HARVARD UNIVERSITY
COMMITTEE ON THE USE OF HUMAN SUBJECTS
Request for Approval of Human Subjects Research*

DIRECTIONS:

1. Download this form into Microsoft Word. Place cursor on the gray boxes and type. Box size will expand as you type.

2. FOR STUDENTS: You must have your faculty sponsor sign a paper copy of the application or email a note that s/he has reviewed the completed application and is satisfied with the adequacy of the proposed research design and the measures proposed for the protection of human subjects.

3. Return the completed application as an attachment to: cuhs@fas.harvard.edu or mail to:

   Committee on the Use of Human Subjects
   FAS Research Administration Services
   50 Church Street, Room 539
   Cambridge, Massachusetts 02138

   Telephone: (617) 496-CUHS (2847); Fax: (617) 496-7400.

   Any of the required attachments not available electronically must be sent or delivered to the Committee Office.

   Thank you!

* Note: There are three IRBs at Harvard University. If in doubt as to the proper Committee to review your project, please ask. The Committee on the Use of Human Subjects reviews projects for the University area (The Faculty of Arts and Sciences, including Harvard College, GSAS, and the Division of Continuing Education; Radcliffe Institute; and all the non-medical professional schools). The other two IRB offices are:

   Office for Research Subject Protection
   Harvard Medical School
   Gordon Hall, 25 Shattuck Street
   Boston, MA 02115
   Phone: (617) 432-3192
   Fax: (617) 432-3169
   Email: orsp@hms.harvard.edu

   Human Subjects Committee
   Harvard School of Public Health
   1552 Tremont Street
   Boston, MA 02120
   Phone: (617) 384-5480
   Fax: (617) 384-5484
   Email: hsc@hsph.harvard.edu
FROM: (name, campus address)  
Randy L. Buckner, PhD  
33 Kirkland St.  
William James Hall, Rm. 254  
Cambridge, MA 02138  

Please direct all correspondence to:  

Marisa Hollinshead  
33 Kirkland St.  
William James Hall, Rm. 264  
Cambridge, MA 02138  

TELEPHONE: (617) 496-7039  

E-MAIL: mhollins@wjh.harvard.edu  

PROJECT TITLE: Correlates of human cognition and memory  

ANTICIPATED FUNDING SOURCE: (include grant or contract number if known):  

FACULTY SPONSOR'S NAME (for non-faculty applicants): Randy L. Buckner  
Supervising lecturer, instructor or graduate student (if applicable): N/A  
SPONSOR'S E-MAIL ADDRESS: randy_buckner@harvard.edu  

DURATION OF ENTIRE PROJECT:  
from 02/2009 to 02/2013.  

APPROVAL REQUESTED FOR (maximum one year; must be renewed annually):  
from 02/2009 to 02/2010  

1. Please give a brief summary of the purpose of the research in non-technical language. Be sure to include a statement of the research problem, its importance, and how your project will address it. Cite two or three references directly relevant to the proposed inquiry.
The proposed experiments will use structural and functional MRI (fMRI) to examine neural processes contributing to human memory and the control of memory processes. The broad hypothesis is that distinct regions of the brain contribute to different phases and processes associated with cognition and memory. We are able to identify these processes by having participants engage in simple behavioral tasks while simultaneously recording (indirectly) brain activity using non-invasive fMRI. Preliminary data indicate that activation in a network of brain regions, including prefrontal, medial temporal, and parietal regions contribute to memory processes. Our experiments will extend these results by varying specific tasks and the kind of material memorized and remembered.

