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Functional connectivity in category-selective brain networks after encoding predicts subsequent memory:

Category selective connectivity predicts memory

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Abstract

Activity in category selective regions of the temporal and parietal lobes during encoding has been associated with subsequent memory for face and scene stimuli. Reactivation theories of memory consolidation predict that after encoding connectivity between these category-selective regions and the hippocampus should be modulated and predict recognition memory. However, support for this proposal has been limited in humans. Here, participants completed a resting-state functional MRI (fMRI) scan, followed by face- and place-encoding tasks, followed by another resting-state fMRI scan during which they were asked to think about the stimuli they had previously encountered. Individual differences in face recognition memory were predicted by the degree to which connectivity between face-responsive regions of the fusiform gyrus and perirhinal cortex increased following the face-encoding task. In contrast, individual differences in scene recognition were predicted by connectivity between the hippocampus and a scene-selective region of the retrosplenial cortex before and after the place-encoding task. Our results provide novel evidence for category specificity in the neural mechanisms supporting memory consolidation.

Keywords

Episodic Memory; Perirhinal Cortex; Hippocampus; Consolidation

Introduction

Memory consolidation theories predict that coordinated activity between the hippocampus and cerebral cortex is responsible for the storage of a long-term memory trace (Buzsaki, 1989; Nadel et al., 2000; Squire, 1992) and that this process is mediated by the reactivation of regions during rest that were active during encoding (Marr, 1971; McClelland et al., 1995; Rasch and Born, 2007; Sutherland and McNaughton, 2000). Once thought to primarily occur during sleep, recent studies in rodents and primates (Diba and Buzsaki, 2007; Foster and Wilson, 2006; Hoffman and McNaughton, 2002; Karlsson and Frank, 2009) and in humans

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(Peigneux et al., 2006; Tambini et al., 2010) have provided evidence supporting the idea that reactivation-mediated memory consolidation occurs during periods of wakeful rest following episodes of memory encoding. In humans, individual differences in associative memory performance have been related to increased hippocampal-cortical connectivity after encoding (de Voogd et al., 2016; Murty et al., 2017; Tambini et al., 2010), and to the reinstatement of multivoxel patterns of activation during rest after encoding (Staresina et al., 2013; Tambini and Davachi, 2013). However, to date no study has directly addressed the following question: do brain regions that “fire together” during the encoding of new faces or scenes subsequently show a modulation in their functional connectivity during reactivation that relates to individual differences in memory retrieval? An affirmative answer to this question would provide additional evidence contributing to our understanding of the mechanisms of human memory consolidation during short wakeful intervals soon after experiences.

A long history of research has supported the existence of specialized cortical regions in the fusiform gyrus and perirhinal cortex (PRC) that are engaged preferentially during the visual encoding of faces (Collins and Olson, 2014). Similar category specificity has been observed in the parahippocampal cortex (PHC) and the retrosplenial cortex (RSC) during the visual encoding of places (Epstein and Kanwisher, 1998). Although typically studied in the context of visual perception, the activity of these category selective regions of the temporal and parietal cortex may also contribute to subsequent item memory. Activity in the PRC and PHC during encoding has been related to successful retrieval performance for faces and places respectively (LaRocque et al., 2013; Staresina et al., 2011). Similar effects have been observed during recognition, with activity patterns in the PRC and PHC differentiating between familiar and unfamiliar faces and places (Martin et al., 2013). The RSC also responds preferentially to familiar relative to unfamiliar scenes (Epstein and Morgan, 2012), and activity in this region during post-encoding rest has been associated with place-object associative memory (Staresina et al., 2013).

Reactivation theories of memory consolidation predict that face- and place-memory encoding and subsequent rehearsal should modulate connectivity between the hippocampus and category selective regions of the temporal and parietal cortex, and that this modulation of connectivity will relate to individual differences in recognition memory performance. The goal of the current study was to test these predictions. Participants completed a baseline resting-state functional MRI (rs-fMRI) run followed by a face- and a place-encoding task (see Figure 1). Each encoding task was followed by an additional rs-fMRI run during which time participants were instructed to think about the stimuli they had just seen in order to encourage the re-activation of brain regions that were active during encoding. Recognition memory for the face and place stimuli was assessed outside of the scanner. We hypothesized that rehearsal of stimuli encoded during the face- and place-encoding tasks would exert dissociable effects on connectivity between category selective regions of interest and that this modulation would predict subsequent memory for the relevant stimulus material.

