessed on two occasions, separated by 7 days. Each session began with the subject ingesting a 10-mg capsule of D-amphetamine sulfate or placebo. One hour later he was administered the procedures described herein. This interval was selected because plasma levels are maximal and approximately stable for 1–3 h after oral administration of D-amphetamine (4). Following EEG and ERP testing, R.E. completed six CogScreen subtests (Visual Sequence Comparison, Symbol Digit Coding, Matching to Sample, Auditory Sequence Comparison, Divided Attention, and Dual Tasking).

Subject Setup

R.E. was prepared for electrode placement using Omni prep pumice cleaner at the site of electrode place-

Address correspondence and reprint requests to V. N. Starbuck, Department of Neurology, Georgetown University Medical School, 3800 Reservoir Rd., N.W., Washington, D.C., 20007, U.S.A.

Received July 5, 1994; first revision November 1, 1994; second revision January 3, 1995; accepted January 3, 1995.

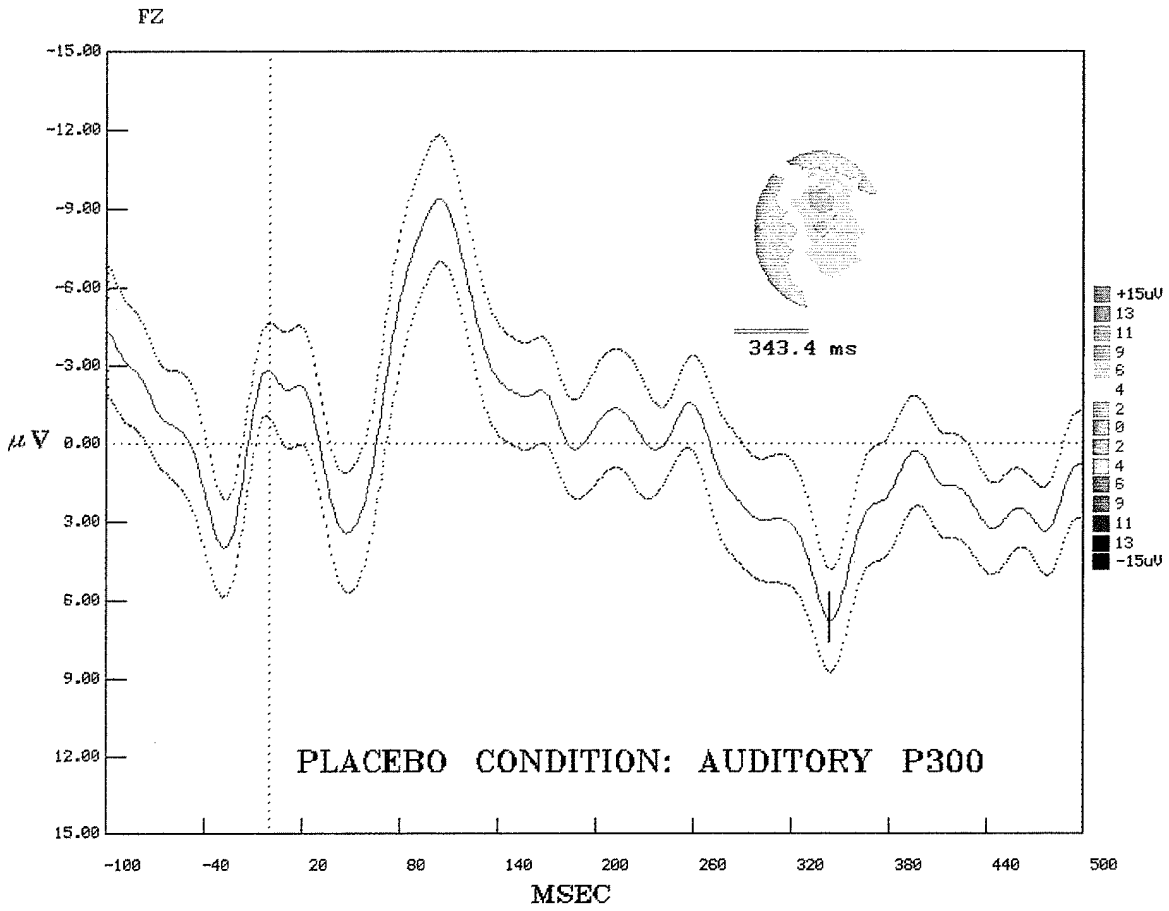


FIG. 1. Solid lines, average evoked response; dotted lines on either side of the solid line, variance ±1 S.D. from the mean.

