

# Memory Formation in Middle-Aged Adults: Dynamics of the BOLD Signal Across Repetitions

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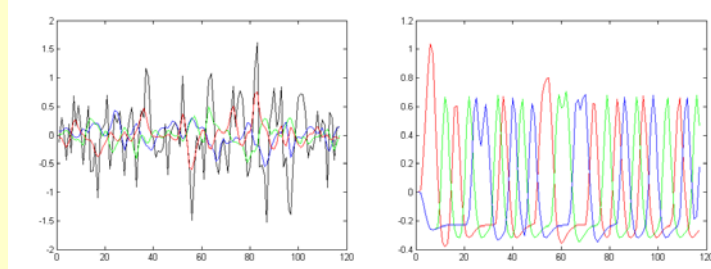


## INTRODUCTION

The past decade of functional imaging research has provided evidence of separable non-unitary systems for encoding and retrieval processes in the domain of episodic memory. Repetition suppression or adaptation paradigms evoke signal in numerous brain regions including the mesial temporal lobe. Here, repeating information has been shown to correspond to progressively decreasing signal in encoding areas such as the hippocampus and entorhinal area. This paradigm has electrophysiological support with depth electrodes in human and nonhuman primates, indicating decreased neural firing and potentially increased neural efficiency as the item or episode becomes encoded. Numerous studies have employed repetition paradigms to document the adaptation response; however, prior studies did not explore how the connectivity within the network is effected by repetition or even during encoding. **AIM:** Investigate the relationships between brain regions during the encoding response using an event-related fMRI paradigm and develop an understanding of how the brain might form a memory.

## METHODS

Two conceptual approaches were used to analyze the fMRI images. First, we used a traditional approach with parametric modulation based on repetition to investigate which regions showed attenuation in the BOLD response over repeated trials. In the second approach, we examined how the hippocampus and amygdala interact with other brain regions across repeated trials. Using an in-house variant of psychophysiological interactions (PPI) to investigate context-dependent connectivity, we were able to identify regions where connectivity with the left and right hippocampus did not change over repetitions (repetition-invariant connectivity [RI]) and regions that changed with repetition (repetition-dependent connectivity [RD]).



PPI uses the seven regressors illustrated to the left to explore task-related connectivity. In the left-most graph: red, green, blue lines represent the interaction of a repetition (right figure) and the hippocampal signal (black line) in the left figure. In the right figure: red, green, and blue lines represent the shape of the response for each repetition. The estimated amplitude of the red, green, and blue lines in the left graph are the change in connectivity related to the task for each repetition. Positive values represent an increase in connectivity, while negative values represent a decrease in connectivity. This model allows the connectivity and BOLD response to fluctuate by repetition.

## IMAGING

Thirty-two participants underwent fMRI scanning. All were middle-aged adults (39 - 64, mean 52 y.o.) cognitively normal and physically healthy and provided written informed consent. The protocol was approved by the local IRB.

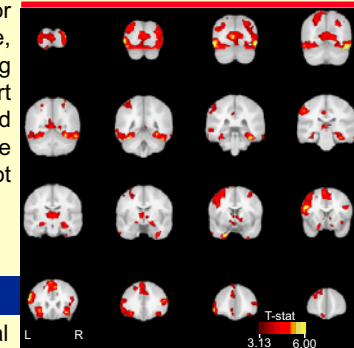
Task: Black line drawings from a standardized picture set were presented. Forty items were presented in 4 counterbalanced sets of 10 during this event-related task. Specific items were presented 3 times each. The participant was instructed to attend to each picture presentation and make a response using an MRI-compatible optical response box. To ensure a deep level of encoding, participants were required to make a semantic decision about each presented object (whether it was natural or man-made) with a yes/no button press. Half of each set were natural objects. The software Presentation and a goggle system, set at 800 X 600 from Resonance Technology (Northridge, CA, USA) were used to deliver the stimuli and log participant responses.