The advent of techniques such as fMRI provides a new opportunity to gain insight into the neural underpinnings of memory by allowing dissection of distinct memory processes not permitted by studies of brain-injured patients. By recording participants during the encoding (study) and retrievals phases of a memory experiment, we can (a) examine which brain regions show increased or decreased activity during particular types of memory tasks, and (b) correlate levels of activity during the encoding phase with levels of subsequent memory performance and activity. In addition, by recording participants during the retrieval phase of a memory experiment, we can (c) dissociate brain regions that show increased activity during successful retrieval from those that show increases during retrieval effort; (d) examine whether reinstatement of patterns of neural activity bolsters retrieval success; and (e) examine the neural correlates of retrieval failures, such as during tip-of-the-tongue episodes, where participants know they know information but are blocked in their access. In this proposal, we will use fMRI to continue a long-standing research program to understand the neural bases of memory processes and networks that control memory processes. Some of our prior work is reported in reviews (Rosen, Buckner, and Dale, 1998 PNAS; Buckner, Kelley, and Petersen, 1999 Nat Neurosci; Buckner and Wheeler, 2001 Nat Rev Neurosci; Buckner, 2003 J. Neurosci.; Buckner, 2004 Neuron).

2. Give details of procedures that relate to subjects' participation.

(a) How are subjects recruited? What inducement is offered? If participants are paid, what amount and when are they paid? Is there partial pay for partial completion? (Append copy of letter or advertisement or poster, if any.)

Participants will be recruited through flyers at local universities and community colleges, churches, libraries, theatres, senior centers, gyms, coffee houses, and other local establishments whom permit flyer posting; newspaper and magazine advertisements, advertising on campus electronic bulletin boards, and by posting to the Harvard Psychology Department’s
Study Pool website. These recruitment procedures are the same as those used previously to recruit individuals to be scanned at MGH in Charlestown; the procedures will now be modified to enroll participants for studies conducted at the new Northwest Science Building imaging facility at Harvard University.

Participants will receive $25.00 per hour for their time and will be provided a pre-assigned parking space at the Northwest Building. Subjects may participate for course credit (1 credit per hour) in replacement of monetary payment. Transportation may be provided to/from the study via taxi at the discretion of the study staff. Subjects will be paid for the full expected amount even if they withdraw during the study.

(b) Salient characteristics of subjects--number who will participate, age range, sex, institutional affiliation, other special inclusion and exclusion criteria (if children, prisoners or other vulnerable subjects are recruited, explain why their inclusion is necessary):

800 adults (normal, cognitively intact individuals, 18+ years, targeting half female) will be enrolled. Potential participants showing initial interest in the study by responding to a study advertisement will be contacted via phone or e-mail and will complete a screening questionnaire containing items related to medical history, medications, and the presence of contra-indicators for MRI research such as metal in the body. While there are no known risks to pregnant women, to be cautious pregnancy is also an exclusion criteria and we ask participants who are pregnant or might be pregnant not to participate. Self report of neurological or psychiatric illness or the presence of contra-indicators for MRI research (such as metal in the body) will result in non-inclusion in the study, as will any sign of cognitive impairment. Following the informed consent procedure, each enrolled participant will complete a questionnaire (e.g., to determine basic demographics and race/ethnicity) and will perform simple behavioral tasks while imaged using fMRI on a 3.0T MRI scanner within the Northwest Science Building at Harvard University.

Minority groups and women are encouraged to participate in the research.

(c) Describe how permission has been obtained from cooperating institution(s)--school, hospital, corporation, prison, or other relevant organization. (Append letters.) Is the approval of other research compliance committees or another Institutional Review Board required?

N/A
d) What do subjects do, or what is done to them, or what information is gathered? (Append copies of instructions, tests, questionnaires, or interview guides to be used.) How many times will observations, tests, etc., be conducted? How long will their participation take? Are interviews to be tape recorded or videotaped?

