The effect of prior knowledge on post-encoding brain connectivity and its relation to subsequent memory

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ABSTRACT

It is known that prior knowledge can facilitate memory acquisition. It is unclear, however, whether prior knowledge can affect post-encoding brain activity to facilitate memory consolidation. In this fMRI study, we asked participants to associate novel houses with famous/nonfamous faces and investigated how associative-encoding tasks with/without prior knowledge differentially affected post-encoding brain connectivity during rest. Besides memory advantages in the famous condition, we found that post-encoding hippocampal connectivity with the fusiform face area (FFA) and ventral-medial-prefrontal cortex (vmPFC) was stronger following encoding of associations with famous than non-famous faces. Importantly, post-encoding functional connectivity between the hippocampus (HPC) and FFA, and between the anterior temporal pole region (aTPL) and posterior perceptual regions (i.e., FFA and the parahippocampal place area), together predicted a large proportion of the variance in subsequent memory performance. This prediction was specific for face-house associative memory, not face/house item memory, and only in the famous condition where prior knowledge was involved. These results support the idea that when prior knowledge is involved, the HPC, vmPFC, and aTPL, which support prior episodic, social-evaluative/schematic, and semantic memories, respectively, continue to interact with each other and posterior perceptual brain regions during the post-encoding rest to facilitate off-line processing of the newly formed memory, and enhance memory consolidation.

Introduction

Making associations between different kinds of information is an important way of building our knowledge system (Halford et al., 2010). Studies have shown that these associative processes can be facilitated by previous experiences or prior knowledge, namely the knowledge one has acquired and brings to bear in acquiring new information (Kan et al., 2009; Poppenk et al., 2010a; Reder et al., 2013; Sharon et al., 2011). At the neural level, it has also been shown that prior knowledge can modulate brain activity during encoding and retrieval to enhance new memory processing (Liu et al., 2017; Maguire et al., 1999; Poppenk et al., 2010b; Staresina et al., 2009; van Kesteren et al., 2010a, 2010b). In addition, there is growing evidence that changes in resting functional connectivity after encoding reflect early memory consolidation (de Voogd et al., 2016; Gruber et al., 2016; Hermans et al., 2017; Staresina et al., 2013; Tambini et al., 2010; Tambini and Davachi, 2013), but there is little research on whether prior knowledge can also influence this process. In this paper we show that prior knowledge can promote post-encoding functional connectivity in regions implicated in memory and perception, and that this effect is related to subsequent associative memory.

A large body of animal literature has shown that post-encoding brain activity, e.g., in the hippocampus (HPC), may reflect memory replay or reactivation and contribute to memory stabilization (Foster and Wilson, 2006; Jadhav et al., 2012; Knauer et al., 2013; Ólafsdóttir et al., 2016; O'Neill et al., 2010, 2008; Oudiette and Paller, 2013; Silva et al., 2015; Singer and Frank, 2009; Sutherland and McNaughton, 2000; Wilson and McNaughton, 1994). Other brain structures such as the striatum, ventral medial prefrontal cortex (vmPFC), visual, and motor cortex are also involved in the replay of previous experiences during post-learning rest or sleep (Gomperts et al., 2015; Hoffman and McNaughton, 2002; Ji and Wilson, 2007; Pennartz et al., 2004; Ribeiro et al., 2004). In line with the animal literature, human functional neuroimaging studies have found that learning experiences can modulate resting-state brain connectivity (Albert et al., 2009; Deuker et al., 2013; Groen et al., 2011; Hasson et al., 2009; Urner et al., 2013; Wang et al., 2012; Zou et al., 2013), and that the HPC activity during post-encoding rest can be correlated with memory performance (Tambini et al., 2010; Staresina et al., 2013; Tambini and Davachi, 2013; de Voogd et al., 2016; Gruber et al., 2016; Hermans et al., 2017). These observations support the idea that post-encoding neural activity may reflect early memory consolidation processes by which newly-encoded memory becomes more stable. Intriguingly, evidence

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from recent animal and human neuroimaging studies has also shown that prior knowledge can facilitate this memory consolidation process (Hennies et al., 2016; Tse et al., 2007). This raises the important question of whether prior knowledge can directly affect brain activity during an immediate post-encoding time window to contribute to memory formation in humans.

Although a recent study found that higher sleep spindle density during post-encoding sleep predicted better schema-related memory (Hennies et al., 2016), to the best of our knowledge, only two human neuroimaging study (van Kesteren et al., 2010a; Schlichting and Preston, 2016) have directly examined prior knowledge effects on brain activity during post-encoding awake rest. However, both studies mainly focused on the connectivity between the HPC and vmPFC, based on the assumption that the vmPFC plays an important role in supporting existing structured mental representations or memory updating (van Kesteren et al., 2012; Zeithamova et al., 2012; Zeithamova and Preston, 2010). While this assumption is reasonable, other regions, such as the anterior temporal pole (aTPL), also have been shown to support prior knowledge (Kan et al., 2009; Liu et al., 2017; Sharon et al., 2011; Staresina et al., 2009) and should be considered in the study of prior knowledge effects on new learning.

