Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2009- 12/31/2012

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA.

4. **Grant Contact Person's Telephone Number:** 814-935-1081

5. **Grant SAP Number:** 4100047645

6. **Project Number and Title of Research Project:** 4 - Functional Brain Imaging of Memory and Language for Epilepsy Surgery

7. **Start and End Date of Research Project:** 6/1/2009 - 6/30/2011

8. **Name of Principal Investigator for the Research Project:** Paul Eslinger, PhD

9. **Research Project Expenses.**

   9(A) Please provide the amount of health research grant funds spent on this project for the entire duration of the grant, including any interest earned that was spent:

   $ 167,073

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost
Hughes	Research Assistant	50% Yrs 1 & 2	$ 30,000

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project
Nguyen	Co-Principal Investigator	5%
Eslinger	Co-Principal Investigator	5%
Acharya J	Co-Investigator	2%
Acharya V	Co-Investigator	1%
Sather	Co-Investigator	1%
Kalapos	Co-Investigator	1%
Cockroft	Co-Investigator	1%
Yang	Co-Investigator	5%
McInerney	Co-Investigator	1%
Flahery-Craig	Co-Investigator	5%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No___X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes___X_____ No_____

If yes, please describe your plans:

There are 2 directions for future research. The first centers around the main aims of the project; that is, the evaluation of epilepsy patients in preparation for surgical treatment and optimizing their outcomes post-surgically. It may make sense to expand the project in the direction of a multicenter collaboration for this portion. The second centers around the functional assessment of neural systems subserving accurate memory consolidation and retention. This holds the potential to inform neuroscientists about the neural components of effective memory function, whether in children, adults or older persons.

12. Future of Research Project. What are the future plans for this research project?

With the recruitment of a new faculty member for the Epilepsy Program, it is expected that the number of patients proceeding to surgical epilepsy treatment will increase. Dr. Frank Gilliam is a well-established epilepsy researcher and clinician coming in at the Professor level who will be joining our research team for completion of this study and extension to new aims. Based on progress to date, it has become clear that functional brain imaging of memory and language offers many advantages over Wada testing and has the potential to be more accurately predictive of post-operative outcomes. Furthermore, surgical epilepsy treatment

has been recently validated in an NIH-funded trial and will continue to be an important option for patients. With the completion of the patient outcome portion of the project, we believe we will be in a strong position to apply for further funding in epilepsy and other surgically treatable brain disorders where language and/or memory functions are vital considerations.

13. **New Investigator Training and Development**. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

    Yes___X_____ No_____

    If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male			1	
Female				
Unknown				
Total			**1**	

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic			1	
Unknown				
Total			**1**	

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian			1	
Other				
Unknown				
Total			**1**	

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

    Yes_____ No___X_____

    If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. **Impact on Research Capacity and Quality**. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes____X____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

No research of this kind had been attempted previously at this institution. The capacity for research in epilepsy and memory disorders has increased.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the entire grant award period. Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Functional Brain Imaging of Memory and Language for Epilepsy Surgery - The purposes of this project were three-fold: (1) to convene a multidisciplinary team of investigators with expertise in functional brain magnetic resonance imaging (fMRI), radiology, cognitive neuroscience, epilepsy and epilepsy surgery to address specific issues pertinent to patient treatment; (2) to develop multiple language and memory activation procedures for fMRI studies in healthy adults; and (3) to begin validating these procedures for localizing language and memory systems in the brain of patients undergoing surgery for epilepsy (i.e., temporal lobectomy). The current Wada procedure, which is used to localize language and memory systems in the brain, was developed over 50 years ago, is highly invasive, and does not always provide interpretable data. We propose to investigate the feasibility of using fMRI procedures as reliable indicators of language and memory localization to replace the Wada Test.

The specific aims of this project are:

(i) Determine the fMRI activation characteristics associated with typical left hemisphere language dominance in adults. We hypothesize that areas where there is no fMRI activity detected across three language tasks can be safely resected during anterior temporal lobectomy for intractable epilepsy.

(ii) Test the hypothesis that asymmetric activation in the medial temporal lobe region during memory retention tasks will be concordant with Wada memory test result and of greater predictive value than the Wada for post-surgical memory function.

(iii) Test the hypothesis that pre-operative fMRI language and memory asymmetries will be predictive of 6-month post-operative re-organization of function.

We planned to study 10 healthy adult volunteers and 10 patients who are diagnosed with Temporal Lobe Epilepsy (TLE) and undergo Anterior Temporal Lobe Resection (ATLR) for

relief of intractable seizures. The fMRI and cognitive tests will be given to the clinical subjects prior to and 6 month post surgery in addition to the standard clinical tests used for preoperative surgery planning.

We have developed or adapted eight (8) cognitive fMRI paradigms to achieve the aims of this study. The experimental tasks, along with high resolution T1 anatomical imaging, requires a total scan time of 65 minutes, which has proven feasible for patients and controls. The tasks include: Word Encoding *(6 minutes)*, Picture Encoding *(6 minutes*), Word Recognition *(8 minutes)*, Picture Recognition *(8 minutes)*, Face-Name Encoding/Recognition *(8 minutes)*, Letter Fluency *(6 minutes)*, Category Fluency *(6 minutes)*, and Sentence Completion *(6 minutes).*

METHODS

Participants

Ten healthy adults have been recruited for standardization studies and all have completed fMRI studies. In addition, we have completed presurgical fMRI studies on 6 temporal lobe epilepsy patients (all completed without difficulty) and 2 of these patients post-lobectomy. The Clinical Surgical Epilepsy Program has been reorganizing (with 2 faculty departures and recruitment of new faculty) and recruitment of temporal lobe epilepsy and anterior temporal lobectomy patients has been much slower than expected. These factors have been beyond our control and quite frustrating, but Drs. Eslinger and Nguyen have been working with this program to increase the number of study participants. The completion of ATLR surgery is not under the control of the principal investigators and is subject to a great number of constraining clinical, personal and even insurance variables such as need for depth electrode and grid insertion recording studies in patients, managing co-morbid conditions, and family support systems. However, the fMRI studies to date have become an increasingly important component of the epilepsy surgical conference discussions. The Epilepsy Surgery Team is committed to completing treatment of the TLE patients and collecting the full sample of post-operative fMRI studies in order to correlate findings with clinical outcomes. This aim will be enhanced by the addition of a new faculty member in epilepsy, Dr. Frank Gilliam. All investigators and support personnel are completing the study protocol at no additional costs to the program.

Experimental Language Paradigms

Letter-word Test (L): Each letter-word task was performed in a block-periodic design. Participants were first presented three letters one at a time and instructed to associate words to the letter. Specifically, each letter was viewed for 30 seconds during which time participants silently generated words beginning with that letter. (Example: S →_____e.g., "sauce", "shoe", "sundae"…… etc). The baseline condition was a fixation cross.

Semantic-category Test (C): Each semantic-category task was performed in a block-periodic design. Participants were presented three separate semantic categories one at a time and instructed to retrieve the names of members of that category for 30 seconds (Example: Fruits → _____ "apple" "banana" "watermelon"……etc). The baseline condition was a fixation cross.

Sentence Comprehension Test (S): Each sentence-embedded task was performed in a block-periodic design. Participants were presented 8 simple sentences (experimental condition) and eight pseudo-sentences (baseline condition), with the simple sentence and pseudo-sentences

presented in separate sessions. Within the simple sentences, a word was missing and subjects were instructed to retrieve the word and complete the sentence (Example: Doctors usually wear_____ ____ clothes. On my hand I have ten _____). The pseudo-sentence was composed of nonsense words designed to stimulate similar visual processing but without the comprehension (e.g., "Rdse sdkln seke _____ lewo lskd."). For both blocks, each stimulus is viewed for 3 seconds, separated by a 0.5 second crosshair. Each block lasts for 28 seconds, and there are 6 baseline blocks and 6 experimental blocks.

Experimental Memory Encoding and Memory Recognition Paradigms

Word Recognition and Picture Recognition: Tasks are also designed similarly, differing only by the verbal vs. visuospatial material. They are programmed in a mixed design. The experimental stimuli are presented using an event-related design and the baseline stimuli are presented using block design. The TR is 2000. In both tasks, participants see strings of words (or pictures), but now they must decide (using a keyboard) if they saw words (pictures) from the previous encoding task or if it is a novel word (picture). Each experimental block contains 6 stimuli lasting 4 seconds each, separated by 2 – 10 second blanks. In total, there are 15 "learned" stimuli and 15 "novel" stimuli in each task. During the baseline blocks, participants see strings of 4 stimuli lasting 4 seconds each, separated by a 0.5 second blank (either a pseudo word or scrambled picture). The instructions are presented in the same manner as the Encoding tasks.

Face/Name Encoding & Recognition: Tasks are programmed in a block design, with a TR of 3000. Participants view a string of 4 faces (one at a time); each face has a name below it and they are instructed to memorize each face and the associated name. Next they have a Distractor period lasting for 48 seconds. During this block, they see alternating "+" and "0", lasting for 3 seconds and 1 second, respectively. Finally, they see the same 4 faces (one at a time), but now all 4 names are listed below each face. Participants are instructed to decide which of the 4 names was associated with each face. During the Recognition block the faces are never presented in the same order as initially presented and the names are in a scrambled order. The task cycles through Encoding → Distractor → Recognition 4 times, twice with male faces and twice with female faces (16 faces total). Stimuli in Encoding and Recognition blocks are presented for 4 seconds each, without any separation.

Equipment and fMRI Scan Parameters

Using the Siemens Magnetom Trio 3-T whole body MRI scanner. Whole-brain imaging data were acquired on T2*-weighted gradient-echo echo-planar imaging (EPI) sequence at Pennsylvania State College of Medicine Hershey Medical Center. Imaging parameters were: repetition time (TR) = 2000ms; echo time (TE) = 30ms; flip angle (FA) = 90°; field of view (FOV) = 230 × 230 × 120mm^3; Matrix size = 80 × 80; 30 layer axial slices were acquired parallel to the AC-PC line; each slice thickness = 4mm; Repetitions scan number was: for letter-word test and Semantic-category test all was 162; for Sentence-embedded Test is 175. High-resolution (1 × 1 × 1 mm^3) anatomical images were acquired using a T1-weighted, 3D gradient-echo sequence. All cognitive testing paradigms were presented using Eloquence fMRI Software (Invivo).

Data Processing and Analysis

Functional images data obtained for each participant were analyzed with SPM5 (http://www.fil.ion.ucl.ac.uk / SPM /software/spm5/) running under Matlab 7.7.0(R2008b) (Math Works, Natick, MA). All functional images data were first processed with realignment for motion correction within the time-curve to remove movement-by-susceptibility induced variance, co-registration with high resolution T1 images. Then the parameter estimate images for each subject were spatially normalized to the Montreal Neurological Institute (MNI) brain EPI template to standardize in a resolution of $2 \times 2 \times 2$ mm^3 based on the ICBM152 (International Consortium for Brain Mapping) stereotactic space. All functional data images also were smoothed by an isotropic Gaussian kernel of $8\times8\times8mm^3$, full width at half-maximum (FWHM) to increase the signal – noise ratio. Activation maps were generated by using the General Linear Model (GLM) in which time series were convolved with the canonical hemodynamic response function. Results were analyzed in a random effects model to create a group-level statistical map with the voxels threshold set at $P < 0.001$(uncorrected) and an extent threshold = 10. Individual contrast images between experimental conditions and baseline condition were assessed for each task.