We will conduct fMRI experiments that explore the neural bases of memory. Each enrolled participant will perform simple behavioral tasks while imaged using fMRI on a 3 tesla MRI scanner within the Northwest Science Building, Harvard University. Imaging consists of six to ten brief tasks, each lasting 4-10 min. During these tasks, subjects view words or pictures, listen to sounds, or make memory decisions about words, pictures and sounds. For example, a participant will be asked whether he/she remembers seeing the word ‘tree’ from the earlier study list or to predict where a previously studies object will be located in a virtual environment. Tasks are also designed to measure memory as well as general cognitive control processes that are associated with control of memory. For these tasks, participants are presented simple stimuli (circles, squares, or arrows) and make prespecified responses (e.g., press the left key when you see a circle or the right key when you see a left pointing arrow). The goal of these tasks is to engage brain networks used generally to solve cognitive tasks. These brain networks are also hypothesized to be used during memory. Behavior in the form of accuracy and speed of response is recorded.

The second kind of task is used as a baseline for the imaging study. During these tasks, simple visual stimuli are presented (e.g., a flickering checkerboard, or simply a fixation cross-hair) and participants view them passively or make a key press when they appear. These tasks are used a baseline tasks to measure brain responses under the simplest conditions as a control for the more demanding tasks where memory and higher-cognitive functions are explored. Behavior in the form of accuracy and speed of response is recorded.

All tasks are designed to be interesting to the participants and minimize stress. Stimuli avoid strong emotional components and frequent breaks are given to minimize fatigue. The total time inside the scanner will not exceed two hours. Each scan will not exceed 10 minutes in order to maximize comfort and minimize motion artifact due to restlessness during scans.

1) MRI/fMRI
The MRI/fMRI study will be performed at the Northwest ScienceBuilding, Harvard University. The subject will be asked to fill out the “MR Screening Form” to rule out any conditions that preclude MR scanning. Safety is paramount and no participant is allowed to enter the MRI scanning room
that has any indication of risk. A trained MR technologist, Tammy Moran, will assist in any safety decisions.

Imaging will be performed on a 3 tesla Siemens Trio scanner (Trio, Siemens Ltd., Enlargen, Germany). Subjects’ heads will be immobilized with pillows, cushions, and/or a restraining strap to reduce motion artifact, and ear protection (earplugs or headphones) will be mandatory. Each MRI scanning session will last up to two hours.

High-resolution 3-dimensional T1 structural MRI scans will be obtained from each subject, then motion-corrected and averaged to optimize the SNR. These data will be used for registering functional scanning sessions (fMRI) to the subject's anatomy. In all fMRI experiments, the subject will lie supine in an MR imager, facing the ceiling of the bore, while auditory and visual stimuli are presented. Standard statistical techniques for analyzing the functional imaging data are in use at Harvard University for analysis of fMRI and structural data. Activation maps are generated by co-varying the resulting hemodynamic response function with predicted response functions (Dale & Buckner, 1996 Hum Brain Mapp). Additional algorithms are available for identification and further examination of significant clusters of activation (Wagner et al., 1998 Science).

3. Describe your research experience and your research ethics training.

   (a) Cite your experience with this kind of research and/or this population. List any assistants who will be working with you and cite their experience also.

The PI (Randy L. Buckner) has been designing, conducting and overseeing memory experiments for nearly 20 years. He has supervised over 3000 imaging sessions, including over 500 session since becoming faculty at Harvard in 2006. Yun-Ching Kao, Jessica Andrews-Hanna, Fenna Krienen, Trey Hedden, Yael Shrager, Justin Vincent, Itamar Kahn, Jorge Sepulcre, Eun Young Choi, Marisa Hollinshead, Angel Mehta, Katherine Powers, and Renee Poulin are well trained in fMRI data collection and have their HETHR certification. All members of the study staff will obtain training and certification at Harvard University before operating the scanner (see attached document that describes CBS Neuroimaging Training Levels).

(b) Where have you received research ethics training? (check boxes) (Note for NIH funded projects, only (i), (ii), or (iii) satisfy training requirements.

   ☒ (i) HETHR
   ☒ (ii) CITI
   ☐ (v) CUHS – led training class
   ☐ (vi) Research methods course (specify) _______

(a) Do subjects sign a written consent form and receive a copy for their records? If not, do they receive an information sheet that provides what they need to know before deciding to participate? (In addition to answering parts a. – e., append a copy of consent form, information sheet, or script for oral explanation to subject.)

