AA

Form Approved Through 2/28/01
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

FEB 16 200

702511

...d on sample.

* PI: MARION, DONALD
Council: 10/2001
1 R01 ~~NS042704-01~~
IPF:2059802
Dual: HD,MH
HD42386-01
IRG: ZNS1 SRC(99)
Received: 02/01/2001

1. TITLE OF PROJECT *(Do not exceed 56 characters, including spaces an...*
fMRI and Sports-Related Concussion

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES *(If "Yes," state number and title)*
Number: NS-01-007 Title: Functional MRI and Intervention for Cognitive Deficits after Traumatic Brain Injury

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR — New Investigator ☐ Yes

3a. NAME *(Last, first, middle)*	3b. DEGREE(S)	3c. SOCIAL SECURITY NO.
Marion, Donald W.	MD	*Provide on Form Page KK*

3d. POSITION TITLE	3e. MAILING ADDRESS *(Street, city, state, zip code)*
Professor	University of Pittsburgh Department of Neurological Surgery Suite B400, UPMC Presbyterian 200 Lothrop Street, Suite B400 Pittsburgh, PA 15213
3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Neurological Surgery	
3g. MAJOR SUBDIVISION School of Medicine	
3h. TELEPHONE AND FAX *(Area Code, number and extension)* TEL: (412) 647-0956 FAX: (412) 647-7337	E-MAIL ADDRESS: dmarion@neuronet.pitt.edu

4. HUMAN SUBJECTS	4a. If "Yes," Exemption no. or IRB approval date		4b. Assurance of compliance no.	5. VERTEBRATE ANIMALS	5a. If "Yes," IACUC approval date	5b. Animal welfare assurance no.
☐ No ☒ Yes	12/21/00	☐ Full IRB or ☒ Expedited Review	M1259	☒ No ☐ Yes		A3187-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year--MM/DD/YY)*		7. COST REQUESTED FOR INITIAL BUDGET PERIOD		8. COST REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs
9/1/01	8/31/06	367,704	546,260	1,920,071	2,856,387

9. APPLICANT ORGANIZATION	10. TYPE OF ORGANIZATION
Name: University of Pittsburgh Address: Office of Research 350 Thackeray Hall Pittsburgh, PA 15260	Public: → ☐ Federal ☐ State ☐ Local Private: → ☒ Private Nonprofit Forprofit: → ☐ General ☐ Small Business
	11. ORGANIZATIONAL COMPONENT CODE: 01
	12. ENTITY IDENTIFICATION NUMBER: EIN/TIN Number — Congressional District: 14

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE	14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Michael M. Crouch Title: Director, Office of Research Address: 350 Thackeray Hall Pittsburgh, PA 15260	Name: Michael M. Crouch Title: Director, Office of Research Address: 350 Thackeray Hall Pittsburgh, PA 15260
Telephone: (412) 624-7400 FAX: (412) 624-7409 E-Mail Address: ornih@orserver.off-res.pitt.edu	Telephone: (412) 624-7400 FAX: (412) 624-7409 E-Mail Address: offres@orserver.off-res.pitt.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)* — DATE: 2/13/01

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fradulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)* — DATE: 2/14/01

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

Participants in organized sports—particularly football, hockey, and soccer—are at increased risk for sustaining one, and often multiple, concussions. Not only can multiple concussions cause long-term or permanent neurologic dysfunction, but there is evidence that athletes who suffer a second concussion before they have fully recovered from the first, are vulnerable to acute, severe brain swelling or death. However, there are no reliable standards for determining when an athlete can safely return to play after a concussion nor whether different criteria are needed depending on their age or gender. Such guidelines await elucidation of the pathophysiology and long-term effects of concussion, which are poorly understood. Current standards of care vary widely and are based on subjective experiences. They do not utilize physiological or neurocognitive measures. Two years ago, we developed a battery of neurocognitive tests (ImPACT) that assesses memory and attention, the two most common cognitive functions impaired by concussion. We have field tested ImPACT and found that this battery accurately reflects the onset and resolution of concussion-induced symptoms. During the next 5 years, we plan to use functional MRI (fMRI) to study 200 high-school and college athletes who have suffered a concussion, in order to characterize post-concussive abnormalities in brain activation patterns. We will correlate changes in fMRI activation patterns with changes detected using a conventional test of working memory (N-Back), and also with the ImPACT battery. Using this paradigm, we will measure the effects of single vs. multiple concussions. The influences of age and gender on these abnormalities will be determined. Finally, we will assess how well changes in fMRI activation patterns, symptoms of concussion, and objective cognitive abnormalities correlate with each other and with academic performance 3 and 6 months after injury. We expect the results of this study to provide a physiologic and anatomic underpinning for the cognitive deficits observed after one or more concussions in different at-risk groups. Such information should enable the development of better guidelines for return to play, school, or work. The results of this study also will help determine which medications or other therapies are most likely to benefit victims of concussion in subsequent therapeutic trials.

PERFORMANCE SITE(S) *(organization, city, state)*

University of Pittsburgh
Pittsburgh, PA

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed to provide the required information in the format shown below.*

Name	Organization	Role on Project
Donald W. Marion, MD	University of Pittsburgh	Principal Investigator
Mark R. Lovell, MD	University of Pittsburgh	Co-Investigator
Michael W. Collins, PhD	University of Pittsburgh	Co-Investigator
Fernando Boada, PhD	University of Pittsburgh	Co-Investigator
V. Andrew Stenger, PhD	University of Pittsburgh	Co-Investigator
Melvin Field, MD	University of Pittsburgh	Co-Investigator
James Becker, PhD	University of Pittsburgh	Co-Investigator
Freddie Fu, MD	University of Pittsburgh	Consultant
Joseph Maroon, MD	University of Pittsburgh	Consultant
William Eddy, PhD	Carnegie Mellon University	Consultant

TABLE OF CONTENTS

DD Principal Investigator/Program Director *(Last, first, middle):* Marion, Donald W.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 9/1/01 THROUGH 8/31/02

PERSONNEL *(Applicant organization only)*		TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED *(omit cents)*		
NAME	ROLE ON PROJECT				SALARY REQUESTED	FRINGE BENEFITS*	TOTALS
Donald W. Marion, MD	Principal Investigator	#	%	$	28,260	5,482	33,742
Mark R. Lovell, MD	Co-Investigator				49,687	9,639	59,326
Michael W. Collins, PhD	Co-Investigator				12,422	2,410	14,832
Fernando Boada, PhD	Co-Investigator				9,834	1,908	11,742
V. Andrew Stenger, PhD	Co-Investigator				1,882	365	2,247
Melvin Field, MD	Co-Investigator				8,436	675	9,111
James Becker, PhD	Co-Investigator				No Salary Support Requested		
Leann Thomas-Bullian	Study Coordinator				23,294	5,777	29,071
Jennifer Bakal	Research Assoc				35,384	8,775	44,159
Denise Davis	Research Assoc				51,758	10,041	61,799
	SUBTOTALS →				220,957	45,072	266,029

CONSULTANT COSTS			
William Eddy, PhD, Biostatistician, CMU (20% FTE)		28,800	28,800
EQUIPMENT *(Itemize)*			
2 Pentium III PCs for use by Research Associates		8,000	
A28-UNF1 - Sun Blade 1000		9,995	
			17,995
SUPPLIES *(Itemize by category)*			
fMRI Study			
Concussion Patients (200 patients, 80 studies/yr @ $433 each)		34,640	
Control Patients (50 patients, 10 studies/yr @ $433 each)		4,330	
Impact Study			
All Patients (250 patients, 80 studies/yr @ $150 each)		12,000	
			50,970
TRAVEL			
Investigator(s) travel to scientific meeting		2,500	2,500
PATIENT CARE COSTS	INPATIENT		0
	OUTPATIENT		0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*			0
OTHER EXPENSES *(Itemize by category)*			
Patient Parking (130 patients/yr @ $7 each)		910	
Control Patient Incentive (10 patients/yr @ $50 each)		500	
			1,410
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$**	**367,704**
CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS		0
	FACILITIES AND ADMINISTRATION COSTS		0
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)*		**$**	**367,704**

= Number of Months Devoted to Project
% = Percentage of Effort
$ = Insitutional Based Salaries

BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD *(from Form Page 4)*	ADDITIONAL YEARS OF SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL: Salary and fringe benefits *Applicant organization only*		266,029	274,010	285,584	311,421	320,764
CONSULTANT COSTS		28,800	29,664	30,554	31,471	32,415
EQUIPMENT		17,995	0	0	0	0
SUPPLIES		50,970	52,499	54,074	55,696	57,367
TRAVEL		2,500	2,575	2,652	2,732	2,814
PATIENT CARE COSTS	INPATIENT	0	0	0	0	0
	OUTPATIENT	0	0	0	0	0
ALTERATIONS AND RENOVATIONS		0	0	0	0	0
OTHER EXPENSES		1,410	1,452	1,496	1,541	1,587
SUBTOTAL DIRECT COSTS		367,704	360,200	374,360	402,861	414,947
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT	0	0	0	0	0
	F & A	0	0	0	0	0
TOTAL DIRECT COSTS		367,704	360,200	374,360	402,861	414,947

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT *(Item 8 a, Face Page)* → **$ 1,920,071**

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

PLEASE SEE JUSTIFICATION ON THE FOLLOWING PAGES.

BUDGET JUSTIFICATION

PERSONNEL

Principal Investigator: Donald W. Marion, M.D., FACS, % Effort, Salary Support Requested

Since 1992, Dr. Marion has served as the Team Neurosurgeon for the University of Pittsburgh Athletic Department, and is the primary neurosurgical provider for all of the University's college athletes, both male and female, who sustain concussion or more severe head or spinal cord injuries. Dr. Marion will be immediately responsible for the conduct of this study. He will assure proper coordination of all neuropsychological and fMRI studies and proper evaluation of the data. Dr. Marion has a long history of coordinating complicated and multifaceted neurotrauma and injury prevention programs. Since 1990, he has had funding for a Program Project grant which forms the basis for the University of Pittsburgh Brain Trauma Research Center. As such, he oversees the research of more than 10 primary investigators and during the past 10 years has been author or co-author of over 100 publications produced from these efforts. Dr. Marion is Professor of Neurological Surgery, Director of the Brain Trauma Research Center and Director of the Center for Injury Research and Control at the University of Pittsburgh

Co-Investigator: Mark R. Lovell, Ph.D. % Effort, Salary Support Requested

Dr. Lovell will be primarily responsible for conducting the ImPACT and modified symbol matching module test batteries which are part of this project. Together with Dr. Collins, they also will be the people primarily doing the initial intake of candidates for the study. They will be in direct contact with all the high school and college athletic programs in the region and already have established professional relationships with most. These two investigators will be conducting the preseason ImPACT studies for all of these athletes, far more than those who will likely become candidates for this study. They will keep the primary database for the neuropsychological test studies and will be responsible for the interpretation of those studies. Dr. Lovell is the Director of the UPMC Sports Medicine Concussion Program at the University of Pittsburgh Medical Center within the Department of Orthopaedic Surgery. Dr. Lovell is currently a Fellow of the National Academy of Neuropsychology and serves as a reviewer for numerous scientific journals. He recently co-edited a book entitled *Sports-Related Concussion*.

He was the first neuropsychologist to utilize neuropsychological testing in professional sports with the Pittsburgh Steelers and developed the neuropsychological test protocols that are currently being utilized with the National Football League (NFL) and National Hockey League (NHL). Dr. Lovell serves as Director of the Neuropsychology Program for the NFL and Co-Director of the NHL Neuropsychology Advisory Board and administers league-wide neuropsychological testing programs for both the NFL and NHL. Dr. Lovell also serves as a consult to numerous individual professional sports organizations.

Co-Investigator: Michael W. Collins, Ph.D, % Effort, Salary Support Requested

Dr. Michael W. Collins is the Assistant Director of the UPMC Sports Medicine Concussion Program and will be collaborating with Dr. Lovell. Together with Dr. Lovell, Dr. Collins will be obtaining the preseason ImPACT studies and doing the initial intake of candidates for this study including determining inclusion and exclusion criterion. Dr. Collins will work with Dr. Lovell to administer the ImPACT and modified symbol matching test batteries and will interpret this data for use in the study.

Co-Investigator: Fernando Boada, Ph.D., % Effort, Salary Support Requested

Dr. Fernando E. Boada, Ph.D. is Assistant Professor of Radiology at the University of Pittsburgh. He has performed research in MRI techniques for over eight years and is an author of thirty peer-reviewed papers, and over 40 conference abstracts related to MRI. He has extensive expertise in MR data acquisition and reconstruction. Over the past 5 years, he has developed customized data acquisition and reconstruction techniques for quantitative MRI of low concentration metabolites (sodium, lithium and phosphorous). Dr. Boada will serve as our primary fMRI consultant in terms of helping to assure high quality performance of the fMRI studies and dealing with any technical MR issues that may arise.

% = Percentage of Effort

Co-Investigator: V. Andrew Stenger, Ph.D. [%] **Effort, Salary Support Requested**

V. Andrew Stenger, Ph.D. is Assistant Professor of Radiology at the University of Pittsburgh and physicist at the University of Pittsburgh's MR Research Center. He has performed research in MRI techniques for several years and his work focuses on the development of new methods for the acquisition of functional MR images, including spiral imaging techniques. He is an author of over 20 peer-reviewed papers, and over 30 conference abstracts related to MRI. Assistance with fMRI data acquisition will be obtained though collaboration with Dr. Stenger. Dr. Stenger's current single-shot spiral imaging protocol, designed for the LX MRI system, allows for the acquisition of up to 24 3.2 mm thick 64x64 slices with a 20 cm field of view in 1.2 seconds. This protocol provides nearly full brain coverage with isotropic voxel dimensions (3.2 mm on a side) in a time rapid enough to produce well defined hemodynamic time courses. The spiral protocol also includes a spectral-spatial excitation pulse which produces images with a large reduction in contamination from lipid signal.

Co-Investigator: Melvin Field, M.D. [%] **Effort, Salary Support Requested**

Dr. Field will work closely with Drs. Lovell and Collins in this project in coordinating and conducting the ImPACT and Modified Symbol Matching studies to be done at the Center for Sports Medicine. He will help conduct the screening interviews for candidates for the study and assist in identifying control subjects. Dr. Field is a senior neurosurgical resident at the University of Pittsburgh School of Medicine. Over the past three years, he has served as the assistant team neurosurgeon for the University of Pittsburgh Panther college football team. His current research interests include analyzing the impact of sports-related concussion on long-term cognitive function and identifying objective means by which return-to-play decisions can safely be made after a concussion. Over the past year he has been working closely with Drs. Lovell and Collins in determining age-related differences of recovery in the concussed athlete.

Co-Investigator: James Becker, Ph.D., [%] **Effort, Salary Support Requested**

James T. Becker, Ph.D. is Professor of Psychiatry and Neurology. Dr. Becker is an experienced neuropsychologist and has extensive experience in the study of brain behavior relationships. He is the Co-Director of the Neuroimaging Core of the University of Pittsburgh Alzheimer's Disease Research Center. He has extensive experience completing functional neuroimaging studies of patients with neurodegenerative disorders using both PET and fMRI techniques. He has also collaborated on a study of n-back performance and brain functional activation in elderly patients with Major Affective Disorder. He is experienced in using SPM99, and has taught it's usage to junior faculty. His contribution to this project will focus on the implementation of the fMRI component of the study, and he will work with Professor Eddy to analyze the fMRI data. He will assist the PI with interpretation of the fMRI data, and will assist in the presentation of the data.

Study Coordinator: Leann Bullian, R.N., [%] **Effort, Salary Support Requested**

Ms. Bullian will be responsible for overall coordination of both the neuropsychological test battery administration and fMRI studies. She will assure that patients are properly screened and will accompany these patients through all phases of the testing. Ms. Bullian is a senior research nurse who has worked closely with Dr. Marion over the past several years as the computer database specialist for the Brain Trauma Research Center. As such, she has coordinated data entry and management for nearly 400 patients with severe traumatic brain injury. She is quite familiar with the research methods described in this study.

Research Associate: Jennifer Bakal, [%] **Effort, Salary Support Requested**

Jennifer Bakal will be a Research Associate in Dr. Eddy's group. She has an MS in Applied Mathematics and has used and developed FIASCO software for the last one and one-half years. With Dr. Eddy's guidance, Ms. Bakal will be [%] devoted to the acquisition and statistical analysis of the fMRI data acquired during this study. Such data acquisition and analysis has been found by our group to be quite

% = Percentage of Effort

time consuming and statistical analysis of the 450 fMRI studies we expect to obtain over the next five years will clearly require the full-time effort of a sophisticated biostatistical associate.

Research Associate: Denise Davis, BS, RT, % Effort, Salary Support Requested

Denise Davis is a Registered Radiologic Technologist with advanced certification in Magnetic Resonance Imaging and a Bachelor of Science degree in Health Sciences from the University of Pittsburgh. She is currently working as a Research Instructor in the Department of Anesthesiology and Critical Care Medicine at the University of Pittsburgh Medical Center. She has been performing fMRI studies including patient preparation, data acquisition, image management and data analysis for the last seven years under the supervision of Keith Thulborn, M.D., Ph.D. She has extensive experience with many of the details required in developing fMRI protocols including fMRI paradigm design and implementation, brain anatomy and subject preparation. She understands basic UNIX commands and has worked on both SUN and Silicon Graphic workstations. Denise is an instructor for the General Electric Master Series: Clinical fMRI at 3.0T and 1.5T. She is a member of the International Society for Magnetic Resonance, Section for Magnetic Resonance Technologists and has organized and chaired regional meetings for the society both in Pittsburgh and Chicago. She has presented posters at the society's annual meeting, recently ranking 1st and 2nd place. She has co-authored 14 publications and recently finished a book chapter (with Dr. Thulborn), currently in press: Clinical fMRI in: Current Protocols in MR Imaging, Wiley and Sons.

For this research protocol she will assume responsibility for assessment and obtaining informed consent, explaining and practicing the fMRI paradigm with the subject, supervision of data acquisition, data management, and initial data analysis. She will assume timely transfer of data to Dr. Eddy's group for statistical analysis.

Fringe Benefits are 19.4% for Medical Faculty and 24.8% for Staff per the University of Pittsburgh DHHS Agreement proposal submitted for fiscal year 2002, effective 7/1/01.

CONSULTANT: William Eddy, PhD. (Biostatistician), FTE % Salary Support Requested

William F. Eddy is Professor of Statistics, Department of Statistics, Carnegie Mellon University. He holds additional appointments in the Center for Automated Learning and Discovery, the Center for the Neural Basis of Cognition, and the Center for Cognitive Brain Imaging. He has served on the editorial boards of the Journal of the American Statistical Association, Society for Industrial and Applied Mathematics Review and was the founding co-Editor of CHANCE magazine and the Journal of Computational and Graphical Statistics. He is the author or editor of ten books and over one hundred scientific papers. Dr. Eddy's role in this study will be as our primary statistical consultant, particularly with regard to the FIASCO software application to our research efforts. Dr. Eddy has a unique understanding of fMRI data analysis and we consider him key to the proper interpretation of the fMRI data acquired in this study.

CONSULTANT: Freddie Fu, M.D., No Salary Support

Dr. Fu is Director of the University of Pittsburgh Center for Sports Medicine and Professor and Chairman of the Department of Orthopaedic Surgery. He has had a longstanding interest and a professional commitment to sports medicine as evidence by numerous text books and journal articles that he has authored or co-authored. He is the Team Physician for the University of Pittsburgh Athletic Programs including the football team, and is Company Orthopaedic Surgeon for the Pittsburgh Ballet Theater. As such, Dr. Fu will be invaluable in the direct referral of many of the patients enrolled in the study, and will provide valuable input in data analyses and interpretation.

CONSULTANT: Joseph C. Maroon, M.D., No Salary Support

Dr. Maroon is Professor and Vice Chairman of the Department of Neurological Surgery, University of Pittsburgh School of Medicine and is Team Neurosurgeon for the Pittsburgh Steelers professional football team. Dr. Maroon has had a very longstanding history of research in the area of mild traumatic brain injury and sports-related concussion. He has written numerous articles in this regard including a recent manuscript in *Neurosurgery* entitled Cerebral Concussion in Athletes: Evaluation and Neuropsychological Testing (Neurosurgery 47:659-672, 2000). Dr. Maroon has been very supportive in the development of this proposal and will undoubtedly provide valuable input as we analyze and interpret the data.

EQUIPMENT:

Two Pentium III PC
These computers will be used by Denise Davis and Jennifer Bakal for preliminary data analysis for the *f*MRI data.

A28-UNF1 – Sun Blade 1000
This server is necessary for the acquisition and data analysis and acquisition from *f*MRI studies to be done in this proposal. We need a server for analysis because we will be obtaining a total of 450 *f*MRI studies and we will need to do a relational analysis on those studies.

SUPPLIES:

***f*MRI Study:**
The MR Research Center charges a research price of $433.00 for each of these studies and we will be obtaining a total of 450 studies.

ImPACT© Study:
The ImPACT© studies cost a total of $150.00 per study and we will be obtaining a total of 400 studies per year.

TRAVEL:
We are requesting $2,500 per year to defray travel expenses incurred by attending scientific meetings related to this study.

OTHER EXPENSES:

Patient Parking:
The parking cost will be $7.00 for a total of 650 times parking will be needed as part of the study for our patients and we intend to reimburse our study subjects for this.

Control Patient Incentive
$50.00 per patient.

BIOGRAPHICAL SKETCH

Give the following information for all *new* key personnel.
Copy this page for each person.

NAME	POSITION TITLE
Donald W. Marion, M.D.	Professor of Neurological Surgery

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
St. John's University, Collegeville, MN	BS	1975	Biology
University of California, Medicine, San Francisco, CA	MD	1982	Medicine
University of Pittsburgh, Medicine, Pittsburgh, PA	MS	1989	Neurobiology
University of Pittsburgh, Medicine, Pittsburgh	Resident	1983-89	Neurosurgery

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Positions Held:

1990-1995 Assistant Professor of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA
1995-1998 Associate Professor of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA
1998-present Professor of Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, PA
1999-present Interim Chief of Neurosurgery, UPMC-Presbyterian Hospital, Pittsburgh, PA

Awards and Honors:

1985 First Prize, Clinical Research, Southwestern Pennsylvania Chapter American College of Surgeons
1989 Jacob Jarvits Head-Injury Fellowship
1992 The Young Investigator Award, The National Head Injury Foundation
1992 & 1993 Outstanding Faculty Award, University of Pittsburgh
1997 Finalist, Health Care Hero Award, Pittsburgh Business Times
1998 & 1999 Best Doctors in America, Woodward/White
1999 & 2040 Who's Who in Medicine and Healthcare, 2nd & 3rd Editions
2000 America's Top Doctors, Castle Connolly Guide
2001 Who's Who in America, 59th Edition

Publications (selected from over 105 publications):

Marion DW, Pollack IF, Lund RD: Patterns of immune rejection of mouse neocortex transplanted into neonatal rat brain, and effects of host immunosuppression. Brain Res 519:133-43, 1990.

Marion DW, Crosby K: The effect of stable xenon on ICP. J Cereb Blood Flow Metab 11:347-50, 1991.

Marion DW, Darby JM, Yonas H: Acute regional cerebral blood flow changes caused by severe head injuries. J Neurosurg 74:407-14, 1991.

Marion DW, Bouma GJ: The use of stable xenon/CT CBF studies to define changes in cerebral CO2 vasoresponsivity caused by severe head injury. Neurosurgery 29:869-73, 1991.

Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM: The use of therapeutic moderate hypothermia for patients with severe head injuries: A preliminary report. J Neurosurg 79:354-62, 1993.

Marion DW, Carlier PM: Problems with initial Glasgow coma score assessment caused by the prehospital treatment of head-injured
patients: results of a national survey. J Trauma 36:89-95, 1994.

Palmer AM, **Marion DW**, Botscheller ML, Bowen DM, DeKosky ST: Increased transmitter amino acid concentration in human ventricular CSF posttrauma. Neuroreport 6:153-56, 1994.

DeKosky ST, **Marion DW**, Goss J, Miller P, Styren S, Kochanek PM: Upregulation of nerve growth factor following cortical trauma. Experimental Neurology 130:173-77, 1994.

Marion DW, Firlik A, McLaughlin M: Hyperventilation and severe traumatic brain injury. New Horizons (supplement to J Crit Care Med) 3:439-47, 1995.

Kochanek PM, **Marion DW**, Zhang W, Schiding JK, White M, Palmer AM, Clark RSB, O'Malley ME, Styren SD, Ho C, DeKosky ST: Severe controlled cortical impact in rats: assessment of cerebral edema, blood flow, and contusion volume. J Neurotrauma 12:1015-25, 1995.

Marion DW, White M: Treatment of experimental brain injury with moderate hypothermia and 21-aminosteroids. J Neurotrauma 13:139-47, 1996.