Regions-of-interest (ROI) analysis was conducted to examine the nature of the neural responses in different tasks. We selected the peak activation coordinates from those contrast clusters as the center of ROI and defined each ROI as a sphere with a 6-mm radius. Once selected, the ROIs were employed as masks to extract the mean percent signal change (averaged over the ROI) in the blood oxygen level dependent (BOLD) responses based on the contrasts between experiment conditions and their control tasks.

All the statistical maps were superimposed on the high-resolution, normalized, T1-weighted, SPM5 structural template image for viewing, and the MNI coordinates from SPM5 were derived.

RESULTS

Memory Paradigms

Representative results are shown because of the large dataset. Among the encoding and memory recognition tasks, *word learning and retention* paradigms have generated clear findings. These are shown in Figure 1. Specifically, medial temporal activation was predominantly on the left and in the region of the hippocampus, which is a main site of anterior temporal lobectomy. In a patient with left temporal lobe epilepsy, who showed a clinical deficit in word recognition memory, there was a specific lack of left medial temporal (hippocampal) activity during this task (see Figure 2 below). Thus, initial results raise the possibility that the word recognition memory task may provide sensitive and specific differences in brain organization subserving verbal short-term memory and may be a viable predictor of post-surgical outcome after left temporal lobectomy.

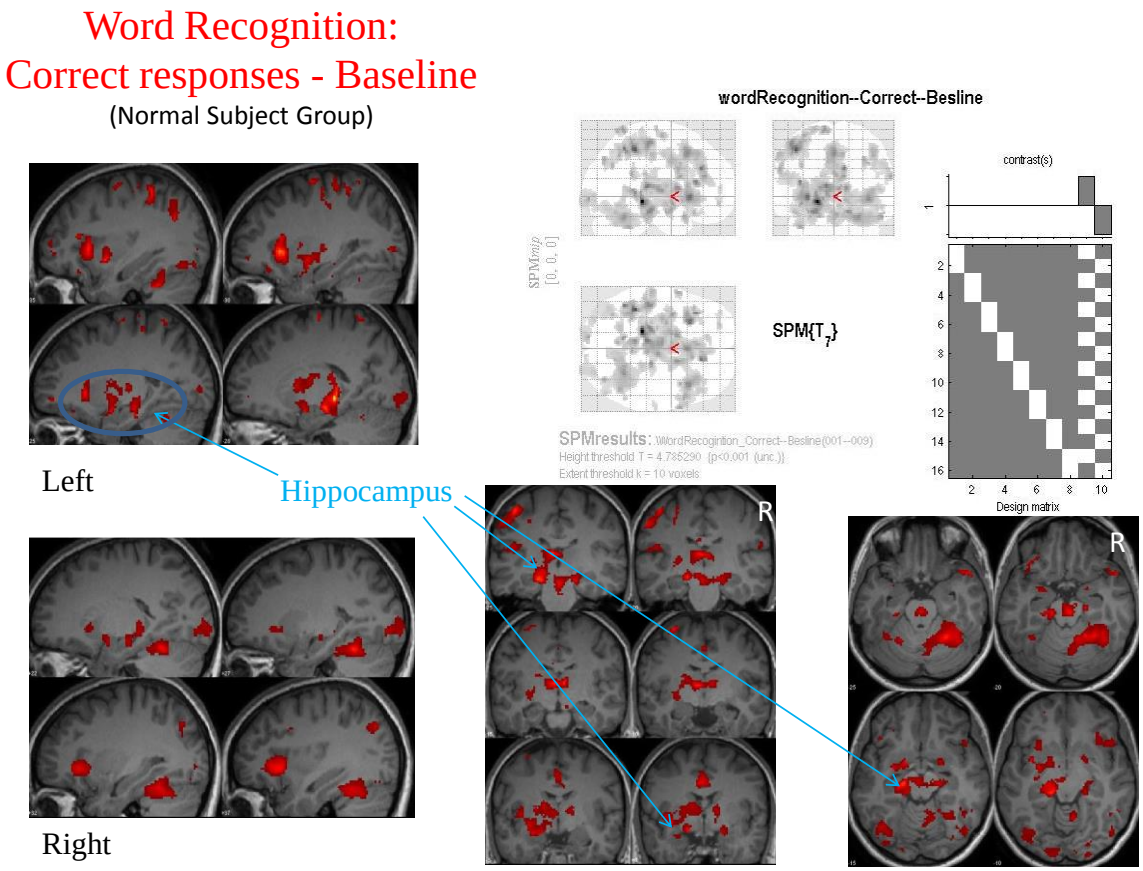
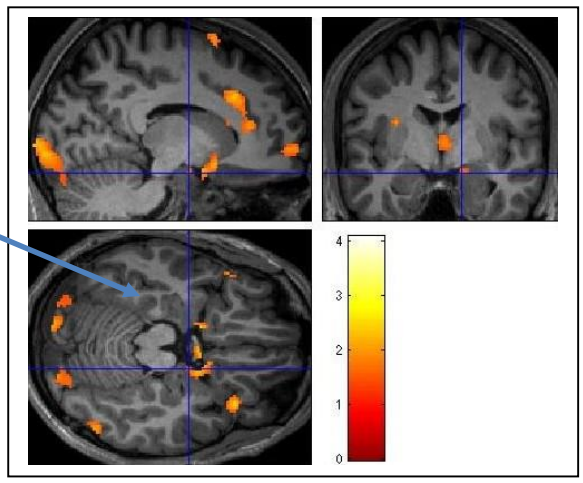


Figure 1. Activation maps of healthy control sample generated by word recognition memory task.

Figure 2. Pre-operative activation map of a patient with left temporal lobe epilepsy showing lack of expected left medial temporal activation during the word recognition task. Only a small cluster of activity was detected in the right medial temporal region which may represent an ineffective compensatory response as the patient's verbal memory testing outside the magnet was deficient.



The *picture recognition memory* generated specific medial temporal lobe activations as well. As expected, these clusters were predominantly in the right hemisphere (see Figure 3). The activation map of a patient with right temporal lobe epilepsy showed lack of typical activity in the right medial temporal lobe region during this task (See Figure 4 below). Thus, initial results raise the possibility that the picture recognition memory task may provide sensitive and specific paradigm to detect differences in brain organization subserving visuospatial short-term memory and may be a good predictor of post-surgical outcome after right temporal lobectomy.

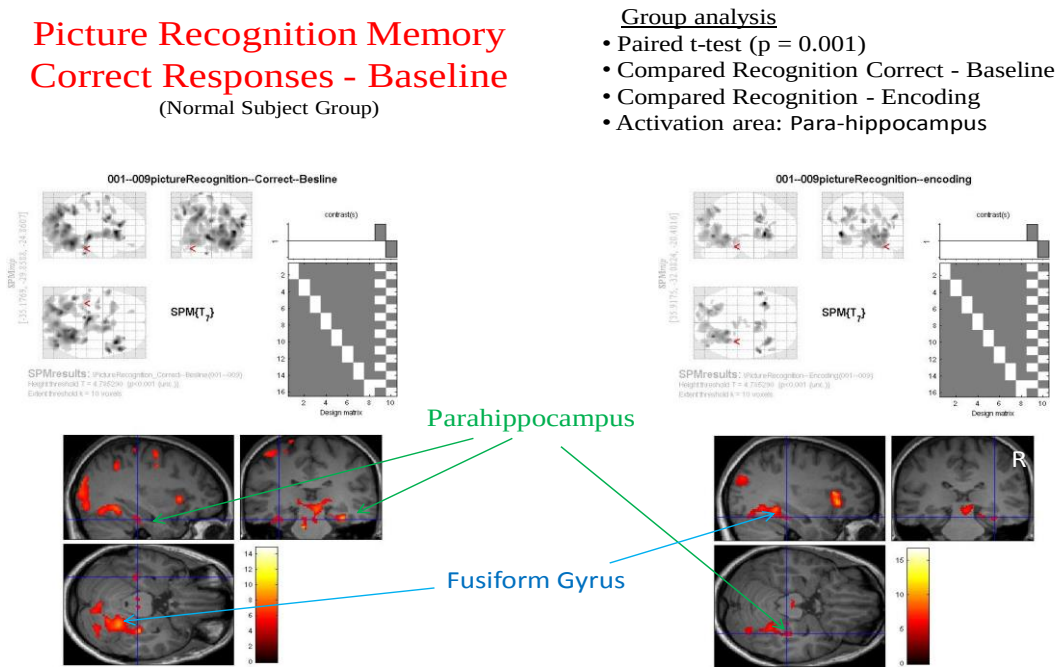
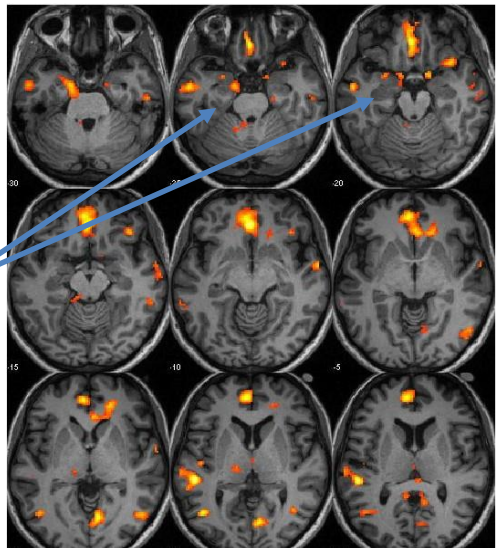


Figure 3. Activation maps of healthy control sample generated by picture recognition memory task, comparing activations under 2 different contrast conditions (i.e., correct recognition responses only on left and all recognition responses on right).

Figure 4. Activation map of patient with right temporal lobe epilepsy showing mainly left medial temporal lobe recruitment during the picture recognition memory task. This is the opposite pattern from what healthy controls show.



With the *face-name associative learning and memory* paradigms, we are pursuing an exciting line of inquiry that is different from the word and picture memory tasks. This is a cognitively more demanding task that generates errors in memory recall in healthy controls. We have decided to focus on differentiating brain activations associated with successful memory performance (i.e., correctly identifying the face-name associations in the memory condition) vs. unsuccessful memory performance. After initial data analysis, we realized that combining all responses (correct and incorrect) into a single analysis was likely yielding a fuzzy picture of the role of the hippocampus in functional memory performance. The difference may conceptually be a subtle one, but we were persuaded that identifying the key medial temporal activations associated with being able to *accurately* remember associative learning was more important than activations associated with performances that were mediocre. Indeed when we compared activations during highly correct blocks ($\geq$75% accuracy) vs. baseline we confirmed consistent bilateral hippocampal activity (Figure 5). However, there were no hippocampal activations detected during low accuracy blocks ($\leq$ 25%), as seen in Figure 6 below.

