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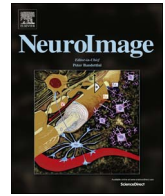
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Retrieval of high-fidelity memory arises from distributed cortical networks



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ABSTRACT

Medial temporal lobe (MTL) function is well established as necessary for memory of facts and events. It is likely that lateral cortical regions critically guide cognitive control processes to tune in high-fidelity details that are most relevant for memory retrieval. Here, convergent results from functional and structural MRI show that retrieval of detailed episodic memory arises from lateral cortical–MTL networks, including regions of inferior frontal and angular gyri. Results also suggest that recognition of items based on low-fidelity, generalized information, rather than memory arising from retrieval of relevant episodic details, is not associated with functional connectivity between MTL and lateral cortical regions. Additionally, individual differences in microstructural properties in white matter pathways, associated with distributed MTL-cortical networks, are positively correlated with better performance on a mnemonic discrimination task.

Introduction

Long-term memory (LTM) is believed to emerge from complex interactions between multiple regions of the cerebral cortex and subcortical structures. Details of the functional relationships between regions in lateral cerebral cortex that support cognitive control processes (Donoso et al., 2014; Barredo et al., 2015) and those in the medial temporal lobe (MTL) that are necessary for retrieval of LTM (Squire et al., 2007), however, are not well understood. The LTM literature suggests that processes supporting mnemonic selection, which resolves interference among overlapping memories (Kostopoulos and Petrides, 2016; Nee and Jonides, 2008; Badre et al., 2005), and judgment of the relevance of episodic details (Cabeza et al., 2008), are amongst key contributions from cognitive control during retrieval that are associated with increased engagement of lateral cortical regions. Our goal here is to elucidate the role of distributed cortical networks that arise during episodic memory retrieval and examine whether interactions between cognitive control regions in lateral cortex and MTL memory regions differ depending upon the qualitative experience of memory retrieval. Specifically, we distinguish between memory when retrieval is based on discrimination of specific details (i.e., high fidelity information) versus when old/new recognition for items is based on more generalized information.

Behavioral classification of these different qualitative experiences of LTM retrieval have been subject to different interpretations according to competing psychological models (Yonelinas et al., 2010; Wixted,

2007), and substantial controversy remains related to concepts about neural activity associated with explicit recognition (Wais, 2013; Yassa and Stark, 2011; Norman, 2010). We adopted an approach, therefore, using a neurocomputational model (Norman and O'Reilly, 2003) aimed at revealing neural activity evoked when memories were retrieved with objective and accurate information for the specific details of common visual objects—high-fidelity memory. Retrieval of such detailed information from prior experiences is commonly characterized as a function of the hippocampal formation (Brown and Aggleton, 2001; Squire and Zola-Morgan, 1991), an area of the MTL that includes the dentate gyrus, hippocampus proper, subicular complex and entorhinal cortex.

The ability to separate the traces associated with each of millions of distinct elements in episodic memory has been attributed to neurocomputational processes in the hippocampus in both humans and rodents (Bakker et al., 2008; Fortin et al., 2004). At the computational or representational level, this process is called pattern separation (Norman and O'Reilly, 2003; McClelland et al., 1995) and is made possible by the unique organization in the dentate gyrus of the hippocampus that supports sparse coding and potentially benefits from life-long neurogenesis (Aimone et al., 2011). Results from human neuroimaging studies have identified increased activity in the hippocampal formation associated with behavioral responses thought to be based on pattern separation processes during memory retrieval (Suthana et al., 2015; Bakker et al., 2008; Kirwan and Stark, 2007).

We collected event-related functional MRI (fMRI) data during an old/new recognition task in order to generate activity and connectivity

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maps for MTL and lateral cortical regions associated with task-related remembering of object memoranda. Specifically, we focused on lateral cortical regions that have been identified as centers of cognitive control contributing to episodic retrieval (Kostopoulos and Petrides, 2016; Bellana et al., 2016; Barredo et al., 2015; King et al., 2015; Kuhl and Chun, 2014; Hutchinson et al., 2014; Frithsen and Miller, 2014; Wagner et al., 2005; Badre et al., 2005). The analyses included regions of the ventrolateral prefrontal cortices (VLPFC) that have been associated with processes that resolve interference during mnemonic selection and regions of lateral parietal cortices that have been associated with processes that direct attention to awareness of details held in memory. Data were also collected during an independent functional localizer task in order to identify regions in lateral occipital cortex with increased sensitivity for representation of the memoranda (Schwarzlose et al., 2008).

Our working framework was that high-fidelity memories arise from bringing into mind detailed information for a particular retrieval goal (i.e., retrieval of sufficient details to support discrimination), which involves processes to tune awareness and selection of the most relevant information. In order to identify distributed networks that we hypothesized to be intrinsic for such processes, methodologically, we examined functional connectivity with lateral cortical regions seeded from univariate results for memory regions of the MTL. Low-fidelity memories, according to this framework, arise from simple item memory or generalized recognition. Low-fidelity retrieval might result from several mechanisms including: a failure to properly cue the system for detailed retrieval, a failure of the system to retrieve details that had been encoded and cued, or a failure to initially encode the relevant details. Regardless of the mechanism(s), we expected these more general, low-fidelity memories would also be associated with MTL signals. We aimed to test the hypothesis that the behavioral distinction in retrieving high-fidelity discrimination-based memory, relative to recognition based on low-fidelity item memory, is associated with increased functional connectivity in discrete MTL-cortical networks. Diffusion-weighted MRI data were also collected to explore the possible relationship between microstructural properties in white matter (WM) pathways related to functional MTL-cortical networks we aimed to identify and discrimination-based memory performance.

Methods

Participants

Twenty-one healthy younger adults between the ages of 20 and 29 years (10 males; mean age 22.8 ± 2.5 years) participated in this study. Inclusion criteria were: native speakers of English, completion 14 or more years of education, right-hand dominant, normal or corrected-to-normal vision, and free from any psychotropic medications and/or conditions contra-indicated for fMRI. Participants gave their informed consent in accordance with the Institutional Review Board of the University of California, San Francisco, and received a small fee in compensation for their time. One participant's data were excluded from analysis because he fell asleep during one block of the task and then presented excessive head movement.

Stimuli

330 object images were displayed at 1024×768 pixel resolution on an LCD computer monitor. Each image contained a photograph of a common object, in color and centered on a white screen, from a subset of the Mnemonic Similarity Task (Stark et al., 2012). 140 of these images were paired with very similar objects (i.e., lures) and the remaining 50 images were distinctly novel objects. Stimuli were presented using E-prime 2.0 (Psychology Software Tools, Inc.; Pittsburgh, PA).

Procedure

We presented the task in two sessions with a delay interval between the study and test sessions of approximately 60 min. In the study session outside of the MRI scanner, participants viewed one image from each of the 140 object pairs (stimulus presentation was 2.5 s) while responding to two incidental questions designed to promote in-depth visualization of each object: 1) “yes or no, will the object fit inside a ladies medium shoe box?”; and 2) “yes or no, can you carry the object across the room using only your right hand?”. The two questions were presented in separate runs so that participants viewed each object image (i.e., target for the test session) twice. Participants were kept naïve to the memory test until being instructed for the test session immediately prior to their scan.

The test session involved ten blocks, each of which contained 33 trials. On each trial, participants viewed one object image on the LCD monitor via a mirror installed on the scanner headcoil (stimulus presentation was 2 s). Immediately following presentation of the object image, a response screen was presented that cued the participant to enter an old/new recognition rating on the response box held in the right hand according to a four-level confidence scale (response collection duration was 2 s). Participants were instructed to respond whether each item was 1=definitely old, 2=maybe old, 3=maybe new, or 4=definitely new (Fig. 1). A 2 s odd/even numbers task followed in order to end participants' engagement in the recognition task before the next trial. Following the odd/even task, a fixation stimulus was presented for 2–12 s to jitter the onset for the next trial and optimize signal deconvolution in our rapid-event-related design. Fourteen targets (i.e., studied objects), fourteen lures (i.e., very similar objects) and five novel items (i.e., distinctly new objects) were presented in each block for a total run time of 380 s. A target and its paired similar lure were never presented in the same test block, and the order of target first or similar lure first was counter-balanced across all the trials. Presentation of target, lure and novel trials was randomized within each block, and block order was counter-balanced across of participants. For analysis, trials were later sorted into hits (“old” responses to targets), misses (“new” responses to targets), lure correct rejections (“new” responses to lures), lure false alarms (“old” responses to lures), novel correct rejections (“new” responses to novel items), and novel false alarms (“old” responses to novel items) on the basis of participants' responses.