Materials and Methods

Participants

An initial cohort of fourteen (four male) cognitively normal native English speakers between the ages of 20 and 30 participated in the fMRI experiment. Four participants (2 male) from this sample failed to complete the recognition task portion of the experiment, and so their data was excluded from all resting state analyses. In order to increase the power and examine the reliability of our results, a second cohort of 10 participants (5 male) was recruited. All participants in this second sample were also cognitively normal native English speakers between the ages of 20 and 30. Due to technical upgrades, we were forced to scan this second sample on a different MRI scanner than the first sample. In the present manuscript we will present all results from the larger combined participant sample. All participants gave written informed consent in accordance with the institutional review board of the Massachusetts General Hospital and Partners Healthcare System Human Research Committee.

Procedure

All participants completed a baseline resting state scan, followed by three encoding tasks and three additional resting state runs conducted in an alternating order. The order of the encoding tasks was faces-objects-places for half of the participants, and places-objects-faces for the other half. Due to time constraints some participants did not complete a resting state run following the object-encoding task, and so we chose to focus all analyses on the face and place encoding tasks and their subsequent resting state runs. After the scanning session, participants completed a memory test for the face, place, and object stimuli that they encountered during the three encoding tasks. In addition, a high-resolution anatomical scan was collected prior to the functional runs.

Stimuli

Face stimuli consisted of images of 20 famous and 20 non-famous individuals. Place stimuli consisted of images of 20 famous and 20 non-famous landmarks. Object stimuli consisted of 20 manmade and 20 natural objects taken from the Snodgrass set of black and white line drawings (Snodgrass and Vanderwart, 1980). Twenty images from each category were used in the encoding tasks (evenly distributed across famous/non-famous and manmade/natural categories), and all stimuli were used in the recognition task.

Encoding tasks

Participants completed the face, place, and object encoding tasks in separate runs that were 5 minutes long each. Each encoding task consisted of 20 trials in which a face, place, or object image was presented for 3 seconds followed by a 12 second fixation. All stimuli were presented in the center of the screen and were unique to that trial. For the object encoding task participants indicated via button press whether the presented image was natural or manmade with each answer being correct on 10 trials. For the face- and place- encoding tasks participants indicated via button press whether the presented image was familiar (famous) or unfamiliar (non-famous) with each answer being correct on 10 trials.

Participants were told to pay attention to the stimuli and that their memory would be tested outside of the scanner.

Resting state runs

Each resting state run lasted 6 minutes and 20 seconds. Participants viewed an empty black screen and were instructed to lie still and think about the stimuli they had seen in the previous encoding task.

Recognition test

Participants completed a recognition test for the material learned during the encoding tasks immediately after the scanning session, 10–15 minutes after the second encoding task and 30–40 minutes after the first encoding task. On each of 120 trials participants indicated whether the presented face, place, or object was old (seen during one of the encoding tasks) or new. For each stimulus category, 20 old and 20 new images were presented. Each image was presented once for 3 seconds followed by a 1 second fixation, and trial order was randomized across all participants. Participants were instructed to respond as quickly and accurately as possible with the response period being limited to the duration of the stimuli on screen (3 seconds).

To account for false alarms to non-studied items, we derived a measure of discriminability, d' , which was calculated in a standard fashion based on classic signal detection theory (Snodgrass and Corwin, 1988). Additionally, because d' is undefined when either proportion is 0 or 1, we used standard formulas to convert these values: $Hits = (\#Hits + 0.5) / (\#studied\ items + 1)$ and $FA = (\#FA + 0.5) / (\#unstudied\ items + 1)$.

fMRI data acquisition

All imaging data for both samples was acquired on one of two 3T Magnetom Tim Trio systems at Massachusetts General Hospital (Siemens), using a 32-channel phased-array head coil. High-resolution structural data was acquired using a T1-weighted 3D MPRAGE sequence ($n=7$, TR/TE/flip angle = 2.53 s/3.48 ms/7°, resolution = 1 mm isotropic) or a T1-weighted 3D MEMPRAGE sequence ($n=7$, TR/TE/flip angle = 2.2 s/1.54 ms/7°, resolution = 1.2 mm isotropic). fMRI data for the resting state runs were acquired using the following parameters: TR = 5 s; TE = 30 ms; flip angle = 90°, 55 slices; voxel resolution: 2 mm isotropic. fMRI data for the encoding task runs were acquired using the following parameters: TR = 3 s; TE = 30 ms; flip angle = 90°, 36 slices; voxel resolution: 3 × 3 × 3.6 mm. Seventy-six volumes were acquired during each resting state run and 100 volumes were acquired during each encoding task run.