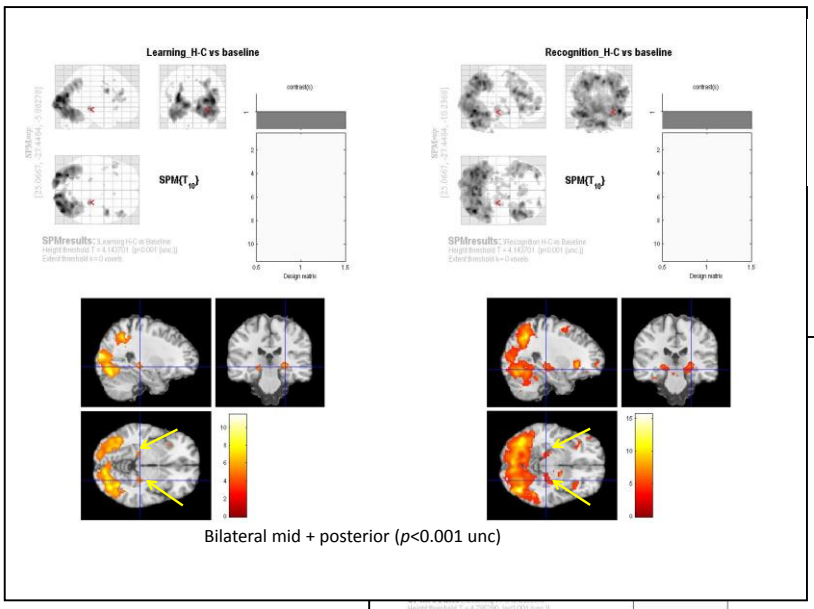


Figure 5. Bilateral hippocampal activity detected during successful (high recall) associative memory trials (yellow arrows)

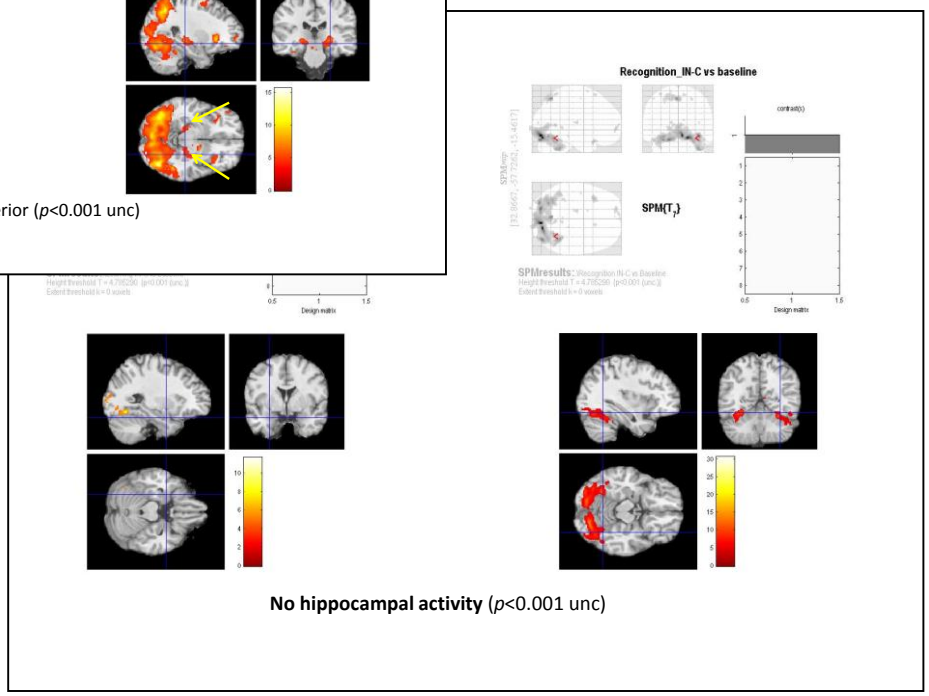


Figure 6. No activations in hippocampus were detected during unsuccessful (low recall) associative memory trials

When successful and unsuccessful associative memory trials were specifically contrasted, the results can be seen in Figure 7 below. Activations during successful recall trials were detected in right and left anterior regions of the hippocampus, and in the bilateral posterior regions. Our data analysis plan at this point is two-fold:

1. For stimulus associations that were accurately retained, analyze the activations that occurred during the *encoding phase* to determine if something was different at that stage of processing to predict later retention vs. later forgetting.
2. Analyze the activations from the accurate associative memory trials with connectivity methods to determine network activation effects of accurate vs. inaccurate retention. By placing a seed in the anterior hippocampal and posterior hippocampal regions, we are interested in determining what other regions might have been interacting with the hippocampus to permit the higher associative retention (e.g., prefrontal cortex). Such analyses may help inform fundamental questions about the neural bases for retention vs. forgetting in healthy adults.

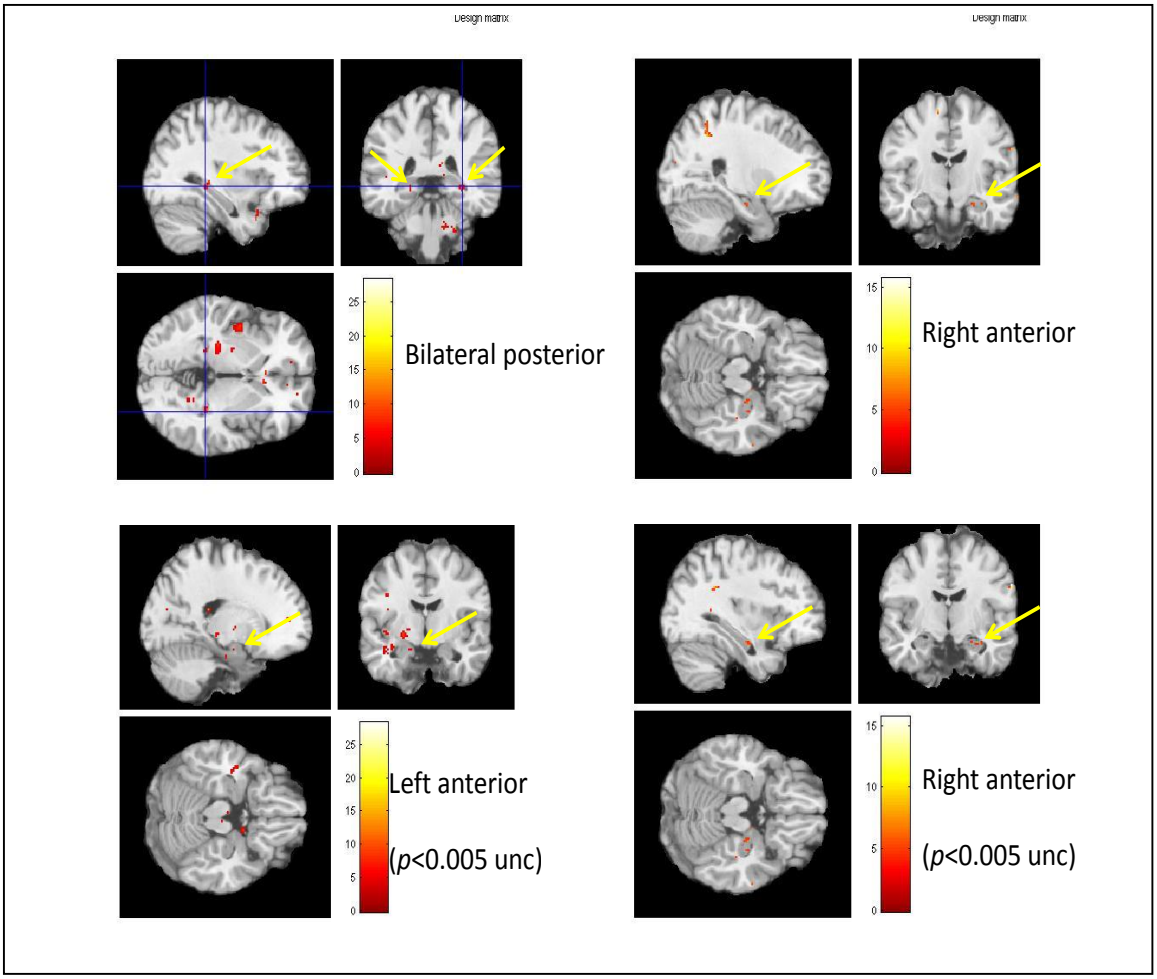


Figure 7. Contrast map of activations occurring during successful associative memory retention vs. unsuccessful retention in healthy adults.

Case Example of fMRI Memory Results Compared to Wada Memory Test

Figure 8 below shows the word memory activation map from a TLE patient who underwent Wada testing with sodium brevitol. The results of the Wada test were ambiguous with regard to memory functions due to uneven drug effects during memory encoding (i.e., drug effects wearing off too quickly). The fMRI activation clusters associated with memory processing were found to be clearly asymmetric in the anterior-medial temporal regions, with greater volume of activation in the left hemisphere (see top 8 slices). The fMRI language lateralization findings were found to be fully consistent with the Wada test results.

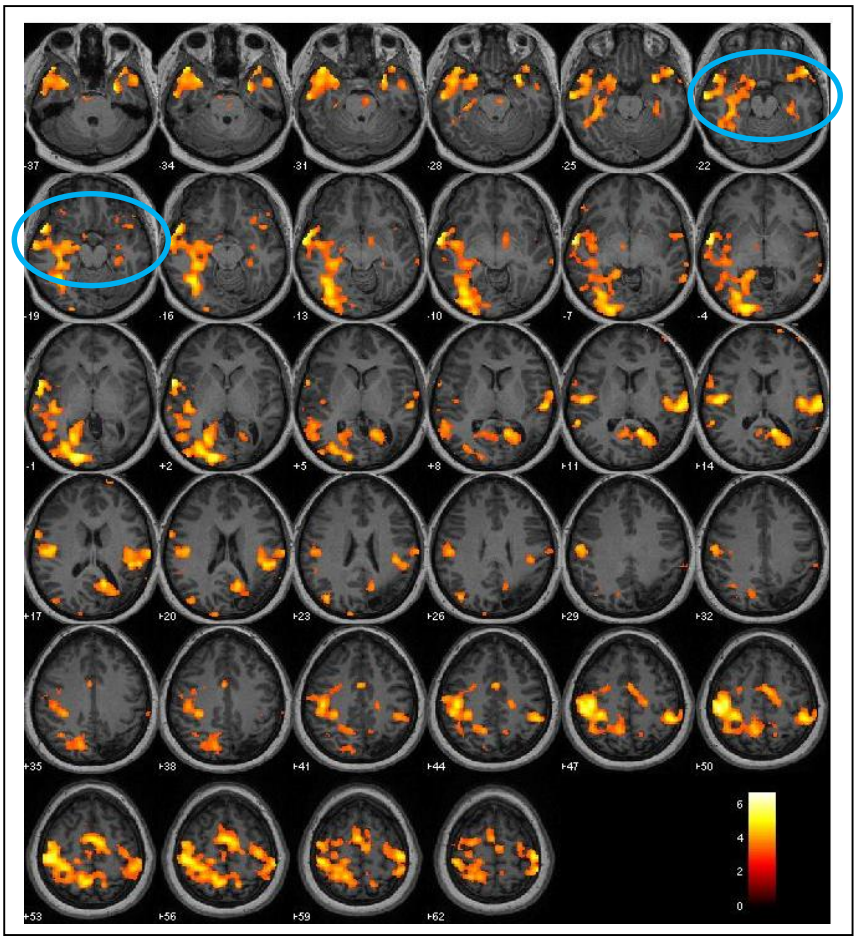


Figure 8. Word memory activation map from a TLE patient who underwent Wada testing with sodium brevitol. The results of the Wada test were ambiguous with regard to memory functions. The activation clusters associated with memory processing are clearly asymmetric in the anterior-medial temporal regions, with greater volume of activation in the left hemisphere (see top 8 slices). The fMRI language lateralization findings were fully consistent with the Wada test results.