Verbal instructions and brief practice runs preceded both the study and test sessions, and participants were encouraged to repeat the practice runs until they were comfortable with the timing and procedure of the experiment sessions. Verbal instructions for the participant's first practice run made clear that some test images were the same, relative to those viewed during the study session, some were very similar and a few were completely novel. Once participants were comfortably situated in the scanner, they completed one high-resolution structural scan, one independent region of interest (ROI) localization run (described below in the fMRI data analysis), 10 test runs, and a diffusion-weighted imaging (DTI) scan. The test practice run was also repeated during the structural scan.

Mnemonic similarity task: discrimination and generalization

Our study utilized a behavioral paradigm that provides both a traditional measure of explicit recognition, as well as measures of discrimination and generalization. Discrimination requires memory of specific details that make an episode unique, while generalization results from an overall match with information stored in LTM. Recognition of a target as “old” can be based on contributions from both processes, although memory judgments based on discrimination likely involve more specific details relevant to the retrieval goal. This old/new recognition test requires the ability to discriminate highly similar lures from the actual targets so as to reflect a behavioral readout

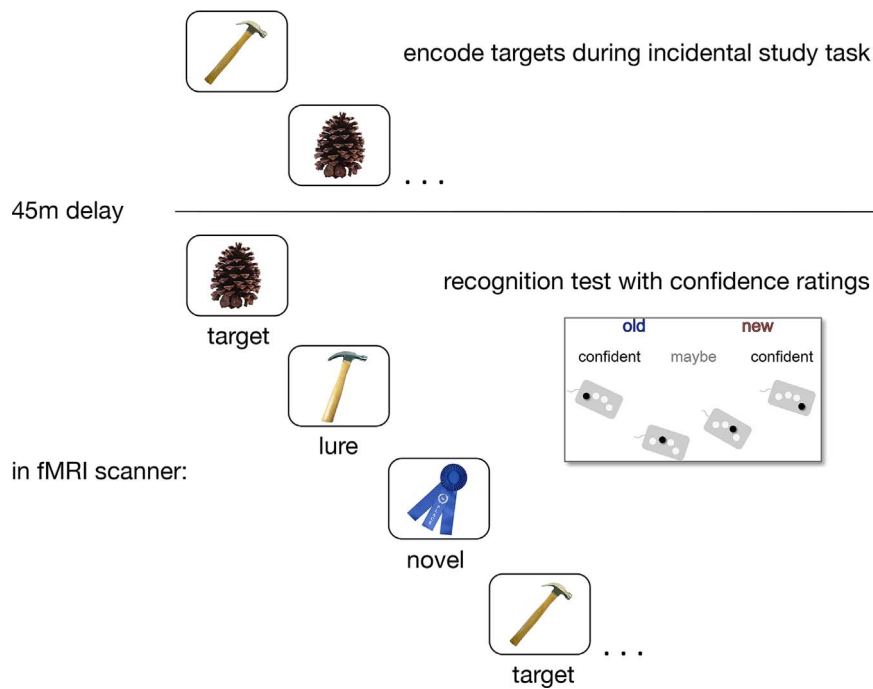


Fig. 1. Experimental procedure. A schematic shows the two sessions used in the behavioral paradigm. In the study session, participants viewed one image from each of 140 object pairs while responding to two incidental questions, which were presented in separate runs. The study questions promoted in-depth visualization of each object (i.e., yes or no: will the object fit inside a ladies medium shoe box; and can you carry the object across the room using only your right hand?). Images not shown during the study session were used as lures in the test session (i.e., lures similar to studied target images). During test sessions in the MRI scanner, approximately one hour after the study session, participants gave an “old” or “new” response with a confidence rating as target, similar lure and novel objects were presented. A 2 s odd/even numbers task followed in order to end participants’ engagement in the recognition task before the next trial was presented.

of, or proxy for, the efficacy of an underlying pattern separation process (Stark et al., 2012). Thus, in our paradigm, correct rejections of similar lures indicated when retrieval during the recognition test most likely relied more on discrimination, which involved remembering details of the targets versus no memory for the details of the similar lures. In contrast, false alarms to similar lures, considering the lack of specificity underlying these responses, likely indicated generalization-based memory (i.e., old/new recognition based on low-fidelity memory) or possibly guesses about old/new decisions on trials when no memory for the type of object presented was retrieved. Consequently, we characterized memory retrieval based on discrimination as having high fidelity and retrieval of generalized memory as having low fidelity.

Although it is tempting to map discrimination and generalization, along with associated fMRI activity, directly onto pattern separation and pattern completion processes, respectively, several factors here preclude a simplified interpretation. First, during explicit recognition, responses based on discrimination may involve concurrent input from both pattern separation and pattern completion. Second, a false alarm to a lure could arise from pattern completion or the failure of pattern separation. Finally, as both pattern completion and separation are thought to occur in the hippocampal formation (Kirwan and Stark, 2007), and even in adjacent subfields of the hippocampus (Bakker et al., 2008), the spatial resolution of traditional fMRI methods (rather than high-resolution methods) precludes the ability to isolate these processes. Thus, as we address our central hypothesis, we refer to memory performance in terms of discrimination and high-fidelity retrieval, or generalized recognition and low-fidelity retrieval.

Behavioral discrimination index

Our analysis of memory performance focused on a behavioral measure of each participant’s discrimination of the Lures as new during an old/new recognition task. Recognition of Targets as “old” could be based on underlying processes for discrimination, for general-

ization, or, most likely, contributions from both processes. Correct rejection of Lures as “new,” however, indicates memory judgments driven by underlying discrimination (i.e., any given correct rejection may have identified differences between a Lure and its paired Target, or between a Lure and all other objects presented in the procedure). Thus, we used a Lure Discrimination Index (LDI) to assess each participant’s qualitative performance in discriminating Lures during the memory test, such that $LDI = (\text{proportion Lure CR} - \text{proportion Novel FA})$. The LDI we used is similar to behavioral measures applied in other work using the Mnemonic Similarity Task, but which included “old,” “similar” and “new” response options during the memory test, such as Reagh and Yassa (2014) and Clemenson and Stark (2016).

By augmenting the simple proportion for responses to Lures based on discrimination (i.e., Lure CR) with the subtraction of the proportion of false alarms to an independent class of novel stimuli (i.e., Novel FA), the LDI provides a more specific scale for each participant’s effectiveness in discriminating details in memory and how their effectiveness may have been influenced by their overall response bias in the old/new task (i.e., bias to respond “old” to targets and to lures, Macmillan and Creelman, 2005).

fMRI acquisition

All images were acquired on a Siemens 3 T Magnetom Trio. Thirty-three 3 mm T2*-weighted gradient-echo slices (no skip, voxel size=3 mm isotropic, TR=2000 ms, TE=28 ms, flip angle 80°, and 240 mm² FoV) were acquired in an axial oblique orientation parallel to the longitudinal axis of the hippocampus. In order to achieve 3 mm slices, no skip, within our desired 2 s repetition time, the field of view resulted in a small sacrifice of whole-brain coverage for some participants. The EPI slice prescription coverage always included the ventral extent of the temporal lobes and sacrificed a limited area of superior prefrontal cortex for approximately half of the participants. Images were corrected for slice timing, motion artifacts and co-registered to

the middle volume of the first functional run. Functional data were modeled using a general linear model (GLM) in Analysis for Functional NeuroImages (AFNI_2011) software (Cox and Hyde, 1996). In addition, high-resolution anatomical (T1-MPRAGE) data sets were collected. Finally, diffusion weighted imaging was acquired with 64 directions and five b-zero volumes, and these data were processed with FSL tools before analysis with probabilistic tractography in a participant's native space.

fMRI localizer task and analysis

The scanner session began with an independent localizer task that was used to identify stimulus-sensitive ROIs in the lateral occipital cortex (Schwarzlose et al., 2008; Grill-Spector and Weiner, 2014). Participants performed a one-back task during three repetitions of 17.5-s blocks that presented either 35 object stimuli from categories other than the targets, grid-scrambled object stimuli, or natural scene stimuli. Each stimulus block was separated by a 17.5-s rest period (fixation). Participants were instructed to indicate when an image matched the preceding image with a button press. Based on the conclusions from Schwarzlose et al. (2008), the contrast of objects > grid-scrambled objects was used in an analysis independent of the GLM for the main LTM task to localize object-selective areas in lateral occipital cortex (LOC) bilaterally. These results identified ROI's associated with visual imagery that supports representations of mnemonic information instantiated during goal-directed retrieval (Wing et al., 2014; Wais et al., 2010).