Definition of ROIs

All fMRI data from the face- and place- encoding tasks were first pre-processed using the following steps: non-brain removal using FSL's brain extraction tool (BET), motion correction using FSL's MCFLIRT linear realignment tool, spatial smoothing using a 5mm FWHM Gaussian kernel, and high-pass temporal filtering with a 15 second cutoff. EPI data was registered to each participant's T1-weighted anatomical scan using FSL's boundary-

based registration tool (BBR), and normalized to a standard Montreal Neurological institute (MNI-152) template.

To identify category selective visual ROIs in the temporal and parietal lobes the preprocessed fMRI time-series from each participant in the first sample's face- and place-encoding runs were submitted to a fixed effects general linear model, with one predictor that was convolved with a double-gamma model of the hemodynamic response function (HRF) for each of the following contrasts: faces > fixation and places > fixation. Single-subject maps were then submitted to a random-effects group-level general linear model. The FFA was defined as a region in the fusiform gyrus that responded more to faces than to places. To compensate for reduced signal to noise ratio in the ventral temporal lobes (Devlin et al., 2000; Visser et al., 2010) a face-responsive PRC ROI was defined as a region within perirhinal cortex that responded more to faces than to fixation. The PPA and RSC ROIs were defined as the regions that responded more to places than to faces within parahippocampal and retrosplenial cortex respectively. All ROIs were located in clusters that survived a threshold of $p < .05$ using cluster-mass correction (cluster forming threshold, $z = 2.3$). For each ROI, a sphere with a 4mm radius was generated, centered on the voxel showing the maximal response to the relevant contrast of interest. We chose to restrict our analysis of category-selective ROIs to the right hemisphere because of the wealth of data suggesting that the face-processing network is strongly lateralized to the right hemisphere (Duchaine and Yovel, 2015; Gainotti, 2013; Kanwisher et al., 1997; Rossion et al., 2012; Sergent et al., 1992).

To identify regions with greater BOLD response at encoding for stimuli that were subsequently remembered (regardless of category) we performed an additional group-level general linear model with regressors for face and place stimuli at encoding that were later correctly remembered (hits) versus forgotten (misses) during the subsequent memory task. Two 4mm radius spheres were generated centered on the voxels in the right and left hippocampus with the maximal response to the contrast hits > misses. Both ROIs were located in clusters that survived a threshold of $p < .01$ using cluster-mass correction (cluster forming threshold, $z = 2.3$).

Resting state analysis

All resting state data was first pre-processed using the following steps: removal of the first four functional volumes to allow for T1-equilibration effects, slice timing correction (SPM2, Wellcome Department of Cognitive Neurology, London, UK), motion correction using FSL's MCFLIRT linear realignment tool, spatial normalization to a standard (MNI-152) atlas space, resampling to 2 mm isotropic voxels, spatial smoothing with a 6mm FWHM Gaussian kernel, and low-pass temporal filtering to remove frequencies > .08 Hz. Sources of spurious variance and their temporal derivatives were removed from the pre-processed data using linear regression. These sources of spurious variance included the 6 parameters derived from head-motion correction, the signal averaged over the whole brain, the average signal from a region located deep in white matter, and the average signal from ventricular CSF. These pre-processing parameters are consistent with what has been done in previous resting state functional connectivity analyses (Bickart et al., 2012; Collins et al., 2017;

Touroutoglou et al., 2015; Touroutoglou et al., 2014; Touroutoglou et al., 2012; Van Dijk et al., 2010; Wang et al., 2010a; Wang et al., 2010b)