Marion DW, Leonov Y, Ginsberg M, Katz LM, Kochanek PM, Lechleuther A, Nemoto EM, Obrist W, Safar P, Sterz F, Tisherman SA, White RJ, Xiao F, Zar H: Cerebral resuscitation from cardiac arrest: Treatment potentials. Crit Care Med 24:S69-S80, 1996.

McLaughlin MR, **Marion DW**: Cerebral blood flow and vasoresponsivity within and around cerebral contusions. J Neurosurg 85:871-76, 1996.

Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST: Treatment of traumatic brain injury with moderate hypothermia. N Eng J Med 336:540-46, 1997.

Resnick DK, Subach B, **Marion DW**: The significance of carotid canal involvement in basilar skull fractures. Neurosurg 40:1177-81, 1997.

Kerr ME, Rudy EB, Weber BB, Stone KS, Turner BS, Orndoff PA, Sereika SM, **Marion DW**: Effect of short duration hyperventilation during endotracheal suctioning on intracranial pressure in severe head injured adults. Nursing Research 46(4):1-7, 1997.

Resnick DK, **Marion DW**, Carlier PM: Outcome analysis of patients with severe head injuries and prolonged intracranial hypertension. J Trauma 46(6):1108-11, 1997.

Marion DW: Therapeutic moderate hypothermia for severe traumatic brain injury. A Review. J Int Care Med 12:239-48, 1997.

Dixon CE, Ma X, **Marion DW**: Reduced evoked release of acetylcholine in the rodent neurocortex following traumatic brain injury. Brain Res 749:127-50, 1997.

Whalen MJ, Carlos TM, Clark RSB, **Marion DW**, DeKosky ST, Graham ST, Heineman S, Schiding JK, Memarzadeh F, Kochanek PM: The effect of brain temperature on acute inflammation after traumatic brain injury in rats. J Neurotrauma 14:561-72, 1997.

Forbes ML, Clark RSB, Dixon CE, Graham SH, **Marion DW**, DeKoskey ST, Schiding JK, Kochanek PM: Hyperventilation early after controlled cortical impact augments neuronal death in CA3 hippocampus. J Neurosurg 88:549-56, 1998.

Henker RA, Brown SD, **Marion DW**: Comparison of brain temperature with bladder and rectal temperatures in adults with severe head injury. Neurosurg 42:1071-75, 1998.

Ciallella JR, Yan HQ, Ma X, Wolfson BM, **Marion DW**, DeKosky ST, Dixon CE: Chronic effects of traumatic brain injury on vesicular acetylcholine transporter and M_2 muscarinic receptor protein in rats. Exp Neurol 152:11-19, 1998.

Resnick DK, Graham SH, Dixon CE, **Marion DW**: The role of cyclooxygenase 2 in acute spinal cord injury. J Neurotrauma 15:1005-13, 1998.

Kerr ME, **Marion DW**, Orndoff PA, Weber BB, Sereika SM: Evaluation of near infrared spectroscopy in patients with traumatic brain injury. Adv Exp Med Biol 454:131-7, 1998.

Wahlig JB, McLaughlin MR, Burke JP, **Marion DW**: The role of xenon-enhanced computed tomography in the management of a traumatic carotid-cavernous fistula: a case report. J Trauma 46(1):181-5,1999.

Bell MJ, Kochanek PM, Heyes MP, Wisniewski SR, Sinz EH, Clark RSB, Blight AR, **Marion DW**, Adelson PD: Quinolinic acid in the cerebrospinal fluid of children after traumatic brain injury. Crit Care Med 27:493-7, 1999.

Dixon CE, Kochanek PM, Yan HQ, Schiding JK, Griffith RG, Baum E, **Marion DW**, DeKosky ST: A one-year study of spatial memory performance, brain morphology and cholinergic markers after moderate controlled cortical impact in rats. J Neurotrauma 16:109-22, 1999.

Clark RSB, Kochanek PM, Chen M, Watkins SC, **Marion DW**, Chen J, Hamilton RL, Loeffert JE, Graham SH: Increases in Bcl-2 and cleavage of caspase-1 and caspase-3 in human brain after head injury. FASEB J 13:813-21, 1999.

Shao L, Ciallella JR, Yan HQ, Ma X, Wolfson BM, **Marion DW**, DeKosky ST, Dixon CE: Differential effects of traumatic brain injury on vesicular acetylcholine transporter and M_2 muscarinic receptor mRNA and protein in rat. J Neurotrauma 16:555-66, 1999.

Whalen MJ, Carlos TM, Kochanek PM, Clark RSB, Heineman S, Schiding JK, Franciola D, Memarzadeh F, Lo W, **Marion DW**, DeKosky ST: Neutrophils do not mediate blood-brain barrier permeability early after controlled cortical impact in rats. J Neurotrauma 16:583-94, 1999.

Dixon CE, Kraus MF, Kline AE, Ma X, Yan HQ, Griffith RG, Wolfson BM, **Marion DW**: Amantadine improves water maze performance without affecting motor behavior following traumatic brain injury in rats. Restorative Neurol Neurosci 14:285-94, 1999.

Whalen MJ, Clark RSB, Dixon CE, Robichaud P, **Marion DW**, Vagni V, Graham S, Virag L, Hasko G, Stachlewitz R, Szabo C, Kochanek PM: Reduction of cognitive and motor deficits after traumatic brain injury in mice deficient in poly(ADP-ribose) polymerase (Rapid Communication). J Cereb Blood Flow Metab 19:835-42, 1999.

Sinz EH, Kochanek PM, Dixon CE, Clark RSB, Carcillo JA, Schiding JK, Chen M, Wisniewski SR, Carlos TM, Williams D, DeKosky ST, Watkins SC, **Marion DW**, Billiar TR: Inducible nitric oxide synthase is an endogenous neuroprotectant after traumatic brain injury in rats and mice. J Clin Invest 104(5):647-56, 1999.

Slade J, Kerr ME, **Marion DW**: Incidence of CSF drainage and Mannitol usage in the treatment of intracranial hypertension with severe head injured patients using moderate therapeutic hypothermia. J Neurosurg Nursing 31(5)264-69, 1999.

Kerr ME, Weber BB, Sereika SM, Darby J, **Marion DW**, Orndoff PA: Effects of endotracheal suctioning on cerebral oxygenation in traumatic brain-injured patients. Crit Care Med 27(12)2776-81, 1999.

Marion DW, Spiegel TP: Changes in the management of severe traumatic brain injury: 1991-1997. Crit Care Med 28(1)16-8, 2000.

Witham TF, Thompson TP, **Marion DW**: Prevention of wound infections in neurosurgery. Contemporary Neurosurg 22(5):1-6,2000.

Whalen MJ, Carlos TM, Kochanek PM, Wisniewski SR, Bell MJ, Clark RSB, DeKosky ST, **Marion DW**, Adelson PD: Interleukin-8 is increased in cerebrospinal fluid of children with severe head injury. Crit Care Med 28(4):929-34, 2000.

Kilpatrick MM, Lowry DW, Firlik AD, Yonas H, **Marion DW**: Hyperthermia in the Neurosurgical Intensive Care Unit. Neurosurg 47(4)850-56, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
James T. Becker, Ph.D.	Professor of Psychiatry and Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Washington and Lee University, Lexington, VA.	B.A.	1975	Physiol. Psychol.
Northeastern University, Boston, MA	M.A.	1977	Neuropsychology
Johns Hopkins University, Baltimore, MD	M.A./Ph.D.	1979/1980	Physiol. Psychol.

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1980-1982 Postdoctoral Research Fellow, Department of Neurology, Boston University School of Medicine and the Boston VA Medical Center, MA

1982-1984 Clinical Research Associate, Boston VA Medical Center and Neurology Department, Boston University School of Medicine, Boston, MA

1982-1984 Assistant Professor of Psychiatry, Alcohol Research Center, University of Connecticut School of Medicine, and the Newington VA Medical Center

1984-1990 Assistant Professor of Psychiatry and Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA

1985-Present Associate Director, Alzheimer Disease Research Center, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA

1990-1996 Associate Professor of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, PA

1996-Present Professor of Psychiatry and Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA

HONORS

1973-1975 Robert E. Lee Research Scholar, Washington and Lee University

1980-1982 Postdoctoral Fellowship awarded by the National Institute for Alcohol Abuse and Alcoholism, sponsored by Nelson Butters, Ph.D.

1987 Diplomate, American Board of Clinical Neuropsychology

SELECTED PUBLICATIONS (From 116 Research Reports and 18 Non-Experimental Articles)

J.T. Becker, F. Boller, O.L. Lopez, J. Saxton, K. McGonigle: The natural history of Alzheimer's disease: I. Description of study cohort and accuracy of diagnosis. **Arch Neurol**, 1994, **51,** 585-594.

O.L. Lopez, R. Larumbe, J.T. Becker, D. Rezek, J. Rosen, W. Klunk, S.T. DeKosky: Reliability of the NINDS/AIREN criteria for the diagnosis of Vascular Dementia. **Neurology**, 1994, **44,** 1240-1245.

J.T. Becker, M.A. Mintun, D. Diehl, A. Martidis, S.T. DeKosky, J. Dobkin: Functional neuroanatomy of verbal free recall: A replication study. **Human Brain Mapping**, 1994, **1,** 284-292.

J.T. Becker, O.L. Lopez, F. Boller: Understanding impaired analysis of faces by patients with Probable Alzheimer's disease. **Cortex,** 1995, **31,** 129-137.

J.T. Becker, M.A. Mintun, K. Aleva, M.B. Wiseman, T. Nichols, S.T. DeKosky: Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. **Neurology**, 1996, **46,** 692-700.

M.A. Butters, O.L. Lopez, J.T. Becker: Focal temporal lobe dysfunction in Probable Alzheimer's disease predicts a slow rate of decline. **Neurology,** 1996, **46,** 687-692.

O.L. Lopez, M.P. Gonzalez, J.T. Becker, C.F. Reynolds, A. Sudilovsky, S.T. DeKosky: Symptoms of depression in Alzheimer's disease, frontal lobe type dementia, and subcortical dementia: Exploration of underlying mechanisms and psychosis. **Neuropsychiatry, Neuropsychol Behav Neurol,** 1996, **9,** 154-161.

A.N. Herbster, T.E. Nichols, M. Wiseman, M.A. Mintun, S.T. DeKosky, J.T. Becker: Functional connectivity in auditory verbal short-term memory in Alzheimer's disease. **NeuroImage,** 1996, **4,** 67-77.

O.L. Lopez, J.T. Becker, C.A. Jungreis, S. Weidman, C.F. Reynolds, S.T. DeKosky: Psychiatric correlates of MR deep white-matter lesions in Probable Alzheimer's disease. **J Neuropsychiat Clin Neurosc,** 1997, **9,** 246-250.

A.N. Herbster, M.A. Mintun, R.D. Nebes R, J.T. Becker: Regional cerebral blood flow in word and nonword reading. **Human Brain Mapping,** 1997, **5,** 84-92.

O.L. Lopez, S. Wisniewski, J.T. Becker, F. Boller, S.T. DeKosky: Extrapyramidal signs as predictors of progression institutionalization and death in Alzheimer's disease. **Arch Neurol**, 1997, **54,** 969-975.

O.L. Lopez, J.T. Becker, M.I. Kamboh, D.I. Kaufer, S.T. DeKosky: The apolipoprotein E4 allele is not associated with extrapyramidal signs or psychiatric symptoms in probable AD. **Neurology**, 1997, **49,** 794-797.

K.S. Graham, J.T. Becker, J.R. Hodges: On the relationship between knowledge and memory for pictures: Evidence from the study of patients with semantic dementia and Alzheimer's disease. **J Inter Neuropsychol Soc,** 1997, **3,** 534-544.

B.J. Zelkowicz, A.N. Herbster, R.D. Nebes, M.A. Mintun, J.T. Becker: An examination of regional cerebral blood flow during object naming tasks. **J Inter Neuropsychol Soc,** 1998, **4**:160-166.

O.L. Lopez, R.P. Brenner, J.T. Becker, R.F. Ulrich, S.T. DeKosky: Electroencephalography and survival in patients with Alzheimer's disease (Letter). **Neurology**, 1998, **51**:918-919.

P.T. Ricci, B. J. Zelkowicz, R.D. Nebes, C.C. Meltzer, M.A. Mintun, J.T. Becker: Functional neuroanatomy of semantic memory: Recognition of semantic associations. **NeuroImage**, 1999, **9**:88-96.

M.B. Wiseman, J.A. Sanchez, C. Buechel, M.A. Mintun, O.L. Lopez, D. Milko, J.T. Becker: Patterns of relative cerebral blood flow in minor cognitive motor disorder in HIV infection. **J Neuropsychiat Clin Neurosci**, 1999, **11**:1-12.

M.A. Conway, J.D. Turk, S.L. Miller, J. Logan, R.D. Nebes, C.C. Meltzer, J.T. Becker: A positron emission tomography (PET) study of autobiographical memory retrieval. **Memory**, 1999, **7(5/6)**:679-702.

J.T. Becker, R.G. Morris: Working memory(s). **Brain and Cognition**, 1999, **41**:1-8.

J.T. Becker, D.K. MacAndrew, J.A. Fiez: A comment on the functional localization of the phonological storage subsystem of working memory. **Brain and Cognition**, 1999, **41**: 27_38.

O.L. Lopez, S. Zivkovic, G. Smith, J.T. Becker, C.C.Meltzer, S.T. DeKosky: Psychiatric symptoms associated with cortical-subcortical dysfunction in Alzheimer's disease. **J Neuropsychiat Clin Neurosci**, 2000; **12(4)**.

O.L. Lopez, J.T. Becker, W. Klunk, J. Saxton, R.L. Hamilton, D. Kaufer, R. Sweet, C.C. Meltzer, S. Wisniewski, S.T. DeKosky: Research, evaluation, and diagnosis of Alzheimer's disease in the last two decades: I. Characteristics of probable AD. **Neurology**, 2000, **55(12)**: 1854-1862.

O.L. Lopez, J.T. Becker, W. Klunk, J. Saxton, R.L. Hamilton, D. Kaufer, R. Sweet, C.C. Meltzer, S. Wisniewski, S.T. DeKosky: Research, evaluation, and diagnosis of Alzheimer's disease in the last two decades: II. Characteristics of possible AD. **Neurology**, 2000, **55(12)**: 1863-1869.

M.A. Butters, J.T. Becker, R.D. Nebes, M.D. Zmuda, B.H. Mulsant, B.G. Pollock, C.F. Reynolds: Changes in cognitive functioning following treatment of late-life depression. **Am J Psychiatry**, 2000, **157(12)**: 1949-1954.

O.L. Lopez, S. Wisniewski, R.L. Hamilton, J.T. Becker, D.I. Kaufer, S.T. DeKosky: Predictors of progression in patients with Alzheimer's disease and Lewy bodies. **Neurology**, 2000; **54**:1780-1787.

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Fernando E. Boada, Ph.D.	Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Universidad Simon Bolivar, Caracas, Venezuela	B.S.	1985	Physics
Case Western Reserve University, Cleveland, Ohio	M.S.	1989	Physics
Case Western Reserve University, Cleveland, Ohio	Ph.D.	1990	Physics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Professional Experience

1983-84	Laboratory Assistant, Universidad Simon Bolivar, Caracas, Venezuela
1984-84	Research Trainee, Instituto Technologico Venezolano del Petroleo, Los Teques, Venezuela
1985-86	Physics Instructor, Universidad Simon Bolivar, Caracas, Venezuela
1987-88	Teaching Assistant, Case Western Reserve University, Department of Physics, Cleveland, OH
1988-89	Research Assistant, Case Western Reserve University, Department of Physics, Cleveland, OH
1990-91	Postdoctoral Fellow, University Hospitals of Cleveland, Department of Radiology, Cleveland, OH
1991-92	Postdoctoral Research Fellow in Metabolic Imaging Laboratory, Harvard University Medical School and Massachusetts General Hospital, Department of Radiology, MGH-NMR Center, Boston, MA
1992-93	Instructor in Radiology, Harvard University Medical School and Assistant in Physics, Massachusetts General Hospital, Department of Radiology, MGH-NMR Center, Boston, MA
1993	Assistant Professor in Radiology, University of Pittsburgh Medical Center, Pittsburgh, PA
1999-2000	Acting Co-Director, MR Research Center, University of Pittsburgh Medical Center, Pittsburgh, PA.
2000-	Acting Director, MR Research Center, University of Pittsburgh Medical Center, Pittsburgh, PA.
2000-	Associate Professor of Bioengineering, University of Pittsburgh, Pittsburgh, PA.
2000-	Associate Professor of Radiology, University of Pittsburgh Medical Center, Pittsburgh, PA.

Selected Publications

F. E. Boada, E. M. Haacke, W. Tobocman, K. Santosh and Z.-P. Liang. Superresolution Imaging applied to Ultrasonic Scattering. *Inverse Problems*, Vol. 5, L21-L26, 1989.

E. M. Haacke, Z.-P. Liang, **F. E. Boada**. Constrained Reconstruction Using Linear Prediction and Projection onto Convex Sets for the removal of Motion, Phase and Gibbs Artifacts in Magnetic Resonance and Ultrasound Imaging. *Optical Engineering*, Vol. 29, 555-556, 1990.

S. Amartur, Z. -P. Liang, **F. E. Boada** and E. M. Haacke. Phase Constrained Data Extrapolation Method for Reduction of Truncation Artifact, Journal of Magnetic Resonance*Imaging,* Vol. 1, 721-724, 1991.

Z.-P. Liang, **F. E. Boada**, R. T. Constable, E. M. Haacke, P. C. Lauterbur and M. R. Smith. Constrained Reconstruction Methods in MR Imaging. *Reviews of Magnetic Resonance in Medicine*, Vol. 4, 67-185, 1992.

F. E. Boada, J. D. Christensen, F. R. Huang-Hellinger, T. G. Reese, K. R. Thulborn. Quantitative *in vivo* Tissue Sodium Concentration Maps: the effects of biexponential relaxation. *Magnetic Resonance in Medicine*, 32: 219-223, 1994.

J. D. Christensen, B. J. Barrere, **F. E. Boada**, J. M. Vevea and K. R. Thulborn. Quantitative Tissue Sodium Concentration Mapping of Normal Rat Brain. *Magnetic Resonance in Mediceine,* 36: 83-89, 1996.

F. E. Boada., J. D. Christensen, J. S. Gillen and K. R. Thulborn. Three Dimensional Projection Imaging with Half the Number of Projections. *Magnetic Resonance in Medicine,* 37: 470-477, 1997.

F. E. Boada, J. S. Gillen, G. X. Shen, S. Y. Chang and K. R. Thulborn. Fast Three Dimensional Sodium Imaging. *Magnetic Resonance in Medicine.* 37: 706-715, 1997.

F. E. Boada, G. X. Shen GX, S. Chang and K. R. Thulborn. Spectrally Weighted Twisted Projection Imaging: reducing T2 signal attenuation effects in fast three dimensional sodium imaging. *Magnetic Resonance in Medicine.* 38: 1022-1028, 1997.

G. X. Shen, **F. E. Boada** and K. R. Thulborn. Dual-Frequency, dual-quadrature, birdcage RF coil design with identical B1 pattern for sodium and proton imaging of the human brain at 1.5T. *Magnetic Resonance in Medicine.* 38: 717-725, 1997.

D. C. Noll, **F. E. Boada**, W. F. Eddy. A Spectral Approach to Analyzing Slice-Selection: Optimization for Through-Plane Interpolation. *Magnetic Resonance in Medicine.* 37: 151-160, 1997.

F. E. Boada, J. J. Gillen, D. C. Noll, G. X. Shen, and K . R. Thulborn . Data Acquisition and Post-Processing Strategies for Fast Quantitative Sodium Imaging. *International Journal of Imaging Systems and Technology* . 8: 544-550, 1997.

F. E. Boada, Z-P Liang and E. M. Haacke. Improved Parametric Reconstruction Using Variable Projection Optimization. *Inverse Problems.* 14: 19-27, 1998.

K. R. Thulborn, **F. E. Boada**, G. X. Shen, J. D. Christensen and T. G. Reese.Correction of B1 inhomogeneities using echo-planar imaging of water. *Magnetic Resonance in Medicine* . 39: 369-375, 1998.

V. A. Stenger, D. C. Noll and **F. E. Boada**. Partial k-space reconstruction for 3D gradient echo functional MRI: a comparison of phase correction methods. *Magnetic Resonance in Medicine.* 40:481-490, 1998.

D. C. Noll, S. J. Peltier and **F. E. Boada**. Simultaneous Multislice Acquisition using Rosette Trajectories (SMART): A New Imaging Method for Fucntional MRI. *Magnetic Resonance in Medicine.* 39:709-716, 1998.

G. X. Shen, J. F. Wu, **F. E. Boada** and K. R. Thulborn. An Experimentally Verified Theoretical Design of Dual-Tuned, Low-Pass Birdcage RF Resonators for MRI and MRS of Human Brain at 3.0 Tesla. *Magnetic Resonance in Medicine.* 41: 268-275, 1999.

V. A. Stenger, S. J. Peltier, **F. E. Boada and** D. C. Noll. 3D Spiral Cardiac/Respiratory Ordered fMRI Data Acquisition at 3T. *Magnetic Resonance in Medicine.* 41:983-991, 1999.

I. Hancu, **F. E. Boada**, G. X. Shen. Three-Dimensional Triple-Quantum-Filtered 23Na Imaging of In vivo Human Brain. *Magnetic Resonance in Medicine.* 42:1146-1154, 1999.

J. C. Soares, **F. E. Boada**, M. S. Keshavan. Brain Lithium measurements with 7Li magnetic resonance spectroscopy (MRS): a literature review. *European Neuropsychopharmacology.* 10:151-158, 2000.

I. Hancu, J. R. C. van der Maarel, **F. E. Boada**. A Model for the Dynamics of Spins 3/2 in Biological Media: Signal Loss during Radiofrequency Excitation in Triple-Quantum Filtered Sodium MRI. *Journal of Magnetic Resonance.* 147: 179-191, 2000.

BIOGRAPHICAL SKETCH

Give the following information for all ***new*** key personnel.
Copy this page for each person.

NAME	POSITION TITLE
Michael W. Collins, Ph.D.	Clinical Instructor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Henry Ford Health System, Detroit, Michigan	Fellow	1998-2000	Clinical Neuropsychology
University of Florida/Shands Hospital, Gainesville, FL	Internship	1997-1998	Clinical Psychology
Michigan State University, East Lansing, MI	Ph.D	1998	Clinical Psychology
Michigan State University, East Lansing, MI	M.A.	1995	Master of Arts in Psychology
University of Southern Maine, Portland, ME	B.A.	1991	BA in Psychology and Biology

PROFESSIONAL EXPERIENCE:

2000 – Present Clinical Instructor, University of Pittsburgh School of Medicine, Department of Orthopaedic Surgery, UPMC Sports Medicine Concussion Program, Pittsburgh, PA.

HONORS AND AWARDS

2000 Certificate of Commendation from the Michigan Hospital Association for Shiawasse County High School "Concussion Safety Program"

1991 Graduated Summa Cum Laude, University of Southern Maine

1989 Participated in NCAA Baseball College World Series for the University of Southern Maine, placing fourth in the nation.

1989 Presented the New England Pepsi-Cola Scholar/Athlete of the Year Award

1988 Presented the New England Pepsi-Cola Scholar/Athlete of the Year Award

PUBLICATIONS and TEXT BOOK CHAPTERS

Collins MW, Lovell MR, McKeag DB. Current Issues in Managing Sports-Related Concussion. Journal of the American Medical Association. 1999;282(24):2283-2285.

Collins MW, Grindel SH, Lovell MR, Dede DE, Moser DJ, Phalin BR, Nogle S, Wasik M, Cordry D, Klotz Daughtery M, Sears SF, Nicolette G, Indelicato P, McKeag, DM. Relationship between concussion and neuropsychological performance in college football players. Journal of the American Medical Association. 1999;282(10):964-970.

Lovell MR, **Collins MW**, Maroon J, Burke C, Fu, F. New developments in the evaluation of sports-related concussion. Pittsburgh Orthopaedic Journal. In press.

Lovell, MR & **Collins MW**. Neuropsychological assessment of the head injured professional athlete. In J.E. Bailes and A. Day (eds). Sports Medicine and Neurosurgery. Neurosurgical topics book series of the American Association of Neurological Surgeons. In press.

Lovell MR, Iverson GL, **Collins MW**, McKeag DM, & Maroon JC. Does loss of consciousness predict neuropsychological decrements following concussion? Clinical Journal of Sport Medicine. 1999;9(4):193-198.

Lovell, MR & **Collins, MW.** Neuropsychological assessment of the college football player. Journal of Head Trauma Rehabilitation. 1998; 13(2) 27-35.

BIOGRAPHICAL SKETCH

Give the following information for all ***new*** key personnel.
Copy this page for each person.