Across participant normalization

The high-resolution structural images for each participant were combined to create a study-specific template (based on Talairach space) for across-participant normalization of structural and functional data. The template brain was processed using Advanced Normalization Tools (ANTS; Avants et al., 2009), a large deformation diffeomorphic transformation tool. For each participant, all functional data maps (univariate and functional connectivity) and probabilistic tractographic maps were normalized from native space to the template using that participant's unique transformation matrix and vector field.

Univariate analyses

Each participant's GLM was based on five task-related regressors and six nuisance variables, including three translational (X, Y, Z) and three rotational (pitch, roll, yaw) motion parameters. Task-related regressors modeled the amplitude of the impulse response for the 20 s (10 TR's) following stimulus onset and were categorized according to hits, misses, lure correct rejections, lure false alarms, novel correct rejections. A sixth category, which included all other volumes (including from the very few trials for which no behavioral response was recorded), served to model baseline. Volumes associated with novel false alarms were categorized into the censor list because the majority of participants had too few of these types of trials to model reliably. After computing the GLM with AFNI 3dDeconvolve, the fit coefficients maps for the five critical task-related regressors were extracted, re-sliced to match the spatial grid for T1 anatomical files in 2.5 mm isotropic voxels, and then smoothed with a 4 mm FWHM Gaussian kernel. Finally, these coefficient maps were passed through ANTS in order to normalize all of the functional data onto the same study-specific template. Statistical maps for pair-wise comparisons were determined by a voxel-wise threshold of $p < 0.005$, and then corrected to parameters determined in AFNI 3dClustSim (i.e., 2.5 mm isotropic voxels, smoothed 5.2 mm FWHM as estimated by AFNI 3dFWHMx, 10,000 iterations, Dec 2015 version), which showed reliable clusters of activation to be greater than 27 voxels, p -corrected < 0.05. For purposes of comparing group-level statistics associated with significant

regions of interest (ROI), mean fMRI signal intensities for the task-related regressors are plotted on a scale where zero (0.00 signal intensity) reflects the constant (mean) level of activity over the entire functional run in that ROI.

An additional analysis of responses given with high confidence (i.e., “definitely” old or new) used specific GLMs that modeled nine regressors: hits, lure correct rejections and lure false alarms made with high confidence; hits, lure correct rejections and lure false alarms made with low confidence; misses; novel correct rejections and a censor list that included all other volumes. The remainder of this high-confidence analysis followed the same procedure as the original analysis.

Functional connectivity analyses

A trial-wise β -series correlation method was developed using AFNI tools to analyze whole-brain functional connectivity based on seed regions of interest (ROIs) obtained in the univariate analyses (Rissman et al., 2004). For each participant, a new GLM design matrix was constructed to model each trial with a unique covariate, resulting in a total of 330 covariates of interest (33 trials per run \times 10 runs), and processed in AFNI 3dSynthesize for each task-related category. The six motion parameters were factored into the GLM design matrix. Whole-brain maps of β -series correlation coefficients were estimated for each task-related category, and these maps were re-sliced to match the grid for T1 anatomical files before being smoothed with a 4 mm FWHM Gaussian. Seed ROIs from the main task and object localizer task analyses were inverse-warped to a participant's native brain space, and AFNI 3dfim+ was used to calculate cross-correlations of ideal reference waveforms with the measured time series (i.e., 20 s) for each voxel for each category (i.e., hits, misses, lure correct rejections, lure false alarms and novel correct rejections). β -coefficient values of R-correlation maps were z-transformed using Fisher's algorithm in AFNI 3dcalc, and then passed through ANTS in order to normalize all of the functional data onto the same study-specific template. Statistical maps for pair-wise comparisons were determined by a voxel-wise threshold of $p < 0.005$, and then corrected to parameters determined in AFNI 3dClustSim (i.e., 2.5 mm isotropic voxels, smoothed 5.2 mm FWHM as estimated by AFNI 3dFWHMx, 10,000 iterations, Dec 2015 version), which showed reliable clusters of activation to be greater than 27 voxels, p -corrected < 0.05.

An additional functional connectivity analysis was based on the seed regions of interest (ROIs) obtained after the high-confidence univariate analysis. For this functional connectivity analysis, a new GLM design matrix was constructed to model each trial with a unique covariate according to the same procedure as in the original analysis. Correlation coefficients were estimated for eight task-related categories: hits, lure correct rejections and lure false alarms made with high confidence; hits, lure correct rejections and lure false alarms made with low confidence; misses; and novel correct rejections.

Analyses of resting state functional connectivity fMRI data have revealed that head motion can produce spurious but spatially structured patterns in connectivity between distant voxels (Power et al., 2014). Although this movement-related artifact has not been associated with event-related whole-brain functional connectivity analyses such as we have conducted here, we examined the relationship in our data between participants' head motion during the two conditions of interest: lure correct rejections and lure false alarms. Our control analysis computed the spatial movement along six motion parameters for each trial of interest (i.e., lure correct rejection or lure false alarm trial) in comparison to the immediately preceding trial and summated the absolute values of those shifts as a total displacement value for each trial of interest. The mean displacement values for lure correct rejection trials and lure false alarm trials were calculated for each participant and then submitted to a group comparison. For the group, mean displacement during lure correct rejections (0.130 ± 0.021 mm)

was not different than mean displacement during lure false alarms (0.136 ± 0.025 mm). Therefore, we are confident that our group functional connectivity results are not confounded with spurious systematic correlations associated with participants' head motion.

DTI microstructure analysis

Diffusion weighted images were collected for 19 of 20 participants, and these data were corrected for motion and eddy current effects, realigned and co-registered to high-resolution structural T1 images using FSL tools (64 gradient directions, b -value=2000 s/mm², TR=7300 ms, and TE=86 ms). An MR scanner software malfunction precluded collecting DTI data for one participant. Segmentation and parcellation of the T1 images was accomplished using the Freesurfer 5.3.0 software library, and these outputs were used to define principal WM pathways via atlas-constrained probabilistic tractography with TRACULA tools (Yendiki et al., 2011). Spurious results were removed by thresholding the DTI maps to include only those voxels through which at least 50 tracts passed (out of 5000 samples from the seed voxel).

Given the difference in axial oblique alignment between the DTI and EPI slice prescriptions, the 19 structural datasets for participants in the analysis of microstructural properties contributed to the development of an additional study-specific template for across participant normalization of DTI data. Each participant's DTI data was transformed to this study specific ANTS template, and then converted into binary values and summed across the 19 participants in order to develop a group probability map for illustrative purposes with the FSL Probtrackx program (van Schouwenburg et al., 2013).

Results

Behavioral results

Overall recognition performance was assessed via accuracy for old/new responses given for three stimulus categories: Targets (i.e., object stimuli previously presented during the encoding session), Lures (i.e., the paired object stimuli presented only during the test session), and Novels (i.e., completely novel object stimuli presented only during the test session). Table 1 shows the group mean proportions for hits and false alarms, which resulted in a mean group estimate of $d' = 1.54 \pm 0.10$. When the level of confidence indicated with old/new responses was considered, accuracy varied in each category according to confidence (Table 1). Group mean accuracy was $53 \pm 3\%$ for correct rejection Lures given with low confidence (i.e., "maybe"), as 7 of 20 participants were at the level of chance for their low confidence responses for Lures. Analyses based only on responses given with high confidence are presented following the main analyses of fMRI data that considered all trials collapsed across confidence ratings.

Behavioral LDI

In order to test our main hypothesis about differences in distributed

functional networks underlying retrieval based on high-fidelity discrimination and low-fidelity generalized recognition processes, our analyses focused on the lure discrimination index of each participant's performance during the memory test, such that $LDI = (\text{proportion Lure CR} - \text{proportion Novel FA})$. The index score also facilitated comparisons of individuals' differences in behavioral and neural measures. Group results showed the mean $LDI = 0.56 \pm 0.04$.