Potential participants are first screened on the telephone for eligibility. This process includes a complete explanation of the protocol procedures. At that time, a potential participant can refuse to participate. Prior to scanning, the purposes, procedures, and risks of the study, and the subject’s right to withdraw from a test at any time will be explained verbally to the subject by a study investigator or staff, with details provided in a written document to be read and signed by the subject. The subject will receive a copy of this informed consent document. Participants’ questions about the protocol will be answered thoroughly and there will be no time limit placed on this procedure. This consent procedure is carried out in a comfortable waiting area near the imaging facility. The subject’s right to withdraw from the study at any time is emphasized. See consent form.

(b) Where (In a lab? Online?) , when (immediately before participation, eg), and by whom (anyone other than investigator?) is consent obtained?

Consent will be obtained at the scanning facility immediately before participation in the proposed study. Consent will be obtained by one of the specified research staff members. A quiet, private room is located just next to the scanner waiting area so that participants can ask questions about the study in privacy. All of the staff members have completed undergraduate education; undergraduates will not consent participants and will not have access to the confidential information provided as part of the consent process.

(c) Are subjects children, mentally infirm, or otherwise not legally competent to consent? If so, how is their assent obtained, and who consents on their behalf?

We will not include children, mentally infirm or those individuals who are not legally competent to consent. Only individuals who are fully able to consent themselves will be eligible to participate.
(d) If subjects are vulnerable due, e.g., to legal status, economic status, illiteracy or other circumstance, describe steps to minimize the risk of coercion or undue influence. Include in your answer how you ensure subjects understand that participation is voluntary.

Participation results in a modest monetary compensation ($25 per hour) or course credit (1 per hour), which we feel could not be construed as coercive. Further, it is emphasized during the consent process that participation is voluntary and that the subject is free to withdraw from the study at any time without penalty.

(e) Is there any language barrier that could affect the consent process (your explanation of the research and the subject’s agreement to participate)? If so, please provide details, such as plans for use of translators or translating documents.

Non-native English speaking individuals will be excluded from the study as the study stimuli are based on English words. Past studies have shown differences in organization for second language acquisition. For this reason, studies that use normal visual word stimuli as a primary component of their study will use only native-English speakers as is the standard for the field.

5. Give details of possible risks of harm to participants.

(a) Are the risks necessary?

fMRI is a safe and painless procedure and there are no known health risks associated with scanning when appropriate precautions are taken. The magnetic field strengths to be used are routinely used clinically without harm and our fMRI scanning procedures fall within the FDA guidelines for radiofrequency electromagnetic field exposure. We feel these are safe levels and less hazardous than a comparable x-ray computed tomography examination. Exceptions include if a person has electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), has clips on blood vessels in their brain, or other metallic objects in their body such as shrapnel, bullets, buckshot, or metal fragments. Therefore, subjects will be carefully screened for previous exposure to metallic fragments or to implanted devices. The loud gradient noise of the MRI scanner could cause hearing damage if no hearing protection is used. Therefore, all subjects will be required to wear earplugs or headphones that reduce scanner noise to safe levels. The 3 tesla has been approved by the FDA and will be operated within the operating parameters reviewed and accepted by the FDA.

(b) What are the possible risks—physical, psychological, legal, social?

There are no known foreseeable risks or side effects associated with conventional scanning procedures except for those people who have electrically, magnetically or mechanically activated implants (such as cardiac pacemakers).
pacemakers) or those who have intracerebral vascular clips (surgically implanted metal clips in any blood vessels within the brain). Therefore, subjects will be carefully screened for previous exposure to metallic fragments or to implanted devices. They will also be asked to place all metallic and magnetic objects in their possession (e.g. keys, jewelry, credit cards) in a drawer outside the magnet room. Although there are no known risks of an fMRI scan to the unborn fetus, we do not permit participation by any female who is or suspects she may be pregnant.