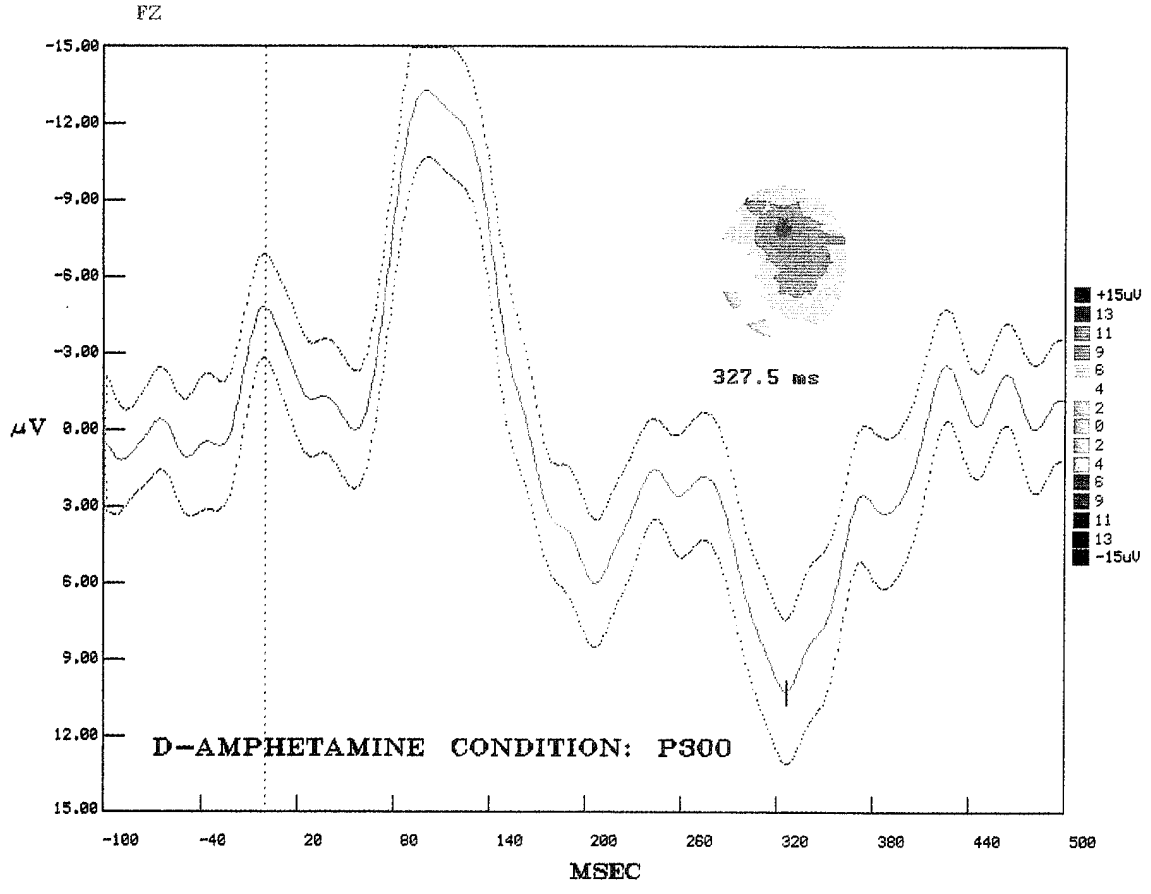


FIG. 2. Solid lines, average evoked response; dotted lines on either side of the solid line, variance ±1 S.D. from the mean.