Case Example of Pre- vs. Post-Operative Memory Test Results in a TLE Patient

To date, two TLE patients have come to the 6-month post-operative phase and we have been able to analyze one patient's post-operative fMRI data. Despite their *right* ATLR, the patient has shown improvement in measured word and face-name memory functions in the post-operative phase, as follows:

Word Recognition:	Pre = 73% vs. Post = 87%
Picture Recognition:	Pre = 90% vs. Post = 83%
Face Name Recognition:	Pre = 38% vs. Post = 44%

The preoperative activation map of the TLE patient taken from the fMRI Face-Name encoding condition is shown in Figure 9. The patient had right anterior medial temporal lobe pathology which is reflected in the asymmetric *hypoactivation* in that region during this learning task (see top 6 slices where left is on left and right on right).

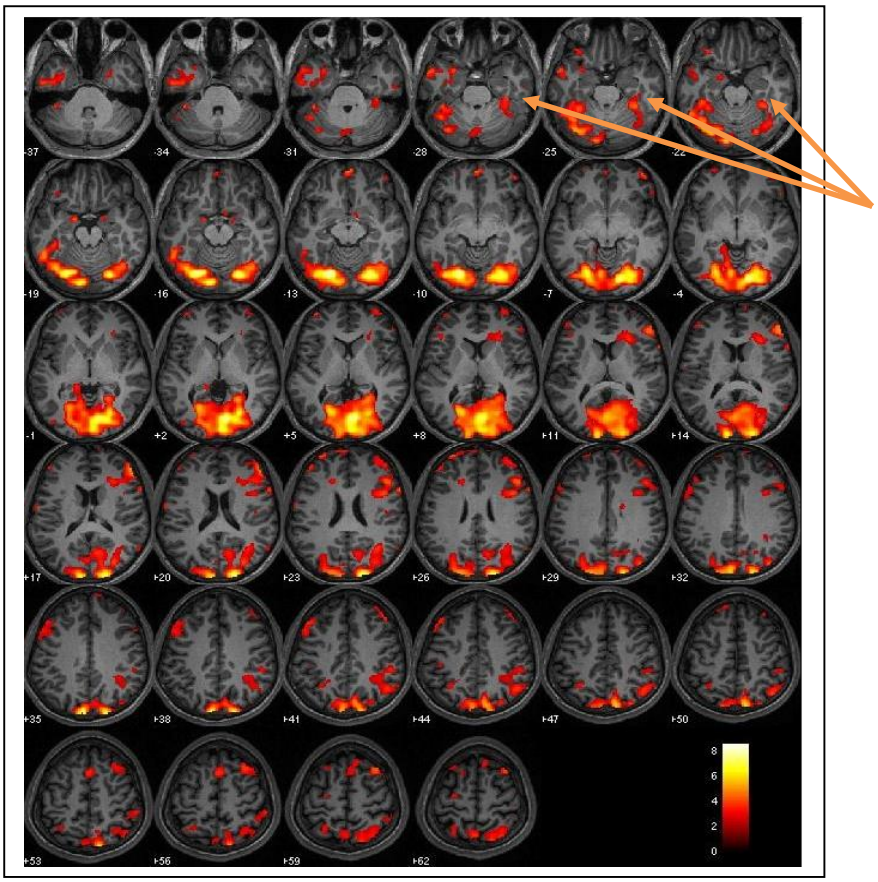
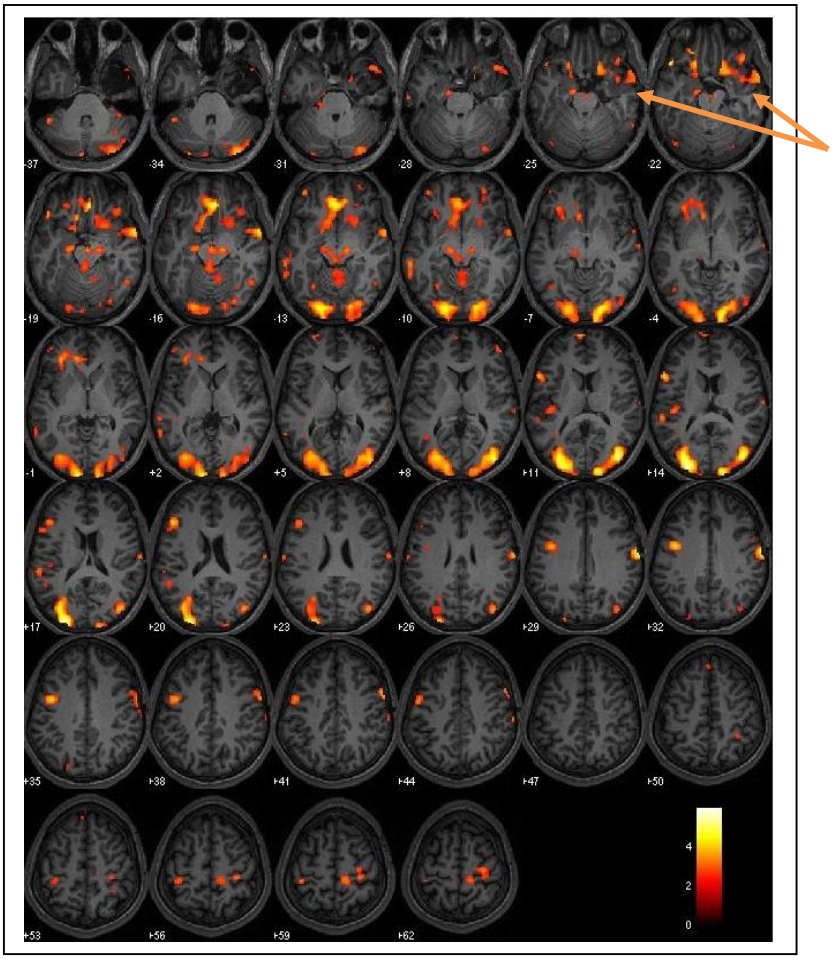


Figure 9. Preoperative activation map of a TLE patient taken from the fMRI Face-Name encoding condition. The patient had right anterior medial temporal lobe pathology which is reflected in the asymmetric hypoactivation in that region during this learning task (see arrows and top 6 slices where left is on left and right on right).

Figure 10 shows the postoperative vs. preoperative activation map of the same right ATLR patient undertaking the Face-Name encoding task. The darkened area of surgical resection can be seen in the right anterior medial temporal lobe in the 4 upper left brain slices. As a result of the surgery and relief of seizures, the right anterior and medial temporal lobe was found to be much more active during the learning process. The patient's accuracy score also improved.

Figure 10. In follow-up to the pre-operative activation map above, this is the fMRI postoperative vs. preoperative activation map of the ATLR patient undertaking the Face-Name encoding task. The region of surgical resection can be seen as a dark area in the right anterior medial temporal lobe in the 4 upper left brain slices. The results show that when post-operative vs. pre-operative brain activation patterns are statistically compared, the right anterior and medial temporal lobe is now much more active during the learning process (see arrows). The patient's accuracy of learning also improved.



There is notable activation in areas connected to ATL including the visual cortex and prefrontal cortex. These regions interact with the ATL during learning and memory tasks. Hence, the improved memory appears to be at the neural network level.

Language Paradigms

Measures of language activation showed significant asymmetric activity of the cerebral hemispheres such as the predominant left hemisphere activations observed during the Sentence Completion task (see Figure 11 below, see also Figure 12 for axial slice series). Across the several language tasks, statistical analyses revealed no clear differences between patient and healthy controls in eloquent language areas in the left cerebral hemisphere, confirming the expected left hemisphere language dominance patterns in TLE patients. However, we did identify one patient with left temporal lobe epilepsy who showed additional recruitment of right hemisphere resources during this task (Figure 13). Detecting such differences may be extremely important in guiding certain neurosurgical treatment of temporal lobe epilepsy and predicting language outcome after surgery. By following the larger TLE sample through to post-operative outcome, we should be able to clarify this issue.

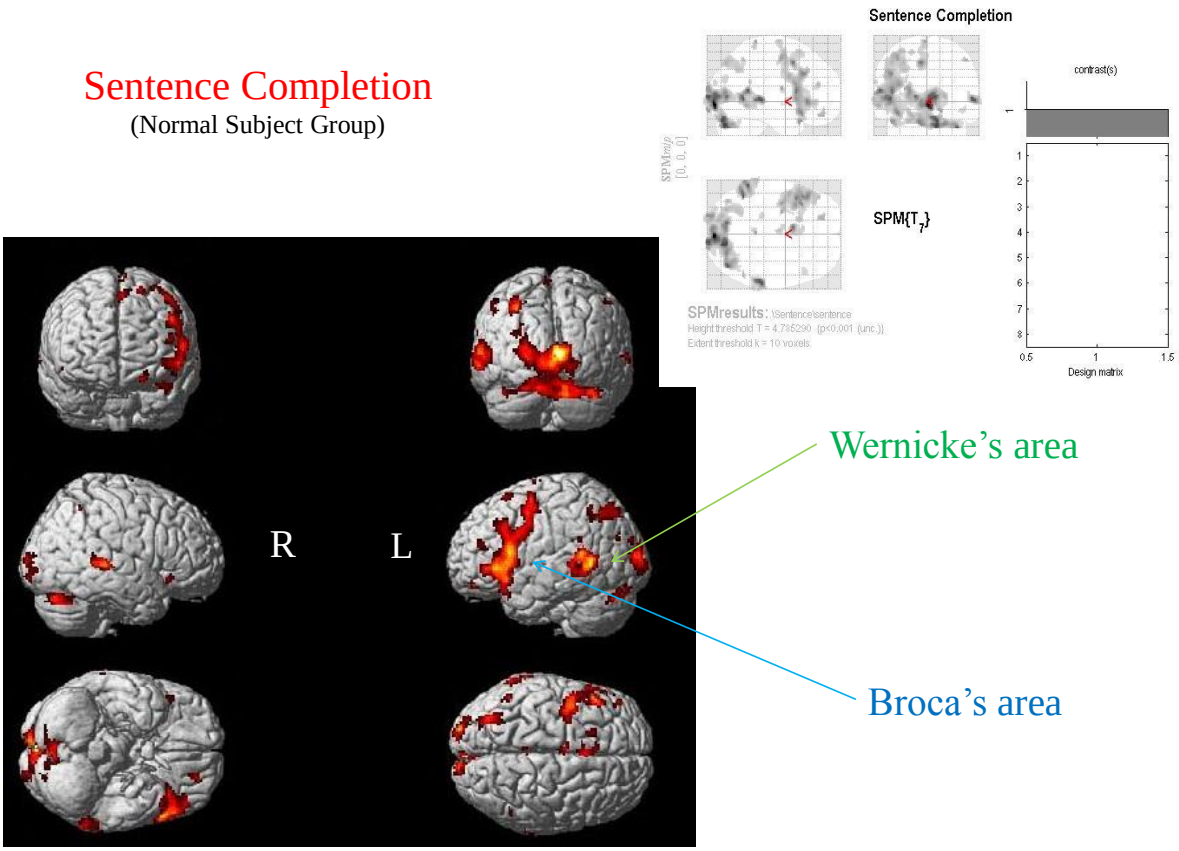


Figure 11. Brain activation map of healthy controls during the sentence completion task. Findings confirm highly asymmetric left hemisphere activity typically associated with dominant hemisphere mediation of language