NAME	POSITION TITLE
William F. Eddy	Professor of Statistics; Carnegie Mellon University

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Yale University, New Haven, CT	Ph.D.	1976	Statistics
Princeton University		1971	Statistics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

CURRENT POSITION:
Carnegie Mellon University, Professor, Department of Statistics; Associate Head, Department of Statistics; Professor, Center for Automated Learning and Discovery; Director, Institute for Statistics and Its Applications; Professor, Center for the Neural Basis of Cognition; Professor, Center for Cognitive Brain Imaging.

PROFESSIONAL EXPERIENCE:
Visiting Appointments: Bell Communications Research, 1987; Massachusetts Institue of Technology, 1985; University of Heidelberg, 1984; IAMI, Milan, 1982; Brown University, 1981
Member, ASA Board of Directors, 1988-1990, 1992
Founding Editor, Journal of Computational and Graphical Statistics, 1990-1994
Fellow, AAAS, 1987
Fellow, ASA, 1982
Fellow, IMS, 1987
Elected Member, ISI, 1982
Former Chairman of the Board and Executive Director, Interface Foundation of North America, 1987-1990
Former Member, Board of Directors, AFIPS, 1988-1990
Founding Editor, CHANCE magazine, 1987-1991
Chairman, Committee on Applied and Theoretical Statistics, National Research Council, 1990-1993

HONORS:
1977 Elected Fellow, Royal Statistical Society
1982 Elected Fellow, American Statistical Association
1982 Elected Member, International Statistical Institute
1987 Elected Fellow, American Association for the Advancement of Science
1987 Elected Fellow, Institute of Mathematical Statistics
1988 Elected Member, Mu Sigma Rho

SELECTED PUBLICATIONS

Goddard, N.H., Hood, G., Cohen, J.D., Nystrom, L.E., Eddy, W.F., Genovese, C.R., and Noll, D.C., 2000. Functional Magnetic Resonance Imaging Dataset Analysis, Industrial Strength Parallel Computing (A.E. Koniges, Ed.), Morgan Kaufmann Publishers, 431-451.

Eddy, W.F., Fitzgerald, M., Genovese, C., Lazar, N., Mockus, A., and Welling, J., 1999. The Challenge of Functional Magnetic Resonance Imaging, Journal of Computational and Graphical Statistics, 8, 3, 545-558.

Young, T.K. and Eddy, W.F., 1999. A Tale of Two Imaging Methods -- Magnetic Resonance and Seismic Reflection, submitted to Statistical Science.

Carpenter, P.A., Just, M.A., Keller, T.A., Eddy, W.F., and Thulborn, K.R., 1999. Time Course of fMRI-Activation in Language and Spatial Networks During Sentence Comprehension, NeuroImage, 10, 216-224.

Eddy, W.F. and Young, T.K., 1999. Optimizing MR Resampling, to appear in Handbook of Medical Image Processing.

Carpenter, P.A., Just, M.A., Keller, T.A., Eddy, W.F., and Thulborn, K.R., 1999. Graded Functional Activation in the Visuo-Spatial System with the Amount of Task Demand, Journal of Cognitive Neuroscience, 11, 1, 9-24.

Noll, D.C., Genovese, C.R., Vazquez, A.L., O'Brien, J.L., and Eddy, W.F., 1998. Evaluation of Respiratory Artifact Correction Techniques in Multishot Spiral Functional MRI Using Receiver Operator Characteristic Analyses. Magnetic Resonance in Medicine, 40, 633-639.

Goddard, N.H., Hood, G., Cohen, J.D., Eddy, W.F., Genovese, C.R., Noll, D.C., and Nystrom, L.E., 1997. Online Analysis of Functional MRI Datasets on Parallel Platforms. Journal of Supercomputing, 11, 295-318.

Noll, D.C., Boada, F.E., and Eddy, W.F., 1997. Multi-Shot Rosette Acquistions: Application to Spectrally Selective Imaging and Functional MRI. Proceedings of International Society for Magnetic Resonance in Medicine Fifth Scientific Meeting, 1, 133.

Noll, D.C., Boada, F.E., and Eddy, W.F., 1997. A Spectral Approach to Analyzing Slice Selection in Planar Imaging: Optimization for Through-Plane Interpolation. Magnetic Resonance in Medicine, 38, 151-160.

Noll, D.C., Genovese, C.R., Nystrom, L.E., Vazquez, A.L., Forman, S.D., Eddy, W.F., and Cohen, J.D., 1997. Estimating Test-Retest Reliability in Functional MR Imaging II: Application to Motor and Cognitive Activation Studies. Magnetic Resonance in Medicine, 508-517.

Genovese, C.R., Noll, D.C., and Eddy, W.F., 1997. Applications of Reliability Estimates in fMRI. Proceedings of International Society for Magnetic Resonance in Medicine Fifth Scientific Meeting, 3, 1658.

Fan, X., Eddy, W.F., Noll, D.C., and Genovese, C.R., 1997. Visual Analysis of Variance: A Method for Quantitative Assessment of fMRI Data Processing Procedures. Proceedings of International Society for Magnetic Resonance in Medicine Fifth Scientific Meeting, 3, 1659.

BIOGRAPHICAL SKETCH

Give the following information for all ***new*** key personnel.
Copy this page for each person.

NAME	POSITION TITLE
Melvin Field	Resident in Neurosurgery (PGY-5)

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
University of Florida, Gainesville, Florida	BS	1993	Basic Medical Sciences
University of Florida College of Medicine, Gainesville Florida	MD	1996	Medicine
University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania	Resident	1997-present	Neurosurgery

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Positions Held:

1997 – Present Resident in Neurosurgery (PGY-5), University of Pittsburgh School of Medicine, Pittsburgh PA

Awards and Honors:

1992 Junior Honors Medical Program, Palm Beach County Medical Auxiliary Scholarship
1993 Graduated with Highest Honors, University of Florida
1993 Phi Beta Kappa
1991 Golden Key National Honor Society
1991-1992 Presidential Annual Spring Recognition for Outstanding Students
1990 Alpha Epsilon Delta Honor Society
1989-1993 Florida Academic Scholar

Memberships:

1997 – Present Allegheny County Medical Society, member
1997 – Present American Association of Neurological Surgeons, candidate
1992 – Present American Medical Association, member
1996 – Present Congress of Neurological Surgeons, resident member
1992 – Present Florida Medical Association, member
1997 – Present Pennsylvania Medical Society, member

Publications:

1. Emil Kozarov, Hanke van der Wel, Melvin Field, Mikelina Gritzali, Ross Brown, and Christopher West; "Characterization of FP21, a Cytosolic Glycoprotein from *Dictyostelium*." *Journal of Biological Chemistry*. Vol. 270. No. 7, 3022-3030, 1995
2. Melvin Field, Donald W Marion; "Systemic Infections in the Neurosurgical Critical Care Patient." in Infections in Neurosurgery – Neurosurgical Topics; Hall WA, IE McCutcheon (eds); AANS; Park Ridge, Ill; Ch 11, 155-172, 2000
3. Melvin Field, Timothy F Witham, John C Flickinger, Douglas Kondziolka, L Dade Lunsford; " A Comprehensive Assessment of Clinical and Radiologic Outcomes after Stereotactic Brain Surgery." *Journal of Neurosurgery* Submitted for publication May 2000; Accepted 12-2000; For Publication 4-2001

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Freddie H. Fu, M.D.	Blue Cross of Western Pennsylvania Professor, Executive Vice Chairman, Department of Orthopaedic Surgery

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Dartmouth College, Hanover, NH	A.B.	1974	Biology
Dartmouth Medical School, Hanover, NH	B.M.S.	1975	Medicine
University of Pittsburgh, Pittsburgh, PA	M.D.	1977	Medicine
Brown University, Providence, RI	Internship	1977-78	General Surgery
University of Pittsburgh, Pittsburgh, PA	Fellowship	1978-79	Orthopaedic Research
University of Pittsburgh, Pittsburgh, PA	Residency	1979-82	Orthopaedic Surgery
Hanover Trauma Center, West Germany	Fellowship	1981-82	A.O.

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications DO NOT EXCEED TWO PAGES.

PROFESSIONAL EXPERIENCE

Assistant Professor	Dept. of Ortho. Surg., U. of Pittsburgh, Pittsburgh	1982-1988
Director	Sports Medicine, U. of Pittsburgh, Pittsburgh	1982-present
Medical Director	Center for Sports Med., U. of Pittsburgh, Pittsburgh	1985-present
Assistant Professor	Sch. of Health Related Professions, U. of Pittsburgh, Pittsburgh	1986-present
Associate Professor	Dept. of Ortho. Surg., U. of Pittsburgh, Pittsburgh	1988-present
Professor	Dept. of Ortho. Surg., U. of Pittsburgh, Pittsburgh	1989-present
Blue Cross of West. Penn.		
Associate Professor	Sch. of Health Related Professions, U. of Pittsburgh, Pgh	1989-present
Vice Chairman (Clinical)	Dept. of Ortho. Surg., U. of Pittsburgh, Pittsburgh	1990-1994
Professor	Dept. of Ortho. Surg., U. of Pittsburgh, Pittsburgh	1992-present
Professor	Sch. of Education, Dep. of Phys. and Recreation Education	1994-present
Executive Vice Chair	Dept. of Ortho. Surg., U. of Pittsburgh, Pittsburgh	1994-1997
Chairman	Dept. of Ortho. Surg., U. of Pittsburgh, Pittsburgh	1998-present

HONORS

Sports Med. Traveling Fellow, AOSSM and European Soc. of Knee Surgery and Arthroscopy	1988
Young Investigator Award, American Orthopaedic Society for Sports Medicine	1989
Inaugural holder of Blue Cross of Western Pennsylvania Chair in Orthopaedic Surgery	1989
J.Joyce Award, International Arthroscopy Association	1991
Chancellor's Public Service Award, University of Pittsburgh, Pittsburgh	1993
Herodicus Award, AOSSM Annual Meeting	1994
Charles S. Neer Award, American Shoulder and Elbow Surgeons	1994
Kappa Delta (Young Investigator) Award of the American Academy of Orthopaedic Surgeons	1996
National Athletic Trainers' Assoc. President's Award for Outstanding Contribution to Sports Medicine	1996
Biersdorf/GOTS Research Award (GOTS: German-Austrian-Swiss Society for Orthopaedic Traumatologic Sports Medicine), 1st Place, 2nd Place and 3rd Place	1996
The Best Doctors in America, 1999, Orthopaedic Surgery, Woodward/White, Inc.	1999
Albert Trillat Award, International Society of Arthroscopy	1999
Godfather, AOSSM-WPOA Traveling Fellowship, Australia/New Zealand	1999
Honorary Member, Royal College of Orthopaedic Surgeons of Thailand	2000

SELECTED PUBLICATIONS

1. Day C, Kasemkijwattana C, Menetrey J, Floyd S, Booth D, Moreland M, Fu F, and Huard J, Myoblast-Mediated Gene Transfer to the Joint, *Journal of Orthopaedic Research*, 15 (6):894-903, 1997.
2. Borsa P, Lephart Sm, Irrgang J, Safran M, Fu F, The effects of joint position and direction of joint motion on proprioceptive sensibility in anterior cruciate ligament deficient athletes, *American Journal of Sports Medicine* 25 (3):336-40, 1997.
3. Kasemkijwattana C, Menetrey J, Somogyi G, Moreland M, Fu F, Buranapanitkit B, Watkins S, and Huard J, Development of Approaches to Improve the Healing Following Muscle Contusion, *Cell Transplantation*, 7 (6):585-598, 1998.
4. Mandelbaum B, Browne J, Fu F, Michele L, Mosely J, Erggelet C, Minas T, and Peterson L, Articular cartilage lesions of the knee, AMERICAN JOURNAL OF SPORTS MEDICINE 26:853-861, 1998.
5. Menetrey J, Kasemkijwattana C, Fu FH, Moreland M, and Huard J, Suturing Versus Immobilization of a Muscle Laceration, AMERICAN JOURNAL OF SPORTS MEDICINE 27(2):222-229, March April 1999.
6. Rozzi S, Lephart S, Gear W, Fu FH, Knee joint laxity and neuromuscular characteristics of male and female soccer and basketball players, AMERICAN JOURNAL OF SPORTS MEDICINE 27(3):312-319, 1999.
7. Day C, Bosch P, Kasemkijwattana C, Menetrey J, Moreland M, Fu F, Ziran B, and Huard J, Use of Muscle Cells to Mediate Gene Transfer to the Bone Defect, TISSUE ENGINEERING 5(2):119-125, 1999.
8. Safran M, O'Malley D, and Fu F, Peroneal tendon subluxation in athletes: new exam technique, case reports, and review, MEDICINE & SCIENCE IN SPORTS & EXERCISE, 31(7):S487-S492, July 1999.
9. Goto H, Shuler F, Lamsam C, Moller H, Niyibizi C, Fu F, Robbins P, and Evans C, Transfer of LacZ Marker Gene to the Meniscus, JOURNAL OF BONE AND JOINT SURGERY 81-A(7):918-925, July 1999.
10. Menetrey J, Kasemkijwattana C, Day C, Bosch P, Fu F, Moreland, M and Huard J, Direct, fibroblast- and myoblast-mediated gene transfer to the anterior cruciate ligament, TISSUE ENGINEERING 5(5):435-442, 1999.
11. Hoher J, Livesay G, Ma C, Withrow J, Fu F, and Woo S, Hamstring graft motion in the femoral bone tunnel when using titanium button/polyester tape fixation, KNEE SURGERY, SPORTS TRAUMATOLOGY, ARTHROSCOPY 7:215-219, 1999.
12. Safran M, Allen A, Lephart S, Borsa P, Fu F, and Harner C, Proprioception in the posterior cruciate ligament deficient knee, KNEE SURG, SPORTS TRAUMATOL., ARTHROSC 7(5):310-317, 1999.
13. Fu F, Bennett C, Lattermann C, and Ma CB, Current trends in anterior cruciate ligament reconstruction, Part 1: Biology and Biomechanics of Reconstruction, AMERICAN JOURNAL OF SPORTS MEDICINE 27(6):821-830, 1999.
14. Debski R, Wong E, Woo S, Sakane M, Fu F, and Warner J, In situ force distribution in the glenohumeral joint capsule during anterior-posterior loading, JOURNAL OF ORTHOPAEDIC RESEARCH 17(5):769-777, 1999.
15. Boss A, Klimkiewicz, Fu F, Technical innovation: creation of a peripheral vascularized trough to enhance healing in cryopreserved meniscal allograft reconstruction, KNEE SURG, SPORTS TRAUMATOL, ARTHROSC 8:159-162, 2000.
16. Kasemkijwattana C, Menetrey J, Goto H, Niyibizi C, Fu F, Huard J, The use of growth factors, gene therapy and tissue engineering to improve meniscal healing, MATERIALS SECIENCE AND ENGINEERING C 13 (2000) 19-28.
17. Menetrey J, Kasemijwattana C, Day C, Bosch P, Vogt M, Fu F, Moreland M, and Huard J, Growth factors improve muscle healing in vivo, JOURNAL OF BONE AND JOINT SURGERY (Br), 82-B (1):131-137, 2000.
18. Kasemkijwattana C, Menetrey J, Bosch P, Somogyi G, Moreland M, Fu F, Buranapanitkit B, Watkins S, and Huard J, Use of growth factors to improve muscle healing after strain injury, CLINICAL ORTHOPAEDICS AND RELATED RESEARCH 370:272-285, January 2000.
19. Cao M, Stefanovic-Racic M, Georgescu H, Fu F, and Evans C, Does nitric oxide help explain the differential healing capacity of the anterior cruciate, posterior cruciate, and medial collaterl ligaments?, AMERICAN JOURNAL OF SPORTS MEDICINE 28(2):176-182, March April 2000.

BIOGRAPHICAL SKETCH

Give the following information for all ***new*** key personnel.
Copy this page for each person.

NAME	POSITION TITLE
Mark Robert Lovell	Director, UPMC Sports Medicine Concussion Program

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Northern Michigan University, Marquette, MI	B.S.	1977	Psychology/Biology
Finch University of Health Sciences Chicago Medical School, North Chicago, IL.	Ph.D.	1984	Clinical Psychology
University of Nebraska Medical Center, Omaha, NE	Internship	1983-1984	Clinical Neuropsychology
University of Nebraska Medical School, Omaha, NE	Post-Doc.	1984-1985	Clinical Neuropsychology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

ACADEMIC/CONSULTING POSITIONS:

1993-present	Pittsburgh Steelers Football Club-Consultant
1995-present	National Football League Subcommittee on Concussion- Consultant member
1995-present	Director, Neuropsychology Program-National Football League
1996-present	Philadelphia Eagles Football Club-Neuropsychological Consultant
1997-present	National Hockey League (NHL)-Chairman, Neuropsychology Advisory Board
1997-1998	Buffalo Sabres Hockey Team-Consultant
1997-2000	Detroit Red Wings Hockey Team-Neuropsychological Consultant
1999-2000	Detroit Lion Football Club-Neuropsychological Consultant
1996-2000	Director, Division of Neuropsychology-Henry Ford Health System
2000-present	Pittsburgh Penguins Hockey Club-Neuropsychological Consultant
2000-present	Director, UPMC Sports Medicine Concussion Program

SELECTED PUBLICATIONS

1. Coffey, C.E., Cummings, J., Lovell, M.R. & Pearlson, G. Textbook of Geriatric Neuropsychiatry (Associate Editor). Washington, D.C: American Psychiatric Press, 1994.
2. Schuster, J., Lovell, M.R. & Tracta, T. (eds.) Training Mental Health Professionals in the Era of Managed Care. San Francisco, Jossey-Bass, 1997.
3. Bailes, J., Lovell, M.R. & Maroon, J. (eds.) Sports-Related Concussion. St. Louis, Quality Medical Publishers, 1998.
4. Coffey, C.E., Cummings, J., Lovell, M.R. & Pearlson, G. (Associate Editor). Textbook of Geriatric Neuropsychiatry- 2nd. Edition. American Psychiatric Press, 2000.
5. Franzen, M.D. and Lovell, M.R. Neuropsychological Assessment. In R.E. Hales and S.C. Yudofsky (eds.) Textbook of Neuropsychiatry. Washington, D.C: American Psychiatric Press, 41-54, 1987.
6. Price, T.R.P., Goetz, K. & Lovell, M.R. The neuropsychiatry of brain tumors. In R.E. Hales and S.C. Yudofsky (eds.) Textbook of Neuropsychiatry, 2nd. Edition. Washington, D.C: American Psychiatric Press, 473-498, 1992.
7. Lovell, M.R. and Starratt, C. Cognitive rehabilitation. In R.E. Hales and S.C. Yudofsky (eds.) Textbook of Neuropsychiatry, 2nd. Edition. Washington, D.C: American Psychiatric Press, 741-754, 1992.
8. Lovell, M.R. and Franzen, M.D. Neuropsychological Assessment. In R.E. Hales, S.C. Yudofsky and J. Silver (eds.) Neuropsychiatric Aspects of Traumatic Brain Injury. Washington, D.C: American Psychiatric Press, 133-162, 1994.
9. Lovell, M.R. and Nussbaum, P.D. Neuropsychological Assessment In C.E. Coffey, J. Cummings, M.R. Lovell, and G. Pearlson (eds.) Textbook of Geriatric Neuropsychiatry. Washington, D.C: American Psychiatric Press, 129-144, 1994.
10. Price, T.R.P., Goetz, K. & Lovell, M.R. The neuropsychiatry of brain tumors. in R.E. Hales and S.C. Yudofsky (eds.) Synopsis of Neuropsychiatry. Washington, D.C: American Psychiatric Press, 361-380,1994.
11. Franzen, M.D. and Lovell, M.R. Cognitive Rehabilitation and Behavior Therapy of Patients with Neuropsychiatric Disorders. In S. Yudofsky and R. Hales (eds.) The American Psychiatric Press Textbook of Neuropsychiatry - Third Edition, 1997.
12. Price, T.R., Goetz, K. & Lovell, M.R. The Neuropsychiatry of Brain Tumors. In S. Yudofsky and R. Hales (eds.) The American Psychiatric PressTextbook of Neuropsychiatry -Third Edition, 1997.
13. Lovell, M.R. and Smith, S.S. Subcortical Dementias. In P.D. Nussbaum (Ed.)The Handbook of Neuropsychology and Aging. Plenum Press, 1997.

14. Lovell, M.R. Neuropsychological assessment of the professional athletes. In J. Bailes, M.R. Lovell & J. Maroon (eds) Sports-Related Concussion, Quality Medical Publishers, 1998.
15. Anderson, P. & Lovell, M.R. Neuropsychological assessment and hockey. In J. Bailes, M.R. Lovell & J. Maroon. (eds). Sports-Related Concussion, Quality Medical Publishers, 1998.
16. Pending Publication
17. Podell, K. And Lovell, M.R. Neuropsychological Assessment. In C.E. Coffey and J. Cummings (Eds.) Textbook of Geriatric Neuropsychiatry, 2nd. Edition, Washington, American Psychiatric Press, 2000.
18. Finlayson, M.A.J. and Lovell, M.R. Neuropsychology in Sport. In D.A. Kumbhare and J.V. Basmajian (Eds.). Clinical Decision Making and Outcomes in Sports Rehabilitation, Philadelphia, Saunders, 2000.
19. O'Leary, D.S., Lovell, M.R., Sackalleres, C.J., Berent, S., Giordani, B., Seidenberg, M. & Boll, T.J. The effects of age at onset of partial and generalized seizures on neuropsychological performance in children. Journal of Nervous and Mental Disease, 171, 624-629, 1983.
20. Franzen, M.D., and Lovell, M.R. Behavioral treatments of aggressive sequelae of brain injury. Psychiatric Annals, 17, 389-396, 1987.
21. Lovell, M.R: Pediatric head trauma. Trauma Alert, 1989.
22. Goetz, K., Lovell, M.R. & Price, T.R.P. Neuropsychiatric Aspects of brain tumors. Neuroscience Journal, Vol. 1 (3), 1990.
23. Lovell, M.R: Neuropsychological testing in the epilepsies. Neuroscience Journal, Vol. 1 (4), 1990.
24. Goldberg, E., Podell, K., Harner, R., Lovell, M.R. & Riggio, S. Cognitive bias, functional cortical geometry, and the frontal lobes: laterality, sex, and handedness. Journal of Cognitive Neuroscience, 276-296, 1994.
25. Goldberg, E, Podell, K. & Lovell, M.R. Lateralization of frontal lobe functions and cognitive novelty. Journal of Neuropsychiatry and Clinical Neuroscience, Special Issue: The Frontal Lobes and Neuropsychiatric Illness, 371-378, 1994.
26. Brillman, J., Davis, D.A., Clark, R.E., Lovell M.R., Price, T.R.P. & Benckart, D.H. Increased MCA flow during the initial phase of cardiopulmonary bypass may cause neurological dysfunction, Neuroimaging, 135-141, 1995.
27. Clark, R.E., Brillman, J., Davis, D.A., Lovell, M.R., Price, T.R.P. & Magovern, G. Microemboli during CABG: genesis and effect on outcome Journal of Thoracic and Cardiovascular Surgery, 249-257, 1995.
28. Coffey, C.E., Cummings, J.L., Duffy, J.D., Fink, M., Lauterbach, E.C., Lovell, M.R. Malloy, P., Nussbaum, P.D., Royall, D.R. & Salloway, S.S. Assessment of treatment outcomes in neuropsychiatry: A report from the committee on research of the American Neuropsychiatric Association. Journal of Neuropsychiatry and Clinical Neuroscience, 287-289, 1995.
29. Podell, K., Lovell, M.R., Zimmerman, M. & Goldberg, N. The Cognitive Bias Task and lateralized frontal lobe functions in males Journal of Neuropsychiatry and Clinical Neuroscience, 491-501, 1995.
30. Smith-Seemiller, L., Lovell, M.R. & Smith, S. Cognitive dysfunction after closed head injury: contributions of demographic, injury severity and other factors. Applied Neuropsychology, 3, 41-47, 1996.
31. Smith-Seemiller, L., Lovell, M.R., Smith, S., Markosian, N. & Townsend, R. Impact of skull fracture on neuropsychological functioning following closed head injury, Brain Injury, 11, 191-196, 1997.
32. Smith-Seemiller, L., Lovell, M.R.,Franzen, M.D., S. & Townsend, R. Neuropsychological function in restrained versus unrestrained motor vehicle occupants who suffer closed head injury, Brain Injury, 11, 735-742, 1997.
33. Lovell, M.R. and Collins, M. Neuropsychological evaluation of the college football player. An invited review paper for a special issue on sports-related head injury presented in the Journal of Head Trauma Rehabilitation, 13 (2) 9-27, 1998.
34. Arffa, S., Lovell, M.R., Podell, K & Goldberg, E. Wisconsin Card Sorting Test performance in above average and superior school children: relationship to intelligence and age. Archives of Clinical Neuropsychology, 13(8), 1998.
35. Lovell, M.R. Evaluation of brain injury in the professional athlete. Playing safe: Neuropsychological testing in professional sports, Recovery, 9 (3), 1998.
36. Collins, M.W., Grindel, S., Lovell, M.R., Dede, D., Phalin, B., Moser, D., Nogle, S., Wasik, M., Cordry, D., Daugherty, M., Sears, S., Nicilette, G., Indelicato, P., & McKeag, D. The neuropsychological impact of concussion in college football players. Journal of the American MedicalAssociation, 1999; 282(10), 971-976.
37. Lovell, M.R., Iverson, G.L., Collins, M.W., McKeag, D. & Maroon, J.C. Does brief loss of consciousness predict neuropsychological decrements following concussion? Clinical Journal of Sports Medicine, 1999; 9(4), 193-198.
38. Collins, M.W., Lovell, M.R. and McKeag, D. Current issues in managing sports-related Concussion. Journal of the American Medical Association, 1999; 282, 2283-2285.
39. Maroon, J.C., Lovell, M.R., Norwig, J., Podell, K., Powell, J.W. & Hartl, R. Cerebral concussion in athletes: evaluation and neuropsychological testing, Neurosurgery, 2000; 47:659-672.
40. Wojtys, E., Bailes, J., Boland, A., Bomberger, I., Burke, C., Cantu, R., Griffin, L., Hovda, D. Ireland, M., Kelly, J., Landry, G., Lovell, M., McCrea, M., McKeag, D., Mathews, J., Miller, D., Minkoff, J., Papadopoulis, S., Pellman, E., Quincy, R., Ross, H. & Smith, B. Concussion in Sports:Proceeds of a workshop on the Diagnosis and treatment of concussion. American Journal of Sports Medicine, 1999; 27(5), 676-687.