Pearson correlation coefficients were then computed for the BOLD signal time courses of each ROI pair for the baseline resting state run, and for the resting state runs following the face- and place- encoding tasks. Correlation coefficients were converted to z-scores using a Fishers r to z transformation prior to further statistical analyses. The magnitude of change between the connectivity of each ROI pair at baseline, and following the face- and place- encoding runs was assessed using paired-sample t-tests. Partial correlations were used to assess the relationship between individual differences in face- or place- memory performance (d' prime), and z-transformed connectivity between ROI pairs at baseline and following the encoding tasks, controlling for variability in average movement in the x,y, and z directions across all resting state scans (mm^3). We additionally computed correlation coefficients between face or place d' prime and the difference in connectivity between ROIs at baseline and following each of the encoding tasks, again using partial correlations to control for variability in movement across scans. All analyses of connectivity-behavior relationships were restricted to ROIs we hypothesized would be specifically involved in face- or place- memory. Because we expected the hippocampus to play a domain-general role in recognition memory, our hippocampal ROIs (LHipp and RHipp) were included in all connectivity-behavior analyses. We first assessed the relationship between recognition memory for faces and connectivity between the FFA, PRC, LHipp, and RHipp at baseline, following the face encoding run, and the modulation of connectivity between these ROIs by face encoding. We next assessed the relationship between place memory and the connectivity of the PPA, RSC, LHipp, and RHipp at baseline, following the place encoding run, and the modulation of connectivity between these ROIs by place encoding. We report all significant effects.

Results

Defining regions of interest

A face-selective regions of interest (ROI) was defined in fusiform gyrus (fusiform face area; FFA) and a face- responsive region was defined in PRC. Place-selective ROIs were defined in the parahippocampal gyrus (parahippocampal place area; PPA) and RSC (see Experimental Procedures). Additional ROIs were defined in the left and right hippocampus (RHipp and LHipp) that maximally responded to stimuli that were later remembered vs. those that were not, regardless of stimulus category (see Table 1).

Group level influences of face- and place-encoding on functional connectivity

To assess the relative influence of the face- and place-encoding tasks on subsequent functional connectivity, we first calculated pairwise correlations between the BOLD signal time course of all functional ROIs during the baseline resting state scan (prior to the performance of any task), and during the rest periods following each of the encoding runs. Following the face-encoding task there was no significant group-level change in connectivity between any ROI pair from baseline, however, a modest decrease in connectivity between the PPA and FFA was observed ($r = -.09$, $t_{18} = 2.04$, $p = .057$). There were no significant

group-level changes in connectivity from baseline following the place-encoding task. All statistics were performed on Fisher Z-transformed correlation values. No other significant effects were observed.

We additionally assessed whether differences in the order of the learning tasks (i.e. learning faces first versus learning places first) influenced the effect of the learning tasks on connectivity. A one-way ANOVA was performed on the difference scores between the connectivity of all ROIs during the baseline resting state run, and following the face- or place-encoding runs. The degree to which connectivity between the FFA and PPA was affected by the place encoding task differed significantly between participants who encoded faces versus places first [faces first: $M = -.15$; places first: $M = .05$; $F(1,17) = 5.18$, $p = .036$]. In addition, the degree to which connectivity between the PRC and PPA was affected by the face encoding task differed significantly between participants who encoded faces versus places first [faces first: $M = -.11$; places first: $M = .07$; $F(1,17) = 7.91$, $p = .012$].

Modulation of connectivity between face-responsive ROIs predicts face memory performance

We next assessed the relevance of individual differences in the modulation of connectivity by the face-encoding task to subsequent recognition memory performance for face stimuli. As predicted, individual differences in face recognition memory (d') were predicted by the modulation of connectivity between the FFA and PRC (Figure 2, $r = .57$, $p = .014$). Importantly, the modulation of connectivity between the FFA and PRC did not predict individual differences in place recognition memory (Figure 2, $r = .15$, $p > .5$), and the correlation between modulated PRC-FFA connectivity and face memory was greater than that for place memory with this difference being marginally significant ($z = 1.4$, $p = .08$), suggesting that this effect is specific to face stimuli. There was no relationship between face recognition memory and PRC-FFA connectivity at baseline or following the face-encoding task (all p s $> .05$).

We further analyzed the persistence of the relationship between PRC-FFA connectivity and face recognition beyond the post-face encoding resting state run (see Supporting Information Figure 1). For participants who encoded faces first ($N=9$), modulated connectivity between the FFA and PRC continued to predict face memory even after the place encoding task 23 minutes later ($r = .70$, $p = .037$), suggesting that this relationship between modulated connectivity and recognition memory can persist despite interfering task demands. For participants who encoded places first ($N = 10$), there was no relationship between modulated connectivity between the PRC and FFA after the place encoding task and subsequent memory for faces ($p > .19$).