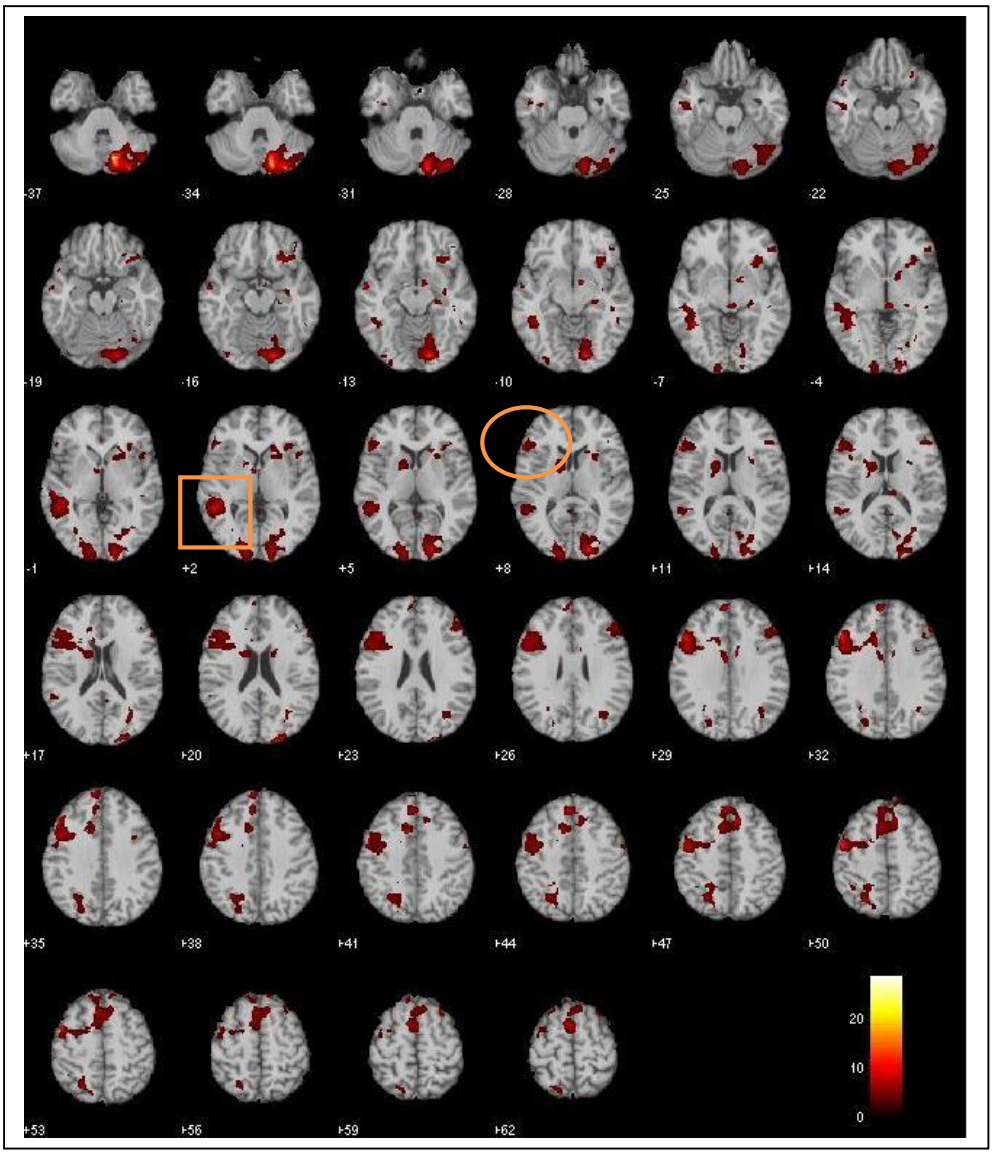


Figure 12. Average activation map of the TLE sample generated during the Sentence Completion Task. These results confirm that specific clusters of activity occurred in the left cerebral hemisphere (left on left in this image), specifically including Broca's area (highlighted circle) and Wernicke's area (highlighted square). Hence, this task produces a reliable and highly significant asymmetry of language activity consistent with expected left hemisphere dominance for language in right-handed patients with TLE.

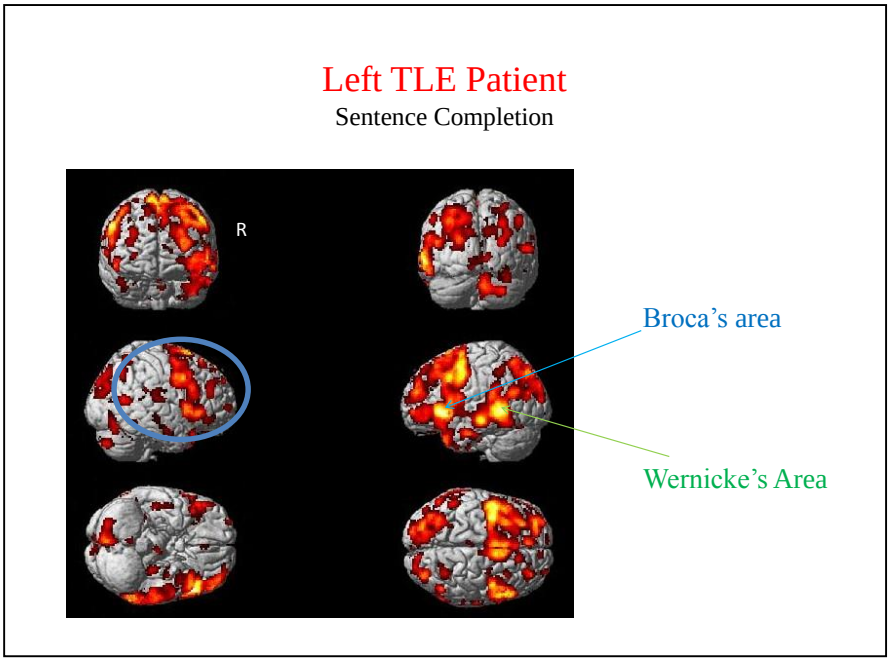


Figure 13. Activation map of left temporal lobe epilepsy patient during the sentence completion task showing bilateral recruitment of frontal-temporal regions, unlike the highly left asymmetric pattern of healthy controls seen above. This may have important implications for language recovery after surgery.

Comparisons Between Language Activation Tasks

We compared lexical-semantic verbal processing during letter fluency, category fluency, and sentence comprehension tasks in order to evaluate differential involvement of specific neural regions of human brain for functional selectivity.

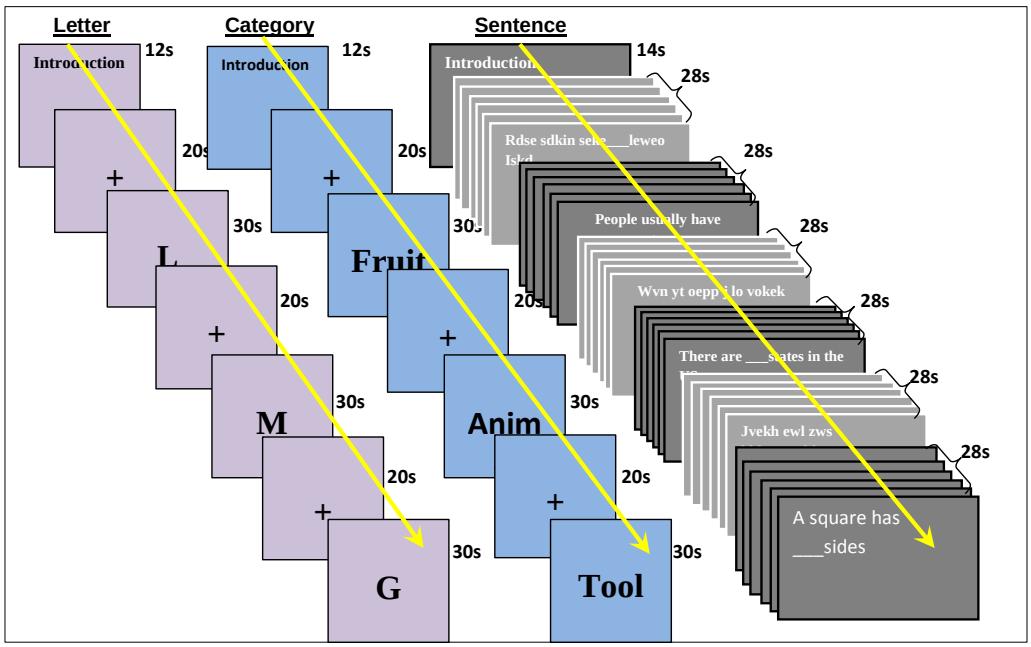


Figure 14. Task paradigms for letter, category and sentence comprehension tasks

Each task was performed in a block-periodic design. fMRI scanning parameters were: TR/TE/FA = 2000ms/30ms/90^0; FOV = 230×230×120 mm^3; matrix 80×80; 30 axial slices; slice thickness = 4mm. Number of repetitions were 162 for the letter and semantic fluency paradigms and 175 for the sentence comprehension paradigm.

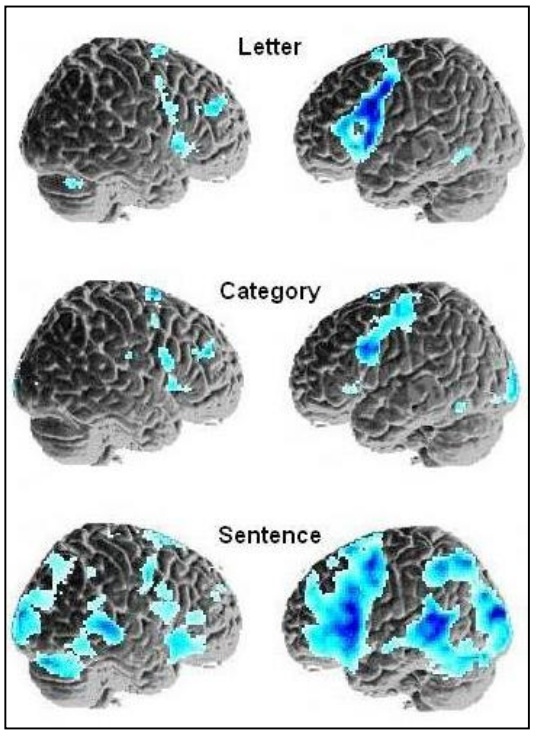


Figure 15. Average activation patterns for each language task on lateral brain views.