Univariate fMRI results

The first step in the group analyses of the fMRI data examined all responses to Targets and Lures, collapsed across high and low confidence, in order to identify regions of the MTL associated with memory retrieval processes. A pairwise t-test identified regions in the MTL where activity associated with hits was greater than activity associated with misses. Although memory retrieval can be associated with reductions in MTL activity to levels below that for learning trials (e.g., repetition suppression), we adopted the general view that positive-going differences are proxies for signals associated with successful recognition. Another, independent pairwise t-test identified regions where activity associated with LureCR (correct rejection of lures) was different than activity associated with LureFA (false alarms to lures). We interpreted MTL clusters showing a difference in activity such that $LureCR > LureFA$ as proxies for signals underlying discrimination, and we took MTL clusters showing a difference in activity such that $LureFA > LureCR$ as proxies for signals underlying generalization. Although false alarms for similar lures on some trials may have been based on guesses about old/new decisions, we believe the behavioral results showing a far lower mean miss rate than mean LureFA rate (Table 1) substantiate using $LureFA > LureCR$ as a fair proxy for signals underlying low-fidelity generalized recognition.

A conjunction of the two independent contrast maps identified the regions of MTL activity associated with recognition memory signals (i.e., hit > miss) that involved underlying discrimination (i.e., $LureCR > LureFA$) or involved underlying generalization (i.e., $LureFA > LureCR$). After cluster-extent parameters were applied (p -corrected < 0.05), two clusters in the hippocampal formation were observed (Fig. 2): one cluster in right entorhinal cortex (ERC) associated with both successful LTM retrieval and accurate discrimination of Lures (fMRI activity: hits > misses, $t_{19} = 2.22$, $p < 0.05$; and $LureCR > LureFA$, $t_{19} = 3.39$, $p < 0.005$), and one cluster in left hippocampus proper associated with both successful LTM retrieval and generalized responses to Lures (fMRI activity: hits > misses, $t_{19} = 2.71$, $p < 0.02$; and $LureFA > LureCR$, $t_{19} = 2.58$, $p < 0.02$).

In addition to identifying the regions of MTL that showed signals associated with memory retrieval based on underlying discrimination or underlying generalization processes (Fig. 2), we examined activity maps in the lateral cortical areas for the contrast of $LureCR$ versus $LureFA$ to identify regions associated with cognitive control processes contributing to episodic retrieval. Specifically, we were interested in activity in regions of inferior frontal gyrus (IFG) (Barredo et al. 2015; Badre and D'Esposito, 2009) and lateral parietal cortex (Bellana et al., 2016; King et al., 2015; Hutchinson et al., 2014; Cabeza et al., 2008)

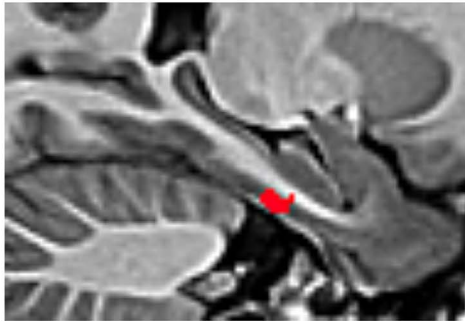
Table 1

Summary of behavioral results. Mean values are shown for performance in each category of the responses during the memory test (SEM). Proportion values were used in analysis of accuracy. In the analysis of confidence ratings, values were used such that 2=definitely and 1=maybe. Mean values in bold face indicate a difference between the group means in that category ($p < 0.05$) and accuracy above the level of chance. For Lures and Novels, FA=false alarms and CR=correct rejections.

[n=20]	Targets		Lures		Novels	
	<i>hit</i>	<i>miss</i>	<i>FA</i>	<i>CR</i>	<i>FA</i>	<i>CR</i>
Proportion	0.81 ± 0.02	0.19 ± 0.02	0.37 ± 0.02	0.63 ± 0.02	0.07 ± 0.01	0.93 ± 0.01
Confidence	1.65 ± 0.04	1.33 ± 0.05	1.49 ± 0.05	1.63 ± 0.03	1.32 ± 0.13	1.90 ± 0.02
	<i>definitely</i>	<i>maybe</i>	<i>definitely</i>	<i>maybe</i>	<i>definitely</i>	<i>maybe</i>
Accuracy	88 ± 2%	69 ± 3%	69 ± 4%	53 ± 3%	90 ± 2%	47 ± 8%

a. discrimination seed:

right ERC (22 -18 -23)



b. generalization seed:

left hippocampus (-22 -13 -18)

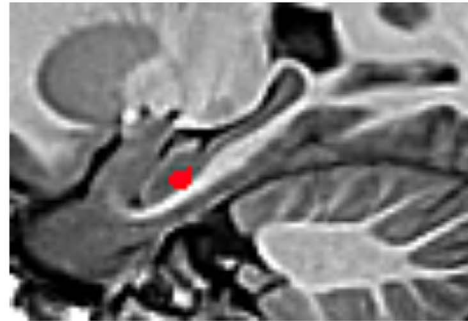


Fig. 2. Conjunctions of statistical maps of MTL fMRI activity. Pairwise comparisons of signals associated with recognition memory and underlying processes identified two regions of interest in the hippocampal formation. A conjunction map was generated for results from independent univariate contrasts showing areas of intersection for activity associated with hits vs. misses and activity associated with correct rejections vs. lures. The conjunction analysis identified one region associated with LTM retrieval and discrimination (a. right entorhinal cortex fMRI activity: hits > misses, and LureCR > LureFA) and one region associated with LTM retrieval and generalization (b. left hippocampus fMRI activity: hits > misses, and LureFA > LureCR). Sagittal views of the group normalized brain template indicate coordinates based on Talairach space.

Table 2

Regions of activity associated with discrimination and generalization. Paired t-tests contrasted fMRI activity associated with correct rejection of similar lures (LureCR) versus false alarms to similar lures (LureFA) (voxel-wise threshold, $p < 0.005$), and results were visually masked to include all clusters in inferior frontal gyrus (IFG) and lateral parietal cortex, which are regions that have been implicated in cognitive control processes guiding episodic retrieval, as well as memory regions in the medial temporal lobe (MTL). Cluster-extent parameters were applied (p -corrected < 0.05). A number of clusters showed activity associated with LureCR greater than LureFA (A), and a few clusters showed activity associated with LureFA greater than LureCR (B). Each cluster is given by anatomical reference, Brodmann Area, coordinates based on Talairach space, peak voxel effect size and total extent in voxels.

Contrasts of univariate activity:			
Region	Coordinates	Peak voxel	Cluster extent
		x y z	t -value
Voxels			
A) MTL and Control regions signaling CR > FA			
Right inferior frontal gyrus (BA47)	45 41 -7	3.37	166
Left inferior frontal gyrus (BA45)	-36 33 8	3.50	54
Left inferior frontal gyrus (BA45)	-43 32 -5	3.66	48
Right inferior frontal gyrus (BA45)	51 32 8	3.54	64
Right entorhinal cortex	22 -18 -23	5.97	72
Left entorhinal cortex	-20 -18 -23	3.40	33
Left parahippocampal cortex (BA27)	-17 -27 -15	3.17	38
Left angular gyrus (BA39)	-53 -64 29	3.95	41
Right angular gyrus (BA39)	57 -55 37	3.13	108
Right angular gyrus (BA39)	51 -61 40	4.81	46
B) MTL and Control regions signaling FA > CR			
Left inferior frontal gyrus (BA44)	-42 23 21	3.37	31
Left hippocampus	-22 -14 -19	4.32	29
Right hippocampus	20 -26 -6	3.37	34
Left intraparietal sulcus (BA39/40)	-48 -61 23	3.54	40

that showed differential activity associated with these effects. We visually masked whole-brain group analysis maps, such that contrast results identified in approximately bilateral inferior frontal gyri and lateral parietal cortices were submitted to further analysis. The analysis revealed a number of regions of IFG and lateral parietal cortex that showed patterns of activity in association with LureCR > LureFA and in association with LureFA > LureCR, after cluster-extent parameters were applied (p -corrected < 0.05) (Table 2, which also includes MTL clusters identified by these contrasts). Univariate activity outside of the visual mask, in approximately right transverse parietal sulcus (BA5/7),

left cingulate sulcus (BA32/33), left thalamus, and right insula, is not analyzed here.