It is interesting to note that some of the participants in our sample showed an apparent decrease in connectivity between the FFA and PRC following the face-encoding task (Figure 2). There was a modest negative relationship between the magnitude of PRC-FFA connectivity at baseline and the magnitude of connectivity change following the face encoding task ($r = -.419$, $p = .074$), such that participants with lower PRC-FFA connectivity at baseline showed the greatest increase in connectivity following the face-encoding task, and participants with higher PRC-FFA connectivity at baseline showed lower increases, and in

some cases decreases, in connectivity following the face-encoding task (see Supporting Information Figure 2). Thus it seems that the behavioral relevance of modulated connectivity following an encoding task is greatest for individuals who have lower connectivity to start with.

Post-encoding connectivity between place-selective ROIs predicts place memory performance

We next assessed the relevance of individual differences in functional connectivity to recognition memory for place stimuli. Contrary to our hypotheses, there was no significant relationship between place memory and the change in connectivity after the place-encoding task for the hippocampus or any of the place-selective ROIs (all p values $> .2$). However, individual differences in place recognition memory (d') were predicted by the magnitude of connectivity between the RSC and LHipp at baseline (Figure 3, $r = .59$, $p = .01$) after the place-encoding task (Figure 3, $r = .47$, $p = .047$). The magnitude of RSC- LHipp connectivity at baseline and following the place encoding task did not predict individual differences in face recognition memory (both $ps > .12$). The correlation coefficients between RSC-LHipp connectivity and place- or face- memory differed significantly at baseline ($z = 1.66$, $p = .049$) but not following the place-encoding task ($p > .5$), and so the specificity of this result should be interpreted with caution.

Discussion

Here, we provide novel evidence that individual variability in the learning of new items is predicted by increased functional connectivity between ventral temporal cortical, MTL cortical, and hippocampal regions in a manner suggestive of a reverberating circuit that subserves early consolidative processes. This relationship between learning-performance and functional connectivity demonstrates content specificity such that the regions engaged during the encoding of faces or places show a stimulus material-specific relationship between connectivity after face or place encoding respectively and individual differences in material-specific memory performance.

Hippocampal-neocortical interactions support memory for places

Our finding that hippocampal-RSC connectivity following the place-encoding task predicts place memory performance is consistent with a large history of research implicating the hippocampus in memory consolidation (Buzsaki, 1989; Nadel et al., 2000; Squire, 1992). In rodents, the reactivation of hippocampal place-cells during post-learning sleep (Wilson and McNaughton, 1994) and awake rest (Carr et al., 2011; Jadhav et al., 2012) has been associated with subsequent memory for spatial locations. In humans, increased hippocampal connectivity (de Voogd et al., 2016; Murty et al., 2017; Tambini et al., 2010; Tompary et al., 2015; Woolley et al., 2015) and the re-activation of hippocampal encoding-related activity patterns (Bird et al., 2015; Tambini and Davachi, 2013) have both been associated with individual differences in subsequent memory performance.

To our surprise, connectivity between the left hippocampus and RSC at baseline also predicted individual variability in recognition memory for places. This finding is consistent

with previous work showing that intrinsic connectivity between task-relevant brain regions predicts individual variability in performance (Baldassarre, 2012; O'Neil et al., 2014; Zhu et al., 2011). One possibility is that the relationship between scene recognition performance and RSC-LHipp connectivity before and after encoding might reflect individual variability in anatomic connectivity that support more efficient encoding and consolidation for scene stimuli. This account is speculative and would be an interesting avenue for future research.

Although there is limited data on connectivity between the RSC and hippocampal subfields in humans, tract-tracing work in non-human primates has revealed dense reciprocal connections between the RSC and the hippocampus (Aggleton et al., 2012; Kobayashi and Amaral, 2003; Kobayashi and Amaral, 2007), entorhinal cortex (Aggleton et al., 2012; Kobayashi and Amaral, 2003; Morris et al., 1999), and parahippocampal cortex (Kobayashi and Amaral, 2003; Lavenex et al., 2002). Supporting a critical role of coordinated hippocampal-RSC activity in memory, it has been shown in rats that hippocampal dependent learning is associated with increased immediate early gene (*Arc*) expression in the RSC (Tse et al., 2011). In humans, familiarity and repetition-related signals in the posterior hippocampus closely mirror those in the RSC (Reagh et al., 2014), and encoding-related activity patterns are reinstated in the RSC during active rehearsal (Bird et al., 2015) and post-encoding rest (Staresina et al., 2013).