Scanning Procedures: After higher order shimming, a T2\* gradient-echo EPI sequence was used. The EPI parameters were as follows: echo time (TE) = 30 ms; repetition time (TR) = 2000 ms; flip angle = 90 degrees; acquisition matrix = 64 x 64 voxels; field of view (FOV) = 240 mm. Thirty sagittal slices of brain were acquired within each TR. Voxel resolution was 3.75 x 3.75 x 5 mm (4mm thick slices with a 1 mm skip). A time course of 120 (x4) of which the initial 3 time-points were discarded. To correct for EPI image distortions, 3D field maps (co-planar with the fMRI slices) were acquired on each subject by measuring the phase of non EPI gradient echo images at two echo times (7 and 10 ms). Static field inhomogeneity correction was achieved using FSL.

Image preprocessing included: correcting for slice-timing, motion-correction, fieldmap correction, spatial normalization to the EPI template in MNI space, resampling to 2mm isotropic voxels, and smoothing with an 8 mm FWHM Gaussian filter. Single subject activation maps and adaptation responses were derived using a general linear model with the following terms: stimulus convolved with a canonical hemodynamic response function, high frequency signal filtering (cutoff = 1/128 Hz), motion parameters and their derivatives, and a parametric term to model a linear change over repetition. Our in-house variant of PPI was used to investigate hippocampal connectivity. All figures represent second-level analyses of contrast images from the two models.

## RESULTS

### Adaptation Response and Hippocampal ROI

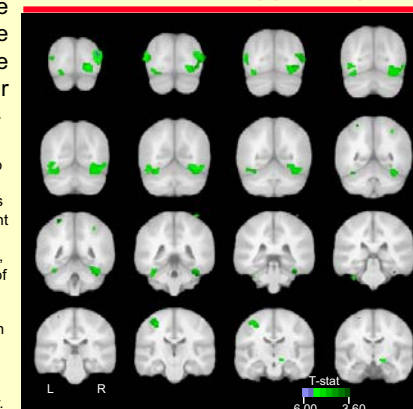


**Left:** Coronal slices from Y= -96 to Y= 54 showing the adaptation response at  $p < .01$  (FDR corrected) in 50 contiguous grey matter voxels. Significant regions included: bilateral hippocampus, amygdala, fusiform gyrus, inferior frontal lobe, thalamus, superior parietal lobule, middle and inferior occipital, left middle cingulate, left inferior parietal lobule, and left precuneus.

**Right:** left and right hippocampal and amygdala regions of interest. The intersection of these ROI and the adaptation responses (left) were used as seeds in the PPI analyses (below).

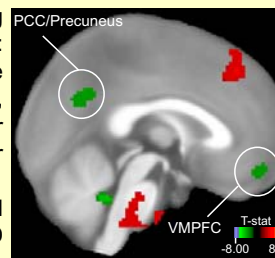


### PPI with the Left Hippocampus and Amygdala

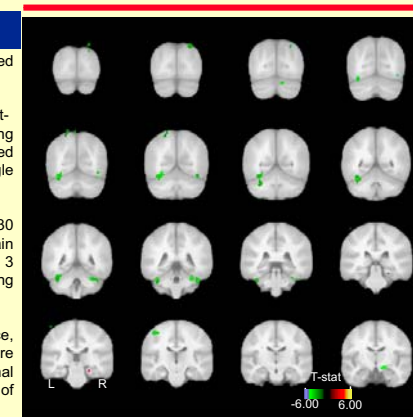


**Left:** Coronal slices from Y= -86 to Y= -11 showing RD connectivity ( $p < .001$ , uncorrected). Decreasing connectivity was observed in: bilateral fusiform gyrus, middle occipital gyrus, right hippocampus, left precentral gyrus, left superior parietal lobule, and the right inferior parietal lobule.

**Right:** RI connectivity maps formed by the conjunction of the RD contrast  $p > .1$  (unc) and the average connectivity contrast  $p < .001$  (unc) in 20 voxels.