A magnetic resonance scan is not uncomfortable but if a person is prone to claustrophobia (fear of enclosed spaces) they may find the environment uncomfortable. There is a loud knocking sound during the imaging; earplugs or headphones will be provided so the sound should not be bothersome.

Occasionally a participant finds the MRI environment confining and stressful, or uncomfortable because they need to use the restroom. On such occasions we simply remove the participant from the scanner and discontinue the study. Payment is not held contingent on the completion of the study to encourage individuals to indicate their discomfort.

A sensitive issue that arises in human research using MRI surrounds discovery of incidental findings. The scanner we use has no history of clinical use and the sequences are not meant for clinical evaluation. The scans will be used only for research purposes and will not be examined for abnormalities. It is common for the data to be deemed unusable and images not examined further. None of the study staff or the principal investigator have clinical experience reading MRI images and are not in a position to note abnormalities.

To avoid any possible confusion that the study is being done for clinical purposes, the consent makes clear that we do not use the sequences for detection of clinical conditions and, if asked, investigators are asked to verbally make clear that we do not examine the scans for abnormalities. That is, all precautions are taken to not imply in anyway that the scans will be checked or evaluated by an expert for the purposes of clinical evaluation.

On occasion, investigators may notice in the course of the research analysis a finding that seems abnormal. If this occurs the study staff noting the potential abnormality is asked to communicate directly with the principal investigator (Dr. Randy Buckner). On rare occasions, Dr. Randy Buckner or knowledgeable designated Harvard faculty member (e.g., Dr. Bruce Rosen or Dr. Greg Sorensen who direct the MGH Martinos Center) will communicate information back to the participant. That information will be communicated confidentially to the participant. Any decisions with regard to seeking further
examination or treatment will remain entirely the choice of the participant. Being told about a potential abnormality may cause anxiety and suggest the need for additional tests and financial costs.

(c) What steps will be taken to minimize the risk? (If the research may involve greater than minimal risk to participants, describe provisions for monitoring data to ensure participant safety.)

The principal investigator is responsible for data monitoring to ensure the safety of subjects. The well being of the subject is constantly monitored using the 2-way intercom system between the scanner operator and subject, and by visual monitoring of the subject through the window into the scan room (the subject is visible to the operator at all times). Participant status is assessed after each scan and any adjustments required to facilitate participant comfort are made when necessary. The study can be discontinued at any time at the subject’s request as is explained to the subject during the informed consent procedure. Subjects will also be instructed on how to use an emergency handheld device to inform the operator if they wish to immediately stop scanning and be removed from the magnet. In addition, as described previously, careful screening for contra-indicators is conducted via written questionnaire and oral interview prior to subject participation.

(d) Should a subject be injured or otherwise harmed, or experience significant distress, what are your plans for addressing the problem? (e.g., emergency care training for lab staff if physical harm is a risk; referral for evaluation or treatment if there are significant psychological risks)

Adverse events will be reported to the CUHS and within 10 working days. Serious adverse effects will be reported within 24 hours by phone, fax or email as stipulated by the CUHS.

If risks are anticipated to be no more than minimal, please state so here and in the consent form, if used.

We do not anticipate any major risks involved in this study.

6. Are subjects deliberately deceived in any way? If so, what is the nature of the deception? Is it likely to be significant to subjects? Is there any other way to conduct the research that would not involve deception, and, if so, why have you not chosen that alternative? What explanation for the deception do you give to subjects following their participation?

The experimental procedure does NOT require participants to be deliberately deceived.
7. How will participation in this research benefit subjects? If subjects will be "debriefed" or receive information about the research project following its conclusion, how do you ensure the educational value of the process? (Append copies of any debriefing or educational materials.)