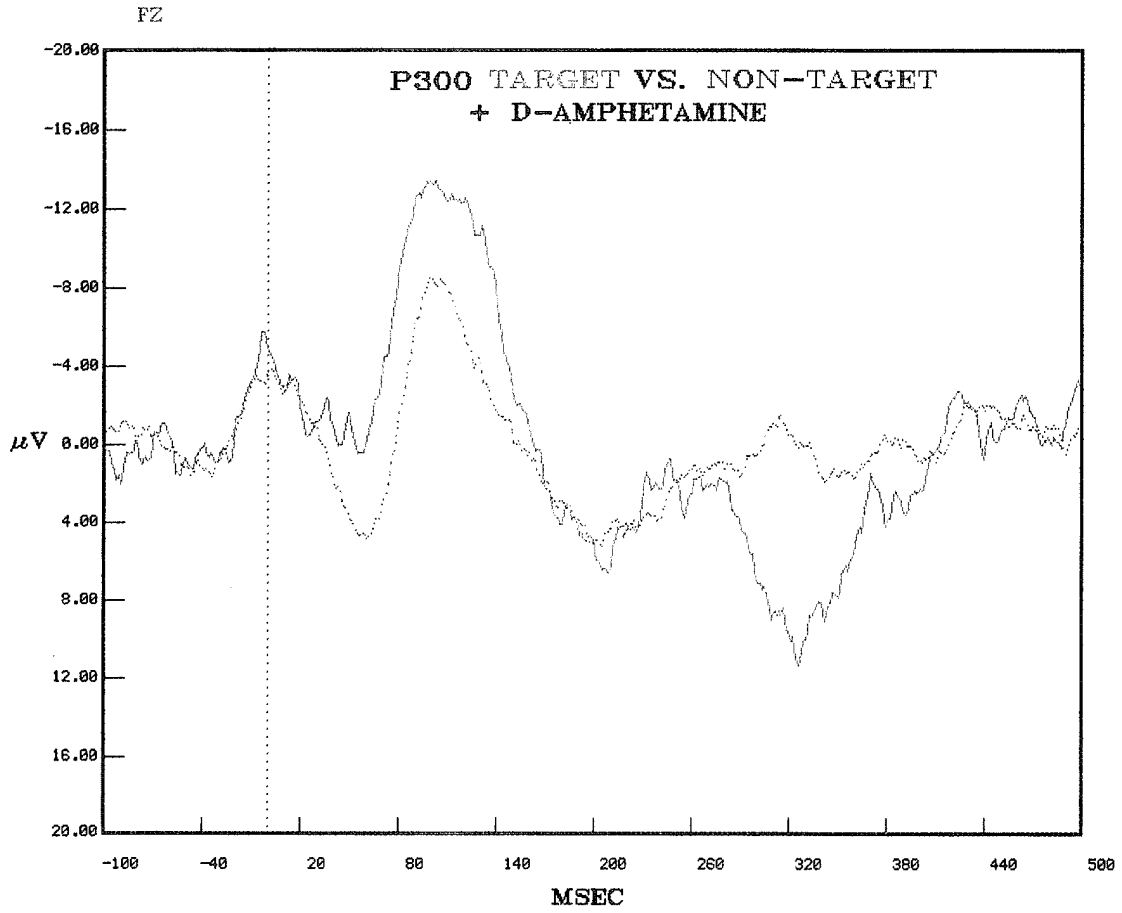


FIG. 3. Green line, average evoked response elicited by targets; red line, average evoked response elicited by non-targets.

ment to reduce impedance. Grass silver silver-chloride electrodes were affixed to the scalp by collodion glue with an electrolyte gel. Electrode placements conformed to the International 10-20 system, with linked ear reference electrodes.

Two 2-min recording sessions of continuous EEG data were acquired at each test session, one with eyes closed and one with eyes open. Raw EEG data was epoched, the baseline was corrected, and an eye-blink algorithm was applied using ± 50 μV cutoff margins. Spectral analysis of EEG bands was generated for each 2-min recording. The effect of the left hemisphere craniotomy performed following head injury was apparent on all EEG and ERP recordings. Left-sided slowing was also apparent on continuous EEG. This finding correlated with increased left hemisphere amplitude on ERP recordings.

Auditory P300 ERPs were acquired over a sweep time of 1 s, beginning 100 ms before stimulus presentation. Artifact was defined by $\pm 80\mu$V, and average waveforms were baseline corrected and filtered at a bandpass of 0.25–40 Hz. ERP averages were generated from 40 to 60 epoch recordings.

RESULTS AND DISCUSSION

Figure 1 shows the average P300 for R.E. under placebo conditions. The variance in the average is shown in the surrounding lines, representing one standard deviation above and below the mean. The upper-right quadrant shows a topographic map of the distribution of the ERP activity. The amplitude of the P300 on placebo is abnormal and would be read as "absent." Furthermore, the topographic distribution of the waveform amplitude is more centro-anterior than is typical (5), although it is not significantly lateralized.