Together, the RSC, medial entorhinal cortex (MEC), and parahippocampal gyrus (PHG) are thought to compose a specialized memory circuit that provides the hippocampus with information about where in time and space an event occurs (Bucci and Robinson, 2014; Ranganath and Ritchey, 2012). All nodes within this circuit are preferentially engaged in tasks that require the processing of spatial (scene) stimuli (Epstein and Kanwisher, 1998; Graham et al., 2010; Marchette et al., 2015; O'Craven and Kanwisher, 2000; Park et al., 2007; Schultz et al., 2012; Troiani et al., 2014; Vann et al., 2009; Zeidman et al., 2014), and it has been argued that this selectivity is driven by the spatial or navigational relevance of the stimuli used (Janzen and Jansen, 2010; Janzen and van Turenout, 2004; Schinazi and Epstein, 2010; Troiani et al., 2014). The RSC in particular is involved in representing the mnemonic context in which a landmark appeared (Maguire et al., 1999; Marchette et al., 2015; Ranganath and Ritchey, 2012; Vann et al., 2009). Here, we showed that variability in memory performance was predicted by connectivity between the RSC and hippocampus, at baseline and following the encoding of place stimuli. Thus, we speculate that connectivity within the place-processing circuit may be a sensitive measure of memory processes. However, it should be noted that the correlation coefficients between RSC-LHipp connectivity and place- or face- memory differed significantly at baseline but not following the place-encoding task, and so the specificity of this result should be interpreted with caution.

PRC-cortical interactions after encoding support memory for faces

Although most discussions of consolidation focus on hippocampal-cortical interactions, attention has increasingly begun to focus on the PRC as a medial temporal cortical region that may also contribute to consolidation-like processes, particularly for objects (as opposed to associations). Rodent studies have used pharmacologic probes (e.g., NMDA or

cholinergic receptor antagonists or the protein synthesis inhibitor lidocaine) immediately after encoding to focally inhibit PRC function, with resultant impairment on object memory tasks (Balderas et al., 2008; Warburton et al., 2003; Winters and Bussey, 2005a; Winters and Bussey, 2005b). Notably, these types of rodent studies do not show such PRC-mediated memory deficits when spatial memory tasks are used (Larkin et al., 2008; Ramos, 2008). In humans, it has been shown that connectivity between the PRC and hippocampus is important for the consolidation of object-based memories after a delay (Vilberg and Davachi, 2013), and that post-encoding dopaminergic input into the PRC, as reflected by increased connectivity with the ventral tegmental area, predicts long-term item, but not associative, memory (Tompary et al., 2015).

It is well-known from monkey tract tracing studies that fusiform cortex provides substantial input to PRC (Suzuki and Naya, 2014), and multiple lines of research point to the importance of this pathway for object and face memory. In humans, recent work has shown that individual variability in the ability to remember unique faces is associated with the microstructural integrity of the inferior longitudinal fasciculus (ILF) (Gomez et al., 2015; Hodgetts et al., 2015; Tavor et al., 2013; Unger et al., 2016) which connects the fusiform gyrus with the ventral ATLs and PRC (Catani et al., 2003; Pyles et al., 2013).

Together, a face sensitive region within the PRC (Nasr and Tootell, 2012; Nestor et al., 2011; O'Neil et al., 2013; O'Neil et al., 2014; Rajimehr et al., 2009; Rossion et al., 2012), the FFA, and the occipital face area (OFA) are thought to form a specialized circuit for processing facial identity (Collins and Olson, 2014). Single-cell recordings in non-human primates have supported the existence of structural connections between face-sensitive regions in the PRC and more posterior face processing regions (Moeller et al., 2008). In humans, it has been shown that activity patterns in the PRC distinguish familiar from unfamiliar faces (Martin et al., 2015; Martin et al., 2013) and that the intrinsic connectivity of the FFA and face-responsive voxels in the PRC predict behavioral performance during a face recognition task (O'Neil et al., 2014). Robust activity was seen in the FFA and PRC during the visual encoding of faces, however this activity did not predict individual differences in subsequent memory performance. Instead, the modulation of connectivity between the PRC and FFA after encoding was more sensitive to variability in underlying memory processes, and may be an early marker of systems consolidation for face stimuli.