BIOGRAPHICAL SKETCH

Give the following information for all ***new*** key personnel.
Copy this page for each person.

NAME	POSITION TITLE
Joseph C. Maroon, M.D.	Clinical Professor and Vice Chairman

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing. Include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Indiana University, Bloomington, IN	A.B.	1961	Anatomy and Physiology
Indiana Univ. School of Med., Indianapolis, IN	M.D	1965	Medicine
Indiana Univ. Medical Center, Indianapolis, IN	Intern.	1966	General Surgery
Indiana Univ. Medical Center, Indianapolis, IN	Resident	1967	General Surgery
Indiana Univ. Medical Center, Indianapolis, IN; Georgetown University Hospital, Washington, D.C.; Oxford University Hospitals, Oxford, England	Resident	1971	Neurological Surgery
University of Vermont, Burlington, VT	Fellow	1972	Microneurosurgery

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

1972-1984	Department of Neurological Surgery University of Pittsburgh Medical Center Pittsburgh, PA		Professor and Chief
1972-1983	The Pitt Panthers Football Team University of Pittsburgh Pittsburgh, PA	T	Team Neurosurgeon
1977-Present	The Pittsburgh Steelers Football Organization Pittsburgh, PA		Team Neurosurgeon
1984-1999	Department of Neurological Surgery MCP/Hahnemann-Allegheny Campus Pittsburgh, PA		Professor and Chairman
1995-1998	Department of Surgery MCP/Hahnemann-Allegheny Campus Pittsburgh, PA		Professor and Chairman
1999-Present	Department of Neurological Surgery University of Pittsburgh Medical Center Pittsburgh, PA		Clinical Professor and Vice Chairman

SOCIETY POSITIONS

1980-83 Secretary, Congress of Neurological Surgeons; 1983-84, Vice President, Congress of Neurological Surgeons; 1984-85, President Elect, Congress of Neurological Surgeons; 1985-86, President, Congress of Neurological Surgeons.

HONORS

1988 Dapper Dan Man of the Year; 1990 The Wakeman Award; 1991 Contributors Recognition Award Allegheny Health Sciences; 1991 Distinguished Alumnist Award; 1993 Clevenger Award; 1994-1999 Best Doctors in America; 1996 Heindl Endowed Chair for Neuroscience Research; 1999 Healthcare Hero Finalist;1991 Arab American Medical Association Award for Excellence in Medicine; 1999 Lou Holtz/Upper Ohio Valley Hall of Fame

PUBLICATIONS (selected)

1. Maroon JC and Healion T: Head and neck injuries in football. J Indiana State Med Assoc, 63:995-999, 1970.
2. Maroon JC: the management of football head and neck injuries. Medical Digest, 18:26-23, 1972.
3. Maroon JC and Gosling C: A head and neck trauma teaching model. J trauma, 13:245-247, 1973.
4. Maroon JC, Kerin T, Rehkopf P and McMaster J: A system for preventing athletic injuries. The Phys and Sportsmed, 5:77-79, 1977.
5. Maroon JC, Steele PB and Berlin R: Football head and neck injuries—an update. Clin Neurosurg, 27:414-429, 1980.
6. Ryan, AJ, Rimel, RW, Maroon JC, Bruno LA and Torg JC: Concussion in athletes. A round table. The Phys. and Sportsmed, 10 (1):95-108, 1982.
7. Bailes JE, Poole CC, Hutchison W, Maroon JC and Fukushima T: Utilization and cost savings of a wide-area computer network for neurosurgical consultation. Telemed J, 3(2):135-139, 1997.
8. Acevedo HF, Hartsock RJ and Maroon JC: Detection of membrane-associated human chorionic gonadotropin and its subunits on human cultured cancer cells of the nervous system. Canc Detect and Prev, 21(4):295-303, 1997.
9. Daffner RH, Yakulis R and Maroon JC: Intraosseous meningioma: A case report. Skeletal Rad, 27:108-111, 1998.
10. Quigley MR, Bost J, Maroon JC: Outcome after microdiscectomy: results of a prospective single institutional study. Surg Neurol, 49(3):263-267, 1998.
11. Fukushima T and Maroon JC: Repair of carotid artery perforations during transsphenoidal surgery. Surg Neurol, 50:174-177, 1998.
12. Maroon JC, Abla AA, Bost J: Association between peridural scar and persistent low back pain after lumbar discectomy. Neurol Research, 21(1):S43-S46, 1999.
13. Lovell MR, Iverson GL, Collins MW, McKeag D, and Maroon JC: Does loss of consciousness predict neuropsychological decrements after concussion? Clin J Sports Med, (4)193-198, October, 1999.
14. Maroon JC, Lovell, MR, Norwig J, Podell K, Powell JW and Hartl R: Cerebral concussion in athletes: Evaluation and neuropsychological testing. Neurosurg, 47(3):659-672, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
V. Andrew Stenger, Ph.D.	Research Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Hawaii, Honolulu, HI	B.S.	1989	Physics
Ohio State University, Columbus, OH	M.S.	1993	Physics
Ohio State University, Columbus, OH	Ph.D.	1996	Physics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Employment

1989-1992 Teaching Assistant, Ohio State University Dept. of Physics, Columbus, OH
1992-1996 Research Assistant, Ohio State University Dept. of Physics, Columbus, OH
1996-1998 Research Associate in Radiology, University of Pittsburgh, Pittsburgh, PA
1998-1999 Research Instructor in Radiology, University of Pittsburgh, Pittsburgh, PA
1999-Present Research Assistant Professor in Radiology, University of Pittsburgh, Pittsburgh, PA

Honors

1989-1991 OSU Physics Departmental Summer Academic Fellowship
1990-1991 Hazel S. Brown Scholarship Fund Award for Teaching Excellence
1992 Shell Oil Company Award for Excellence in Teaching

Selected Publications

V. A. Stenger, C. H. Recchia, J. E. Vance C. H. Pennington, D. R. Buffinger, and R. P. Ziebarth, NMR measurement of superconducting-state spin susceptibility in alkali fullerides, *Physical Review B Rapid Communications* **48**, p. 9942 (1993).

D. R. Buffinger, R. P. Ziebarth, V. A. Stenger, C. H. Recchia, and C. H. Pennington, Rapid and efficient synthesis of alkali metal C60 compounds in liquid ammonia, *Journal of the American Chemical Society* **115**, p. 9267 (1993).

V. A. Stenger, C. H. Recchia, C. H. Pennington, D. R. Buffinger, and R. P. Ziebarth, NMR studies of alkali C_{60} superconductors, *Journal of Superconductivity* **7**, p. 931 (1994).

D. R. Buffinger, S.-M. Lee, R. P. Ziebarth, V. A. Stenger, and C. H. Pennington, *Recent Advances in the Physics and Chemistry, Proceedings of the 185th Meeting of the Electrochemical Society*, May 22-27, 1994.

V. A. Stenger, C. H. Pennington, D. R. Buffinger, and R. P. Ziebarth, Nuclear magnetic resonance of A_3C_{60} superconductors, *Physical Review Letters* **74**, p. 1649 (1995).

C. H. Pennington, V. A. Stenger, C. H. Recchia, C. D. Hahm, K. R. Gorny, V. A. Nandor, D. R. Buffinger, S.-M. Lee, and R. P. Ziebarth, ^{13}C NMR hyperfine couplings, T1 anisotropy, and Korrina relations in Rb^3C_{60}: search for effects of strong correlation, *Physical Review B Rapid Communications* **53**, p. R2967 (1996).

C. H. Pennington and V. A. Stenger, Nuclear magnetic resonance of C_{60} and Fulleride superconductors, *Reviews of Modern Physics* **68**, p. 855 (1996).

C. H. Pennington, C. Hahm, V. A. Stenger, K. Gorny, C. H. Recchia, J. A. Martindale, D. R. Buffinger, and R. P. Ziebarth, "Double resonance NMR probes of structural distortions in alkali fulleride superconductors," *Physical Review B Rapid Communications* **54**, p. 6853 (1996).

V. A. Stenger, D. C. Noll, and F. E. Boada, Partial k-space reconstruction for 3D gradient echo functional MRI: a comparison of phase correction methods. *Proceedings of International Society for Magnetic Resonance in Medicine Fifth Scientific Meeting*, p. 3, 1631.

V. A. Stenger, D. C. Noll, and F. E. Boada, Quantitative comparison of phase correction methods for partial k-space 3D gradient echo functional MRI, Proceedings *of International Society for Magnetic Resonance in Medicine Fast Imaging Workshop*, p. 191 (1997).

V. A. Stenger, D. C. Noll, and F. E. Boada, "Partial k-space reconstruction for 3D gradient echo functional MRI: a comparison of phase correction methods," *Magnetic Resonance in Medicine* **40**, p. 681 (1998).

V. A. Stenger, S. Peltier, F. E. Boada, D. C. Noll, "3D Spiral Cardiac/Respiratory Ordered fMRI Data Acquisition at 3T," in *Proceedings of International Society for Magnetic Resonance in Medicine Sixth Scientific Meeting*, p. 297 (1998).

S. Peltier, V. A. Stenger, D. C. Noll, 3D fMRI physiological noise compensation at 3T, in *Proceedings of 4th International Conference on Functional Mapping of the Human Brain*, 581, 1998.

V. A. Stenger, S. Peltier, F. E. Boada, D. C. Noll, 3D Spiral Cardiac/Respiratory Ordered fMRI Data Acquisition at 3T, in *Proceedings of 4th International Conference on Functional Mapping of the Human Brain*, 582, 1998.

D. C. Noll, V. A. Stenger, A. L. Vazquez, S. J. Peltier, "Spiral scanning in functional MRI." *Medical Radiology: Functional MRI, C.* Moonen and P. Bandettini (Eds.), Springer-Verlag, Heidelberg, pp. 149-160, 1999..

V. A. Stenger, S. Peltier, F. E. Boada, D. C. Noll, "3D Spiral Cardiac/Respiratory Ordered fMRI Data Acquisition at 3 Tesla," *Magnetic Resonance in Medicine* **41**, 983 (1999).

C. S. Carter, A. MacDonald, D. Noll, A. Stenger, J. D. Cohen, Event Related fMRI of Strategic vs. Evaluative Functions of the Anterior Cingulate During Cognition, in *Proceedings of Cognitive Neuroscience Society Annual Meeting*, 21B, 1999.

L. L. Ross, D. B. Barch, J. D. Cohen, A. MacDonald, D. Noll, A. Stenger, C. S. Carter, Anterior Cingulate Cortex Dysfunction and Cognitive Disability in Schizophrenia, in *Proceedings of Cognitive Neuroscience Society Annual Meeting*, 17B, 1999.

C. S. Carter, D. B. Barch, A. MacDonald, L. L. Ross, D. Noll, A. Stenger, J. D. Cohen, Anterior Cingulate Cortex and Cognitive Disability in Schizophrenia, *Biological Psychiatry*, 189, 1999.

C. S. Carter, A. MacDonald, L. L. Ross, A. Stenger, D. Noll, J. D. Cohen, Strategic vs. Evaluative Functions of the Anterior Cingulate During Cognition, *Biological Psychiatry*, 346, 1999.

C. S. Carter, D. B. Birch, A. MacDonald, D. Noll, A. Stenger, J. D. Cohen, Anterior Cingulate Cortex and Cognitive Disability in Schizophrenia: An Event Related fMRI Study, *Schizophrenia Research*, Vol. 36, 219, 1999.

V. A. Stenger, R. Santos, F. E. Boada, D. C. Noll, Simulated Multi-Dimensional RF Excitation for Reduction of Susceptibility Artifacts in fMRI Acquisition at 3 Tesla, in *Proceedings of International Society for Magnetic Resonance in Medicine Seventh Scientific Meeting*, 2080, 1999.

V. A. Stenger, F. E. Boada, D. C. Noll, Gradient Compensation Method for the Reduction of Susceptibility Artifacts for Spiral fMRI Data Acquisition, in *Proceedings of International Society for Magnetic Resonance in Medicine Seventh Scientific Meeting*, 538, 1999.

F. E. Boada, R. Ross, V. A. Stenger, D. C. Noll, B. Goodpaster, and D. Kelley, Absolute Quantification of Skeletal Muscle Lipid Content with MRI, in *Proceedings of International Society for Magnetic Resonance in Medicine Seventh Scientific Meeting*, 297, 1999.

V. A. Stenger, F. E. Boada, D. C. Noll, Three-Dimensional Tailored RF Pulses for the Reduction of Susceptibility Artifacts in Gradient Echo Functional MRI, in *Proceedings of International Society for Magnetic Resonance in Medicine Eighth Scientific Meeting*, 52, 2000.

C. S. Carter, A. M. MacDonald, L. L. Ross, V. A. Stenger, D. C. Noll, and J. D. Cohen, Parsing executive processes: strategic versus evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences of the U.S.A.* **97**:1944-48, 2000.

Pending Publication

Pending Publication

V. A. Stenger, F. E. Boada, D. C. Noll, Three-Dimensional Tailored RF Pulses for the Reduction of Susceptibility Artifacts in T2*-Weighted Functional MRI, *Magnetic Resonance in Medicine*, **44**, 525-531, 2000.

M. H. Sohn, S. Ursu, J. Anderson, V. A. Stenger, and C. S. Carter, The Role of Prefrontal Cortex and Posterial Porital Cortex in Task Switching, in press for *Proceedings of the National Academy of Sciences of the U.S.A.*

Other Support

BECKER, James (Page 1/3)

Name of Individual:	BECKER, James
Active/Pending	Active
Project Number (Principal Investigator):	*5 R01 AG13669-03 (Becker)
Source:	NIA
Title of Project (*and/or Subproject*):	Functional Neuroimaging of Semantic Memory in AD
Dates of Approved/Proposed Project:	6/6/96 - 3/31/01
Annual Direct Costs / Percent Effort:	$124,930 / %

The purpose of this project is to investigate the changes in semantic memory function which occur in normal aging and dementia.

Overlap (*summarized for each individual*): None

Active/Pending	Active
Project Number (Principal Investigator):	5 K02 MH01077-07 (Becker)
Source:	NIMH
Title of Project (*and/or Subproject*):	Natural History of Dementia
Dates of Approved/Proposed Project:	7/1/99 - 6/30/04
Annual Direct Costs / Percent Effort:	$71,010 / %

The data gathered from this project will address the question on how the HIV virus affects higher thought processes and why there is individual variation in the behavioral effects.

Overlap (*summarized for each individual*): None

Active/Pending:	Active
Project Number (Principal Investigator):	5 R01 MH45311-11 (Becker)
Source:	NIMH
Title of Project (*and/or Subproject*):	HIV-I Related Neuropsychological Abnormalities
Dates of Approved/Proposed Project:	8/1/98 - 7/31/03
Annual Direct Costs / Percent Effort:	$207,659 / %

The Allegheny Neuropsychiatric Survey (MH43511) investigates the neuropsychological, psychosocial, and neurological consequences of HIV infection and AIDS among community residents seeking primary medical care.

Overlap (*summarized for each individual*): None

Active/Pending	Active
Project Number (Principal Investigator):	99-G-050 (Supp.2) (Becker)
Source:	FAA
Title of Project (*and/or Subproject*):	The Effect of Shiftwork on Cognition among Air Traffic Control Specialists
Dates of Approved/Proposed Project:	9/24/99 - 9/22/01
Annual Direct Costs / Percent Effort:	$85,796 / %

The purpose of this study is to determine the effects of current shift work patterns and shift rotation practices on cognitive function within the Air Traffic Control Specialist workforce.

Overlap (*summarized for each individual*): None

% = Percentage of Effort

BECKER, James (Page 2/3)

Active/Pending: Active
Project Number (Principal-Investigator): *5 R01 AG15928-02 (Kuller)
Source: NIA
Title of Project (*and/or Subproject*): Cognitive Tests, ApoE, Brain MRI and Risks of Dementia
Dates of Approved/Proposed Project: 9/30/98 - 7/31/01
Annual Direct Costs / Percent Effort: $41,589 / %

We propose to test the hypothesis that MRI changes, including infarct-like lesions are associated with increased risk of dementia.

Overlap (*summarized for each individual*): None

Active/Pending Active
Project Number (Principal Investigator): 2 P30 MH52247-06 (Reynolds, III)
Source: NIMH
Title of Project (*and/or Subproject*): IRC for the Study of Late-Life Mood Disorders
Dates of Approved/Proposed Project: 3/1/00 - 2/28/05
Annual Direct Costs / Percent Effort: $857,601 / %

The goal of the IRC/LLMD is to understand and reduce treatment response variability in geriatric depression and related disorders.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): 2 P50 AG05133-17 (DeKosky)
Source: NIA
Title of Project (*and/or Subproject*): ADRC--Administrative Core
Dates of Approved/Proposed Project: 6/1/00 - 3/31/05
Annual Direct Costs / Percent Effort: $206,165 / %

The Administrative Core provides the organizational structure and leadership for planning and implementation of all activities directed toward the fulfillment of the ADRC aims.

Overlap (*summarized for each individual*): None

Active/Pending Active
Project Number (Principal Investigator): 2 P50 AG05133-17 (DeKosky)
Source: NIA
Title of Project (*and/or Subproject*): ADRC-Clinical Core
Dates of Approved/Proposed Project: 6/1/00 - 3/31/05
Annual Direct Costs / Percent Effort: $218,076 / %

The clinical core will perform clinical and research evaluations at the study entry and at annual follow-up of patients with AD and related dementias and control subjects participant in the ADRC.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): 2 P50 AG05133-17 (DeKosky)
Source: NIA
Title of Project (*and/or Subproject*): ADRC-Neuroimaging Core
Dates of Approved/Proposed Project: 6/1/00 - 3/31/05
Annual Direct Costs / Percent Effort: $51,982 / %

Imaging Core for developing PET and MRI for Alzheimer's Disease.

Overlap (*summarized for each individual*): None

% = Percentage of Effort

Pending Support

***These grants will end before the current proposal would begin.**

****All research effort will be subsumed under the 5 K02 MH01077-07 (Becker) Award. In addition, Dr. Becker will reduce efforts on other grants and adjust in consultation with appropriate NIH personnel.**

Other Support

BOADA, Fernando (Page 1/2)

Name of Individual:	**BOADA, Fernando**
Active/Pending	Active
Project Number (Principal Investigator):	2RO1 NS32756-06 (Boada)
Source:	National Institute of Health
Title of Project (*and/or Subproject*):	Rapid Whole-Brain Functional MR Imaging
Dates of Approved/Proposed Project:	2/1/99 - 1/31/02
Annual Direct Costs / Percent Effort:	$43,261.00 / %

This is a subcontract to the University of Michigan to enhance and evaluate methods for functional magnetic resonance imaging (fMRI) that are capable of high temporal resolution spatial resolution and whole brain coverage.

Overlap (*summarized for each individual*): None

Active/Pending:	Active
Project Number (Principal Investigator):	5R01 AG14051-03 (Nebes)
Source:	National Institute of Health
Title of Project (*and/or Subproject*):	Aging, White Matter Hyperintensities & Cognitive Decline
Dates of Approved/Proposed Project:	4/15/97 - 2/28/02
Annual Direct Costs / Percent Effort:	$37,081.00 / %

The primary goal of this research study is to investigate whether cognitive decrements commonly thought to be a normative component of aging may, in fact, be the result of white matter pathology.

Overlap (*summarized for each individual*): None

Active/Pending	Active
Project Number (Principal Investigator):	R01 HL64205-02 (Boada)
Source:	National Institute of Health
Title of Project (*and/or Subproject*):	Methodology for In Vivo 3D Triple Quantum Sodium MRI
Dates of Approved/Proposed Project:	1/18/00 12/31/02
Annual Direct Costs / Percent Effort:	$20,784.00 / %

This exploratory proposal is aimed at exploring the relationship between triple-quantum filtered sodium signal intensity and tumor mitotic activity *in vivo* using a pool of glioma patients undergoing treatment at the Pittsburgh Cancer Institute. Our aims are to characterize the TQF NMR signal in normal and neoplastic brain tissue, and to study in correlation with mitotic activity in low and high grade gliomas.

Overlap (*summarized for each individual*): None

Active/Pending:	Active
Project Number (Principal Investigator):	1 R21 MH61472-01 (Stenger)
Source:	National Institute of Health
Title of Project (*and/or Subproject*):	Tailored RF Pulses for Reducing Artifacts in fMRI
Dates of Approved/Proposed Project:	5/15/00 4/30/02
Annual Direct Costs / Percent Effort:	$75,000.00 / %

The purpose of this R21 proposal is to develop tailored radiofrequency (RF) pulse methodology for the mitigation of magnetic field inhomogeneity artifacts in gradient echo (GE) functional MR imaging.

Overlap (*summarized for each individual*): None

% = Percentage of Effort

BOADA, Fernando (Page 2/2)

Active/Pending: Active
Project Number (Principal Investigator): 1 R21 CA87805-01 (Boada)
Source: National Institute of Health
Title of Project (*and/or Subproject*): Assessing Tumor Malignancy *In Vivo* Using Sodium MRI
Dates of Approved/Proposed Project: 7/1/00 6/30/02
Annual Direct Costs / Percent Effort: $100,000.00 / %

This exploratory proposal is aimed at exploring the relationship between triple-quantum filtered sodium signal intensity and tumor malignancy *in vivo* using a pool of high and low grade biloma patients undergoing treatment at the Pittsburgh Cancer Institute.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): *1R21 MH59389-02 (Boada)
Source: National Institute of Health
Title of Project (*and/or Subproject*): Three Dimensional Quantitative Lithium MRI in Human Brain
Dates of Approved/Proposed Project: 8/1/98 - 7/31/01
Annual Direct Costs / Percent Effort: $74,872.00 / %

MRI can be used as a noninvasive tool for probing brain metabolism *in vivo*. The metabolic information gathered with MRI can be used for understanding basic mechanisms underlying the function of the human brain during diseased and/or normal condition.

Overlap (*summarized for each individual*): None

Pending Support

Pending Support

***This grant will end before the current proposal wound begin.**

% = Percentage of Effort

Other Support

COLLINS, Michael W.

No Other Support

Other Support

Field, Melvin (Page 1/1)

Name of Individual: **FIELD, Melvin**

Active/Pending: Active

Project Number (Principal Investigator): D2000-0251 (Melvin Field, M.D.)

Source: Private Support

Title of Project (*and/or Subproject*):

Dates of Approved/Proposed Project: 07/01/00 – 06/30/01

Annual Direct Costs / Percent Effort: $23,121.00 / %

The major goals of this project are to establish a model for measuring differential gene expression in cerebrovascular tissue after SAH, determine whether the degree of differential gene expression is tissue dependent or erythrocyte hemolysate dependent, and determine if the changes in gene expression occur in a predictable fashion relative to the onset of angiographic, physiological and symptomatic vasospasm.

Overlap (*summarized for each individual*): None

% = Percentage of Effort

Other Support

LOVELL, Mark R.