Figure 2 demonstrates the average P300 for R.E. on D-amphetamine. Again, the amplitude of the P300 is maximal in the fronto-central region and is not significantly lateralized. The degree of variability is diminished on D-amphetamine compared with placebo. Most striking, however, is the enhancement of P300 amplitude with D-amphetamine treatment. While the P300 in the D-amphetamine condition is of normal amplitude and latency, it is still abnormally distributed in the central anterior region. The anterior shift of the P300 is interesting in light of R.E.'s history of

bilateral temporoparietal subdural hematomas and may represent functional reorganization. To further evaluate the degree to which the D-amphetamine enhancement is specific to attentional mechanisms, Fig. 3 shows a comparison of components evoked by target tones with components evoked by nontarget tones. The enhancement was specific to the target to which he was attending.

Results of CogScreen testing showed a selective enhancement of performance on a measure of divided attention. His performance deteriorated less under the simultaneous task condition, and he also improved in his performance on a measure of impulsivity. These results show that D-amphetamine affects the speed with which one is able to divide or switch attention and the ability to inhibit responses under speeded, simultaneous task conditions.

In summary, we found a topographic reorganization of the P300 component following head injury. The redistribution of the waveform was not specific to drug or placebo conditions. Moreover, D-amphetamine enhanced the amplitude of the P300. This enhancement was specific to P300 targets and was not apparent in response to nontarget stimuli. We believe that D-amphetamine facilitates attentional capacity allocation to targets in the P300 paradigm. These observations support those reported by Bleiberg et al. (1) and further document the beneficial effect of D-amphetamine treatment on attentional mechanisms following brain injury.

REFERENCES

1. Bleiberg J, Garmoe W, Cederquist J, Reeves D, Lux W. Effects of D-amphetamine on performance consistency following brain injury. *Neuropsychiatry, Neuropsychol Behav Neurol* 1993;6(4): 245–8.
2. Kay GG. *CogScreen: software and professional manual.* Odessa, FL: Psychological Assessment Resources, Inc., 1995.
3. Begleiter H, ed. *Evoked brain potentials and behavior.* New York: Plenum Press, 1977.
4. Gualtieri CT, Wargin W, Kandy R, et al. Clinical studies of methylphenidate serum levels in children and adults. *J Am Acad Child Psychiatry* 1982;21:19–26.
5. Picton TW. The P300 wave of the human event-related potential. *J Clin Neurophysiol* 1992;9(4):456–79.

INS

NOTE: FIVE FULL COPIES NEEDED

INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY
TWENTY-FOURTH ANNUAL MEETING
CHICAGO, ILLINOIS, USA
February 14-17, 1996
Abstract Reproduction Form
Deadline For Receipt of Abstracts is JUNE 23, 1995

IMPORTANT
Instructions on the previous pages must be followed COMPLETELY for abstract to be published.

List name, address and telephone number of author who will be responsible for all communications to coauthors.

Name: Victoria N. Starbuck, Ph.D.
Address: Dept. of Neurology
Georgetown Univ. Hospital
3800 Reservoir Road, N.W.
Washington, D.C. 20007
Telephone numbers: (include country, city/area code).
Office: 202-687-8525
Home: 202-337-0756
E-mail: starbucv@medlib.georgetown.edu

Abstracts sent to other national societies or those published previously will not be considered. Authors are asked to exercise discretion in the number of papers submitted due to the difficulties of scheduling.

Check all that apply

Symposium ____

Papers - (Preference)
Poster Session Presentation X
Oral Presentation ____
Will not accept alternate format ____

Eligibility for Rennick or Butters Award
Please check if first author is:
Pre-doctoral student ____
Post-doctoral student X

Please check if presenting/responsible author is a Member of INS. ____

(OVER-PAGE 1 CONTINUES)

Type Abstract Here--Stay within border & 125 words. Symposium organizer should duplicate form & provide a 125 word abstract of each main speaker.

V.N. Starbuck, R.C. Platenberg, J. Bleiberg, C.A. Eberle, C.S. Lin, K. Ward, & A.A. Hartley. fMRI of Working Memory: A Case Study of Signal Enhancement with D-Amphetamine Treatment Following Head Injury. Department of Neurology, Georgetown University School of Medicine, Washington, D.C. 20007, USA.