IFG regions in left pars orbitalis (BA47) and bilateral pars triangularis (BA45) showed greater activity in association with LureCR, relative to LureFA. Bilateral regions of angular gyrus (BA39) also showed greater activity in association with LureCR, relative to LureFA. Analysis also showed greater activity in association with LureFA, relative to LureCR, in a region of left IFG, pars opercularis (BA44), and left intraparietal sulcus (BA39/40).

The results of the functional localizer analysis revealed bilateral LOC regions (BA19/37, middle temporal gyri) that showed activity in association with objects (stimuli from categories other than the targets) > grid-scrambled objects (left LOC, $t_{19}=5.39$, right LOC, $t_{19}=4.97$; both $p < 0.001$). Cluster-extent parameters were applied (p -corrected < 0.05), and these ROIs were used in the functional connectivity analysis.

Functional connectivity results

A critical analysis of fMRI data examined whole-brain functional connectivity between lateral cortical regions and MTL regions that signaled LTM retrieval based on either discrimination or generalization. Independent general linear models were estimated for each participant's fMRI data in order to analyze the trial-wise covariance of activity between voxels within the entire brain volume collected. Critically, the multivariate analysis beta-series correlation method (Rissman et al., 2004; Gazzaley et al., 2004) brought the advantage of comparing covariance of activity between voxels in distributed cortical regions along the entire course of the memory test in the MRI scanner, in comparison to the preceding univariate step that contrasted mean parameter estimates.

Our univariate results identified two key regions in the hippocampal formation: in one region of right ERC, increased activity was associated with recognition based on accurate discrimination of specific details, and, in one region of left hippocampus, increased activity was associated with recognition based on underlying generalization. We focused on connectivity between these two functionally defined seed regions with lateral prefrontal and parietal cortices, which were cortical areas we identified in the results of the univariate analyses (Table 2) and have been previously implicated in cognitive control contributions in LTM retrieval processes (Bellana et al., 2016; Barredo et al., 2015; King et al., 2015; Wang et al., 2014; Wais et al., 2010; Johnson et al., 2009). Pair-wise t-tests contrasted connectivity associated with LureCR versus connectivity associated with LureFA in order to identify net-

works of interest using both the discrimination seed (i.e., right ERC cluster) and the generalization seed (i.e., left hippocampus proper cluster). We followed the same procedure from the univariate analysis and visually masked group functional connectivity maps such that network nodes identified in approximately bilateral inferior frontal gyrii, lateral parietal cortices and MTL memory regions were submitted to further analysis.

Because we do not propose that old/new responses to targets were process pure (i.e., recognition based solely on discrimination or generalization), our approach to masking the functional connectivity data was based on a more obvious interpretation about processes associated with responses for LureCR and LureFA. If we applied the conjunction step used in the univariate analysis to the functional connectivity analysis, results for cognitive control ROIs could be overly restricted to show increased connectivity only when recognition of targets was successful purely because of underlying discrimination or generalization. Instead, the approach based on increased connectivity in association with responses to the similar lures provided a more inclusive analysis of contributions to networks engaged during discrimination and generalization.

After cluster-extent parameters were applied (p -corrected < 0.05), functional connectivity with the right ERC cluster discrimination seed was greater in association with LureCR than with LureFA for the following regions: left IFG (BA45/47, $t_{19}=3.45$, $p < 0.005$); right IFG (BA45, $t_{19}=3.72$, $p < 0.005$); right perirhinal cortex (BA28, $t_{19}=3.23$, $p < 0.005$); and bilateral angular gyrus (BA39, right, $t_{19}=2.88$, $p < 0.01$, and left $t_{19}=2.95$, $p < 0.01$). The immediate regions of these cortical network nodes, which revealed greater functional connectivity with the discrimination seed in association with LureCR, relative to LureFA (Fig. 3), not surprisingly, also showed greater univariate activity in association with LureCR, relative to LureFA (Table 2). Notably, functional connectivity with the discrimination seed was greater in association with LureFA than with LureCR for one region in right hippocampus, but not for any lateral cortical regions.

Functional connectivity with the left hippocampus generalization seed was greater in association with LureFA than with LureCR for two clusters in other regions of the left hippocampus, but no other areas in lateral cortex. Our results, therefore, did not reveal long-range functional networks associated with low-fidelity retrieval, which was based on some form of generalized memory.

LOC object localizer ROI analysis

An additional focus of our functional connectivity analysis was to examine networks with the object-sensitive ROI's in LOC that had been revealed by the object localizer task. Previous fMRI studies that examined episodic retrieval of visual stimuli have identified reactivation of signals associated with previous encoding of the memoranda in stimulus-sensitive regions of LOC (Wing et al., 2014; Wais et al., 2010; and see Grill-Spector and Weiner (2014)). Pairwise t-tests contrasted connectivity associated with LureCR versus connectivity associated with LureFA for each the left and the right LOC ROI's. The results showed that functional connectivity with the left LOC object-sensitive ROI was greater in association with LureCR, relative to LureFA, to both left hemisphere lateral cortical regions identified in the main analysis with the right ERC discrimination ROI (IFG, $t_{19}=2.95$, p -corrected < 0.01 ; angular gyrus, $t_{19}=2.93$, p -corrected < 0.01 ; Fig. 4). The right LOC object-sensitive ROI did not show functional connectivity with lateral cortical regions in association with responses to Lures.

Individual differences

We also examined the relationship between individual differences in functional activity and LDI scores to compare participant-to-participant variations in performance with group mean results from the univariate analysis. While certainly still not able to conclude a causal relationship, the positive correlation across participants of a

particular measure of neural activity with LDI scores would bolster the hypothesis that the factor of interest has an important role in support of discrimination-based retrieval. The difference in discrimination-associated activity (i.e., LureCR - LureFA) in the right ERC ROI for each participant was regressed against his/her respective LDI score. Fig. 5a illustrates the comparison across the group.

Univariate fMRI results associated with high-confidence responses

The behavioral results showed that both recognition of targets and correct rejection of similar lures were more accurate for responses given with high confidence (i.e., definitely old or definitely new, respectively). Regardless of whether high-confidence responses are best viewed as quantitatively or qualitatively different than low-confidence responses, their analysis can provide insight into retrieval mechanisms that are less contaminated by noise, weak retrieval signals, or guessing. Thus, an additional analysis was performed to compare the fMRI data associated with old/new responses based on comparable confidence ratings so that activity could be observed in association with high-fidelity memories retrieved with greater confidence. The analysis took account of having a sufficient minimum number of trials in each condition in each participant's GLM so that data from all participants contributed to the group analysis. These comparisons used contrasts of univariate activity in the MTL associated with memory signals and process signals based on high confidence hit $>$ miss, high-confidence LureCR $>$ high-confidence LureFA for discrimination, and high-confidence LureFA $>$ high-confidence LureCR for low-fidelity generalized recognition.

The pairwise contrast of MTL activity associated with high-confidence hit $>$ miss revealed one region predominantly in the left hippocampus ($t_{19}=2.51$, $p < 0.02$). This region associated with high-confidence recognition was anterior to and not adjoining the left hippocampus generalization ROI identified in the univariate results presented above.

An independent pairwise comparison identified regions where activity associated with high-confidence LureCR was different than activity associated with high-confidence LureFA. Results showed one region in posterior left hippocampus where activity associated with high-confidence LureCR was greater than in association with high-confidence LureFA ($t_{19}=3.26$, $p < 0.005$), which we interpreted as a signal for underlying discrimination. A more rostral region in left hippocampus showed activity associated with high-confidence LureFA that was greater than with high-confidence LureCR ($t_{19}=2.46$, $p < 0.02$), which we interpreted as a signal for underlying low-fidelity, generalized retrieval.

A conjunction of these contrast maps revealed no clusters of MTL activity. This pattern suggests, at least for our data, that increased confidence in retrieval was not signaled by simply increased activity in the same ROIs as associated with underlying discrimination or generalization in the results collapsed across all responses, but instead was signaled by differential activity in distinct clusters upstream within the MTL. Notably, fewer observations contributed to the high-confidence analysis, in particular an average reduction from 51 LureFA trials to 26 high-confidence LureFA trials. However, because no MTL ROIs that signaled high-confidence recognition in conjunction with either discrimination or generalization were identified, we do not report results for functional connectivity associated with high confidence.