Subjects will not receive direct benefits from the present study, except the knowledge that the results of the study will enhance our understanding of the neural substrates underlying learning and memory. Society benefits from research advances in understanding learning and memory. Because there are few risks to the participants in these studies and the data accumulated will provide information about the functional changes associated with learning, the risk versus benefit ratio is high. Copies of seminal papers in memory and links to relevant websites will also be provided (see appended debriefing form).

8. How are confidentiality and/or anonymity assured? Will identifiers be removed from the data? If so, at what point, and if not, please explain why identifiers must be retained.

In order to keep participants’ confidentiality, behavioral and MRI data collected in this study is recorded in a database using a coding system that does not allow for identification. The key to this coding system resides on a password-protected computer accessible only to the PI and research study staff. Screening information, which by nature must include identifying demographics, are kept in locked file cabinets or a locked room that only serves the purpose of storing confidential files. As a further precaution, name fields are not filled in at the scanner console so that the digital data do not contain, in any header field, identifying information. For date or birth, we will enter only the year, while excluding month and date, in effort to minimize the potential of identification. Confidentiality of all results will be preserved within the confines of the law.

9. How is the privacy of subjects protected? (e.g., are questions tailored to the research question so subjects are not asked to provide unnecessary information?)

A quiet, private room is located just next to the scanner waiting area so that participants can ask questions about the study in privacy. Undergraduates will not be involved in the consenting process. Where possible, we ask the subjects to exclude themselves from participation rather than recording sensitive information. For example, we ask participants who are pregnant or think they could be pregnant not to consent to the study but do not ask them to record the information as part of the consent process. We similarly ask individuals who are taking, or have taken, medications for psychiatric illness not to participate. They are explicitly instructed in the consent that they do not need to inform us of
why. This gives the participant ample time to choose not to participate without having to divulge a sensitive reason.

Behavioral tasks that subjects will be asked to complete while inside the scanner are tailored to the research question.

10. Will research data (written or otherwise recorded) be destroyed at the end of the study? If not, where and in what format and for how long will they be stored? To what uses—research, demonstration, public performance, archiving—might they be put in future? How will subjects' permission for further use of their data be obtained?

The data acquired in this study are combined with data from other studies to make comparisons. Numerous discoveries have been made in the field through reanalysis and standards of the field now require making data accessible to other investigators so long as now confidentiality issues are compromised. For these reasons, the coded digital images will be stored indefinitely on a password protected network. The network is only accessible via virtual private network or by computers within locked, secure locations. The network is kept separate from the main Harvard network to further enhance security. Note that this only pertains to coded data. Participant names and other identifying information are not available at all. After the data is no longer required, it will be destroyed by shredding all paper documents and deliberately overwriting all electronic records. We do share data with other investigators for research purposes. Under those conditions, we only share deidentified, coded data. For example, an investigator may request to reanalyze the data in a published study. Under such circumstances we would share the data absent the names or the participant and other potentially identifying information (e.g., we would use age rounded to year rather than exact date of birth).

11. Do you and/or any other investigators associated with the project described in this application have or appear to have any actual or potential conflicts of interest with respect to this research? (see http://cuhs.harvard.edu/conflict for what may constitute a conflict of interest that must be disclosed).

☐ Yes  ☒ No

If yes, a CUHS committee member will contact you to determine the extent of any conflict and assist in the development of a management plan.

By submitting this application, I certify that the study has been adequately designed to protect human subjects.
APPLICANT'S SIGNATURE:

DATE:       January 25, 2008

(For non-faculty applicants)

I have reviewed this completed application and I am satisfied with the adequacy of the proposed research design and the measures proposed for the protection of human subjects.

FACULTY SPONSOR'S SIGNATURE: _________________________________________

ATTACHMENTS:

☐ Recruitment letter, poster, ad
☐ Written consent form, information sheet, or script
☐ Subject instructions
☐ Tests or questionnaires
☐ Interview guides
☐ Debriefing materials
☐ Other institutional approval
☐ Other _____