Functional magnetic resonance imaging (fMRI) was used to measure brain activation for a 54 year old male head-injured subject on two working memory tasks (Location and Identity) and a simple Motor Task. The subject was evaluated on and off d-amphetamine treatment. fMRI analysis demonstrated significantly greater activation when the subject was on drug. Drug effects were most salient for the Location task. The posterior slices yielded more differential fMRI activation compared to the anterior slices. Significant differential activation was also observed for the Motor Task. These findings support prior electrographic and behavioral studies of d-amphetamine-mediated performance changes. Findings also support Baddeley's model of working memory.

fMRI of Working Memory:
A Case Study of Signal Enhancement with D-Amphetamine Treatment following Head Injury

Working memory has been defined as a temporary storage system for information to be manipulated during performance of cognitive tasks (Baddeley, 1992). In Baddeley's model, working memory is composed of two systems, one concerned with phonological information and the other with visuospatial information, both of which are under the control of a central executive system (Baddeley, 1986, 1992). Prior neuroimaging studies have demonstrated increased activation in multiple cortical areas, with specific constellations of activation for different types of tasks involving working memory (Jonides, Smith, Koeppe, Awh, Minoshima, & Mintun, 1993). Specifically, posterior structures appear to mediate task performance on measures requiring visuospatial functions, whereas anterior structures mediate the selection of one line of processing and ignoring other competing demands (Hartley, 1993). Working memory is a primary system subserving attentional processes and may be selectively susceptable to impairment following head injury. The current study used fMRI to examine patterns of activation in the brain during working memory tasks involving visuospatial/location or phonological/identity components in a brain injured subject (R.E.) on and off d-amphetamine.

Prior neurocognitive and electrophysiological studies of this subject (R.E.) demonstrated improvements in attention specific tasks on d-amphetamine treatment compared with placebo (Starbuck, Bleiberg, & Kay, 1995; Bleiberg, Garmoe, Cederquist, Reeves, & Lux, 1993). Bleiberg et. al (1993) demonstrated a reduction in the variability of his response to attention demanding cognitive testing. Starbuck et. al (1995) reported a topographic reorganization of the auditory P300 evoked potential component following his head injury. The redistribution of the waveform was not specific to d-amphetamine or placebo conditions. However, there was a specific enhancement of the amplitude of the P300 to target tones which was unique to the d-amphetamine condition. D-amphetamine appeared to facilitate attentional capacity allocation to targets in the P300 paradigm. Results from CogScreen (Kay, 1995), a computerized cognitive screening battery with demonstrated sensitivity to head injury, showed improved performance on a test of divided attention, as well as reduction in impulsive responding on another measure when tested on d-amphetamine compared to placebo conditions.

Functional magnetic resonance imaging (fMRI) provides a means of imaging the brain during performance of specific cognitive tasks. The fMRI deoxyhemoglobin contrast method (Turner, LeBihan, Moonen, & Despres, 1991) has been successfully used to study brain functioning during cognitive testing. Using this method, focal increases in neuronal activity can be detected and localized to specific regions of the brain. Echo-planar imaging allows for signal detection in slice placements throughout the brain. In view of the high spatial resolution of MRI, it was hypothesized that fMRI techniques would be able to provide a detailed view of brain regions activated during attention-demanding tasks. It was further hypothesized that fMRI would be sensitive to physiological changes mediated by d-amphetamine treatment following head injury.

METHODS

Subject

R.E. is a 57 year old, right-handed, male attorney who sustained a traumatic brain injury in a bicycle accident 7 years before the present study. Initial computed tomography (CT) scans showed bilateral temporoparietal subdural hematomas and a left temporoparietal contusion. Loss of consciousness was only about 5 minutes, but the left sided subdural hematoma required surgical evacuation. Testing 6 months postinjury revealed that his Wechsler Adult Intelligence Scale-Revised Verbal IQ was 126 and his Performance IQ was 108. He attained a Wechsler Memory Scale Memory Quotient of 136 with 100% retention after 30 minutes using the Russell modification. Additional neuropsychological tests showed a similar pattern of average to superior performance.