All fMRI images were processed with SPM5. Activation maps for each paradigm were constructed at the individual subject level using the general linear model (GLM). Analyses revealed common and distinct brain activations among the tasks. Common activation areas occurred in the left superior/inferior frontal gyrus, the anterior cingulate cortex, the supplementary motor area, and the insula. Differential involvement of the occipital lobe, the temporal lobe, thalamus, and cerebellum, according to tasks, occurred as well (Figures 15 & 16).

We concluded that these fMRI stimulation paradigms are capable of identifying both common and distinctive left hemisphere dominant regions across multiple language tasks. Our next step will be to analyze the results in the pre-operative vs. post-operative phases for patients with ATLR.

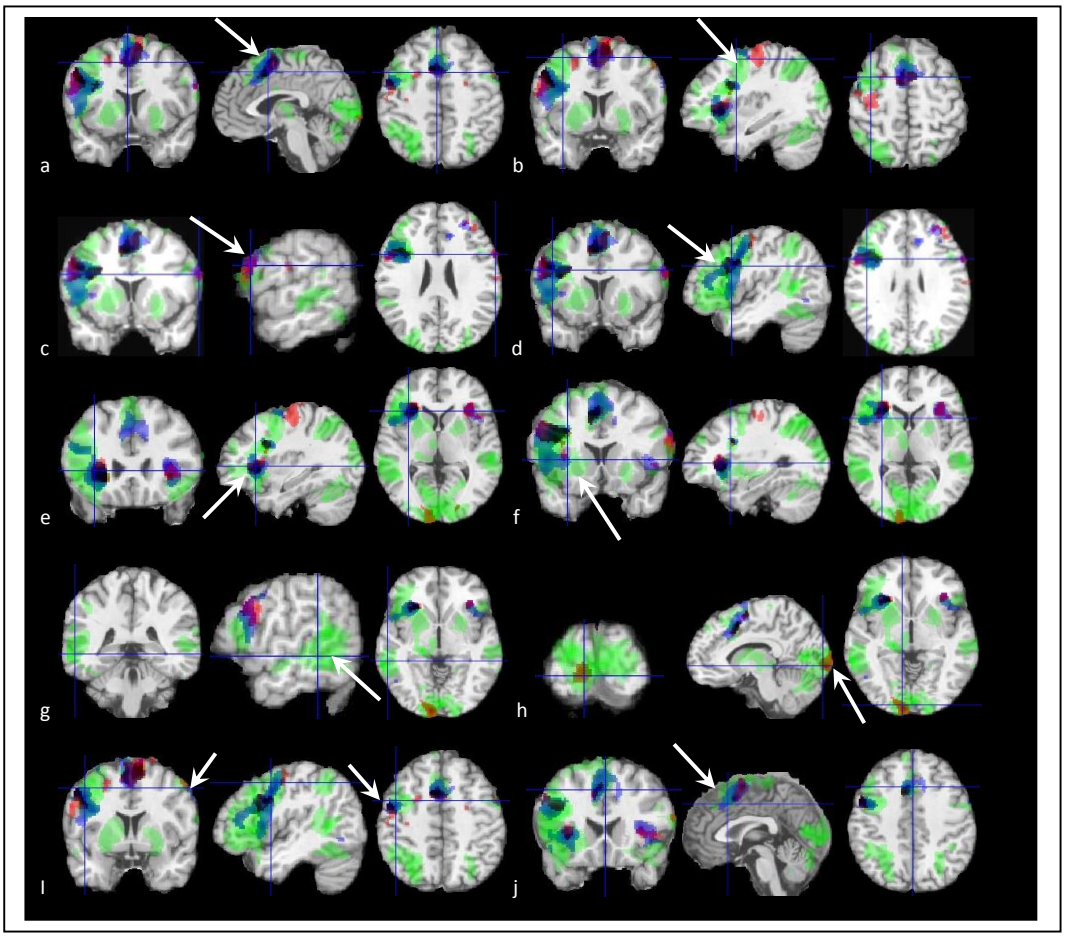


Figure 16. Specific areas of activation associated with letter fluency (blue), category fluency (red) and sentence comprehension (green) tasks. Arrows point out task specific regions, detailed more in the attached manuscript submission (Li et al.).

Presented Abstracts at Scientific Meetings (Summarized below)

ISMRM Annual Meeting November 26, 2012, Chicago

fMRI Study of the Role of the Hippocampal Formation during Face-Name Recognition: Successful vs. Failed Face-Name Associations

Yunqing Li, P. J. Eslinger, Q. X. Yang

Synopsis: This study used fMRI to measure brain activity during encoding and recognition testing of novel face-name pairs, investigating the role of the hippocampal and the nearby MTL cortical areas. We compared the activation for successful versus failed retrieval of the face-name information during the recognition process. The increased response of the pulvinar of left thalamus and left fusiform gyrus (BA35) during successful recognition may indicate a neural substrate for memory consolidation of long-term knowledge and a potentially specific binding pathway. This study suggested that the hippocampal formation is crucial for successful retrieval association and that the degree of coordination between hippocampal and neocortical activity may predict the likelihood of subsequent memory.

Introduction:
The human medial temporal lobe (MTL) is known to be involved in declarative memory, in specifically, the hippocampus is widely thought to play a substantial role in forming associations, the role of surrounding cortical regions in the medial temporal lobe, including perirhinal and parahippocampal cortex, is controversial. We used fMRI to measure brain activity during learning and recognition testing of novel face-name pairs to investigate the role of the hippocampal region and the nearby MTL cortical areas in encoding and retrieval of associative. Eight healthy subjects were measured the activities in their brain during the encoding and recognition of novel face-name associations, and compared to encoding versus viewing repeated face-name pairs, and compared the activity for successful retired information versus no-successful retired the face information during the recognition task, with fMRI. This study suggested that anterior regions of the hippocampal formation, in particular, are crucial for successful retrieval associative and that the degree of coordination between hippocampal and neocortical activity may predict the likelihood of subsequent memory.

Methods:
Subject: Eight, right-handed, native English speaking healthy adults with no history of neurologic or psychiatric conditions volunteered to participated in the study (5 female; age range 21–45 years). All participants gave informed written consent under an approved National Institute of Mental Health protocol, had no reading/vocabulary difficulties, and had normal or corrected-to-normal visual acuity.

Cognitive Stimulation Paradigms:
This task is set up in a block design. Task cycles through Encoding to distracter to Recognition 4 times, twice with male faces and twice with female faces, total were16 faces, total task time were 8 minutes.
Face-name pair encoding task: Participants were first presented with a string of four faces (one at a time), each face has a name below it. Participants were instructed to silently memorize each face and their name associated with it.
Baseline task: after encoding task, they have a distracter period where they see alternation “+” and “0”
Face-name pair recognition task: after baseline task, Participants were separately presented with four faces (one at a time), but now all four name are listed below each face. Participants are instructed to decide which of the four names goes with each face as they remembered in encoding learning task.

fMRI Protocol: fMRI scanning was done data on a 3T MR scanner (Siemens Trio) with echo-planar imaging (EPI). Imaging parameters were: TR/TE/FA = 2000ms/30ms/90^0; FOV = 230×230×120mm^3; matrix 80×80; 30 axial slices; slice thickness = 4mm. Number of repetitions for face-name pair paradigm was 174. A T1-wighted axial structural image with resolution $2 \times 2 \times 2$ mm^3 was also collected from each subject.

Data Processing and Analysis: All fMRI images were processed with SPM5. Data normalization was done using the Montreal Neurological Institute brain template and the functional data was smoothed with a Gaussian kernel of $8 \times 8 \times 8$ mm^3 (FWHM). Activation maps for each paradigm were constructed at the individual subject level using the general linear model (GLM). Activation maps of encoding, successful remember face and name, no remember face and name tasks were compared using a paired t-test.

Results:

For the encoding and recognition face-name pair task, a consistent pattern of activation was observed in the temporal lobe, parahippocampus, pulvinar nucleus of the thalamus, fusiform and bilateral frontal cortices across individual subjects. There were great activities in left temporal lobe and left thalamus during successful and failed remember face-name pair task. Also the bilateral parahippocampus activities were shown in no-successful period. During the recognition task, we found that successfully remembered face-name pairs that were subsequently remembered showed significantly greater activation in the right hippocampal formation and left parahippocampus BA 35 and the pulvinar of left thalamus, compared to face-name pairs that were forgotten.

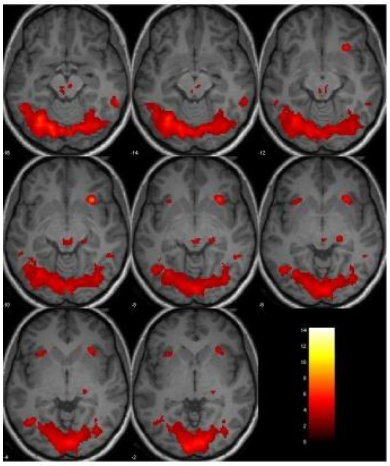


Fig1. Failed retention during recognition

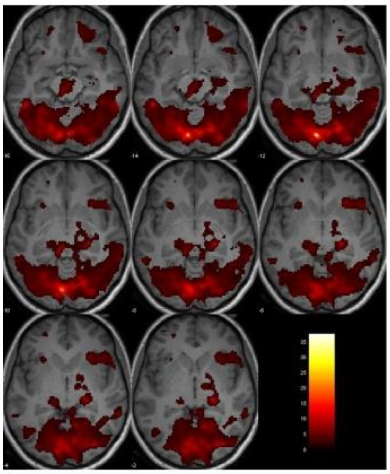


Fig2. Successful retention during recognition

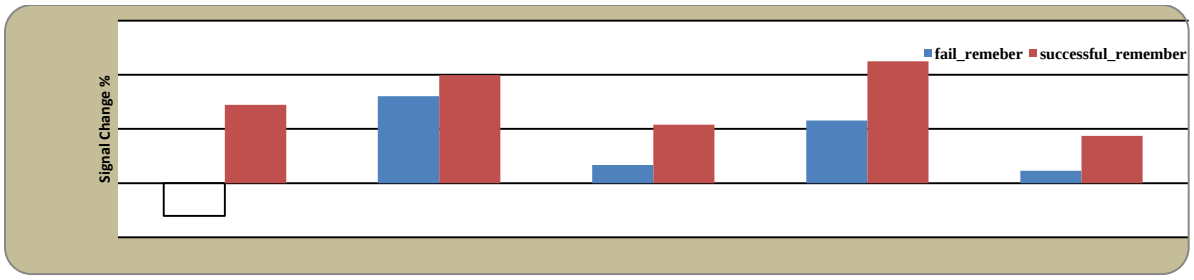


Fig3. Comparison of successful to failed remember activity in

Conclusions: The higher right hippocampal activation during successful face-name association was strongly correlated with activity in cortical regions involved in multimodal integration, supporting the idea that interactions between the hippocampus and neocortex contribute to associative memory. The higher right fusiform gyrus and right hippocampus activation during encoding suggests a potentially specific binding pathway. The increased pulvinar of left thalamus gyrus and left fusiform gyrus (BA35) BOLD response during recognition successful memory may indicate a neural substrate for memory consolidation of long-term knowledge and a potentially specific binding pathway.