No Other Support

Other Support

MARION, Donald W. (Page 1/3)

Name of Individual:	Donald W. Marion, M.D.
Active/Pending	Active
Project Number (Principal Investigator):	P50 NS30318 (Marion)
Source:	NIH/NINDS
Title of Project (*and/or Subproject*):	University Of Pittsburgh Brain Trauma Research Center
Dates of Approved/Proposed Project:	03/01/95 – 06/30/05
Annual Direct Costs / Percent Effort:	$830,493 / %

This is a program project grant which is a continuation of the University of Pittsburgh Brain Trauma Research Center grant. The focus of our investigations are in the molecular mechanisms of secondary injury particular emphases on delayed oxidative stress, programmed cell death, the relationship of amyloid precursor protein with interleukin-1β, the role of inducible nitric oxide synthase as an endogenous neuroprotectant, the role of mesocortical dopamine systems in causing chronic functional and cognitive deficits, and the role of poly(ADP-ribose) polymerase as a mediator of oxidative DNA damage and apoptosis. Our investigations will attempt to correlate findings regarding these molecular mechanisms in the laboratory with patients who have suffered severe traumatic brain injury through recovery of CSF and dialysis samples and brain tissue at surgery.

Overlap (*summarized for each individual*): None

Active/Pending	Active
Project Number (Principal Investigator):	R49/CCR310285 (Marion)
Source:	CDC
Title of Project (*and/or Subproject*):	Grants for Injury Control Research Centers
Dates of Approved/Proposed Project:	09/01/98 – 08/31/03
Annual Direct Costs / Percent Effort:	$662,377 / %

This project is a center project sponsored by the CDC intended to address issues related to injury prevention, acute care, and rehabilitation. As Director of this Center, I coordinate research done by a group of other individuals although I do not have a specific research project of my own.

Overlap (*summarized for each individual*): None

Active/Pending:	Active
Project Number (Principal Investigator):	*D1997-0210 (Marion)
Source:	Private Support
Title of Project (*and/or Subproject*):	
Dates of Approved/Proposed Project:	07/01/98 – 06/30/01
Annual Direct Costs / Percent Effort:	$45,438 / %

This project uses PET imaging to measure regional CMR02, CBF, and CMR glucose in patients following severe traumatic brain injury. For this study, we take advantage of the fact that patients have *in vivo* microdialysis in place and we are able to correlate extracellular lactate and pyruvate levels with CMR glucose as measured by PET.

Overlap (*summarized for each individual*): None

% = Percentage of Effort

MARION, Donald W. (Page 2/3)

Active/Pending: Active
Project Number (Principal Investigator): R01 NS38087 (Kochanek) – Marion Co-Investigator
Source: NIH/NINDS
Title of Project (*and/or Subproject*): Adenosine and Traumatic Brain Injury
Dates of Approved/Proposed Project: 07/01/99 – 06/30/04
Annual Direct Costs / Percent Effort: $10,615 / %

This project investigates the levels of cerebrospinal fluid adenosine following traumatic brain injury in adults and children and also attempts to investigate pharmacologic manipulations at those levels. It is involving primarily basic science research.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): M1999-0080 (Dixon) – Marion Co-Investigator
Source:
Title of Project (*and/or Subproject*): Private Support
Dates of Approved/Proposed Project: 07/01/99 – 06/30/02
Annual Direct Costs / Percent Effort: $16,225 / %

In this project, Dr. Dixon is developing preliminary and pilot data relative to the dopaminergic oxidative mechanisms described in his new proposal.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): 1 R01 NR04801 (Kerr) – Marion Co-Investigator
Source: NIH/NINR
Title of Project (*and/or Subproject*): The Effect of APOE on Outcomes in TBI
Dates of Approved/Proposed Project: 09/30/99 – 06/30/04
Annual Direct Costs / Percent Effort: $46,527 / %

This project will be investigating a genetic marker (APOE) as a possible indicator of predisposition to poor outcome following severe and moderate traumatic brain injury.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): 1 T32 HD40686 (Kochanek) – Marion Co-Investigator
Source: NIH/NINDS
Title of Project (*and/or Subproject*): Training in Pediatric Neurointensive Care and Resuscitation Research
Dates of Approved/Proposed Project: 09/25/00 – 04/30/05
Annual Direct Costs / Percent Effort: $94,003 / %

This is a training grant that has been submitted for the training of pediatric neurointensive care and resuscitation research specialists. I will serve as a consultant and faculty member in this effort.

Overlap (*summarized for each individual*): None

% = Percentage of Effort

MARION, Donald W. (Page 3/3)

Active/Pending: Active

Project Number (Principal Investigator): *N/A (Marion)

Source:

Title of Project (*and/or Subproject*):

Private Support

Dates of Approved/Proposed Project: 8/1/00 – 7/31/01

Annual Direct Costs / Percent Effort: $87,500 / %

The objective of this study is to demonstrate the safety and effectiveness of the Cool Line catheter with the CoolGard system for fever reduction. As an alternative means of managing fever in patients in the neurointensive care unit, Alsius has developed a central venous catheter, the Cool Line, designed for use as an adjunct for fever reduction. Cooled saline solution at a temperature of 4 degrees C is pumped from the CoolGard unit, the external temperature control system, through the Cool Line intravascular heat exchanger catheter, which can be placed in the femoral vein, jugular vein and subclavian vein. The Cool Line catheter has a "closed loop" design, such that the cooled saline from the CoolGard flows into the Cool Line, which contains two small balloons designed for increased exposure of the cooled catheter to the venous blood flow, and then back to the CoolGard system

Overlap (*summarized for each individual*): None

Pending Support

*These grants will end before the current proposal would begin.

In the event that all pending grants are funded, Dr. Marion will reduce efforts on other grants and adjust in consultation with appropriate NIH personnel.

% = Percentage of Effort

Other Support

STENGER, V. Andrew

Name of Individual: STENGER, V. Andrew
Active/Pending: Active
Project Number (Principal Investigator): 1R21 MH61472-01 (Stenger)
Source: National Institute of Mental Health
Title of Project (*and/or Subproject*): Tailored RF Pulses for Functional MRI
Dates of Approved/Proposed Project: 06/01/00 – 05/21/02
Annual Direct Costs / Percent Effort: $75,000 / %

Develop a method using tailored RF pulses for reducing artifacts from magnetic susceptibility variation if functional MRI of the brain.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): 2RO1 NS32756-06 (Boada)
Source: National Institute of Health
Title of Project (*and/or Subproject*): Rapid Whole-Brain Functional MR Imaging
Dates of Approved/Proposed Project: 2/1/99 - 1/31/02
Annual Direct Costs / Percent Effort: $43,261.00 / %

This is a subcontract to the University of Michigan to enhance and evaluate methods for functional magnetic resonance imaging (fMRI) that are capable of high temporal resolution spatial resolution and whole brain coverage.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): 5R01MH47074-08 (Cohen)
Source: National Institute of Health
Title of Project (*and/or Subproject*): Mechanisms of Context Processing in Schizophrenia (Cohen)
Dates of Approved/Proposed Project: 6/6/97 - 5/31/02
Annual Direct Costs / Percent Effort: $22,846.00 / %

This project takes an integrated approach to studying the cognitive and neurobiological disturbances associated with schizophrenia and the relation between these.

Overlap (*summarized for each individual*): None

Pending Support

In the event that all pending grants are funded, Dr. Stenger will reduce efforts on other grants and adjust in consultation with appropriate NIH personnel.

% = Percentage of Effort

Center For Sports Medicine **RESOURCES**

. FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary

Laboratory: The UPMC Center for Sports Medicine, 3200 Water Street, Pittsburgh, PA. Is a free-standing clinical and research facility. This facility opened in September of 2000 and is regarded as one of the most advanced facilities of its kind in the world. The center provides office space for the for neuropsychological testing component of the program as well as office space for study participants (Lovell and Collins).

Clinical: The UPMC Sports Medicine Center provides comprehensive sports medicine services to athletes at the amateur, collegiate and professional levels and serves as the training facility for both the Pittsburgh Steelers and University of Pittsburgh football teams. The Sports Medicine Concussion Program represents the most comprehensive concussion management program of its kind in the country. UPMC staff (Lovell) oversees the concussion evaluation programs for both the National Football League and the National Hockey League.

Animal: No Animals will be utilized as subjects in this study.

Computer: Three Pentium III lap-top computers are available neuropsychological test administration. The neuropsychological testing software (ImPACT) has been installed on these computers to allow for test administration. Two additional Pentium II computers are available to assist in completing the study. No additional computer resources are requested as part of this study.

Office: The Sports Medicine Concussion Program has a secretary who provides administrative support as well as three additional appointment schedulers.

Other:

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

Magnetic Resonance (MR) Research Center RESOURCES

. FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary

Laboratory: The University of Pittsburgh Medical Center (UPMC) has a state-of-the-art MR Research Center on the 8th floor of Presbyterian University Hospital allotting space for imaging systems, support laboratories and office space. This MR Research Program includes 5 academic and 6 support staff. The Program is built around development and application of acquisition and image reconstruction schemes for clinical as well as research MRI studies. The Center opened September 1994.

Animal: No Animals will be utilized as subjects in this study.

Computer: The computational power for the research network is supplied by a 8 processor Silicon Graphics Power Challenge L server, multiple Sun SPARC 10 (Models 40 and 512MP), 20 and Ultra workstations and Silicon Graphics Inc. IRIX workstations (Octane and O2 models). The SPARC workstations and the Power Challenge L server are interconnected by a 100 Mb/s CDDI (Copper DDI) LAN. Commercial software for image analysis (SAGE, IDL, Analyze) complements the development of customized software for individual projects. The administrative LAN runs on 10Mb/s Ethernet (10Base-T) and is connected by router to the CDDI research LAN. It includes Apple Macintosh computers, Windows 95 PC's and 2 high-speed 600dpi laser printers. Available software includes packages for word processing, relational database, image display and processing, presentation graphics and communications. Both LANs can communicate through a router to the Radiology Department's Novell Netware-based Ethernet LAN. The administrative LAN system has access to Novell file server and e-mail systems permitting file sharing and communication with other department members. This connection also provides access to the University of Pittsburgh computer networks and from there to the world-wide Internet network for intra- and extra-mural collaboration, respectively.

Office: >

Other: **Electronics Laboratory:** It contains all the necessary equipment for RF coil design and construction including network analyzer, RF and LF impedance analyzers, frequency synthesizer and oscilloscope. The associated mechanical workshop has a lath and milling machine with accessories for fabrication of metal, fiberglass and plastic supports for coils and phantoms.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

Instrumentation: Two Signa human imaging/spectroscopy systems (General Electric Medical Systems, Milwaukee, WI) operating at 1.5T and 3.0T, respectively. The 1.5 Tesla scanner operates under Version 8.4 software and is equipped with spectroscopy (General Electric NMR Systems, Fremont, CA) and echo planar imaging. Both instruments have Signa patient handling capabilities, detachable patient table and laser land marking. The 3.0T scanner operates under version 8.2.5 of the scanning hardware. Both scanners are capable of 4Gauss/cm peak gradient strength (15,000Gauss/cm/sec slew rate). The instrumentation is designed to handle the high data rates and storage required by fMRI. Both systems are interfaced to a high-speed local area network (CDDI-based LAN) for data transfer to workstations for analysis. All conventional and echo planar MR imaging and MR angiographic functions (both phase contrast and time-of-flight methods) are supported. The magnet rooms are magnetically, acoustically and RF shielded.

Quality assurance procedures are in place for both scanners. These include daily signal stability scans for echo planar imaging (1% maximum RMS over a continuous 30 minute acquisition with a 64x64 matrix size) and daily signal-to-noise measurements with the standard RF head coil. The MR Research Center has maintenance agreements with General Electric Medical Systems that guarantee service in less than 12 hours whenever daily stability scans fail to meet the required specifications

fMRI AND SPORTS-RELATED CONCUSSION

INTRODUCTION/SPECIFIC AIMS

Mild traumatic brain injury (TBI), commonly referred to as concussion, frequently causes a cluster of symptoms that include headaches, short-term memory loss, impaired concentration, and behavioral disturbances. There is no effective treatment for this post-concussion syndrome, in part because little is known about its anatomic and pathophysiologic basis. Elucidation of the neurophysiology and brain locations affected by concussion is the first step in developing effective treatment strategies.

Mild TBI is difficult to investigate, however, because many victims do not come to the hospital for treatment, or they are evaluated and discharged from a primary care facility and receive no further care. But, high-school and college athletes are a fertile group for studying concussion. In addition to their high risk for mild TBI, they are highly motivated to recover (in contrast, for example, to workers, whose pursuit of secondary gain may artificially retard their recovery). We have developed a battery of neurocognitive tests (ImPACT) that focus on working memory and attention, the two elements of cognition most commonly affected by concussion. We administer these as pre-season tests to 90% of the athletes in this geographic region so that we have a baseline for comparison with post-concussive tests. Thus, we have a relatively captive population of individuals at risk for concussion who routinely undergo neuropsychological testing, both before the season and after a concussion, and who are available for this study. We will use functional MRI studies (fMRI), to detect focal abnormalities in brain activation, in conjunction with our neurocognitive tests, to help characterize the neuroanatomic and neurophysiologic basis for the symptomatic and objective cognitive manifestations of concussion.

Specific Aims

1. Describe fMRI patterns of brain activation that typically concur with specific cognitive deficits identified using a traditional (n-back) and a new (ImPACT) neuropsychological test in victims of sports-related concussion.

Hypotheses: Athletes with a sports-related concussion will have working-memory impairment associated with characteristic patterns of abnormal brain activation, particularly in the prefrontal, inferior parietal, and cingulate cortex and the cerebellum. Such abnormalities of brain activation will return to normal as the measured cognitive deficits subside.

2. Describe typical fMRI of activation associated with subjective components of sports- related concussion and post-concussion syndrome (headaches, concentration deficits, memory deficits, dizziness, and behavioral dysfunction).

Hypothesis: Working-memory deficits and brain-activation abnormalities will be more prominent in athletes with the most severe post-concussive symptoms.

3. Determine the effect of multiple sports-related concussions on cognitive function and fMRI activation.

Hypothesis: Working-memory deficits and brain-activation abnormalities will be more prominent in athletes who have had multiple prior concussions than in those who have never had a prior concussion. In addition to depressed brain activation, we anticipate that athletes with multiple concussions will show new cortical areas of abnormal activation.

4. Define gender and age effects on concussion-related changes in fMRI activation and cognition.
Hypothesis: Younger (high-school aged) athletes will recover from brain activation abnormalities and cognitive deficits more slowly than older (college-aged) athletes. Male athletes will have a more rapid and complete recovery than female athletes.

5. Correlate concussion-related fMRI, cognitive, and symptomatic changes with academic performance.
Hypothesis: Academic performance will deteriorate as a result of prolonged post-concussive symptoms or signs or in relation to the number of prior concussions the athlete has suffered.

BACKGROUND AND SIGNIFICANCE

In the United States, over 300,000 sports-related concussions occur annually, and the likelihood of suffering a concussion while playing a contact sport is estimated to be as high as 19% per year of play.[22] More than 62,000 concussions are sustained each year in high-school contact sports,[45] and among college football players, 34% have had one concussion and 20%, multiple concussions.[12] Concussions often cause significant and sustained neuropsychological impairments in information-processing speed, problem solving, planning, and memory, and these impairments are worse with multiple concussions.[11;37;42]

Suffering a second concussion while still having symptoms from a previous concussion can be lethal. In 1973, Schneider was the first to describe the deaths of two athletes who died after suffering a relatively minor head injury during recovery from a previous concussion.[55] In 1984, Saunders and Harbaugh reported the same scenario in a 19-year-old college football player and coined the term "second-impact syndrome" (SIS).[52] Since then, at least 26 deaths have been attributed to SIS, 20 of them occurring in the past 10 years.[36]

Physicians, trainers, and others who care for injured athletes disagree about the amount of time that must pass before an athlete with a concussion can safely return to play or the potential danger of returning too soon.[36] Many athletes resume play prior to resolution of cognitive deficits because, until recently, there were no valid tests available to assess cognitive function during recovery. Thus, there are no widely accepted evidence-based guidelines that coaches or trainers can use to be sure the athlete has recovered.[12] At least 14 different concussion scales have been published since 1973, with widely disparate criteria for grading concussion severity and resuming athletic activity. Moreover, because post-concussive symptoms can be quite subtle, coaches and athletic trainers often miss the diagnosis. In fact, physicians and sports medicine researchers do not even agree on the definition of "concussion." Previous attempts to objectify the diagnosis of concussion or post-concussive syndrome using multiple concussion scales, computed tomography (CT), magnetic resonance imaging (MRI), and EEG have been unsuccessful.

Most experts believe that the signs and symptoms of concussion are related to a metabolic dysfunction in the inferior parietal, prefrontal, and cingulate cortex.[26;27] Decreased cerebral blood flow, hyperglycolysis, glutamate-induced excitotoxicity, and abnormal cellular ionic fluxes occurring after TBI have been implicated as the cause for this dysfunction. Recent studies have suggested that delayed metabolic dysautoregulation is caused by excitatory amino acid-induced ionic shifts with increased Na/K ATPase activation and resultant hyperglycolysis.[6;31;60] The decreased cerebral blow flow that occurs with post-traumatic dysautoregulation is not well understood. Such dysautoregulation may not be seen until 2-3 days after injury and often persists

for more than a week.[16;17;25;43;56] It has also been postulated that metabolic dysregulation, until fully resolved, may make the brain more vulnerable to a second injury,[9;59] thus explaining the severe neurological dysfunction or death when a second impact occurs before these abnormalities resolve. These hypotheses, however, are based primarily on metabolic and physiologic information obtained from animal experiments or studies of *severe* TBI in humans. Quantitative, and possibly also qualitative, differences likely exist for victims of concussion.

The neuropsychological deficits that result from sports-related concussion have been extensively reported. Barth et al. gave baseline neuropsychological tests to 2300 football players from 10 college teams.[3] Approximately 200 players suffered concussions during the period of the study. Re-administration of the tests to each injured player at 24 hours, 5 days, and 10 days showed subtle post-concussive impairments in their ability to process new information, which typically resolved by the tenth day. Macciocchi et al. compared cognitive function and post-concussive symptoms between 183 college athletes with concussions and age-matched control subjects and found impaired performance and increased headaches, concentration difficulties, and behavioral problems in the injured group.[35] Among 33 amateur soccer players, Matser et al. found moderate to severe impairments in memory and planning in 27%, compared with only 7% of swimming or track athletes.[37] They attributed the high rate of deficits in soccer players to concussions sustained during "heading" of the ball. Jordan et al. found impaired concentration, attention, and memory in all 42 boxers they studied.[30] The degree of cognitive dysfunction was proportional to the boxer's sparring exposure, a finding that supports the concept that multiple concussions have a cumulative adverse effect on cognitive function. Collins et al. studied post-concussion recovery in almost 400 athletes.[11] They reported that athletes who suffered multiple concussions performed more poorly on neuropsychological tests and were more likely to have prolonged learning difficulties than those with a single or no concussion.

All of these studies have been of college or professional athletes, and we have not found any studies that examined the effects of concussion in high-school athletes. And yet, most at-risk athletes are at the high-school level or younger. Moreover, the majority of the 17 athletes who died of SIS between 1992-1997 were high-school students.[9] Although current return-to-play guidelines are applied identically to all age groups, no study has examined whether vulnerability to concussive injury differs with age. Such age-related differences are suggested, however, by our previous studies, which showed significant post-concussion differences on standard neuropsychological tests between high-school and college athletes (See Preliminary Data Section).

These age-related neuropsychological differences may well be related to previously described differences in post-traumatic pathophysiology in the adolescent versus the adult brain. Children and teenagers are more likely than adults to have diffuse injury and prolonged brain swelling. This may in part be related to the fact that the immature brain is approximately 60 times more sensitive to glutamate-mediated N-methyl-D-aspartate excitotoxic brain injury.[7;24;40;41] Therefore, high-school athletes might be expected to have a slower recovery than college-aged or older athletes and to be more susceptible to severe neurological deficits should they be re-injured during recovery.[1;8;44;53;54] On the other hand, some argue that younger athletes should have a greater potential for recovery after concussion because of their greater potential for cortical reorganization compared with adults. Studies comparing functional outcome after hemispherectomy found that younger animals had a more complete functional recovery than older ones.[57] This finding supports previous clinical evidence of marked synaptic excess in children,

relative to adults, allowing for neural pathway rerouting during recovery and functional plasticity in the developing brain.[28]

In addition to age, gender appears to affect outcome after a concussion. Females with mild TBI are more likely than males to report sleep disturbances and headaches, and are less likely to be employed or in school 1 year after injury.[10] In their study of individuals who presented to an emergency department after a concussion, Bazarian, et al. also found that females were more likely than males to have post-concussive syndrome at 1, 3, and 6 months after injury, though these differences reached statistical significance only at 3 months.[4] The authors attributed these differences to significant differences in the mechanism of injury: more females were involved in motor-vehicle collisions (57% vs. 22% of males), while more males had sports injuries (33.3% vs. 8.6% of females). Gerberich evaluated the effects of TBI on college academic performance.[21] Individuals with TBI were compared to uninjured controls and to controls hospitalized for other types of injuries. Concussion led to a significant decrease in grade point average (GPA) for the females compared to their controls; this was not observed in the males who had a concussion. Another study looking only at those who were working before injury showed no gender differences in return-to-work rates, but significant differences between males and females in reported capacity for unrestricted employment, as measured through the DRS employability subscale.[58] Most studies to date have found that even after controlling for other demographic, premorbid, and event-related factors, women have worse outcomes than men after a concussion, and a recent meta-analysis involving 8 studies and 20 outcome variables showed outcome was worse in women than men for 85% of the variables studied.[18]

In contrast to the literature citing more symptoms and poorer outcomes for females after TBI, animal studies suggest that female hormones may play a neuroprotective role after TBI. Roof found that endogenous or synthetic progesterone caused a greater reduction of cerebral edema in female rats compared to males.[47] Progesterone also has been shown to limit lipid peroxidation, facilitate cognitive recovery, and reduce secondary neuronal loss after cortical contusion in male rats.[46;50] Estrogen appears to have a protective effect in males, but it increases mortality and worsens motor function in females.[15] Other studies have found that estrogen maintains normal cerebral blood flow and, when given acutely, reduces mortality after experimental TBI.[48] These findings are thought to be due to estrogen-mediated neuroprotective mechanisms such as antioxidant effects and reduction of levels of excitotoxic mediators of secondary brain injury.[15;49]

In clinical drug trials, gender differences have been reported for aspirin efficacy in stroke prevention and for tirilizad efficacy in the treatment of subarachnoid hemorrhage. These drugs were found to be much more beneficial for males than females.[49] However, studies evaluating gender-dependent differences in the treatment of TBI are largely non-existent.

Thus, many questions remain regarding the pathobiology of concussion, the effects of age and gender, and the time course for recovery. One approach would be to examine brain regional activity during cognition as a function of concussion. Functional MRI (fMRI) is a noninvasive means of imaging changes in local cerebral blood flow and in brain activation that occur with cognitive or physical activity. fMRI monitors brain function with a relatively high degree of spatial and temporal resolution.[39;51] The technology is based on the sensitivity of MRI to magnetic effects induced by the modulation of the oxygenation status of hemoglobin (oxy/deoxyhemoglobin) that results from local variations in blood flow. It has been shown that such variations can be induced by task activation or cognitive processes such as language or

mental imagery.[34] The MRI signal is increased by a few percent when physical or mental activity activates a region of the brain, causing a sharp increase in local blood flow and oxygen utilization. The functional activation of brain regions as recorded by fMRI has been shown to correlate quite well with regional brain electrical activity as recorded using event-related evoked potentials, and with regional glucose metabolism as detected with positron-emission tomography (PET).[34]

To date, only one study has been published describing the use of fMRI in patients with TBI. McAllister et al. compared brain-activation during a working-memory task (n-back) between 11 healthy subjects and 12 patients who had a concussion within the past month.[38] They found activation by the two groups to be significantly different for working-memory circuitry in response to different processing loads. In the control subjects, stimulation with a low processing load led to maximum activation in the frontal and parietal lobes, and more difficult tasks produced very little increase in activation in these areas. For the 12 concussion patients, the level of activation stimulated by the low processing load was slightly less than in controls, but the level of activation in the frontal and parietal lobes was significantly higher than for control subjects with the high processing loads. The investigators interpreted their results as suggesting that patients with a concussion perceive a change in their ability to engage working memory, and they experience this change as having to work harder to maintain accurate test performance. These findings also suggest that injury-related changes in the ability to modulate memory processing may underlie the typical findings of worsened memory after a concussion.

Other diagnostic modalities have shown that regional metabolic abnormalities correlate with cognitive dysfunction. Fontaine et al. used PET to measure regional glucose metabolism in 13 TBI patients with deficits in memory, attention, executive function, or behavior.[19] They found cognitive and behavioral disorders to be closely linked to decreased metabolism in the prefrontal and cingulate cortex. Results of memory and executive function tests correlated with regional metabolism in the mesial and lateral prefrontal cortex and the cingulate gyrus. Behavioral disorders correlated with mesial prefrontal and cingulate metabolism.