Design and Procedure

fMRI scans of the brain were performed using a 1.5 Siemens Vision with a standard cp head coil. MRI data was acquired using a single shot gradient-echo planar imaging (EPI) pulse sequence with TE = 50 msec, TR = infinity, flip angle = 90 degrees, FOV = 230 mm, slice thickness = 4 mm, and matrix size = 64x64. Slice positions for working memory tests were localized to maximize regions in the frontal, temporo-parietal and parieto-occipital regions of the brain. Slice positions were localized to the motor strip for motor activation studies. The functional stimulation pattern involved a 2 minute scan of 25 images at each slice location: 5 at rest, 5 during testing, 5 at rest, 5 during testing, and 5 at rest. Pre and post stimulation images were compared using the cross-correlation analyses. Functional maps were obtained using a correlation coefficient threshold of 0.6 which corresponds to a z-score equal to 2. The functional maps were overlaid with anatomical images for better localization.

During fMRI imaging sessions, R.E. was presented with three tasks: a working memory letter identity task (Identity), a working memory letter location task (Location), and a simple motor task. Both the working memory tasks employed a two-back protocol that is very demanding with respect to storage processes. The subject must always have in working memory at least three stimuli to complete the tasks successfully: the present item, and the two immediately preceding ones. The tasks also require constant shifting of items to and from working memory; with the arrival of each new item, the subject must not only insert that item into working memory, but also drop one of the current occupants of working memory while maintaining the other occupant.

For the Identity task, the subject had to determine whether the letter being presented matched the letter presented two items back, regardless of where the letter appeared on the page. For the Location task, the subject had to determine whether the location of the letter was the same as the location two items back, regardless of the letter being presented. Both tests used the same task stimuli, presented in different orders. Thus the physical parameters of the two tasks was identical, only the instructions to the subject changed between the two tests. Extensive practice on each task was conducted prior to imaging to ensure that the subject understood the instructions and was able to do the test.

The third task utilized a simple motor cortex activation protocol. This task involves bilateral sequential finger to thumb taps, and has been demonstrated to activate areas in the motor cortex. The task was included to examine activation effects related to non-attention demanding task performance.

RESULTS

Activation maps of the eleven slices of EPI images were obtained for each test. Both test sessions were subjected to further statistical analysis. The design was a 2 X 3 doubly-repeated measures analysis of variance. The independent variables were drug (off and on d-amphetamine), and test (Identity, Location, or Motor Task). The dependent variable was number of pixels per slice showing significant activation. For the Identity and Location working memory tasks, two doubly-repeated measures analyses of variance were conducted, one for the first seven slices (posterior region) and one for the last four slices (anterior region). Analysis of the Motor Task activation was restricted to the four slice placements closest to the motor strip. Significant drug effects were observed in both posterior and anterior regions. These effects were most pronounced for the Location task. Differential fMRI activation on and off drug was greater in the posterior region for the Location task ($\underline{M}$ = 1.28 off d-amphetamine; $\underline{M}$ = 58.8 on d-amphetamine) compared to the Identity task ($\underline{M}$ = .57 off d-amphetamine; $\underline{M}$ = 10.6 on d-amphetamine). For the anterior region, differential activation was again found for the Location task ($\underline{M}$ = 14.1 on d-amphetamine; $\underline{M}$ = .5 off d-amphetamine). No significant drug effects were found for the Identity task when the analysis was limited to the anterior slices. A main effect of drug for Motor Task performance was found such that there was more activation when the subject was on d-amphetamine ($\underline{M}$ = 44.2) compared to when he was off drug ($\underline{M}$ = 8.25).

Discussion

In summary, fMRI analysis demonstrated significantly greater activation when R.E. was on d-amphetamine compared to when he was off drug. Drug effects were greater for the Location task than the Identity task. Drug effects were more salient in the posterior slices. These findings supplement previous studies of R.E. demonstrating improved electrophysiological response and behavioral performance on attention tasks with d-amphetamine treatment. These findings are also convergent with Baddeley's model of working memory. Specifically, posterior activation during the Location test is consistent with the postulated localization of visuospatial working memory functions. Although there was no differential drug activation for the Identity task in the anterior regions, both working memory tasks elicited activation in the frontal lobes on drug. This finding is consistent with the proposed contribution of the central executive system in working memory. An unexpected finding of the present study was the differential activation found for Motor Task performance. One explanation for this finding may relate to the activation from areas adjacent to the motor strip. Consequently, the increase in activation associated with the on-drug condition may be attributable to factors such as improved motivation or speed of task performance, both of which are mediated by supplementary motor areas. Future studies should attempt to control for the contribution of supplementary motor cortex activation.