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RSNA Annual Meeting 2011

Evaluation of memory lateralization in healthy human brain: A new Mix-block fMRI approach

Yunqing. Li, Dan. Nguyen, P. J. Eslinger, Q. X.Yang

Introduction: In recent years there has been an increased interest in applying fMRI to pre-surgical examination of episodic memory in epilepsy patients with medial temporal lobe (MTL) resection. The MTL surgery may cause verbal memory deficits and decline in language - dependent cognitive tasks [1]. The advent of fMRI has made it possible to study the neural correlates of both encoding and retrieval processes of memory [2]. Whether an event-related or a block paradigm aims to visualize the encoding process may affect the activation patterns in the limbic system and the hippocampus gyrus [3]. Previous fMRI research has raised the possibility that the MTL activation asymmetry may be significantly correlated with memory lateralization by using a complex visual scene-encoding stimulation paradigm[4] Study of patients with lateralized MTL damage has indicated that left MTL lesion is associated with specific and severe word memory deficits (while nonverbal-spatial memory functions are preserved), while right MTL lesion causes comparatively milder deficits in nonverbal-spatial memory (while verbal memory functions are preserved) [5]. Thus, left and right MTL regions may be highly asymmetric in the types of memory functions. In this study, we present a new comprehensive and clinically applicable Mix Block with Event-related design paradigm fMRI test - including both a single word and a complex visual scene task, and including block encoding and mixed block

recognition retrieval task. The application of this paradigm is assessment of hemispheric specific lateralization memory activity in the bilateral MTL memory related structures of healthy subjects. The goal of this study was to determine a suitable fMRI paradigm for pre-surgical examination of MTL memory activation areas.

Methods:

Subjects: Fourteen, right-handed, healthy adults with no history of neurologic or psychiatric conditions participated in the study (7 male, age range 21- 45 years). All participants spoke English as their first language and possessed no reading /vocabulary difficulties, had normal or corrected-to-normal visual acuity and were given informed written consent prior to undergoing an approved National Institute of Mental Health protocol.

Cognitive task design for fMRI:
Block-encoding paradigm: two block paradigm. Participants were first separate presented with two block-encoding memory paradigm (30 single-word or 30 complex visual scenes) and were required to remember each words or scenes on the screen as they can. Each block encoding paradigm presented over six 40s blocks. Each stimulus was displayed for 3.5s followed with 0.5s blank screen and the baseline is 30 pseudo-words or 30 scrambled images by block task. There is a 8s interval of rest after each block. (Fig 1, A)
Mix-recognition retrieval paradigm: two mix paradigm. Participants were separately presented some new words/scenes or old words/scenes (showed in block-encoding paradigm) and were required to perform recognition retrieval for which the word/scenes was shown in the first block-encoding paradigm. In the mix paradigm, each stimulus (word or scene) was presented for 3.5s followed by different intervals of blank screen from 2s to 12s by event-related task. The baseline is 30 pseudo-words or 30 scrambled images by block task . (Fig 1, B)

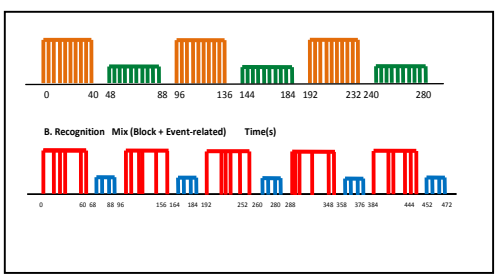

Fig 1. fMRI paradigm.
(A), Block Encoding.
(B), Mix Recognition (Block + Event-related).

fMRI Protocol: fMRI data were obtained on a 3 T Siemens Trio scanner with a fast gradient system for echo-planar imaging (EPI), a 8-channel receive head coil, TR / TE / FA = 2000 ms / 30 ms / 90^0, FOV = 230×230×120 mm^3, matrix 80×80, 30 axial slices, slice thickness = 4 mm. Number of repetitions for the word and scene block encoding memory paradigm was 188 and for the Mix-block recognition retrieval memory paradigm was 233. Axial T_1-wighted structural image and T_2*-sensitive, gradient-echo, echo-planar functional image with BOLD (blood oxygenation level dependent) contrast were collected for each subject.
Data Processing and Analysis: All fMRI images were processed with SPM5 for realignment within the time-course and co-registration with high resolution T_1 images. fMRI data were normalized to the Montreal Neurological Institute brain template [3] at a resolution of $2 \times 2 \times 2$ mm^3 and smoothed with a Gaussian kernel of $8 \times 8 \times 8$ mm^3 (FWHM). Activation maps from

each memory function at the individual level were generated using general linear modeling. Activations in the medial temporal lobe between word and scene recognition memory were compared by paired t-test.

Results: Activations were generated by the word and scene recognition retrieval memory tasks. For word recognition retrieval memory task, there was significant well-localized and highly lateralized activation mostly in the left medial temporal lobe (MTL) and hippocampus (Fig. 2). Some activations are in the left posterior temporal and the inferior prefrontal cortices were also detected (corresponding to specific word processing regions). In contrast, the complex visual scenes recognition retrieval memory task generated greater significant and very different neural activations that mainly localized in the bilateral parahippocampus gyrus and fusiform gyrus (Fig. 3). The right greater clusters were more than left in hemisphere. Finally, all tasks showed similar activity in the bilateral supplementary motor area, and the bilateral pre- and post central gyrus and the bilateral inferior occipital lobe.

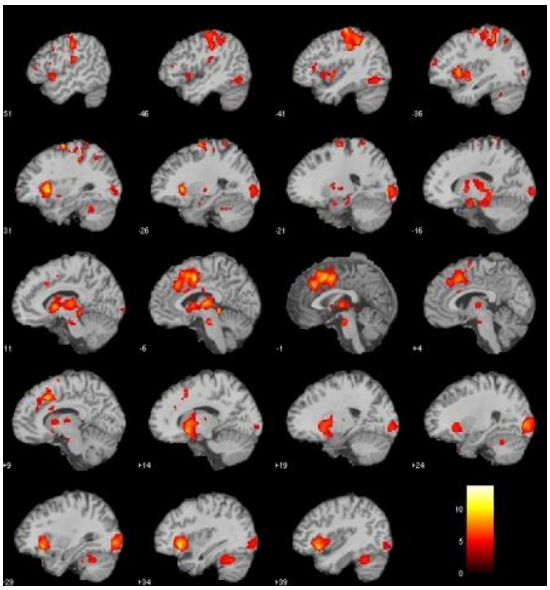

Fig.2. Word Mix recognition retrieval paradigm task

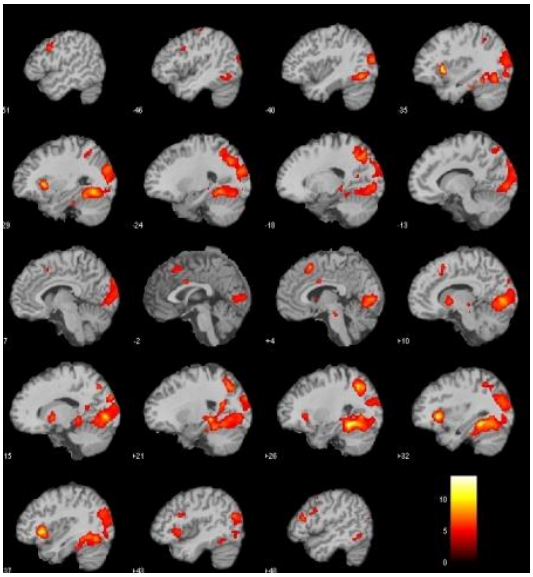

Fig.3. Scene Mix recognition retrieval paradigm task

Discussion: Results reveal substantial and significant differences in the MTL of the human brain for word and scenes recognition retrieval short-term memory tasks in healthy human brain. For word recognition retrieval memory tasks, the activation was associated with highly asymmetric in left hippocampus gyrus. For nonverbal-spatial memory of scenes recruited bilateral MTL and mainly localized the bilateral para-hippocampus gyrus and fusiform gyrus. Overall, our findings show that both the difference location and amount of cortical activity can be modulated by varying Mix-block design paradigm of single-word and complex visual scenes task demands. In particular, the result is more clearly and significant showed the human brain short-memory

processing laterality. So our study suggests that our new Mix-block design paradigm fMRI approach should be feasible to evaluate the neural systems integrity for pre-surgical short-memory examination in epilepsy patients with (MTL) resection. This fMRI study approach potentially importance is predicting post-surgical short-memory outcomes, as suggested by Golby et al [5].

References:

[1] Richardson MP; Neurology 2006, 66:699-705.
[2] Strandberg M; Brain Imaging and Behavior, 23(2010).
[3] Powell HWR; Neuroimage 2005, 27:231–239.
[4] Li P; Cognitive Science, 33 (2009) 629–664.
[5] Marcie L; Brain 2004, 127:2286-2298.
[6] Golby. AJ; Epilepsia, 2002, 43(8):855-863.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

___X_Yes
_____No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X_ No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

__10__Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

___20__Number of subjects originally targeted to be included in the study
___16__Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to

provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
__8___Males
__8___Females
_____Unknown

Ethnicity:
__2___Latinos or Hispanics
__14__Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
__1___Asian
_____Blacks or African American
__1___Native Hawaiian or Other Pacific Islander
_14__ White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

Dauphin County

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X___ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication, listed in the table, in a PDF version 5.0.5 format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1.Functional neuroanatomy of the limbic system.	Eslinger PJ	In Davis AS (Ed.) *Handbook of Pediatric Neuropsychol ogy* [pp. 137-146]. Springer Publishing: New York	August 2010	☐Submitted ☐Accepted X Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X_____ No_____

If yes, please describe your plans:

Three areas of data analysis are being targeted:

1. Hippocampal-cortical connectivity associated with successful memory performance (This plan is achievable with our current data set)
2. Post-temporal lobectomy hippocampal reorganization (This plan will require completing the recruitment and follow-up study of the clinical sample)
3. Post-left temporal lobectomy language reorganization (This plan will require completing the recruitment and follow-up study of the clinical sample)

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The project was geared toward reducing the need for an invasive Wada procedure and improving the cognitive outcomes after temporal lobectomy for intractable epilepsy.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No____X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

The BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Eslinger, Paul J.	Professor/Director of Clinical Neuropsychology and Cognitive Neuroscience Programs
eRA COMMONS USER NAME (credential, e.g., agency login) peslinger	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Fordham University, Bronx, New York	B.S.	05/74	Psychology, Philosophy,
Texas Christian University, Fort Worth, Texas	M.S.	05/78	Chemistry of Behavior & Physiological Psychology
Texas Christian University, Fort Worth, Texas	Ph.D.	12/80	Neuroscience & Chemistry of Behavior
University of Iowa Hospitals, Clinics & College of Medicine, Iowa City, Iowa	Fellowship	06/83	Clinical Neuropsychology & Cognitive Neuroscience

A. Personal Statement

As a clinical neuropsychologist and cognitive neuroscientist, my expertise is in the design, application, and analysis of protocol instruments that assess behavior, cognition, and emotional functioning as well as the localization of acquired lesions from stroke, epilepsy, dementia and other forms of neuropathology. I have been an investigator in studies of structure-function impairments in stroke, concussion, epilepsy, cognitive aging, Alzheimer's disease, frontotemporal dementia, Parkinson's disease and other neurodegenerative conditions as well as multi-center drug treatment trials for Alzheimer's disease, traumatic brain injury, and detection of mild cognitive impairment in Parkinson's disease. My role in this project will be to coordinate the study of temporal lobe epilepsy patients with intractable seizures who will undergo surgical treatment for relief of seizures. This involves coordinating with the Surgical Epilepsy team in the Departments of Neurology and Neurosurgery as well as with the Center for MR/MRI Research for collection and analysis of brain imaging data during functional memory and language tasks in the pre-operative and post-operative phases as well as in healthy control participants.