To tackle these questions, we need to design experiments that can elicit different types or components of prior knowledge, such as semantics, social emotions, perceptions, or episodic memories, which can be supported by well-known distinct brain regions and the connections between them. Then, we can use fMRI to examine how functional connectivity among these different brain regions can be affected by prior knowledge manipulations in the preceding encoding tasks. Following this idea, in this study we designed an associative memory task that required forming associations between two items, a house and a face, for which there are well-delineated and differential localizations in the brain. The houses were always novel, but to manipulate prior experience, the faces were those of famous people or of people unfamiliar to the participants. Specifically, participants were asked to associate pictures of novel houses with pictures of either famous or nonfamous faces in different blocks. After each encoding block, participants rested in the scanner. Because famous faces can elicit rich stores of social/affective, semantic, and perceptual knowledge, as well as episodic memories, each supported by different brain systems (Fairhall and Ishai, 2007; Gobbini et al., 2004; Gobbini and Haxby, 2007; Ishai, 2008; Renoult et al., 2012; Ross and Olson, 2012; Simmons et al., 2010), this fame manipulation created two conditions, famous vs. nonfamous, in which prior knowledge effects at the brain level can be examined during post-encoding rest.

Similar to the previous study that focused on the encoding phase (Liu et al., 2017), we included the HPC, aTPL, vmPFC, parahippocampal place area (PPA), and fusiform face area (FFA) as our regions of interest (ROIs). We chose these ROIs because the literature has shown that the medial temporal lobe, especially the HPC, plays an important role in associative encoding (Davachi, 2006; Davachi and Wagner, 2002; Eichenbaum et al., 2007) and post-encoding memory reactivation (O'Neill et al., 2010). Previous studies have also shown that the vmPFC and aTPL support social evaluative and semantic processing (Etkin et al., 2011; Grabenhorst and Rolls, 2011; Luo et al., 2010; O'Reilly, 2010; Patterson et al., 2007; Roy et al., 2012) and contribute to prior knowledge facilitation effects (Kan et al., 2009; Liu et al., 2017; Ross et al., 2011; Sharon et al., 2011; Staresina et al., 2009; van Kesteren et al., 2012). The two posterior perceptual regions, i.e., the PPA and FFA, support the processing of house and face stimuli, respectively (Kanwisher, 2010), and their activation can be affected by prior knowledge related to familiar faces (Bar et al., 2008; Gobbini and Haxby, 2006; Liu et al., 2014). Importantly, all of these ROIs, which support different components of memory processing, showed increased activity during face-house associative encoding when prior knowledge was involved (Liu et al., 2017), raising the possibility that they also play a role in post-encoding memory processes. Therefore, by comparing the functional connectivity among these ROIs between the famous post-encoding and nonfamous post-encoding rest periods, the current study enables us to investigate how prior knowledge affects post-encoding brain activity and impacts subsequent memory.

The literature on memory consolidation has shown that the medial temporal lobe, especially the HPC, is crucial for supporting new memory processing, whereas neocortical regions may play a greater role in supporting already consolidated memories (Frankland and Bontempi, 2005; Moscovitch et al., 2005; Nadel and Moscovitch, 1997; Squire and Alvarez, 1995). This switch in neural substrates may also underlie changes in the nature of these memories following consolidation (Nadel and Moscovitch, 1997; Wiltgen and Silva, 2007; Winocur and Moscovitch, 2011). Because it has been found that prior knowledge can facilitate memory consolidation (Tse et al., 2011, 2007), we hypothesized that the anterior cortical regions, namely, the vmPFC and aTPL, should form stronger resting connectivity with the HPC, PPA, and FFA after the famous compared to the nonfamous encoding condition, reflecting stronger cortical involvement from anterior brain regions during early memory consolidation when prior social/evaluative or semantic knowledge was involved. These connectivity measures should also better predict associative memory performance in the famous than the nonfamous condition. Moreover, our earlier finding that the HPC and FFA/PPA activations were stronger in the famous than nonfamous encoding condition (Liu et al., 2017), would lead to the prediction that the connectivity between the HPC and PPA/FFA should also be stronger during the famous post-encoding than the nonfamous post-encoding rest, reflecting stronger episodic binding processes when prior knowledge is present.

Method

Participants

Twenty young adults (12 females), between 18 and 24 years of age (*Mean* = 21.3, *SD* = 1.49), were recruited from the University of Toronto's St. George campus. They were all right-handed, native English speakers, and free of any psychiatric or neurological conditions. The participants were paid $76 and gave their informed consent. The study was approved by the Research Ethics Board at Baycrest Center for Geriatric Care (University of Toronto).