These findings support the utility of fMRI as a tool for the investigation of the neuroanatomical substrates of working memory. Further research may help in the selection of individuals who would be likely to respond well to treatment with d-amphetamine following head injury.

References:

Baddeley, A. (1986). Working memory. Oxford University Press, Oxford, England.

Baddeley, A. (1992). Working memory. Science, 255 (556-559).

Bleiberg, J., Garmoe, W., Cederquist, J., Reeves, D., Lux, W. (1993). Effects of d-amphetamine on performance consistency following brain injury. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 6 (4): 245-248.

Hartley, A. (1993). Evidence for the selective preservation of spatial selective attention in old age. Psychology and Aging, 8 (3), 371-379.

Jonides, J., Smith, E.E., Koeppe, R.A., Awh, E., Minoshima, S., & Mintun, M. (1993). Spatial working memory in humans as revealed by PET. Nature, 363 (17).

Kay, G.G. (1995). CogScreen Aeromedical Edition: Professional Manual. Odessa, Florida: Psychological Assessment Resources, Inc.

Starbuck, V.N., Bleiberg, J., & Kay, G.G. (1995). D-Amphetamine Mediated Enhancement of the P300 ERP: A Placebo-Crossover Double-Blind Case Study. In press. Neuropsychiatry, neuropsychology, and behavioral neurology, Vol. 8, Number 3.

Dartmouth-Hitchcock Medical Center

Department of Diagnostic Radiology

One Medical Center Drive
Lebanon, New Hampshire 03756-0001
FAX 603-650-5455

September 5, 1995

Dear Dr. Starbuck,

YES!

Your abstract has been accepted for presentation at The Eastern Neuroradiological Society Annual Meeting at Niagara-on-the-Lake October 6 - 8, 1995.

Each essayist is asked to make his presentation in 7 minutes with an additional 3 minutes for discussion (10 minutes total). Because we have a record number of abstracts it will be necessary for everybody to stay on time as a courtesy to fellow members.

Your talk is scheduled for Saturday 11:35 - 11:45

I have enclosed a camera ready copy of your abstract. Please look it over carefully and get back to me either by FAX (603-650-5455), snail mail (address above), voice mail (603-650-8315) or the Internet (Laurence.D.Cromwell.@Dartmouth.edu) if there are any blatant errors.

I would also ask you to FAX back the enclosed form indicating whether or not you are a member in training. Please indicate who is presenting if it is not the first author.

Dr. terBrugge has arranged a wonderful social program. With what I know from the abstracts we will have a terrific scientific program as well. I am looking forward to seeing you in October. Once again, thank you very much for submitting your abstract.

Sincerely,

Larry Cromwell

Laurence D. Cromwell, M.D.

LDC/lp

Enclosures

fMRI: A Case Study of d-Amphetamine Mediated Signal Enhancement during Working Memory Tests

VN Starbuck, RC Platenberg, JC Bleiberg, C Eberle, C Lin, K Ward, A Hartley, D Schellinger

Georgetown University School of Medicine
Washington, DC

PURPOSE

fMRI was used to measure brain activation on and off d-amphetamine treatment in a 54 year old male head injured subject. Two working memory tasks and a simple Motor task were studied. Prior neurocognitive studies of this subject demonstrated improvements in attention-specific tasks on d-amphetamine treatment. It was hypothesized that fMRI techniques would provide information on brain regions activated during attention-demanding tasks and that fMRI would be sensitive to physiological changes mediated by d-amphetamine treatment.

METHODS AND MATERIALS

fMRI data was acquired using a 1.5 Siemens Vision with a standard cp head coil. MRI data consisted of 11 single shot gradient-echo EPI scans of transverse orientation.

RESULTS

Statistical analysis revealed significantly greater activation when the subject was on drug. Regions in the posterior fronto-temporal areas yielded more differential fMRI activation compared to frontal-parietal areas. Significant differential activation was also observed on the Motor Task.

CONCLUSION

The present findings support the utility of fMRI as a tool for the investigation of the neuroanatomical substrates of working memory. Further research may help in the selection of ~~individual~~ INDIVIDUALS who would be likely to respond well to treatment with d-amphetamine following head injury.