Relevance of our findings to models of memory

The relative contribution of MTL subregions to episodic memory has been a source of considerable controversy (Eichenbaum et al., 2007). Converging evidence from animal studies suggest that the hippocampus receives information from partially segregated anterior (lateral entorhinal cortex, PRC, and ventral visual regions) and posterior (medial entorhinal cortex, PHC, and dorsal regions) pathways (Burwell, 2000; Eichenbaum et al., 2007; Lavenex and Amaral, 2000; Suzuki and Amaral, 1994a; Suzuki and Amaral, 1994b; van Strien et al., 2009). One theory proposes that the functional organization of the MTLs is driven by the differential engagement of subregions in the recognition processes of recollection and familiarity (Diana et al., 2010; Eichenbaum et al., 2007; Ranganath et al., 2004). Another proposal holds that MTL organization is better understood in terms of the

memory processes required for recognizing items versus the context in which they occurred (Brown and Aggleton, 2001; Eichenbaum et al., 2007; Ranganath and Ritchey, 2012). Others have argued that the organization of the brain, and of the MTLs in particular (Litman et al., 2009), is driven by the sensitivity of distinct neural subsystems to the informational content of different stimulus classes (Alvarado and Bachevalier, 2005; Diana et al., 2007; Diana et al., 2010; Spaniol et al., 2009; Staresina et al., 2011). Our results are consistent with this last model and suggest that different types of stimuli may drive the recruitment of anterior versus posterior memory systems during the active consolidation process. However, our results would also be predicted by item and context models of MTL organization, due to the preferential engagement of item and context processing systems by face and scene stimuli. Future research should be aimed at elucidating how functional differences in the sensitivity of MTL substructures to stimulus category relate to the differential involvement of these same structures to item vs. context or familiarity vs. recognition memory processes.

Limitations and Future Directions

The temporal scale of the effects observed in the present study warrants further discussion. Here, connectivity between category selective brain regions immediately after encoding predicted variability in memory performance when tested 10–15 minutes after the second encoding task or 30–40 minutes after the first encoding task. To our surprise, the effect of modulated connectivity between the PRC and FFA on subsequent memory for faces persisted for 23 minutes in the participants who completed the face encoding task first, despite participants completing two different encoding tasks in between. Our results are consistent with previous research in humans showing that consolidative processes, as reflected by altered activity or connectivity within encoding related brain regions, can occur seconds (Ben-Yakov and Dudai, 2011), minutes (Keller and Just, 2016; Tambini et al., 2010; Tompary et al., 2015; Woolley et al., 2015), or 24 hours (Vilberg and Davachi, 2013) after encoding, and that these changes predict subsequent memory when tested immediately (Keller and Just, 2016; Tambini et al., 2010; Tompary et al., 2015), after 24 hours (Tompary et al., 2015; Vilberg and Davachi, 2013), or three days later (Woolley et al., 2015). Research in rodents has supported the hypothesis that the molecular cascade of events leading to systems level consolidation can begin to occur shortly after encoding; the up regulation of immediate early genes has been observed within minutes to hours after learning paired associates that fit within an existing knowledge schema (Tse et al., 2011). Furthermore, the replay of hippocampal firing sequences has been observed in rodents immediately following a learning trial (Carr et al., 2011; Dudai et al., 2015). Imaging methods with better temporal resolution will be required to understand the link between cellular markers of consolidation obtained in rodents, and the imaging markers of consolidation obtained in humans. However, based on this previous research we speculate that post-encoding connectivity changes between functional brain regions in humans reflect the initiation of consolidative processes that support the formation of a stable memory trace.