DTI results

Based on results that revealed increased functional connectivity in a distributed left hemisphere network associated with successful retrieval of discrimination-based memories, we explored microstructural properties of the structural, white matter (WM) (Jones et al., 2013) pathways between nodes of that network. The analysis was focused on WM pathways that spanned regions of the functional high-fidelity

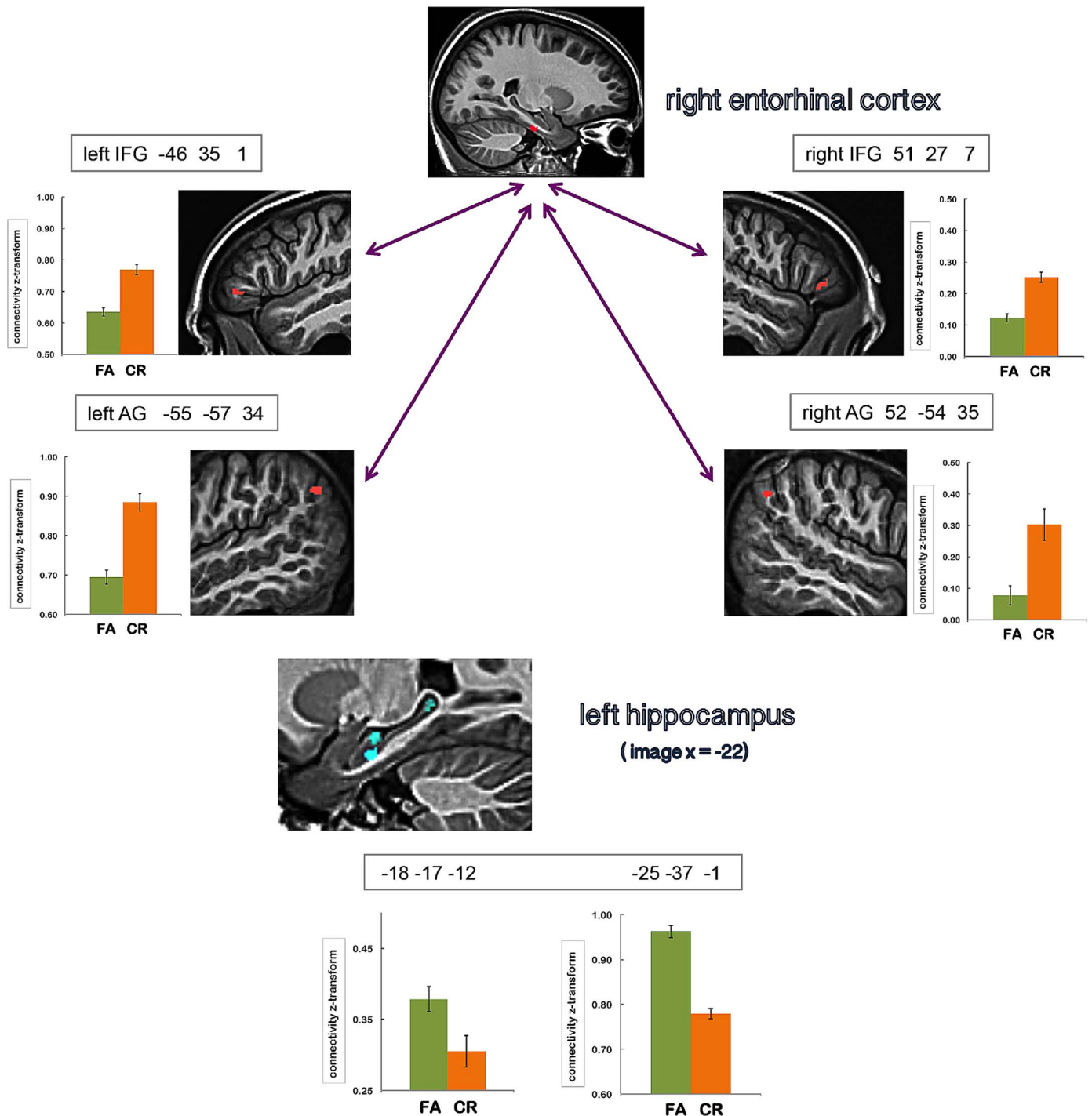


Fig. 3. Functional connectivity. Pair-wise comparison of functional connectivity associated with correct rejection of lures (CR), relative to false alarms to lures (FA). The results were visually masked to include all clusters, bilaterally, in IFG and lateral parietal cortices, as well as memory regions in the medial temporal lobe (MTL). Results in the upper panel show increased functional connectivity between the right entorhinal cortex discrimination seed (Fig. 2a), left and right inferior frontal gyri (IFG), and left and right angular gyri in association with discrimination (i.e., during retrieval of high-fidelity memories). Results in the lower panel show increased functional connectivity between the left hippocampal seed (Fig. 2b) with other regions in the left hippocampus (pale aqua) in association with low-fidelity generalized recognition. Bar graphs show mean fMRI connectivity values (SEM) associated with CR and FA from the identified clusters (p -corrected < 0.05). These functional network nodes are presented on sagittal views of the group normalized brain template, left and right hemispheres respectively, with ROI coordinates indicated based on Talairach space.

memory network, and it examined the correlations of neural measures of fractional anisotropy (FA) with our behavioral measure for discrimination bias index.

Analysis of the diffusion-weighted (DTI) data with TRACULA produced standardized maps of FA values (i.e., mean value over an entire specific tract) for two prominent WM bundles that passed through the memory and cortical control ROIs identified in the

functional networks associated with discrimination-based memory retrieval: the left anterior thalamic radiation (ATR) and the left superior longitudinal fasciculus (SLF). The ATR directly connects IFG regions with the anterior thalamic nuclei, receiving dense inputs from regions of the MTL including the hippocampal formation (Coenen et al., 2012; Wright et al., 2010). Components of the perisylvian SLF connect lateral cortical regions from an anterior extent at the IFG to a