APPENDIX D

FMRI PROTOCOL

Appendix D
(Drs. Starbuck's and Platenberg's FMRI Protocol)

Procedure for Using Functional MRI of Working Memory and Attention to Study the Effects of d-Amphetamine

Functional magnetic resonance imaging (FMRI) is a technique which permits the measurement of microscopic changes in magnetic susceptibility. Using the deoxyhemoglobin method, the BOLD* technique, we are able to measure the regional conversion of oxyhemoglobin, which is diamagnetic, to deoxyhemoglobin, which is paramagnetic. This conversion occurs as a result of neuronal activity and blood flow. Changes in signal intensity result from localized deoxyhemoglobin decreases which are secondary to neuronal activation as well as intrinsic hemodynamic factors. Changes in signal intensity are also related to the, temporal characteristics of the task protocol. Thus, activation is time locked to task-relevant characteristics. As a result, brain function may be mapped in a non-invasive manner, with relatively high spatial resolution, and without the need for radio pharmaceuticals,

This protocol is being developed to examine attention and working memory in a group of pre-selected head injured patients. These patients have demonstrated a positive response to d-amphetamine treatment of attention-related deficits. Using our test protocol, FMRI data will be acquired during cognitive testing, and analyzed for regional areas of activation on and off drug during these tasks.

Design and Procedure:

FMRI scans of the brain will be performed using a 1.5 Tesla Sieman's Vision with a standard circular polarized (cp) head coil. MRI data will be acquired using a single shot gradient-echo planar imaging (EPI) pulse sequence with TE=50 msec, TR=infinity, flip angle=90 degrees, FOV=230 mm, slice thickness =4 mm, and matrix size = 64 x 64. Slice positions for working memory and attention tasks will be localized to maximize regions in the frontal, temporo-parietal, and parieto-occipital regions of the brain. Slice orientation will be transverse.

The functional stimulation pattern includes a 2 minute scan of 25 images at each slice location; 5 epochs rest, 5 task activation, 5 rest, 5 task activation, and 5 rest (A-IB-A-B-A design). Functional activation is derived through a statistical procedure comparing task activation to rest on a pixel by pixel basis. Functional maps will be obtained using a cross correlation coefficient threshold of 0.65 which corresponds to a z-score equal to about 2. Functional maps will be superimposed on anatomical images for better localization.

The cognitive tests will include 2 visual working memory tasks, and a sustained auditory attention and calculation task. The Identity and Location working memory tasks employ a two-back protocol that is very demanding with respect to storage processes. The subject

must always have in working memory at least three stimuli to complete the tasks successfully, the present item, and the two immediately preceding ones. The tasks also require constant shifting of items to and from working memory; with the arrival of each new item, the subject must not only insert that item into working memory, but also drop one of the current occupant!; of working memory while maintaining the other occupant. Preliminary data with normal controls have demonstrated reproducible, consistent activation in the right fronto-parietal area during the Location task. This is consistent with PET data identifying working memory for spatial location in the right hemisphere. Activation in the left frontal lobe is demonstrated during the Identity task, but the degree of activation is not as robust as that seen with the Location task. Activation in the primary visual cortex has also been demonstrated during both tasks, and serves as an internal control for our working memory tasks.

The primary attention and calculation tasks is a modified version of the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977). During this task, numbers are presented auditorily at a constant rate. The subject must add the number being presented to the previous number presented. Preliminary data from normal controls has demonstrated reproducible, consistent activation in the left frontal area. Demonstration of activation in the primary auditory cortex also serves as an internal control to validate this technique.

The reason for re-designing the original project was that the Year 1 data raised questions about the stability of ANAM performance in brain injured populations. , suggesting that developing norms was premature until the within-day and across-day variability was better understood. This issue was discussed at length with the Advisory Board prior to and at the August 12, 1995 meeting. Consensus was that norms development for brain-injured populations should be deferred to Year 3, and replaced by aggressive further study of the variability issue in Year 2. The "Computerized Library of ANAM Reference Cases" makes the entire raw data set available to DOD and other approved scientists. The consensus conference proposed for May, 1996 will determine the summary statistics and graphical displays for the data set, identify persons who should have access, and re-evaluate the issue of developing norms during Year 3.