In summary, mild TBI (concussion) causes significant cognitive deficits that appear to be worse and more prolonged with repeated injury. The few imaging studies done to date implicate abnormal function or metabolism in the prefrontal, parietal, and cingulate cortex as likely causes for these cognitive deficits. However, there have been no large prospective studies that combine cognitive testing with a functional imaging study to elucidate the relationship between specific post-concussive cognitive deficits and abnormalities in various brain regions. In this regard, several studies suggest that there may be significant differences related to age and gender, but it is not clear if the prognosis is better or worse for younger as compared to older individuals or males versus females. As a result, current management of mild TBI is relatively arbitrary and extremely variable. With no standard criteria to assess cognitive damage or recovery, high-school and college athletes who suffer a concussion may return to play too soon and are at risk for SIS. Students who return to school too soon after a concussion may be unable to work to their full potential, become discouraged because of a decline in academic performance, and unnecessarily limit their long-term goals.

There is a need for a large prospective study that will more clearly define the pathobiology of concussion and identify the differences in neuroanatomic and neurophysiologic recovery from concussion that are related to time after injury, age, and gender. The results of such a study

would provide the scientific basis for the formulation of guidelines concerning who can safely return to work, school, or athletic competition after one or repeated concussions. Such guidelines may well be found to be different for individuals of different ages, or for males and females. Information derived from such a study also could be expected to guide the development of therapies aimed at preventing or limiting the symptoms of post-concussive syndrome.

PRELIMINARY STUDIES/PILOT DATA

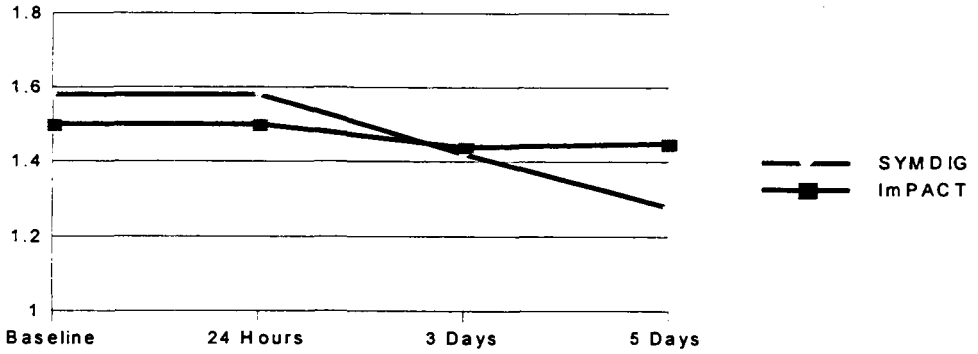
In this section we will describe our considerable experience with the neuropsychological assessment of concussed athletes, and with the use of fMRI in similar patients. We first will describe our experience with the neuropsychological assessment and recovery of deficits in concussed athletes using the ImPACT test battery proposed in this study. Second, we will describe our studies of the effect of age on recovery from concussion. Third, we will briefly report our experience using fMRI in other patient groups. Finally, we will describe the results of fMRI studies and ImPACT neuropsychological assessment in three individuals with concussion who were recently evaluated in our program. Based on these studies we believe we have the necessary neuropsychological evidence to support our general hypotheses, and the ability to require meaningful fMRI data in the acute post-concussion patient.

Measurement of Post-Concussive Cognitive Deficits Using ImPACT

In 1999, we (Lovell and Collins) described "immediate post-concussion assessment and cognitive testing" (ImPACT), a battery of neuropsychological tests specifically for evaluating sports-related concussions.[11] These tests measure multiple aspects of cognitive function including attention span, sustained and selective attention time, response variability, and several dimensions of memory. Before these tests are administered, subjects complete a self-report questionnaire concerning 20 symptoms commonly associated with concussion as well as a concussion-history form (Appendices 2 and 3). ImPACT is a user-friendly, Windows-based computer program that can be administered via a laptop computer by a team coach or athletic trainer with minimal training. Reaction time is reliably measured to within 1/1000 of a second across individual test modules. There are a total of 8 test modules, structured to allow an assessment of processing speed as a subject fatigues. The stimulus array within each module is randomly varied such that a near-infinite number of alternate forms is possible, thereby minimizing practice effects. The battery takes a total of 20 minutes to complete.

Reliability (resistance to practice effects) of ImPACT: To demonstrate the resistance of the ImPACT test battery to practice effects, we administered it to 28 uninjured high-school students on 4 separate occasions over 5 days, and compared their results to the results of a standard memory test (Symbol Digit) given to a separate group of students at the same four intervals (Fig 1). ImPACT scores did not change significantly after repeating the test 4 times, while Symbol Digit scores were significantly improved, presumably because of practice.

Figure 1: Resistance of ImPACT to Practice Effects-Comp. with the Sym-Dig Test



To date, over 1500 high-school and 800 college and professional athletes have undergone baseline (preseason) ImPACT testing, of whom approximately 70 high-school and 50 college athletes have been restudied after suffering a concussion.

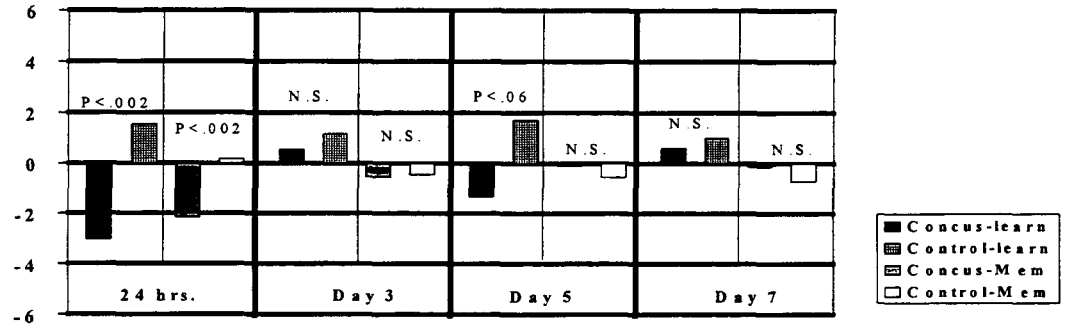
Seventeen local high schools/colleges have purchased ImPACT and plan to implement baseline testing for female and male participants in football, soccer, ice hockey, rugby, lacrosse, basketball, and wrestling. We expect a *minimum* of 200 athletes per school to have baseline testing, *at least* 25% of whom are female. Thus, we anticipate that at least 3400 athletes will have preseason ImPACT testing this year. Since approximately 5% of athletes have a concussion in a given season, we expect to have baseline/post-injury data on *at least* 170 athletes per year, of whom at least 43 will be female.

In just the past 4 months (10/1/00-1/31/01), we have used ImPACT (in addition to other neuropsychological measures) to evaluate 40 high-school and college athletes referred for acute sports-related concussions (see Appendix 4 for demographic details). The evaluation was designed to help determine cognitive/neurobehavioral sequelae and resolve retirement/return-to-play issues. The athletes comprised 29 high-school and 11 college athletes, 31 male and 9 female, aged 13-24. Twelve had had no prior concussion; 7 had one prior concussion; 14 had two to four prior concussions, and 7 had five or more prior concussions. Their most common sports were football (n=19), hockey(n=7), soccer (n=7), and wrestling (n=4).

Effect of Age on Recovery from Concussion: High-School vs College Athletes

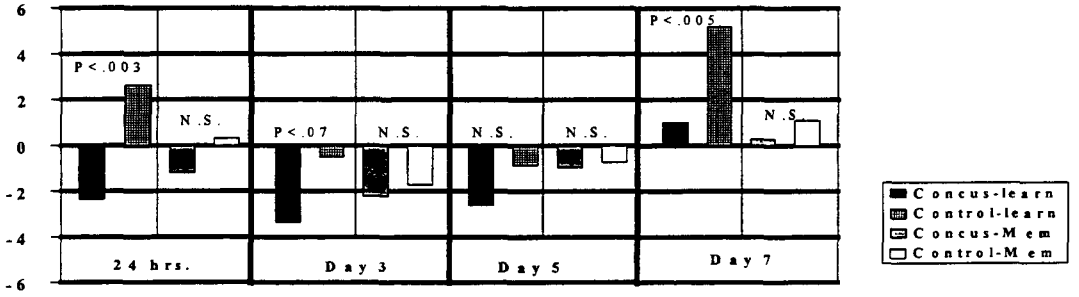
In an earlier study we used the Hopkins Verbal Learning Test (HVLT) and the Brief Visuospatial Memory Test-Revised (BVMT-R) to evaluate 19 high-school and 35 college athletes who suffered a concussion while playing football or soccer (detailed data in Appendix 1). We compared their performance on these tests with that of age-matched uninjured subjects (20 high-school students, 18 college students). Verbal learning and memory (HVLT) recovery patterns are presented for the college and high-school athletes in Figure 2 and Figure 3, respectively. Figure 4 shows visual memory and learning recovery patterns (BVMT-R) for high-school athletes.

Figure 2 Recovery Pattern of Concussed and Control College Athletes Verbal Learning and Memory



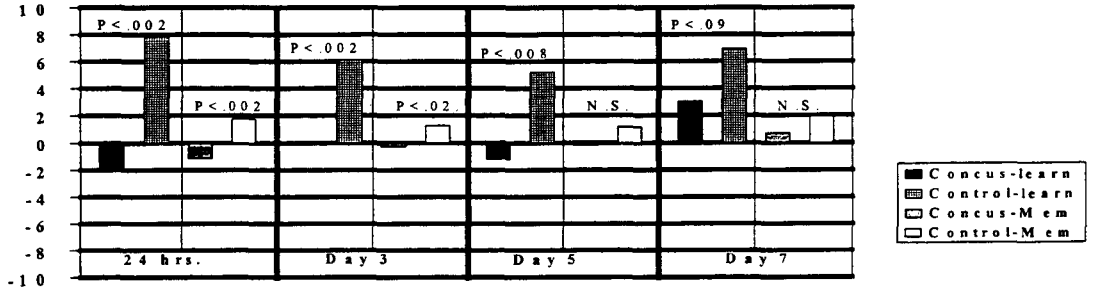
Scores reflect the mean difference of subjects relative to their baseline performance. A lower score reflects poorer performance compared to baseline. Learning and memory scores represent performance on the Hopkins Verbal Learning Test (HVLT).

Figure 3 Recovery Pattern of Concussed and Control High School Athletes Verbal Learning and Memory



Scores reflect the mean difference of subjects relative to their baseline performance. A lower score reflects poorer performance compared to baseline. Learning and memory scores represent performance on the Hopkins Verbal Learning Test (HVLT)

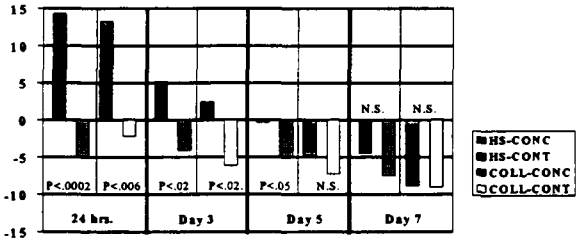
Figure 4 Recovery Pattern of Concussed and Control High School Athletes Visual Memory and Learning



Scores reflect the mean difference of subjects relative to their baseline performance. A lower score reflects poorer performance compared to baseline. Learning and memory scores represent performance on the Brief Visuo-spatial Memory Test-Revised.

Compared with age-matched control subjects, learning performance 24 hours after a concussion was significantly worse for both high-school ($p < 0.003$) and college athletes ($p < 0.002$). This was true for tests of both verbal (Fig. 2 and Fig. 3) and visuospatial memory (Fig. 4). By 3 days after injury, learning returned to nearly normal in the college athletes, but the high-school athletes continued to have difficulties, particularly with visuospatial learning. Both 5 and 7 days after injury, the test results for college athletes remained similar to those of control subjects, but the high-school athletes continued to have significant memory deficits, particularly for visuospatial learning at 5 days ($p < 0.008$) and verbal memory at 7 days ($p < 0.005$).

Figure 5. Symptom Self-Report of Concussed and Control Athletes High School and College



Scores reflect the mean difference of subjects relative to their baseline report of symptoms. A positive score reflects more symptoms compared to baseline on the Post-Concussion Scale-Revised. A negative score indicates less symptoms compared to baseline.

Injured high-school athletes reported a significant incidence of post-concussive symptoms at 24 hours ($F = 16.7$; $p < .0002$), 3 days ($F = 5.8$; $p < 0.02$) and 5 days post-injury ($F = 4.1$; $p < 0.05$). In contrast, college athletes no longer had a significant incidence of symptoms on day 5 (Fig. 5). Notably, several of the high-school and college athletes who had suffered concussions reported a net *decrease* in post-concussive symptoms on days 5 and 7 as compared with their pre-concussion status, raising the possibility that both these groups minimize symptoms in order to resume athletic activity.

This study suggests that high-school athletes have a slower neuropsychological recovery after sports-related concussion than do college athletes. At least 7 days after a "mild" concussion, high-school football and soccer participants had a significant learning impairment. Conversely, college football and soccer players had significant learning deficits only at 24 hours after injury.

Use of fMRI and n-back in Patients with Neuropsychiatric Disorders

We recently completed a study of the effects of a major depressive disorder on working memory in elderly people. Although studies of cognitive function in elderly patients with depression have revealed variable cognitive deficits, executive dysfunction appears to be a prominent feature of the depression syndrome. Functional neuroimaging studies (e.g., PET) consistently have revealed frontal cortical hypometabolism in these patients, but these studies all were performed while the patients were at rest, and their cognitive state at the time of the scan was unknown. We used fMRI to examine the functional integrity of the frontal subcortical brain and chose the n-back as the activation task because successful performance requires the integrity of these frontal circuits.

All subjects tolerated the scans and could perform the tasks. Direct comparison of the 2-back and 1-back conditions enabled us to examine those brain regions whose activity was associated with the increased memory demands of the 2-back task. This showed significant activation in the cingulate gyrus and in the insular cortex on the left. Our data demonstrated that although many of the brain circuits normally associated with visual-verbal working memory are activated in elderly patients with major depression, activation was lacking in the frontal circuits thought to be important for the successful performance of visual-verbal working memory.

Our group also has used the n-back task with fMRI to determine the nature and extent of brain functional abnormalities in AIDS. HIV infection poses a risk for developing a dementia

syndrome secondary to HIV-related central nervous system toxicity. Previous studies using PET imaging have found that HIV-infected individuals have alterations in functional connectivity when performing an auditory-verbal working-memory task. We sought to extend these findings using a verbal recognition memory task (n-back) known to be associated with the dopamine system. We studied 10 young subjects with CDC-defined AIDS and 6 healthy young HIV-seronegative control subjects.

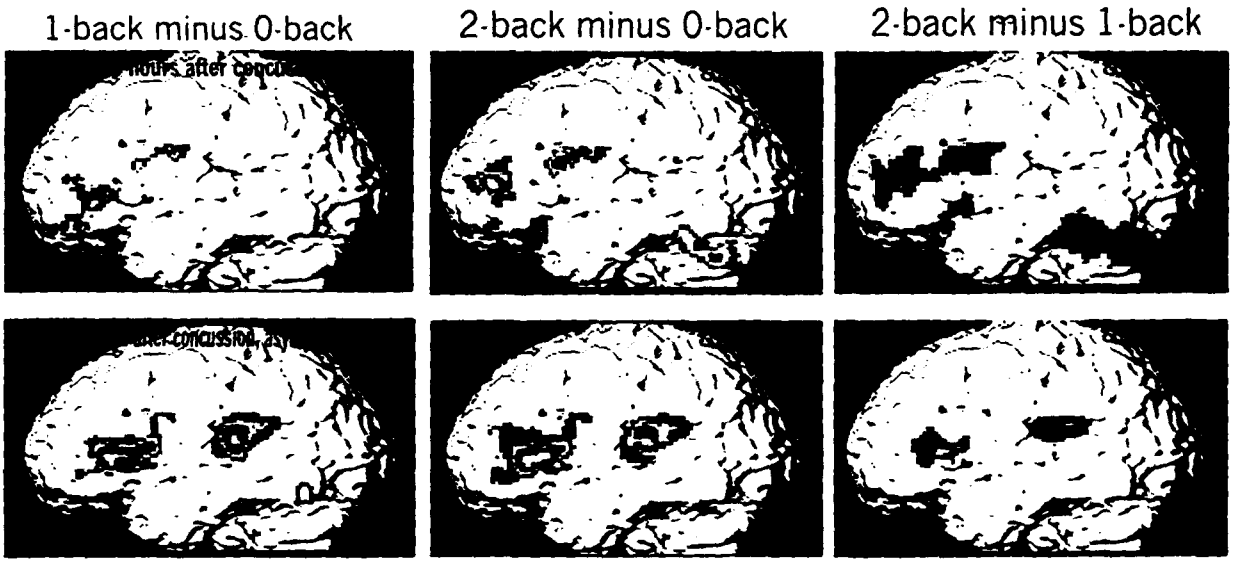
Relative to the 0-back condition, both 1-back and 2-back conditions activated the posterior parietal lobe in both AIDS patients and control subjects. However, compared with the 1-back condition, 2-back led to significant activation in Broadman's area (BA) 6 on the right, and bilaterally in BA10 in the HIV/AIDS patients. There was no significant activation in the regions of the dorsolateral prefrontal cortex.

These data make three important points relative to our current proposal: First, it is possible to use fMRI to study and obtain meaningful data in "difficult" patients (as post-concussive subjects may be perceived). Second, the n-back task is robust, and we could observe normal patterns of activation among elderly subjects, and among young subjects with HIV infection. Third, the patterns of regional activation, and the deviance from normal, can differ between disease groups. For example, the patients with major depression showed normal but attenuated activation of the prefrontal cortex, whereas those with AIDS failed to show normal activation of the prefrontal cortex but did show normal activation of the more posterior brain regions (i.e., inferior parietal lobe).

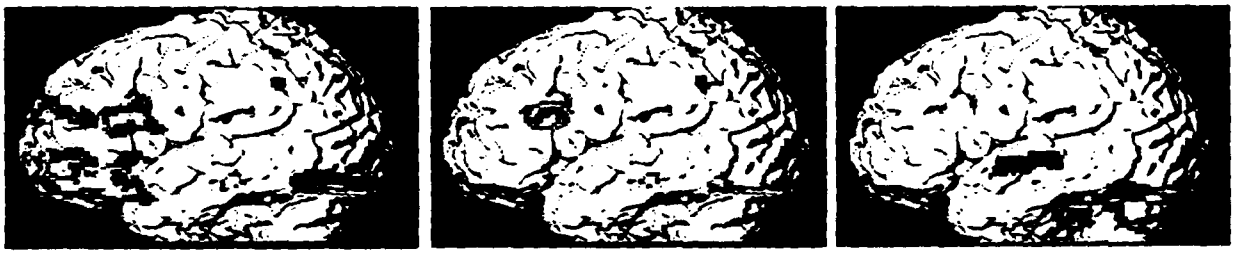
<u>fMRI Activation Patterns After Concussion: Pilot Studies of 3 Subjects</u>

Of critical importance to the success of the present study is our ability to acquire meaningful fMRI data in subjects with a concussion, who may have difficulty lying still in the scanner, be distracted by the noise of the scanner, or be generally irritable. Any of these features could increase the likelihood of significant head movement that could not be completely corrected by the data analysis stream. We completed a series of fMRI studies in three patients referred to the Sports Medicine Concussion Clinic during the last month. The fMRI scans were performed using a GE 1.5-T MRI system equipped for echo-planar imaging. Oblique axial sections were positioned parallel to the AC-PC line, and 14 slices (5 mm, 1 mm skip) were obtained beginning at the superior surface of the brain (TE=3000, TR=50, flip=90). There were eight acquisitions for each of three tasks conditions and a total of 98 epochs per condition. The data were corrected for head movement, the scans aligned, and the data spatially normalized prior to analysis (Fig. 6).

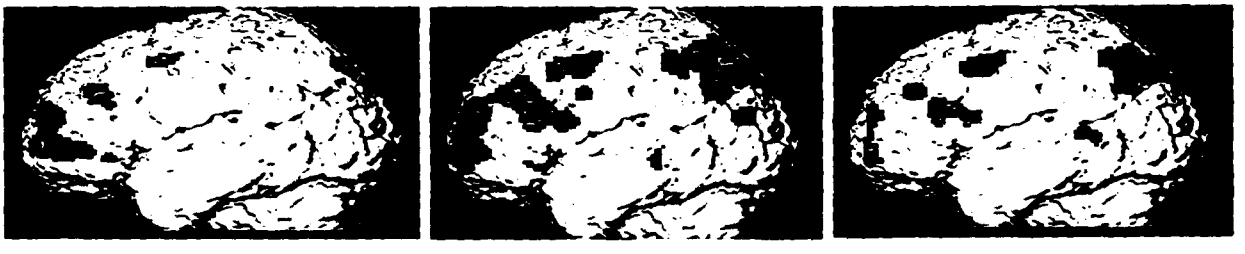
FIGURE 6



These fMRI studies are of a 17-yeaar-old right-handed female athlete who suffered a cncussion while playing basketball 48 hours prior to evaluation. Immediately after injury, she had altered sensorium but no loss of consciousness. She had had one previous concussion, 3 weeks earlier. Series A(48-hour study): Symptoms were general irritability, slowing of mentation, and headache; ImPACT showed deficits in visual memory, attention, reaction time, and speed of information processing. Series B(8 days after injury): asymptomatic; ImPACT results: all modules were normal or high normal.



Two weeks before this fMRI scan, this 36-year-old right-handed man suffered a concussion in a motor-vehicle collision and lost consciousness for 15 minutes. He had minimal post-traumatic amnesia and a normal CT scan of the head. He had one previous concussion, 13 years before. Current symptoms were headache, impaired concentration and memory, sensitivity to noise, and sleep disturbances. ImPACT results: deficits(<30% of normal) in attention, verbal memory, visual memory, and reaction time.



A 17-year-old left-handed male suffered a concussion while wrestling 6 days prior to evaluation. He did not lose consciousness but had immediate dizziness and confusion and had post-traumatic amnesia for 12 hours. He had three previous concussions: 7 weeks ago, 5 weeks ago, and 2 weeks ago. Current symptoms were headache, lethargy, concentration difficulties, and fatigue. ImPACT results: deficits in working memory, visual memory, and speed of information processing.

In the female basketball player, fMRI activation was depressed in the prefrontal and inferior parietal cortex, and abnormal activation was present in the cerebellum, 48 hours after concussion, when she was symptomatic and had cognitive deficits as measured with ImPACT (fMRI Series A, Fig. 6). At 8 days after injury, when she was asymptomatic and her ImPACT results had returned to normal, she had increased fMRI activation in the prefrontal and inferior parietal cortex and virtually no activation in the cerebellum. These findings were most apparent with the 2-back task when contrasted with the 1-back task (fMRI Series B, Fig. 6). Our results are consistent with those of McAllister et al.[38] Like them and others, we also found very different activation patterns in the left hemisphere (posterior parietal, frontal polar) with our left-handed subject and therefore have decided to include only right-handed athletes in the proposed study.

Summary

We have extensive experience with the neuropsychological evaluation of concussion in high-school and college athletes. Our earlier studies demonstrated important differences in post-concussive learning and memory deficits between high-school and college athletes. We currently evaluate a large number of high-school and college athletes and do not anticipate any difficulties in enrolling a sufficient number of male and female subjects of high-school and college ages and with single or multiple concussions. We also have extensive experience with the ImPACT test battery, which we propose to use as our primary measure of cognitive dysfunction; we will have pre-season test results with which to compare post-concussive results. In two previous studies of patients with major depressive disorder or HIV infection, we successfully conducted the fMRI studies that we will use in this investigation. We have used most elements of the proposed protocol to study three patients with concussion during the past month. In one of those patients, we obtained fMRI studies within 48 hours after concussion and a second study after symptoms and cognitive deficits subsided. Thus, we have demonstrated that we can study patients with concussion and can effectively and efficiently process the data.

RESEARCH DESIGN AND METHODS

Overview

The purpose of this study is to examine the nature and extent of abnormalities in cognition and in functional activation of the brain associated with sports-related concussion, and to characterize those changes over time. Over the next 5 years, we will perform neuropsychological and functional neuroimaging studies (fMRI) within 72 hours after a sports-related concussion is sustained in 200 subjects. They will have had a baseline (preseason) neuropsychological evaluation, and post-traumatic neuropsychological testing will be repeated weekly until their symptoms and signs subside, when they will have a second fMRI evaluation. We will compare their results with those obtained in 50 age- and gender-matched control (uninjured) athletes. We will use the resultant data to address a series of linked hypotheses concerning the functional basis of post-concussive syndrome:

1. Athletes with a sports-related concussion will have working-memory impairment associated with characteristic patterns of abnormal brain activation, particularly in the prefrontal, inferior parietal, and cingulate cortex.

2. Such abnormalities of brain activation will return to normal as the measured cognitive deficits subside.

3. Working-memory deficits and brain-activation abnormalities will be more prominent in athletes with the most severe post-concussive symptoms and in those who have had multiple concussions than in those who never had a prior concussion. In addition to depressed brain activation, we anticipate that athletes with multiple concussions will show new cortical areas of abnormal activation, particularly the cerebellum.