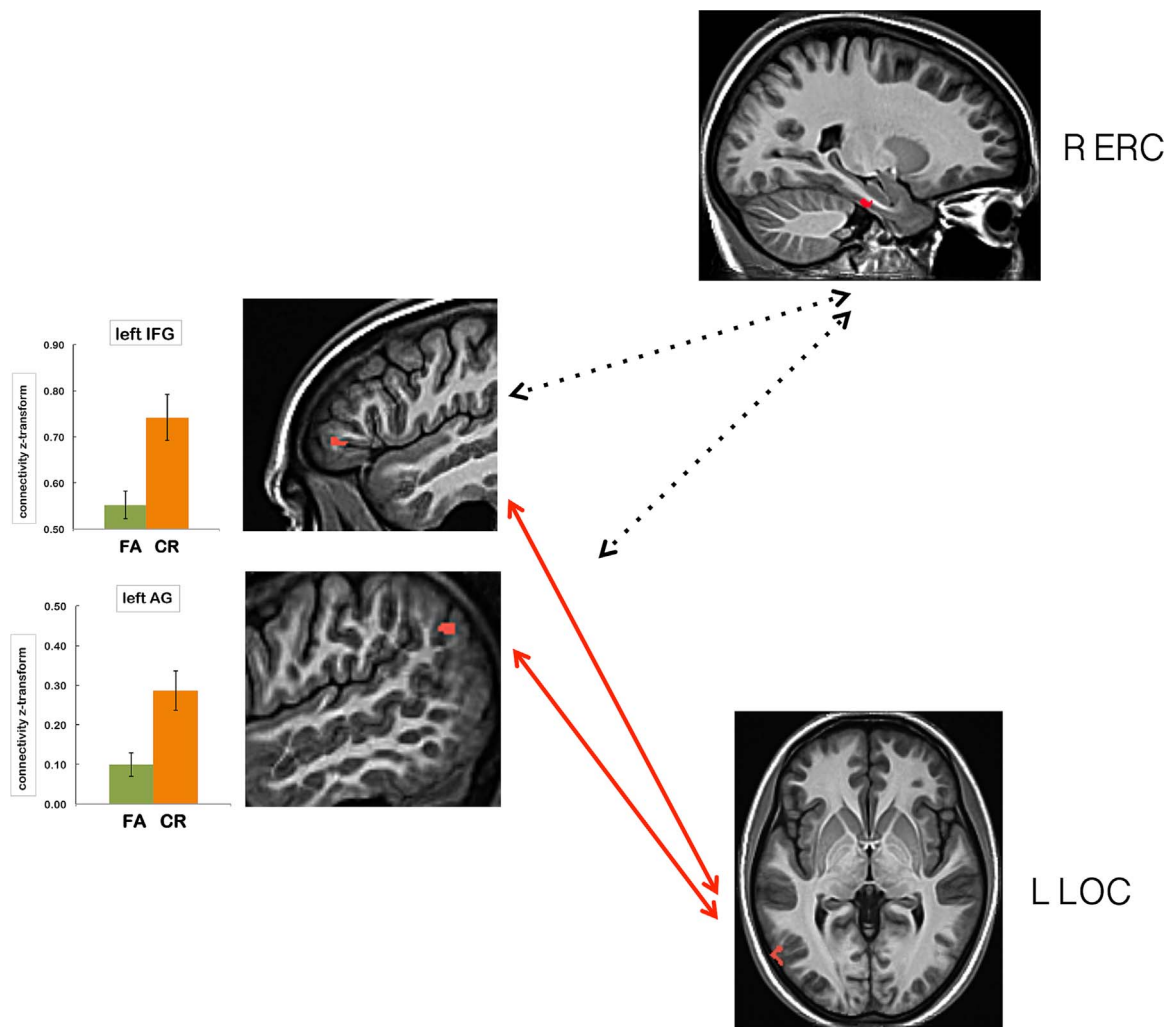


Fig. 4. Functional connectivity with object-sensitive lateral occipital cortex region. Group fMRI results from an independent localizer task identified a stimulus-sensitive ROI in left lateral occipital cortex (LOC). In the multivariate analysis, pair-wise comparisons revealed that functional connectivity (orange connectors) increased in association with correction rejection of lures (CR), relative to false alarms to lures (FA), between the left LOC object-sensitive ROI and both the left IFG and the left angular gyrus nodes of functional networks with the discrimination seed (gray dotted connectors). Bar graphs show mean fMRI connectivity value (SEM) associated with LureCR and LureFA. The nodes of this discrimination network are each presented on left sagittal or axial views of the group normalized brain template. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

posterior extent at angular gyrus (Martino et al., 2012). Using these maps for WM pathway microstructure developed from each participant's data, we compared individual differences in FA in the left hemisphere (i.e., ipsilateral with the functional network supporting discrimination-based retrieval illustrated by Fig. 4) with differences in behavioral discrimination capability. The results showed a positive correlation between FA values in the left ATR and discrimination bias index scores such that greater FA values predicted higher discrimination bias index scores ($r_{18}=0.56$, $p < 0.05$ after Bonferroni correction for multiple comparisons; Fig. 5b). The comparison of individual differences in FA for the left SLF maps with differences in discrimination scores did not show a correlation between differences in WM microstructure and differences in behavioral performance ($r_{18}=0.30$, $p=0.21$).

Discussion

Seminal work that proved the necessary role of the MTL in learning and memory for facts and events (Scoville and Milner, 1957) has been expanded by the development of functional connectivity analysis with event-related fMRI data to elucidate whole-brain networks associated with LTM (Wais et al., 2010, Wang et al. 2014, Vilberg and Rugg,

2013). Here, we tested a framework predicting that successful, high-fidelity episodic retrieval depends upon MTL memory processes in conjunction with lateral cortical function. The basis for our framework is that bringing to mind information of sufficient detail to support high-fidelity memory, as compared to memories having lower fidelity, requires contributions from cognitive control processes associated with lateral cortical function. The results show that increased functional connectivity across MTL-cortical networks was associated with successful retrieval of detailed episodic memory, whereas old/new recognition for items based on low-fidelity, generalized information did not engage functional networks with regions outside of the MTL.

The recent literature associating fMRI results with retrieval of episodic memories has begun identification of cortical regions showing covariance in activity with memory regions of the MTL during tasks that include the Remember/Know procedure and identification of paired-associates (King et al., 2015), source-monitoring (Barredo et al., 2015), and old/new recognition (Kuhl and Chun, 2014). The novelty of our findings is drawn from convergent results in functional, structural and distributed network analyses to make several important advances. The results revealed: (i) discrimination-based memory (i.e., high-fidelity retrieval based on discrimination of episodic details) arises from functional networks of MTL, IFG and parietal regions; (ii) higher

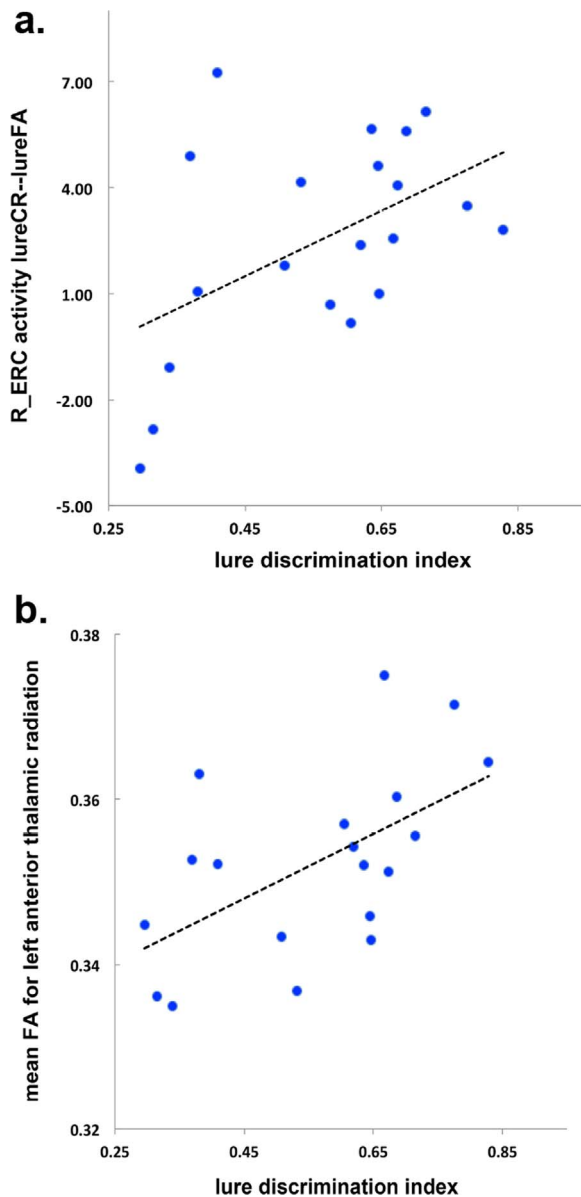


Fig. 5. Comparisons of individual differences. Behavioral discrimination performance was positively correlated with measures of univariate activity and fractional anisotropy (FA). (a) Increased differences in activity associated with discrimination in the right entorhinal cortex (ERC) ROI were positively correlated with increased discrimination bias index scores ($r_{19}=0.49$). The ERC ROI was functionally defined by a conjunction of the two independent contrast maps identifying MTL activity associated with recognition memory signals (i.e., hit > miss) and with underlying discrimination: (i.e., LureCR > LureFA). (b) Individual differences in fractional anisotropy (FA) for the left anterior thalamic radiation (ATR) were positively correlated with discrimination bias index scores ($r_{18}=0.56$).

discrimination-based retrieval performance is associated with greater similarity in WM microstructural properties for the ATR structural pathway; and (iii) low-fidelity retrieval in our task was not associated with increased MTL-lateral cortical connectivity.

The fMRI results identified a region in right ERC where activity increased in association with hits, relative to misses, as well as in association with correct rejection of similar lures, relative to false alarms. This cluster in right ERC signaled memory judgments based on discrimination. It is reasonable to expect, during any given trial, that several discrete clusters in sub-regions of the hippocampal formation were processing pattern separation or pattern completion computations (Bakker et al., 2008), and previous work reports MTL regions outside of the hippocampus proper that show a pattern of activity

consistent with pattern separation underlying continuous recognition (Suthana et al., 2015; Kirwan and Stark, 2007). We interpret the function of the right ERC cluster, therefore, as the summing point of MTL output signaling memory judgments based on discrimination. The comparison of individual differences showed a positive correlation between increases in right ERC activity associated with discrimination and better performance in terms of increased discrimination during the memory test (i.e., LDI scores).