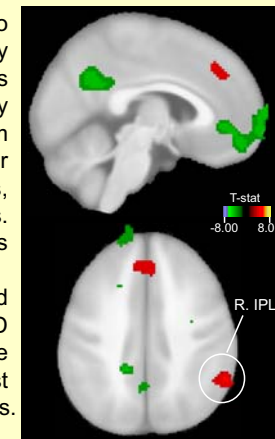


### PPI with the Right Hippocampus and Amygdala

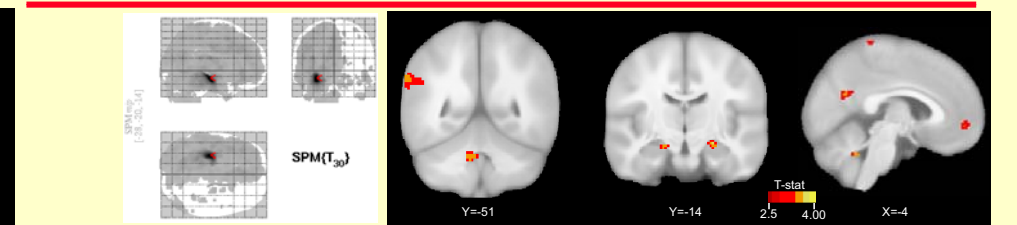


**Left:** Coronal slices from Y= -86 to Y= -11 showing RD connectivity ( $p < .001$ , uncorrected). Regions showing decreasing connectivity include: bilateral fusiform gyrus/cerebellum, left superior parietal lobule, left central sulcus, and left insula/inferior frontal gyrus. The right parahippocampal gyrus exhibits an increase in connectivity.

**Right:** RI connectivity maps formed by the conjunction of the RD contrast  $p > .1$  (unc) and the average connectivity contrast  $p < .001$  (unc) in 20 voxels.

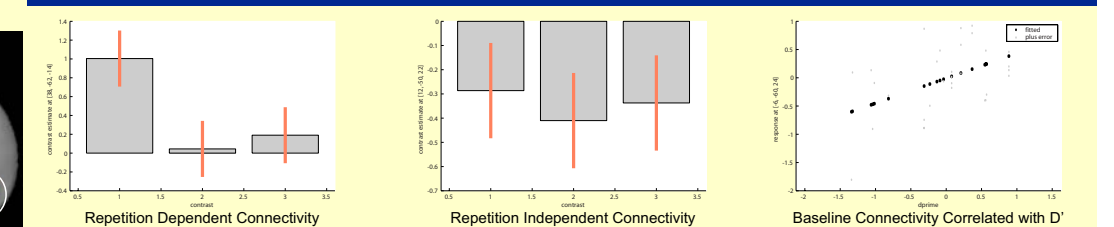


### Baseline Connectivity with the Left Hippocampus Predicts Encoding Success



**Left:** A maximum intensity projection of connectivity with the left hippocampus/amygdala thresholded at  $T \sim 10$ . The intrahemispheric dominance of the connections demonstrates the importance of studying baseline (and resting) connectivity. **Right:** Correlation of  $d'$  and connectivity with the left hippocampus/amygdala. Several known memory areas exhibited a positive correlation including: VMPFC, PCC/Precuneus, bilateral hippocampus, and the left supramarginal gyrus. This finding suggests that the baseline connectivity is critical in memory formation.

## DISCUSSION



This study reveals several important findings:

- (1) there are RD and RI effects on the hippocampal memory network;
- (2) involvement of sensory association regions potentially decreases as the memory becomes stronger;
- (3) memory paradigms should consider the effects of repetition on the BOLD signal when interpreting their results;
- (4) functional brain networks, although they might not exhibit a significant BOLD response, may still contribute to memory formation; and
- (5) the state of the brain prior to encoding influences subsequent memory.

In addition to informing our understanding of normal memory function in terms of functional brain networks, we believe these methods will be critical to investigating memory change in aging and disease. Future studies are aimed at investigating how baseline/resting connectivity might be modulated and how that might impact memory and changes in these networks in aging populations, especially those with risk factors for AD. Many of the regions identified as showing altered connectivity during encoding, compared to rest, are regions that have also been implicated in AD pathology. These findings provide a potential explanation of why memory might be impaired in patients.

## ACKNOWLEDGEMENTS

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