4. Younger (high-school aged) athletes will recover from brain activation abnormalities and cognitive deficits more slowly than older (college-aged) athletes. Male athletes will have a more rapid and complete recovery than female athletes.

5. Academic performance will deteriorate as a result of prolonged post-concussive symptoms or signs or in relation to the number of prior concussions the athlete has suffered.

We have crafted our study such that we will directly address 6 of the 9 "research areas of interest" specifically delineated in the RFA (Functional MRI and Intervention for Cognitive Deficits after Traumatic Brain Injury), in response to which we are submitting this proposal. The specific research areas we will not address are those that involve intervention or treatment. For patients with sports-related concussion, we believe that the studies we propose must be successfully completed before rational treatment strategies can be formulated.

Study Sample

Experimental subjects will be drawn from a pool of male and female high-school and college athletes who are referred for evaluation within 72 hours after a suspected concussion. All subjects (including control) will have had preseason testing with the ImPACT neurocognitive test battery.

Inclusion Criteria (at the time of evaluation for this study):

a. High-school or college athlete involved in an organized contact sport
b. Age 13-25 years
c. Sports-related concussion within 72 hours of presentation*
d. Has undergone pre-season testing with ImPACT, and results are available
e. GCS score of 14 or 15
f. Normal findings on CT scan of the head
g. Right handed (determined according to the Edinburgh handedness inventory)

* Concussion will be defined by the American Academy of Neurology criteria: a trauma-induced alteration in mental status, with or without loss of consciousness.

Exclusion Criteria:

a. Post-traumatic amnesia lasting more than 24 hours after the injury
b. Intracranial CT abnormalities (e.g., contusion, hemorrhage, skull fracture)
c. Left-handed
d. Pre-existing neurologic disease (e.g., seizure disorder, meningitis, encephalitis, cerebral palsy)
e. History of substance abuse or dependence (DSM-IV definition)
f. History of DSM-IV Axis I psychiatric disorder
g. History of learning disorder (DSM-IV definition)
h. History of attention deficit disorder with or without hyperactivity (DSM-IV definition)

i. History of claustrophobia, or inability or unwillingness to undergo fMRI, n-back, or ImPACT testing
j. Ferromagnetic medical implants or shrapnel
k. Refusal of subject (or parent/guardian if age < 18) to sign consent
l. English is their second language[32]
m. No pre-season ImPACT test or results unavailable

In preparation for this study, we have contacted the coaches and/or trainers of all high-school and college athletic programs in our county and in the region. All have received personal letters and have been contacted by telephone or in person. We have given them laminated pocket cards that describe our study and our concussion program and clearly describe the signs and symptoms of concussion. As a result of these efforts, we have evaluated 40 high-school and college athletes with a concussion over the last 4 months (see Preliminary Studies).

In this catchment area, the majority of athletes enrolled in organized high-school and college contact sports are male (approximately 75%), so we anticipate that a larger number of males than females will suffer a concussion and will therefore be enrolled in our study. Although athletes from all sports will be eligible, our experience suggests that the largest number of male subjects will be injured while playing football, and the majority of female subjects will be injured while playing soccer. *No subject will be enrolled in this study more than once, even though it is possible that subjects who have completed the study will have another concussion and again be eligible.*

Control subjects ($n=50$) will be high-school and college athletes who have no history of concussion. They will be invited to participate by their coaches or trainers. Those who wish to participate will be referred to our Sports Medicine Center for screening. Inclusion and exclusion criteria will be the same as for experimental subjects except that control subjects cannot have a history of concussion or other head injury, nor will they undergo head CT scans. Absence of a history of a concussion will be determined by self-report, which is somewhat suspect given that most potential control subjects will have been involved in sports for several years. However, they will complete a detailed questionnaire that we believe will faithfully identify most episodes of concussion (Appendix 3). The proportion of high-school versus college control subjects will be similar to that in the experimental group, as will the proportion of males and females. We also will attempt to match the control and experimental subjects with respect to grade point average, pre-season ImPACT test results, and sport. *Control subjects will receive $50 dollars for participation in this study.*

Conduct of the Study

As part of our routine evaluation of all patients with a suspected concussion, every potential experimental subject will undergo a plain CT scan of the head. *As per our current protocol, they will receive no specific post-concussive treatment other than analgesics for headaches for at least 6 weeks after injury, which is the maximum duration of evaluation for the subjects enrolled in this study.*

Potential subjects will be initially evaluated at our Sports Medicine Center by Dr. Collins or Dr. Lovell and considered for enrollment in this study if they have been referred for a sports-related

concussion or as a control subject. After they are screened for inclusion and exclusion criteria, the purpose of the study will be described to them, and informed consent obtained.

The primary test of cognitive function will be the ImPACT test battery. Because all subjects will have undergone preseason ImPACT testing, we will have pre- and post-concussion test results for within subject comparison. The primary activation stimulus for the fMRI studies will be n-back, but we will attempt to assess the activation effects of ImPACT by using a modified version of its Symbol Matching module together with n-back as activation tasks during the fMRI study. The following is the schedule for studies we will obtain for experimental subjects:

	Pre-season	Within 72 hours of concussion		Every 7 days until normal	At the time of resolution of symptoms or signs, or at 6 weeks	
	SMC	SMC	MRRC	SMC	SMC	MMRC
ImPACT	XX	XX		XX	XX	
Symbol Match		XX	XX		XX	XX
n-back			XX			XX
fMRI			XX			XX

SMC, University of Pittsburgh Sports Medicine Center
MRRC, MR Research Center, Presbyterian University Hospital

Control subjects will have the same cognitive and fMRI studies as the experimental subjects, but only once.

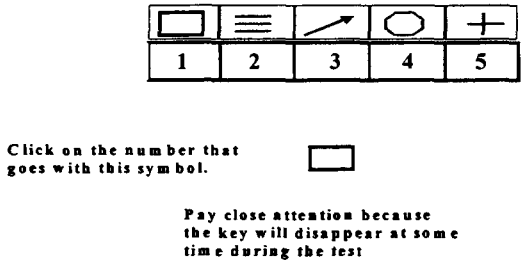
Integration of ImPACT with fMRI

The ImPACT test battery will be our primary measure of cognitive dysfunction after concussion and is a part of routine pre-season testing for most high-school and college athletes in this region. After enrollment as a control subject or referral to the Sports Medicine Center for evaluation of a sports-related concussion, subjects will use a laptop computer to take this cognitive test battery, which begins with a questionnaire asking if they have any of 20 symptoms commonly associated with concussion (Appendix 2). They will then complete 7 other test modules that assess attention span, working memory, sustained and selective attention time, and response variability. The individual modules and cognitive domains tested are as follows:

Modules	**Cognitive Domain**
Symptom Inventory	Self-Report of Symptoms
Word Discrimination	Verbal Memory
X's and O's	Visual Working Memory
Number Tracking	Attention
Visual Span	Visual Attention Span
Symbol Matching	Learning/Recent Memory
Word/Color Discrimination	Choice Reaction Time
Three Letter (Trigrams)	WorkingMemory/Processing Speed

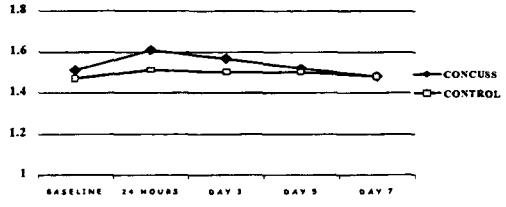
The subjects will receive an overall score as well as scores for each of the 8 modules, all of which will be used for comparison with their pre-season scores (within-subject comparison) and with the scores of appropriately matched control subjects. The entire ImPACT test battery cannot be used as a functional stimulus for fMRI studies because some of the modules require moving a mouse or typing. In order to integrate ImPACT into the fMRI study, we modified its Symbol Matching module for use as part of the cognitive-activation stimulus, together with the n-back test during fMRI (Fig. 7). ImPACT's Symbol-Matching module is a measure of paired associate learning

Figure 7: Modified Symbol Match Task



that is highly sensitive to the effects of concussion. Learning deficits can occur soon after concussion and can remain one of the longest-lived problems in chronic post-concussion syndrome. Additionally, impaired learning may be one of the most highly deleterious consequences of concussion in the context of academic performance. This module requires the subject to match symbols to designated numbers and is similar to the Symbol Digit Modalities Test that is commonly used in concussion research. It has several advantages over the other modules: it can be conducted in the MRI scanner; it measures learning and memory; it can be relatively easily decomposed into component parts; and our pilot studies have shown it to be independently sensitive to subtle changes in brain function. In a group of 55 athletes with a mild concussion and no loss of consciousness, we found that the Modified Symbol Matching module detected slowed response times compared with age-matched control subjects (Fig. 8).

Figure 8: Effect of Concussion on Symbol Matching Response Times



Values=Response time per item (seconds)

During the first year of this study, we will complete an analysis of the modified Symbol Matching module outside of the fMRI scanner environment. Subjects always will undergo the full ImPACT test battery before the modified Symbol Matching module so as not to interfere with the clinically relevant aspects of the former study. This will allow us to evaluate the psychometric characteristics of the task and its relationship to the standard Symbol Matching module of ImPACT, as well as its relationship to other ImPACT modules. More specifically, the concurrent validity of the task will be established via its comparison with the full Symbol Matching task of ImPACT. In addition, the stability of the task will be evaluated by examining the performance of participating control subjects across the multiple administrations of the task. The design of the

Symbol Matching module is such that variables of the presentation stimuli, such as time of stimulus exposure and inter-stimulus interval, can be adjusted to make the task more or less difficult. This will allow us the flexibility to tax the concussed brain sufficiently to display differences in brain activation between experimental and control subjects. We may need to modify the test design or methods by which the test is administered. Such modifications will then be included in the version of the test administered during fMRI studies conducted after Year 1.

fMRI Studies

After completing the ImPACT and modified Symbol Matching studies, subjects will be brought to the MRRC approximately 1 hour before their scheduled scan. Arrangements have been made with the MRRC to accommodate all of our subjects within 48 hours of our request. A research nurse or trained technologist will interview the subject to confirm the absence of contraindications to MRI. Subjects will then be taught to perform the n-back test and modified Symbol Matching module that will be used during the scan. Next they will be placed in the MRI scanner, given earplugs to reduce noise, and the head will be positioned comfortably and securely in the quadrature head rf coil with foam cushioning for motion stability. Subjects will be monitored by audio link and through peripheral pulse monitoring as used for cardiac gating.

All fMRI studies will be obtained in a GE 1.5-T Signa scanner using version 8.4 of GE scanning software and equipped for echo-planar imaging (General Electric Medical Systems, Milwaukee, WI). After acquisition of a sagittal scout view, and a high-resolution coronal view with spoiled gradient recalled acquisition (SPGR) for image alignment and localization, each subject will complete the fMRI protocol. Scout T1-weighted sagittal images will be obtained to localize the brain for graphic description of the coronal and axial images. 3-D gradient echo images (SPGR) will be acquired for quantification of gray and white matter, and cerebrospinal fluid (TR=25 ms, TE=4 ms, flip angle=40°, FOV=24 cm x 18 cm; slice thickness=1.5 mm).

The fMRI study will use Blood Oxygenation Level Dependent (BOLD) contrast with T2-weighted imaging using an enhanced version of the protocol described by Brayer - a spiral pulse sequence will acquire 19 slices in 1.50 seconds (1 single shot. TR 1500. TE = 35. FA = 70) with a total scanning time of 15 minutes for the n-back protocol and 15 minutes for the Symbol Matching protocol. A head coil will be used for image acquisition and oblique axial slices will be positioned approximately parallel to the AC-PC line. The resolution element will be approximately isotropic with a slice thickness of 3.8 mm and an in-plane resolution of 3.75 (field = 240 mm. acquisition matrix 64 x 64).

The fMRI protocol (including n-back and Symbol Matching) will take approximately 30 minutes. This time will be divided into multiple "sessions" of approximately 5 minutes, both to permit downloading of the fMRI data from the scanner and to ameliorate the effects of fatigue, which is especially important in the early post-concussion period. The tasks are structured using a "block" design, that is, stimuli will be presented in a grouped fashion and will be initially analyzed to compare signals measured during each block of trials. Additionally, by extending the length of individual trials, it is possible to later model these data such that we may examine "event-related" brain activation. However, it must be stressed that the initial analysis of the data will proceed as a block design (see also Data Analysis section).

n-back task

We will use a visual n-back test of working memory similarly to the way we have used it for previous studies. Briefly, subjects will view a sequence of upper- or lower-case consonants under three conditions: 0-back, 1-back, and 2-back. For the 0-back, the subject is asked whether the current letter matches a single target letter specified before the epoch began. For 1-back, the subject is asked whether the current letter matches the previous one; and for 2-back, the subject is asked whether the current letter matches the letter presented 2 back in the sequence. Immediately after each letter is presented, subjects are instructed to indicate if the letter does or does not match previous letters by pressing a button under their index finger for "yes" and under their middle finger for "no." In all tasks, the subjects observe random sequences of letters appearing one at a time in the center of a visual display and are instructed to respond by pressing a button on a hand-held fiber optic response box whenever a target appears. Stimuli are presented for 500 ms. with an interstimulus interval of 100 ms. Stimulus presentation is controlled by a Macintosh computer using PsyScopy software. At the completion of the study, a score is assigned that represents the number of correct responses.

After completing the n-back task, a T1-weighted structural image will be acquired (while data are being downloaded from the scanner) so that we can check for movement and permit realignment of the images acquired during the modified Symbol Matching task.

Modified Symbol Matching task

The modified Symbol Matching test will comprise four task conditions, in each of which a visual stimulus is presented within a boundary box on the visual display: LEARNING, which presents a symbol and a digit simultaneously; TEST, which presents a symbol alone; NUMBER, which presents a number (1-5) alone; and SYMBOL, wherein the empty boundary box is presented. In each of the four task conditions, the subject must respond identically as described below. The conditions differ, however, in the extent to which they require processing of different information (i.e., symbols or digits) and the effort they require in learning and memory. The critical dependent variable in terms of performance will be the change in accuracy during the course of the fMRI scanning session. The critical dependent variable in the fMRI component of the paradigm will be the locus and extent of brain activation during the initial recall trials

Each trial will last 6 seconds, during which the stimulus will be on the screen for 4.5 seconds, followed by a 1.5-second inter-trial interval with a small white cross in the center of the field for fixation. The subjects will be instructed to *withhold* a response during this interval and either to think about the response they are about to make, or actively to attempt to encode the symbol-digit pair. Two question marks then will appear on the screen, one on each side of the stimulus. At this point, the subjects will be instructed to respond by pressing a button with one of the five fingers of their right hand. The stimulus will stay on the screen for the entire 4.5-second duration of the test trial. After a block of five trials has been presented, the word "pause" will appear on the screen for 6 seconds, followed by a 1.5-second warning period (cross hair centrally located on the screen), and then the next block of trials will begin. Within a set of four blocks of trials, there will be two sequences of test blocks: NUMBER-LEARN-SYMBOL-TEST and SYMBOL-LEARN-NUMBER-TEST. This means that for each set of four blocks, the LEARN block will always precede the TEST block, and one of the control blocks (i.e., SYMBOL, NUMBER) will be interspersed between the LEARN and TEST blocks. Nine sets of four blocks will be presented in a single fMRI "session". After a break to download data from the scanner, the task will be

repeated, yielding a total of 72 whole brain volumes acquired in each of the four task conditions. A third session then will be conducted, wherein the pairing of the symbols and digits will change (i.e, a "reversal" condition) without warning. All task constraints will be the same, except that the specific symbol-digit pairs will be changed. Only a single session of "reversal" will be acquired. This component of the task differs substantially from that of the standard ImPACT Symbol-Matching module but may provide greater sensitivity for concussion-related cognitive dysfunction.

The n-back test and Modified Symbol Matching tests will be administered with a high-resolution LCD projector that is enclosed in an rf-isolation cabinet. It projects visual stimuli onto a rear-projection screen in the bore of the magnet, and subjects view the stimuli via an angled mirror system. Using the right hand, subjects grasp a glove-like device and respond to visual cues by depressing a button adjacent to their fingers as directed. Dr. Becker has successfully used the projection system, button device, and testing software for several years to conduct n-back/fMRI studies in patients with other cognitive disorders (see Preliminary Studies).

Data Analyses

Specific Aim 1: Describe fMRI of brain activation that typically concurs with specific cognitive deficits identified using a traditional (n-back) and a new (ImPACT) neuropsychological test in victims of sports-related concussion.

This analysis will include only those athletes with no previous concussion and will begin with consideration of the cognitive dysfunction and fMRI activation patterns within experimental subjects. The significance of differences between preseason and immediate post-concussion ImPACT scores (overall score and scores for each module) will be determined using t-tests, with Bonferonni correction for multiple comparisons. By identifying which modules of the ImPACT test battery are most affected (greater than 30% decline from pre-season test score), we will be able to identify the cognitive domains (i.e., visual memory, verbal memory, processing speed, reaction time, or learning) that are most severely affected. Thus, we anticipate identifying five subgroups based on primary post-concussion deficit, as follows: (1) memory, (2) processing speed, (3) reaction time, (4) learning, or (5) two or more cognitive domains are affected ($>$ 30% decline in test scores for associated modules).

For the fMRI analyses, we will include age-matched control subjects as our "normal" comparison group. fMRI analyses will include statistical parametric mapping on a voxel-by-voxel basis using a general linear model approach implemented in FIASCO (described in fMRI statistical analysis section below). This parametric design will be used to test our hypothesis of between-group differences in activation. Three conditions will be considered: change in activation pattern, increased activation, and decreased activation, each as a function of differences in the n-back and the Symbol Match tasks. Initially, our focus will be on the pre-frontal cortex, inferior parietal lobule, and cingulate cortex. We will arbitrarily define as a normal activation pattern any pattern which is within two standard deviations of the average activation for controls. Clusters of voxels with activation greater than two standard deviations of controls will be defined as abnormal. In addition, we will determine the highest or lowest level of activation within those clusters. The neurocognitive task will initially be analyzed for each subject as an individual time series before inclusion in multisubject and covariance analyses. The main analyses will use the random effects procedure reported by Holmes and Friston, which eliminates highly discrepant variances between

and within individuals in constructing an appropriate error term for hypothesis testing and generalizability to the population. For multisubject/between-group analyses, the random effects procedure assumes input of one scan per individual for each condition and then performs a mixed-model analysis to account for both random effects (scan) and fixed effects (task conditions). The mean input images for each individual will be obtained by calculating the mean image for the individual epochs of the n-back test (0, 1, and 2-back) and for the Symbol Matching test in both forward and backward directions, with each epoch offset by 3-6 seconds to account for the hemodynamic response function. Scans during which instructions are given will be discarded.

In the experimental group, the ImPACT test battery will be repeated at 7-day intervals until post-concussive cognitive abnormalities have subsided and performance on the ImPACT study has returned to within normal limits, defined as within ½ standard deviation of the subject's pre-season test scores. At that time, or at 6 weeks after injury if the ImPACT scores have not yet normalized, a second fMRI study will be obtained and the data analyzed in the same manner. Differences in activation patterns for the two fMRI studies obtained for each subject will be determined with general linear modeling to test our hypothesis that abnormal activation patterns will be replaced by normal activation patterns as post-concussive cognitive deficits subside. In a within-subject analysis, we will determine the proportion of subjects who have recovery of normal activation patterns associated with normal ImPACT scores. For those who do not regain normal activation patterns despite normal ImPACT test scores, we will describe the brain location of these persistent activation abnormalities. The five subgroups based on primary post-concussion deficit will be compared to determine if deficits in any of these cognitive domains more strongly correlate with persistent fMRI activation abnormalities. This subgroup analysis also will be used to describe brain locations that show abnormal activation, and level of activation in those locations in the group of subjects that *continue* to have abnormal ImPACT test scores at 6 weeks after injury.

In a post-hoc analysis, we will stratify subjects into groups that had high and low activation levels in the pre-frontal, inferior parietal, and cingulate cortex (2 or more standard deviations from control subjects) during their first fMRI study. Using a multi-subject co-variance analyses, we will determine if the level of activation is related to a specific cognitive deficit or group of deficits.

Specific Aim 2: Describe typical *f*MRI activation associated with *subjective* components of sports-related concussion and post-concussion syndrome, such as headache, confusion, irritability, subjective memory loss, or dizziness.

This analysis will include only those athletes with no prior concussion. Individual and group analyses will be implemented as described above, with each symptom (i.e., headache, memory loss, dizziness, and behavioral dysfunction) serving as the independent variable, and pattern of fMRI activation as the dependent variable.

The ImPACT test battery includes a pretest self-report questionnaire that asks the athlete to indicate whether he or she has any of 20 symptoms characteristic of post-concussion syndrome and to rank the severity of each symptom on a standard 0-6 Likert scale. (See Appendix 2 for a complete listing of the symptoms and an example of the form we use.) For the purposes of this analysis, we will consider a symptom "present" only if the subject indicates that its severity is 2

or more points higher on the scale than his or her preseason assessment. This is necessary because we have found that most athletes indicate the presence of at least 1 of the 20 symptoms during preseason testing. We then will compare fMRI activation patterns between groups of athletes who have only one symptom and those with two or more of the symptoms. We also will compare each of these groups with the control group. Based on our previous experience, we anticipate that most subjects will have a cluster of symptoms, typically including headache, memory difficulties, and impaired concentration. Linear regression modeling will be used to identify which symptoms are most commonly associated with abnormal fMRI activation. For analysis of the fMRI studies we will again use a general linear model analysis on a voxel-by-voxel basis. A parametric design will be used to test the hypothesis that there will be abnormal activation patterns characteristic of subjects as a function of each of the predominant post-concussive symptoms. By repeating the fMRI studies when the symptoms subside, we will be able to determine if resolution of the symptoms coincides with resolution of abnormal fMRI activation patterns, as well as with return to baseline performance on ImPACT, within individual subjects.

Specific Aim 3: Determine the effect of multiple sports-related concussions on cognitive function and fMRI activation.

This analysis *will* include subjects who indicated on the ImPACT concussion screening form that they have had one of more prior concussions (see Appendix 3). Studies by our group and others suggest that the likelihood of suffering severe or prolonged cognitive dysfunction after a second concussion is related to the time between the first and second injury. Also, those with several prior concussions are more likely to have worse and more prolonged deficits than those with a single prior concussion. Therefore, we will stratify these subjects into two groups: those who have suffered one or more concussions within the past 3 months, and those whose prior concussions were incurred more than 3 months ago. Within each of these groups, we will further stratify the subjects into three subgroups: (1) 1 prior concussion, (2) 2-4 prior concussions, or (3) 5 or more prior concussions.

We will first identify patterns of cognitive deficits that might be characteristic of each of these six subgroups by comparing pre-season and immediate post-concussion ImPACT sum scores within subjects. The mean time from injury to return to baseline will be determined for each subgroup, as will subgroup differences in the number of subjects who have not recovered by 6 weeks after injury. Multi-subject co-variance analyses will be used for comparisons between these subgroups, and for comparing each subgroup to the group of subjects who have had no prior concussions, and to matched control subjects. fMRI activation patterns for these groups also will be compared, with particular attention given to the level of activation in the individual brain regions (pre-frontal, parietal, and cingulate cortex) as well as to adjacent brain regions and cerebellum that may have abnormal activation due to multiple concussions. We will describe the relationship between such abnormal loci of brain activation and both the timing and frequency of prior concussions.

Specific Aim 4: Describe the effects of age and gender on concussion-related fMRI activation and recovery from cognitive deficits.

To determine the effect of age on cognitive dysfunction, fMRI activation abnormalities, and recovery of these deficits, we will compare high-school athletes with college athletes. We will begin by defining the differences in pre- and post-concussion ImPACT test sum scores and the scores for the individual test modules for each subject. The frequency of abnormal scores for each test module will be determined separately for high-school athletes and college athletes. Between-group analysis using paired t-tests will then be used to identify differences between high-school and college athletes in mean performance for each ImPACT module, and for the test sum scores, with Bonferonni corrections for multiple comparisons. We also will compare the mean duration from injury to recovery of normal cognitive function between the two groups, and will determine the relative proportion of each group that has not regained normal function by 6 weeks after injury. The fMRI activation patterns for these two groups also will be compared, with particular attention to the mean level of activation of clusters of voxels in the pre-frontal, inferior parietal, and cingulate cortex.

To determine gender differences, the male athletes will be compared to female athletes using the same analysis scheme but after substratifying the high-school and college athletes by sex. Between-group (male vs female) comparisons will focus on high-school athletes separately from college athletes since age is considered a significant contaminating factor.

Specific Aim 5: Correlate concussion-related fMRI and neuropsychological changes with academic performance.