B. Positions and Honors

Employment

1979-1981	NRTA-AARP and NINCDS Fellowships in Clinical Neuropsychology, Department of Neurology, University of Iowa College of Medicine
1983-1986	Chief Neuropsychologist, Assistant Professor, Neurobehavior Clinic, Benton Laboratory of Neuropsychology, and Alzheimer's Disease Research Center, Department of Neurology, University of Iowa College of Medicine
1986-1990	Assistant Professor, Brown University Program in Medicine, Department of Psychiatry and Behavioral Sciences, Director-Neurobehavior Diagnostic and Research Laboratory
1987-1990	Consulting Neuropsychologist, Virks Rehabilitation Unit, Rhode Island Medical Center

1990-1996	Associate Professor, Departments of Medicine (Neurology) and Behavioral Science, College of Medicine, Hershey Medical Center, Pennsylvania State University (PSU)
1990-2005	Director of Clinical Neuropsychology and Cognitive Neuroscience Programs, University Hospital Rehabilitation Center, Milton S. Hershey Medical Center, PSU
1996-present	Professor (Tenured), Departments of Neurology, and Neural & Behavioral Sciences Graduate Faculty, Interdisciplinary Neuroscience Program, PSU
2000-present	Professor, Department of Pediatrics (Developmental Pediatrics and Learning), PSU
2004-present	Professor, Department of Radiology and NMR/MRI Research Center, PSU
2011-present	Professor, Department of Public Health Sciences, PSU

Other Experience and Professional Memberships

1980-present	Member, International Neuropsychological Society, American Psychological Association
1982-1984	National Research Science Award, NINCDS
1990-present	Reviewer for NIH Scientific Review Branch, NINDS & NICHD
1992-1996	Consultant to Program in Health Science, Stanford Research Institute (Dr. Gary Swan)
1994-1995	NIH Consensus Conferences – Invited Presenter (1/94, 3/94, 9/94, 4/95)
1994-1998	Merit Review Committee, U.S. Department of Veteran Affairs
1994-present	National Scientific Advisory Council, American Federation for Aging Research
1998-2002	Sponsor, Mentored Clinical Scientist Development Award (KO8-NS02085: Dr. Anna Barrett)
1998-99	Consultant and Lecturer, Education Commission of the States
1998-present	Editorial Boards, *Developmental Neuropsychology*; *Cognitive & Behavioral Neurology*
1999-present	World Federation of Neurology Research Group on Aphasia and Cognitive Disorders
2000	Technical Expert Advisory Group – Agency for Healthcare Research and Quality and UNC-RTI Evidence-Based Practice Center. Project on Social Security Criteria for Speech and Language Disorders in Adults and Children
2002-present	Consultant/Collaborator, University of Pennsylvania Center for Study of Neurodegenerative Diseases, Department of Neurology (Dr. Murray Grossman)
2004	NIH Expert Advisory Group on Cognitive Rehabilitation ("Cognitive Rehabilitation Interventions: Moving from Bench to Bedside")
2010-present	Data Safety Monitoring Board, University of Iowa Program on Obstructive Sleep Apnea and Driving Safety (Rizzo M, PI)
2011-12	External Advisory Committee for the Faculty of Human Sciences, University of Cologne, in the selection of Professorship in Biological Psychology and Cognitive Neuroscience
2012-present	Editor-in-Chief, *Social Neuroscience*

C. Selected peer-reviewed publications (from a total of 130)

1. Benton AL, **Eslinger PJ**, Damasio AR: Normative observations on neuropsychological test performances in old age. Journal of Clinical Neuropsychology 1981; 3: 33-42.
2. **Eslinger PJ**, Damasio AR, Van Hoesen GW. Olfactory dysfunction in man: Anatomical and behavior aspects. Brain and Cognition 1982; 1: 259-85.
3. **Eslinger PJ**, Damasio AR. Severe disturbance of higher cognition after bilateral frontal lobe ablation: Patient EVR. Neurology 1985; 35: 1731-41.
4. **Eslinger PJ**, Damasio AR, Benton AL, Van Allen M: Neuropsychologic detection of abnormal mental decline. Journal of the American Medical Association, 253 (5), 670-4, 1985.
5. **Eslinger PJ**, Easton AE, Grattan LM, Van Hoesen GW: Distinctive forms of partial retrograde amnesia after asymmetric temporal lobe lesions: Possible role of the occipitotemporal gyri in memory. Cerebral Cortex 1996, 6, 530-539.
6. Ng VWK, **Eslinger PJ**, Williams SCR, et al: Hemispheric preference in visuospatial processing: A complimentary approach with fMRI and lesion studies. Human Brain Mapping 2000; 10:80-86.
7. **Eslinger PJ**, Swan GE, Carmelli D: Changes in mini-mental state exam in community dwelling older persons over 6 years: Relationship to health and neuropsychological measures. Neuroepidemiology 2003; 22: 23-30.
8. **Eslinger PJ**, Robinson-Long M, Realmuto J, Moll J, Oliveira-Souza R de, Moll F, Wang J, Yang QX. Developmental frontal lobe imaging and moral judgment: Arthur Benton's enduring influence 60 years later. Journal of Clinical and Experimental Neuropsychology 2009; 31: 158-169.
9. Wang J, **Eslinger PJ**, Doty RL, Zimmerman EK, Grunfeld R, Sun X, Meadowcroft MD, Connor JR, Price JL, Smith MB, Yang QX. Olfactory deficit detected by fMRI in early Alzheimer's disease. Brain Research 2010; 1357: 184-94.
10. Grossman M, **Eslinger PJ,** Troiani V, Anderson C, Avants B, Gee JC, McMillan C, Massimo L, Khan A, Antani S. The role of ventral medial prefrontal cortex in social decisions: Converging evidence from fMRI and frontotemporal lobar degeneration. Neuropsychologia 2010; 48: 3505-12.
11. **Eslinger PJ**, Moore P, Anderson C, Grossman M. Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. Journal of Neuropsychiatry and Clinical Neurosciences 2011; 23: 74-82.
12. Zappala G, Thiebaut de Shotten M, **Eslinger PJ**. Traumatic brain injury and the frontal lobes: What can we gain with diffusion tensor imaging? Cortex 2012; 48: 156-165.
13. Wang J, Shaffer ML, **Eslinger PJ**, Sun X, Weitekamp CW, Patel MM, Dossick D, Gill DJ, Connor JR, Yang QX. Maturational and aging effects on human brain apparent transverse relaxation. PLoS ONE 2012; 7: e31907.
14. **Eslinger PJ**, Moore P, Antani S, Anderson C, Grossman M. Apathy in frontotemporal dementia: behavioral and neuroimaging correlates. Behavioural Neurology 2012; 25: 127-136.
15. Armstrong MJ, Naglie G, Duff-Canning S, Meaney C, Gill D, **Eslinger PJ** et al. Roles of Education and IQ in Cognitive Reserve in Parkinson s Disease-Mild Cognitive Impairment. Dementia and Geriatric Cognitive Disorders Extra 2012; 2: 343-352 (DOI: 10.1159/000341782)

D. Research Support

Ongoing Research Support

National Science Foundation	Baker (PI)	09/01/08—7/30/13

The Education Effect and Demography of Risk: Reasoning and Decision-making about Alcohol Use
Role: Co-Investigator:
The goal of this project is to establish the causal effects of formal education on health decisions.

Canadian Institutes of Health Research Marras (PI) 03/01/13-02/28/17
Predicting outcome in Parkinson's disease cognitive impairment
Role: Co-Inestigator
This project investigates the role of select genes and varying cognitive phenotypes in progression to cognitive impairment in Parkinson's disease

The Hershey Company Karunanayaka(PI) 12/01/11-6/30/13
Neurofunctional Network Involving Affective Responses of Chocolate
Role: Co- Principal Investigator
This project characterizes the affective attributes of chocolate odor on human reward neural networks utilizing integrated behavioral, fMRI and EEG methodologies.

R01 AG027771-04 Yang (PI) 04/01/08-03/28/13
Neuroimaging Study on Function-Structure Relationship of the Olfactory Deficit in AD
Role: Co-Investigator
This project examines an olfactory fMRI biomarker of early Alzheimer's disease.

R01 NS060722 Huang (PI) 05/01/09-04/31/14
Role: Co-Investigator
Structural Marker(s) of Parkinson's Disease Progression
This is a longitudinal study to delineate structural changes and their function correlations during PD progression

RO1 ES019672 Huang (PI) 08/01/11-07/30/15
Regional Brain Manganese Accumulation and Functional Consequences in Welders
Role: Co-Investigator
This is a longitudinal study to measure the regional brain Mn deposition in response to environmental exposure, delineate its functional correlations in "asymptomatic" welders.

U01 NS082151 Huang (PI) 10/01/12-9/30/17
Multimodal MRI markers of nigrostriatal pathology in Parkinson's disease
Role: Co-Investigator
This is a longitudinal study to investigate multimodal MRI techniques in combination with fluid-based iron (Fe) protein profiles to serve as *in vivo* markers for PD-related nigrostriatal pathology

Completed Research Support (within the past 3 years)

Pennsylvania Department of Health Eslinger/Nguyen (PI) 07/01/09-12/31/12
Functional Brain Imaging of Memory and Language in Epilepsy Patients Undergoing Anterior Temporal Lobectomy: Predictions of Cognitive Outcomes
This project examines functional localization of memory and language abilities and their changes in patients before and after temporal lobectomy

Michael J. Fox Foundation Marras (PI) 09/01/08-08/31/12
Validating the Montreal Cognitive Assessment (MoCA) for the Diagnosis of Mild Cognitive Impairment (MCI) in Parkinson's Disease
Role: Co-Investigator
This project investigated early cognitive changes in Parkinson's disease

Clinical and Translational Science Institute Pilot Project Grants/Penn State University
Effect of Bright Light Treatment on Depression of Elders in Long-term Care
Ballentine (PI) 09/01/09-06/30/12
Role: Co-Investigator
This project examines the benefit of bright light therapy on the sleep and cognition of institutionalized elderly at a local retirement village.

Woodward Endowment for Medical Science Education/PSU College of Medicine
The Influence of Metacognition on Second Year Medical Students' Mental Representations of Knowledge Eslinger (PI) 07/01/08-06/30/11
This project assessed the use of metacognitive strategies in medical student learning.

Children's Miracle Network Eslinger (PI) 07/01/08-06/30/11
Functional Brain Imaging Resources for Childhood Cancer Survivors
The project applied cognitive fMRI brain morphometric and analyses to post-treatment effects in a large sample of acute lymphoblastic leukemia survivors