Some of the participants in our sample showed negative correlations between the hippocampus and RSC both before and after the place-encoding task (Figure 3). The interpretation of these negative correlations is difficult because we chose to use global signal regression (GSR) in the pre-processing of our resting state data, which can artificially

increase the number of negative correlations seen (Murphy et al., 2009; Saad et al., 2012; Weissenbacher et al., 2009). This choice was motivated by the fact that GSR is by far the most effective method for dealing with noise introduced by head motion, hardware artifacts, and respiratory patterns when conducting resting state functional connectivity analyses (Ciric et al., 2017; Parkes et al., 2018; Power et al., 2017). This is especially important for analyses aimed at understanding the individual differences in connectivity, as was the case in the present study.

In the present study participants were told to think about the stimuli they had just seen during the resting state runs, and so the reactivation effects we were testing were explicit rather than implicit. This differs from most conceptualizations of resting state scans, where participants are only told to keep their eyes open and stay still. Based on previous research demonstrating reactivation effects during resting state runs with an explicit memory component (Vilberg and Davachi, 2013), and during the performance of other tasks (Tomparry et al., 2015), we expect that the effects observed in the present study would occur even if the encoded stimuli were not purposefully brought to mind. This is further supported by the persistence of the relationship between modulated PRC-FFA connectivity and face recognition in participants who encoded faces first. However, whether reactivation effects that are driven by explicit task demands reflect the same mechanisms as those that occur implicitly remains an open question.

We chose to use a yes/no recognition memory task because we were specifically interested in whether connectivity between category-selective regions in the medial temporal and parietal lobes would predict variability in memory for items belonging to specific categories. A limitation of this decision is that with the present design we are unable discern whether participants were engaging in familiarity or recollection-based memory judgments for the stimuli they encountered. Future research should be aimed at understanding the relevance of connectivity for recognition based on familiarity versus recollection.

Conclusions

In the present study, we showed that increased connectivity between regions that were active during the encoding of faces predicted subsequent recognition performance for those stimuli. In contrast, individual variability in recognition performance for places was predicted by the connectivity of place-encoding regions at baseline and after a place-encoding task. Thus, our results suggest that the encoding of faces and places exert dissociable effects on connectivity between nodes of distinct neural circuits, with consequences for subsequent memory for the relevant stimulus category. These results offer the first report of a direct correspondence between the connectivity of the brain regions that were active during encoding and a behavioral measure of memory consolidation for novel items. Our results provide strong support for reactivation theories of memory consolidation (Marr, 1971; McClelland et al., 1995; Rasch and Born, 2007; Sutherland and McNaughton, 2000), and contribute to a growing body of literature supporting the behavioral relevance of post-encoding changes in functional connectivity (de Voogd et al., 2016; Deuker et al., 2013; Murty et al., 2017; Schlichting and Preston, 2014; Tambini et al., 2010; Woolley et al., 2015).

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A. Experimental protocol: **B. Task defined ROIs:** **Figure 1.**

Overview of experimental procedure. (A) Schematic representation of experimental protocol. (B) Task defined regions of interest. Abbreviations: FFA = Fusiform Face Area, PRC = Perirhinal Cortex, PPA = Parahippocampal Place Area, RSC = Retrosplenial Cortex, RHipp = Right Hippocampus, LHipp = Left Hippocampus. Photographs in Figure 1 were taken from public domain sources on Flickr.

Figure 2.

Modulation of connectivity vs. memory. Individual differences in the increase in FFA-PRC connectivity after both regions activate during face encoding predicts individual differences in face recognition memory (left), but not place recognition memory (right). Pearson product-moment correlation coefficients are reported. FFA = Fusiform Face Area, PRC = Perirhinal Cortex.

Figure 3.

Connectivity vs. memory. Individual differences in RSC-LHipp connectivity at baseline (top) and after both regions activate during place encoding (bottom) predicted individual differences in place recognition memory (right), but not face recognition memory (left). Pearson product-moment correlation coefficients are reported. RSC = Retrosplenial Cortex, LHipp = Left Hippocampus.

Table 1.

MNI Coordinates and average z-scores of task defined ROIs.

ROI	Contrast	Z-Score	MNI Coordinates		
			X	Y	Z
FFA	Faces > Places	4.67	42	-52	-18
PRC	Faces > Fixation	5.18	32	-2	-38
PPA	Places > Faces	5.15	26	-42	-10
RSC	Places > Faces	4.45	14	-58	16
LHipp	Hits > Misses	3.93	-32	-24	-16
RHipp	Hits > Misses	3.72	22	-16	-14