Academic performance will be measured as the GPA per academic term (either quarter or semester), based on grades obtained directly from the school with the subject's permission. The GPA will be calculated by assigning a point value to each letter grade as follows: A=4; B=3; C=2; and D=1, using only grades for core academic subjects (math, science, social sciences, English, foreign language). The average GPA for two consecutive terms that ended before the term during which the concussion occurred will be used as the subject's baseline GPA. The GPA for the current and next academic term will then be used to calculate an academic change. Subjects will be grouped into three categories: (1) negative change, a decline in GPA by 0.2 or more; (2) positive change, an improvement in GPA by 0.2 or more, or (3) no change.

The mean post-concussion ImPACT scores will be calculated for each of the three groups and compared using paired t-tests. The mean duration of abnormal ImPACT test performance also will be compared among the three groups. Finally, using the immediate post-concussion fMRI results, we will compare the level of activation in the three brain regions of interest between the three groups of subjects. Logistic regression analysis will be used to determine the effect of confounding variables such as age (high school vs college), gender, or single vs multiple concussions. Interactions between these variables are likely.

Statistical Analyses of fMRI Data

To analyze the data collected in the fMRI experiments, we will use a package called Functional Image Analysis Software - Computational Olio (FIASCO).[13;33] FIASCO is easy to use because it provides for "default" analyses for simple designs based on t-statistics. Users only have to provide a very small number of parameters to describe their data and obtain a default analysis. FIASCO is modular and hence easily extensible; this allows us to include other software in the FIASCO processing stream. FIASCO provides sophisticated signal processing, reconstruction,

and statistical analysis methods. For example, it incorporates the best known methods for rigid-body motion correction[14] and incorporates a sophisticated spline-based statistical modeling procedure known as BRAIN.[20] FIASCO delivers highly detailed user output including plots and summary statistics for evaluation of data quality. It supports different kinds of input data, different data formats, and different computing platforms, including parallel supercomputers, and it includes tools to evaluate the effectiveness of various processing steps.[23]

In the analysis of *f*MRI experiments run as a block design (vs an event-related design), to accommodate the rise and fall time of the hemodynamic response, we discard from the analysis the first 6 seconds of each epoch within an experimental condition and analyze only the remaining images.[2] A voxel is considered activated in an experimental condition if a t-test comparing its activation in that condition to its level at baseline reaches a threshold value. For many years we have used a fixed threshold of 4 for data collected from the 1.5-T GE scanner. Because the analysis focuses on relatively small anatomically defined regions of interest, these thresholds correspond to Bonferroni corrected p-values that are smaller than 0.01 and are inherently conservative. Recently we have begun experimenting with an alternative procedure known as the "false discovery rate."[5] In this method, the expected proportion of falsely rejected hypotheses (the ratio of the number of incorrectly active voxels to the total number of active voxels) is controlled, leading to a gain in statistical power. The technique is easily implemented using a Bonferroni-type procedure. To test K hypotheses, the first step is to order the p-values from smaller to largest. These are denoted as p1, p2, ..., pK, letting Hi denote the null hypothesis with p-value pi. The desired rate of false discovery is designated as q, and r is the largest i for which pi is less than or equal to iq/ln(K). Then we reject H1, H2, ... Hr. This procedure does not require that the test statistics be independent and is thus appropriate for selecting activated voxels in an fMRI experiment. When all tested hypotheses are true, the false discovery rate is the same as the familywise error rate, so the controlling parameter q may be chosen at conventional levels for significance testing (such as 0.05). This has the advantage of providing a threshold that does vary with the data and yet preserves a constant rate of false discoveries.

FIASCO's flexibility enables us to analyze data from a block design using standard general linear modeling methods, to model the data using polynomial splines in the BRAIN package, or to perform simple "event-related" analyses. The main analysis we plan will fit a mixed fixed/random effects model, treating the experimental stimuli (task conditions) as fixed effects and the scans as random effects within subjects. We will eliminate from the analysis the first 3 to 6 seconds of each block to account for the hemodynamic change. We can then fit the general linear model on a voxel-by-voxel basis. For between-subject comparisons, we are concerned about the extreme loss in spatial resolution caused by transformation to a common brain atlas such as Talairach. Instead, we will calculate several measures of activity for each subject within each region of interest (measures such as signal strength, and fraction of active voxels within a region). We will then fit a random effects model to these derived measures; the fitted effects can be superimposed on the original subject images, thereby retaining the original anatomical resolution and configuration. Thus, we will avoid collecting high-resolution data only to destroy the spatial resolution by transforming it to Talairach coordinates. Additionally, these derived measures can be modeled as a function of the differences in scores on the n-back and Symbol Matching tests.

Number of Subjects Needed for Study

The decision to include 200 subjects with concussion and 50 control subjects was to some extent arbitrary but takes into consideration several factors. Post-concussive syndromes vary substantially in their symptom manifestations, and it seems reasonable to expect a similar degree of variability in fMRI activation patterns. We are aware of only one other study that described changes in fMRI activation patterns in patients with mild TBI.[38] In that study, the range of signal change in the brain locations of interest was quite large, both for the concussion group and for the control group. In both groups, the range for parietal activation was from at least -0.05 to +0.05, and for the concussed group it exceeded +0.18. In a study of 12 normal (uninjured) subjects, Jansma et al. also found significant differences in hemispheric lateralization of activation with the n-back test despite all individuals being right-handed.[29] Thus, we believe that meaningful conclusions will not be possible with a smaller study.

Timeline

Year 1: Publicize the study and recruit subjects through verbal contact with all coaches and trainers of regional high-school and college sports teams; complete any necessary modifications of the Symbol Digit test module; train the research specialists on the conduct of the study and fMRI procedures specific to the study. We expect to enroll 40 athletes with concussion and 10 control subjects and to obtain a total of 90 fMRI studies: two for each experimental subject and one for each control subject. fMRI data will be processed and analyzed immediately after each subject is studied.

Years 2-4: Enroll 40 to 50 experimental subjects and 10 control subjects/year, and process and analyze their fMRI data. We will obtain and analyze 90-110 fMRI studies each year.

Year 5: Enroll the remaining athletes necessary to reach a total of 200 experimental subjects (estimated to be 20-30), and the final 10 control subjects; process and analyze their *f*MRI data; complete statistical analysis and comparisons needed to test the hypotheses as described in *Data Analyses*." Prepare reports of results and submit for publication.

Potential Shortcomings of the Study

1. *Imbalance in the number of subjects with 1 vs multiple concussions, college vs high-school athletes, or males vs females*: Based on our experience to date, we anticipate evaluating many more subjects each year than budget constraints will enable us to enroll. We will limit enrollment to the first 50 subjects who present each year; after enrolling the first 35, we will review the distribution of those subjects in terms of single vs multiple concussions, age, and gender. For the remaining 15 subjects, we will correct for any imbalances observed by biasing our enrollment as necessary. Ten control subjects will be selected each year after the experimental subjects have been enrolled to allow for appropriate matching.

2. *Lack of pre-concussion fMRI studies*: We recognize that specific fMRI activation patterns can vary among both normal individuals and those with a concussion, particularly with regard to hemispheric lateralization of working memory.[29] Thus, the ideal study would compare fMRI activation patterns before and after concussion in the same individual. Unfortunately such a study would be cost prohibitive because it would require fMRI studies of several hundred athletes, less than 5% of whom would suffer a concussion during a sports season. In a prior PET study, Dr. Lovell attempted this and had to abort the study because none of more than 25 athletes studied with PET pre-season had a concussion during the season.

HUMAN SUBJECTS

General Characteristics--Minority Inclusion and Nondiscriminatory Statements
Male and female high-school and college athletes (ages 13-25) will be invited to participate in this study. Based on the expected proportion of males to females who are involved in contact sports, it is expected that more men will be enrolled in the study than women (approximately 3-to-1). The experimental subjects in the study will have suffered at least one and often times multiple concussions. The inclusion and exclusion criterion for these subjects are described in the first portion of the methods section. The reasons for involvement of children and young adults is described below (Participation of Children).

The source for research data for individual identifiable living human subjects will be from preseason and post-concussion neuropsychological testing. Much of the neuropsychological testing is a part of our routine assessment of high-school and college athletes who are referred to us for sports-related concussion. Experimental and control subjects who are participants of this study will have informed consent obtained by one of the co-investigators of this study. The prospective subjects will have the entire conduct of the study as well as the rationale for the study clearly explained to them and the individuals who choose to participate in the study will be required to sign a consent form that has been authorized by the University of Pittsburgh Institutional Review Board.

Potential risks of this study are considered minimal. The patients will undergo two types of tests: neuropsychological assessment and fMRI studies. The neuropsychological assessment information will describe the nature and severity of their concussion. The fMRI studies are noninvasive diagnostic studies during which the only known complication is that of claustrophobia. Individuals who suffer from claustrophobia or state that they are unwilling to undergo the fMRI will be excluded from the study. No individuals with feromagnetic implants, either medical or other, will be included in the study.

We will minimize potential risks with the fMRI studies by excluding patients who have feromagnetic implants and those who have a history of claustrophobia. Information regarding their neuropsychological evaluations (ImPACT) will be freely available to the subjects.

The study is expected to provide important new information regarding the pathobiology of sports-related concussion which can be helpful in developing rational guidelines for return-to-play, work, or school. The findings of the study also will elucidate potential differences in pathobiology and proposed guidelines between individuals of different ages, sexes, and individuals who had single versus multiple concussions. As such, it should greatly expand our understanding of sports-related concussion and mild traumatic brain injury. Because none of the procedures proposed in this study are invasive, we do not view the risks involved in the study as major and therefore believe that the benefits clearly outweigh the risks.

Participation of Children
The NIH (Instructions for PHS 398) defines children as individuals under the age of 21 years. It mandates that they be included in research unless there are compelling reasons for excluding them. The RFA we are responding to emphasizes that it is soliciting proposals for adults. However, we seek to measure changes caused by sports-related concussions and have found high-

school and college athletes (i.e., ages 13-25) to be the most appropriate subjects for such a study. We have been advised by Mary Ellen Cheung, PhD, the author of this RFA and its lead contact person at the NIH, that the intent of limiting it to adults was to exclude young children. She advised us that the study of high-school and college-aged subjects was consistent with the intent of the RFA. Professional athletes also suffer concussions, but, although we have a professional relationship with the National Football League and the National Hockey League, league unions have not been eager to allow their members to participate in this study for a variety of political and financial reasons.

VERTEBRATE ANIMALS: Not applicable

LITERATURE CITED

1. Aldrich EF, Eisenberg HM, Saydjari C, et al: Diffuse brain swelling in severely head-injured children. J Neurosurg 76:450-454, 1992

2. Bandettini P, et.al.: Magnetic Resonance in Medicine. New York: Churchill Livingston, 1992, pp 25-390ff

3. Barth JT, Alves WM, Ryan TV, et al: Mild head injury in sports: neuropsychological sequelae and recovery of function, in Levin HS, Eisenberg HM, Benton AL (eds): Mild head injury. New York: Oxford University Press, 1989, pp 257-275

4. Bazarian J, Wong T, Harris M, et al: Epidemiology and predictors of post-concussive syndrome after minor head injury. Brain Inj 13:173-189, 1999

5. Benjamini Y, Hochberg Y: Controlling the false discovery rate: A practical and powerful approach to multiple testing. J Roy Stat Series B 57:289-300, 1995

6. Bergsneider M, Hovda DA, Shalmon E, et al: Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. J Neurosurg. 86:241-251, 1997

7. Biagas KV, Grundl PD, Kochanek PM, et al: Posttraumatic hyperemia in immature, mature and aged rats: autoradiographic determination of cerebral blood flow. J Neurotrauma 86:241-251, 1996

8. Bruce DA, Alavi A, Bilaniuk L, et al: Diffuse cerebral swelling following head injuries in children: the syndrome of malignant brain edema. J Neurosurg 54:170-178, 1981

9. Cantu RC, Voy R: Second impact syndrome: a risk in any sport. Physician Sports Med 34:2327-2336, 1995

10. Clinchot D, Bogner JA, Mysiw WJ, et al: Defining sleep disturbances after brain injury. American Journal of Physical Medicine and Rehabilitation 77:291-295, 1998

11. Collins MW, Grinnell VS, Lovell MR, et al: Relationship between concussion and neuropsychological performance in football players. JAMA 282:989-991, 1999

12. Collins MW, Lovell MR, McKeag DB: Current issues in managing sports-related concussion. JAMA 282:2283-2285, 1999

13. Eddy WF, Fitzgerald M, Genovese CR, et al: Functional imaging analysis software-Computational Olio, in Prat A (ed): Proceedings in Computational Statistics. Heidelberg: Physica-Verlag, 1996, pp 39-49

14. Eddy WF, Young T: Optimizing the resampling of registered images, in Bankman IN (ed): Handbook of Medical Image Processing and Analysis. Academic Press, 2000, pp 603-612

15. Emerson CS, Headrick JP, Vink R: Estrogen improves biochemical and neurologic outcome following traumatic brain injury in male rats, but not in females. Brain Res 608:95-100, 1993

16. Enevoldsen EM, Cold G, Jensen FT: Dynamic changes in regional CBF, intraventricular pressure, CSF pH and lactate levels during the acute phase of head injury. J Neurosurg 44:191-214, 1976

17. Enevoldsen EM, Jensen FT: Autoregulation and CO2 responses of cerebral blood flow in patients with acute severe head injury. J Neurosurg 48:689-703, 1978

18. Farace E, Alves WM: Women fare worse: a metaanalysis of gender differences in traumatic brain injury outcome. J Neurosurg 93:539-545, 2000

19. Fontaine A, Azovi P, Remy P, et al: Functional anatomy of neuropsychological deficits after severe traumatic brain injury. Neurol 53:1963-1968, 1999

20. Genovese CR: A bayesian time course model for functional magnetic resonance imaging data. Journal of the American Statistical Association 95:691-719, 2000

21. Gerberich SG, Gibson RW, Fife D, et al: Effects of brain injury on college academic performance. Neuroepidemiology 16:1-14, 1997

22. Gerberich SG, Priest JD, Boen JR: Concussion incidences and severity in secondary school varsity football players. Am J Pub Health 73:1370-1375, 1983

23. Goddard NH, Hood G, Cohen JD, et al: Functional magnetic resonance imaging dataset analyses, in Koniges AE (ed): Industrial Strength Parallel Computing. Morgan Kaufmann, 2000, pp 431-451

24. Grundl PD, Biagas KV, Kochanek PM, et al: Early cerebrovascular response to head injury in immature and mature rats. J Neurotrauma 11:135-148, 1994

25. Houlden DA, Schwartz ML, Klettke KA: Neurophysiologic diagnosis in uncooperative trauma patients: confounding factors. J Trauma 33:244-251, 1992

26. Hovda DA, Lee SM, Smith ML, et al: The neurochemical and metabolic cascade following brain injury: Moving from animal models to man. J Neurotrauma 12:143-146, 1995

27. Hovda DA, Prins M, Becker D, et al: Neurobiology of concussion, in Bailes JE, Lovell MR, Maroon JC (eds): Sports-related concussion. St. Louis: Quality Medical Publishers, 1999, pp 12-51

28. Huttenlocher PR: Synaptic density in human frontal cortex: developmental changes and effects of aging. Brain Res. 163:195-205, 1979

29. Jansma JM, Ramsey NF, Coppola R, et al: Specific versus nonspecific brain activity in a parametric N-back task [In Process Citation]. Neuroimage. 12:688-697, 2000

30. Jordan BD, Master EJT, Zimmerman RD, et al: Sparring and cognitive function in professional boxers. Physician Sports Med 24:87-94, 1996

31. Kawamata T, Katayama Y, Hovda DA, et al: Administration of excitatory amino acid antagonists via microdialysis attenuates the increase in glucose utilization seen following concussive brain injury. J.Cereb.Blood Flow Metab. 12:12-24, 1992

32. Kim KHS, Relkin NR, Lee KM, et al: Distinct cortical areas associated with native and second languages. Nature 388:171-174, 1997

33. Pending Publication

34. Le Bihan D: Functional MRI of the brain principles, applications and limitations. J Neuroradiol. 23:1-5, 1996

35. Macciocchi S, Barth JT, Alves WM, et al: Neuropsychological functioning and recovery after mild head injury in collegiate athletes. Neurosurg 39:514, 1996

36. Maroon JC, Lovell MR, Norwig J, et al: Cerebral concussion in athletes: Evaluation and neuropsychological testing. Neurosurg 47:659-672, 1999

37. Master EJT, Kessels AG, Lezak MD, et al: Neuropsychological impairment in amateur soccer players. JAMA 282:971-973, 1999

38. McAllister TW, Saykin AJ, Flashman LA, et al: Brain activation during working memory 1 month after mild traumatic brain injury: a functional MRI study. Neurol 53:1300-1308, 1999

39. McCarthy G: Event-related potentials and functional MRI: a comparison of localization in sensory, perceptual and cognitive tasks. Electroencephalogr Clin Neurophysiol 49:3-12, 1999

40. McDonald JW, Johnston MV: Physiological pathophysiological roles of excitatory amino acids during central nervous system development. Brain Reseach Review 15:41-70, 1990

41. McDonald JW, Silverstein FS, Johnston MV: Neurotoxicity of N-methyl-D-aspartate is markedly enhanced in developing rat central vervous system. Brain Res 459:200-203, 1988

42. Mueller FO, Cantu RC: The annual survey of catastrophic football injuries: 1977. Exercise & Sports Science Reviews 19:261-312, 1988

43. Muizelaar JP, Ward JD, Marmarou A, et al: Cerebral blood flow and metabolism in severely head-injured children. Part 2: Autoregulation. J Neurosurg 71:72-76, 1989

44. Pickles W: Acute general edema of the brain in children with head injuries. New England Journal of Medicine 242:607-611, 1950

45. Powell JW, Barber-Foss KD: Traumatic brain injury in high school athletes. JAMA 282:958-963, 1999

46. Roof RL, Duvdevani R, Braswell L, et al: Progesterone facilitates cognitive recovery and reduces secondary neuronal loss caused by cortical contusion injury in male rats. Experimental Neurology 129:64-69, 1994

47. Roof RL, Duvdevani R, Stein DG: Gender influences outcome of brain injury: progesterone plays a protective role. Brain Res. 607:333-336, 1993

48. Roof RL, Hall ED: Estrogen-related gender differences in survival rate and cortical blood flow after impact acceleration head injury in rats. J Neurotrauma 17:1155-1169, 2000a

49. Roof RL, Hall ED: Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. J Neurotrauma 17:367-388, 2000b

50. Roof RL, Hoffman SW, Stein DG: Progesterone protects against lipid peroxidation following traumatic brain injury in rats. Mol.Chem.Neuropathol. 31:1-11, 1997

51. Rosen BR, Buchner RL, Dale AM: Event-related functional MRI: past, present and future. Proc Natl Acad Sci 95:773-780, 1998

52. Saunders RL, Harbaugh RE: The second impact in catastrophic contact-sport head trauma. JAMA 252:538-539, 1984

53. Scheinker IM: Vasoparalysis of the central nervous system, a characteristic syndrome: significance in the pathology of the central nervous system. Arch.Neurological Psychiatry 52:43-56, 1944

54. Scheinker IM: A syndrome of cerebral concussion in children. Journal of Pediatrics 35:557-560, 1949

55. Schneider R: Mechanism of injury, in Schneider R (ed): Head and neck injuries in football: mechanisms, treatment, and prevention. Baltimore: Williams & Wilkins, 1973, pp 77-126

56. Sutton RL, Hovda DA, Adelson PD: Metabolic changes following corical contusion: Relationships to edema and morphological changes. Acta Neurochir 60 (Suppl):446-448, 1994

57. Villablance JR, Burgess JW, Olmstead CE: Recovery of function after neonatal or adult hemispherectomy in cats. Behavioral Brain Research 19:205-226, 1986

58. Wagner AK, Hammond FM, Sasser H, et al: The use of injury severity variables to predict disability and community integration after traumatic brain injury. J Trauma 49:411-419, 2000

59. Wilberger JE: Traumatic brain injuried in athletes, Traumatic Brain Injury. New York: Thieme Medical Publishers, 1999, pp 165-172

60. Yoshino A, Hovda DA, Kawamata T, et al: Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: evidence of a hyper- and subsequent hypometabolic state. Brain Res 561:106-119, 1991

CHECKLIST

TYPE OF APPLICATION *(Check all that apply)*

[X] NEW application. *(This application is being submitted to the PHS for the first time.)*

[ ] REVISION of application number: _____
(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

[ ] COMPETING CONTINUATION of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

INVENTIONS AND PATENTS *(competing continuation appl.only)*
[✓] No
[ ] Yes. If "Yes," [ ] Previously reported [ ] Not previously reported

[ ] SUPPLEMENT to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

[ ] CHANGE of principal investigator/program director.
Name of former principal investigator/program director: _____

[ ] FOREIGN application or significant foreign component.

1. ASSURANCES/CERTIFICATIONS

The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications begin on page 27 of Section III. If unable to certify compliance where applicable, provide an explanation and place it after this page.

*Human Subjects; *Vertebrate Animals; *Debarment and Suspension; Drug Free Workplace (applicable to new [Type 1] or revised [Type 1] applications only); *Lobbying; *Delinquent Federal Debt; *Research Misconduct; *Civil Rights (Form HHS 441 or HHS 690); *Handicapped Individuals (Form HHS 641 or HHS 690); *Sex Discrimination (Form HHS 639-A or HHS 690); * Age Discrimination (Form HHS 680 or HHS 690); *Financial Conflict of Interest

2. PROGRAM INCOME *(See instructions, page 32.)*

All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

3. INDIRECT COSTS

Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal Agency, it should, immediately upon notification that an award will be made, develop a tentative indirect cost rate proposal.

This is to be based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent DHHS Guide for Establishing Indirect Cost Rates, and submitted to the appropriate DHHS Regional Office or PHS Agency Cost Advisory Office. Indirect costs will not be paid on foreign grants, construction grants, grant to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Service Awards, and specialized grant applications.

[X] DHHS Agreement dated: 3/31/99,12/31/99,6/29/00 [ ] No Indirect Costs Requested.

[ ] DHHS Agreement being negotiated with _____ Regional Office.

[ ] No DHHS Agreement, but rate established with _____ Date _____

CALCULATION *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as CONFIDENTIAL information. Supplying the following information on indirect costs is OPTIONAL for forprofit organizations.)*

a. Initial budget period:
Amount of base $ 357,709 X Rate applied 50,49.5 % = Indirect Costs (1) 178,556

b. Entire proposed project period:
Amount of base $ 1,910,076 X Rate applied 50,49.5,49,48.5 % = Indirect Costs (2) 936,316

(1) Add to total direct costs from form page 4 and enter new total on FACE PAGE, Item 7b.
(2) Add to total direct costs from form page 5 and enter new total on FACE PAGE, Item 8b.

* Check appropriate box(es):
[ ] Salary and wage base [X] Modified total direct costs base [ ] Other base (Explain below)
[ ] Off-site, other special rate, or more than one rate involved (Explain below)

Explanation *(Attach separate sheet, if necessary.)*:
See attached.

4. SMOKE-FREE WORKPLACE

Does your organization currently provide a smoke-free workplace and/or promote the nonuse of tobacco products of have plans to do so?
[X] Yes [ ] No *(The response to this question has no impact on the review of funding of this application.)*

Indirect Cost Calculation

Description		Budget Period Year 1	Year 2	Year 3	Year 4	Year 5	Total
	Start:	9/1/01	9/1/02	9/1/03	9/1/04	9/1/05	
	End:	8/31/02	8/31/03	8/31/04	8/31/05	8/31/06	
Category Totals by Year:							
Personnel		266,029	274,010	285,584	311,421	320,764	1,457,808
Consultants		28,800	29,664	30,554	31,471	32,415	152,903
Equipment		17,995	0	0	0	0	17,995
Supplies		50,970	52,499	54,074	55,696	57,367	270,606
Travel		2,500	2,575	2,652	2,732	2,814	13,273
Other Expenses		1,410	1,452	1,496	1,541	1,587	7,486
Total Direct Costs		**367,704**	**360,200**	**374,360**	**402,861**	**414,947**	**1,920,071**
Less exclusions:							
Equipment (over $5,000)		9,995	0	0	0	0	9,995
Animal Maintenance		0	0	0	0	0	0
GSR Fringe Benefits		0	0	0	0	0	0
Post Doc Salaries & Fringe		0	0	0	0	0	0
Subcontracts >$25,000		0	0	0	0	0	0
MTDC Base		**357,709**	**360,200**	**374,360**	**402,861**	**414,947**	**1,910,076**
Indirect Cost Rate @:	50.0%	149,045					149,045
	49.5%	29,511	148,583				178,094
	49.0%		29,416	152,864			182,280
	48.5%			30,261	195,387	201,249	426,897
Total Indirect Costs		**178,556**	**177,999**	**183,125**	**195,387**	**201,249**	**936,316**
Total Costs		**546,260**	**538,199**	**557,485**	**598,248**	**616,196**	**2,856,387**