Functional connectivity with the right ERC discrimination ROI included bilateral regions in inferior prefrontal and lateral parietal cortices. Both of these cortical areas have been associated in previous reports with cognitive control processes implicated in guiding goal-directed memory retrieval (Barredo et al., 2015; King et al., 2015; Donoso et al., 2014). Most recently, fMRI results similarly show that mid-IFG regions interact during episodic retrieval with posterior cortical areas that are sensitive for the selective details in auditory memory experience (Kostopoulos and Petrides, 2016). The requirements of our behavioral paradigm increased demands for top-down processes to retrieve contextual and visual details from the study session. Indeed, the univariate analyses of our data found bilateral regions in IFG and angular gyrus where activity increased in association with correct rejections (i.e., LureCR), relative to false alarms (i.e. LureFA) (Table 2). We interpret the results showing increased functional connectivity in association with discrimination-based retrieval (Figs. 3a and 5b) as evidence for interactions of different cognitive functions that are engaged in tandem by memory search.

We did not find increased functional connectivity between lateral cortical regions and the left hippocampus region where activity increased in association with hits, relative to misses, as well as in association with false alarms to similar lures, relative to correct rejections. Therefore, our results showed memory judgments based on low-fidelity retrieval were associated narrowly with regions within the hippocampal formation. These low-fidelity memories may have been the result of generalization-based retrieval, ineffective encoding at study, or the sort of familiarity processes attributed to threshold models for recognition (Yonelinas and Jacoby, 1996; Yonelinas, 1994). Although our null finding for MTL-cortical networks associated with low-fidelity retrieval should be taken with caution, given it is evidence from one report based on our operationalization of generalized remembering, this finding is consistent with our hypothesis that memories retrieved without high-fidelity information might arise from processes supported by memory regions of the MTL not tapping cognitive control processes guiding goal-directed retrieval. Yet, as appealing as it might be to attribute such low-fidelity retrieval narrowly to failure in processes that resolve mnemonic interference, our results cannot definitively adjudicate between the possibilities of retrieval errors or ineffective encoding. Notably, results from another recent report based on concepts of recollection and familiarity, which do not map directly onto our concepts of discrimination and generalization, show MTL-cortical functional connectivity selectively in association with recollection (King et al., 2015) and is, therefore, generally convergent with our finding here.

The findings in our data for discrimination-associated connectivity with the IFG (approximately BA45/47) are convergent with previous fMRI reports that showed increased IFG activity in association with processes that support mnemonic selection (Donoso et al., 2014; Badre and D'Esposito, 2009). Mnemonic selection resolves interference between competing or overlapping memory representations (Nee and Jonides, 2008; Badre et al., 2005), and it has the effect of tuning in awareness about information from prior experience most relevant for a memory retrieval goal. Similarly, our findings for discrimination-based connectivity with angular gyrus converge with previous work that associates this region with processes that direct attention to awareness of details held in memory (Kuhl and Chun, 2014; Gilmore et al., 2015), positively track retrieval outcomes (Hutchinson et al., 2014), and support awareness of task-relevant contextual information (Bellana

et al., 2016; Cabeza et al., 2008) and source memory (Frithsen and Miller, 2014). One possible contribution from these angular gyrus network nodes, in association with discrimination of similar lures (i.e., correct rejections), is as a convergence zone from which details specific to paired-targets are projected for judgment of memory, which is suggested by the output buffer account (Kuhl and Chun, 2014, Hutchinson et al., 2014; Vilberg and Rugg, 2008).

Taken together with functional connectivity results for the left LOC object-sensitive region, the fMRI results suggest that a left hemisphere network supported reconstruction of visual imagery for mnemonic information relevant for our stimuli and memory task. Engagement of these functional networks, which connected centers of control for mnemonic selection and awareness with an area selective for object representation (i.e., pars triangularis, angular gyrus and LOC, respectively), can be interpreted as evidence that participants retrieved specific details from visual imagery they had encoded for target objects (Wais et al., 2010). Our key finding is that successful retrieval of high-fidelity memories was associated with the contributions between particular MTL-cortical networks supporting mnemonic selection, awareness of task-relevant details and reconstruction of visual details, all required in concert to achieve accurate discrimination-based judgments.

Results from the independent object localizer task identified bilateral LOC regions with increased stimulus-selective sensitivity, although functional connectivity with MTL-lateral cortical networks in association with discrimination-based retrieval was evident solely from the left LOC ROI. This left hemisphere pattern suggests a particular role for left LOC in fine-grained representations in mental imagery of the object stimuli in our task. A large literature shows bilateral engagement of LOC, in younger adults, in association with recognition and mental imagery for the objects (Bracci and Op de Beeck, 2016; Grill-Spector and Weiner, 2014) and, consequently, offers no particular clue about the laterality effects in our network data. We suppose that the nature of the incidental encoding tasks at the beginning of our procedure likely encouraged sub-vocalization, which, for our right-hand dominant sample, would predictably engage left hemisphere language function for the elaboration of memoranda represented in visual imagery.

The DTI data provided additional evidence for the distributed network associated with discrimination-based memory. The analysis of atlas-defined WM pathways took account of differences in their microstructure associated with the assessment of FA. Our results show that individual differences in FA in the principal atlas-defined WM pathway emanating from the ERC discrimination cluster (i.e., via the ATR) (Coenen et al., 2012; Wright et al., 2010) had a positive correlation with participants' LDI scores. This neural-behavioral correlation provides additional support for our interpretation from the functional data that signals from the ERC discrimination-based cluster interacted with engagement of networks with lateral cortical regions.

In our results, evidence that participants had retrieved high-fidelity memory came from their correct rejection of similar lures as “new” (i.e., meaning an object did not match a previously studied target). Notably, correct rejection of a similar lure could have been based on either accurate memory for the specific details of its target pair, or absence of memory for anything similar (i.e., the novel stimuli). On the other hand, a false alarm to a similar lure showed a mistaken match for a target, or possibly failure to encode the paired target during the study session. Such memory errors indicated that the specific details about a previously studied object were not retrieved successfully and the participant generalized about the object category. In the fMRI results, we interpreted these false memories as responses based on underlying low-fidelity, generalized recognition, considering that misattribution of encoding failure as such a form of generalization, if that occurred for a handful of trials, did not significantly dilute reliability of the conjunction of increased univariate activity for both hit > miss and LureFA >

LureCR (Fig. 2b).

The key behavioral measure in our analysis was an index that tracked participants' performance as a function of memory judgments based on information from discrimination (i.e., LDI). Together with the LDI, findings from the neuroimaging data revealed the function of and microstructural differences associated with networks between MTL and lateral cortical regions that form the neural substrates associated with retrieval of high-fidelity memories. The index score normalized results for participants who used liberal or conservative strategies on our task by scaling individual lure rejection rates with relative false alarm rates for the independent set of novel stimuli. Consequently, we intended the LDI to account for differences in response bias (i.e., much as provided by the calculation of d' for assessment of overall recognition) and provide for a valid evaluation of memory performance based on underlying discrimination. The mean false alarm rate for novel images was small (0.07 ± 0.01), as expected for younger adults, but with sufficient variance to provide an indication of the range in participants' bias to respond “old” to unstudied images (i.e., 0.00 – 0.18 NovelFA).

Further work to investigate distributed networks that support LTM retrieval is necessary to address interesting points that our study is not able to answer. Although our results found a clear dissociation between the neural substrates that subserved discrimination-based memory via distributed functional networks and those subserving low-fidelity generalization via what appear narrowly as MTL activations, determination of causal roles of MTL-cortical networks in LTM retrieval requires direct evidence of functional necessity and depends on methods such as repetitive transcranial magnetic stimulation (rTMS). Further, we should note that in being based on thresholds in various stages of analyses, we cannot conclude (nor would want to advocate) that findings such as the highly-restricted scope of generalization-related activity represents the true limit of the extent of this activity. Thus, the results point to evidence of a broader network of activity related to discrimination than to low-fidelity retrieval, more so than to a sharp limit to generalization related activity. Finally, the MRI methods we applied cannot speak to the directionality of signal in functional or structural networks, which limits any interpretation about mechanistic flow in the networks revealed here. Based on our results, which identified functional networks associated with retrieving, tuning and signaling memory retrieval, one can only speculate whether IFG processes implicated in mnemonic selection influenced angular gyrus processes implicated in awareness of memory, or the other way around, during discrimination-based retrieval.

Authors contributions

PEW led the design of the research, collected and analyzed the data, and wrote the paper. CELS and AG advised in the design, analysis, and manuscript preparation. SJ and DS assisted in data collection and analysis.

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The authors declare no competing financial interests.

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