Procedure

Overview

There were 3 resting scans in this experiment (Fig. 1A). After the structural MRI scan, participants underwent the first (pre-encoding) resting scan which provided a baseline measure of resting brain activity. Participants then performed a face-house associative encoding task for one fame condition in two repeated runs (10 min/run), which was followed by a second resting scan. Participants then performed the associative encoding task for the other fame condition twice in two consecutive runs, which was again followed by a third resting scan. Each resting scan lasted 6 min during which participants were required to keep their eyes closed, remain still, and relax. Under these conditions, they were allowed to think freely. The participants were also informed that the same instructions should be applied to all 3 rests and they were reminded of the instructions before each resting scan started. After the third resting scan, participants also performed a face/house localizer fMRI task.

The order of the two fame conditions was counter-balanced across the participants, with half the participants being given the AA-BB order (A: famous encoding run; B: nonfamous encoding run) and the other half, the BB-AA order. After the MRI session, participants were asked to perform a multiple-step retrieval task in another testing room. The average time delay between the encoding and the retrieval tasks was 54.4 min (*SD* = 4.5 min).

After the retrieval task, participants were asked to rate the famous faces on different dimensions (see *face evaluation* section). At the end of the experiment, participants were also asked to estimate how much time
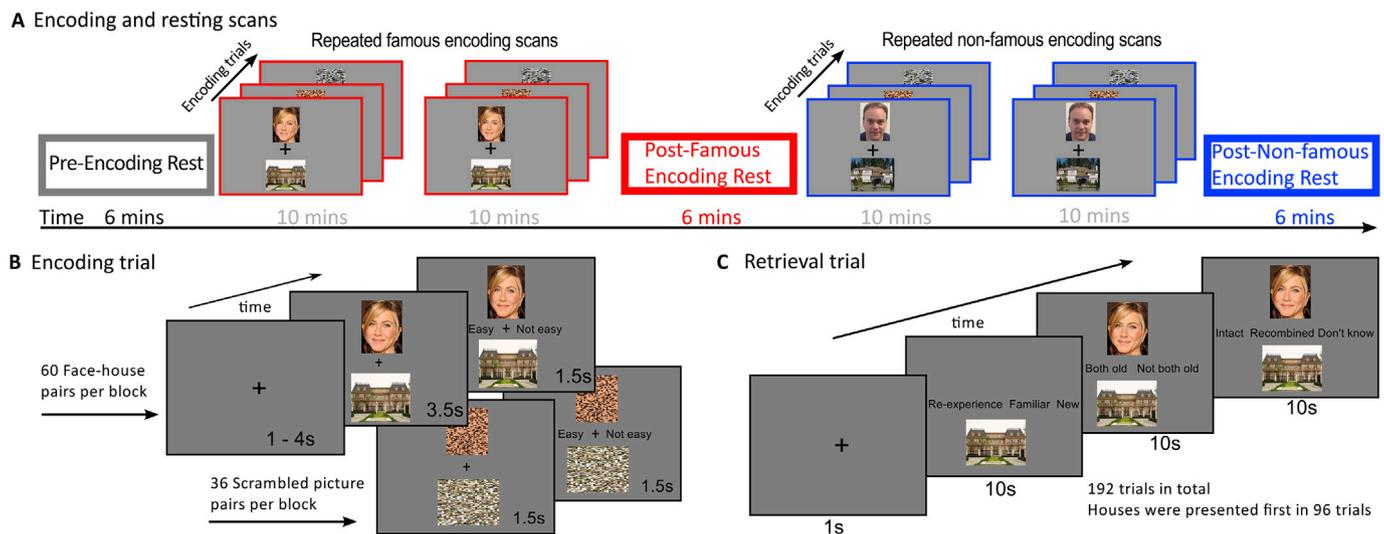
A Encoding and resting scans

Fig. 1. A. Schematic overview of the encoding and resting scans. The order of the famous and nonfamous condition was counter-balanced across the participants. **B.** An example of encoding trials from the famous condition. Identical trial structure was used for the nonfamous condition. **C.** An example of retrieval trials in the famous condition. Identical trial structure was used for the nonfamous condition.

they spent during each rest in thinking about their past and planning for their future (see *Post-experiment interview* section).

Face-house associative encoding task

The details of the encoding task were reported in a separate study that focused on encoding brain activity (Liu et al., 2017). Briefly, 192 colour pictures of Caucasian faces (210 × 300 pixels) and 192 of houses (350 × 300 pixels) were obtained from the Internet using Google Image Search. Half of the face pictures were of famous Hollywood actors (48 females and 48 males). Among the 96 famous face pictures, 60 (30 females) were used in the scanned encoding task each of which was paired with a house picture randomly chosen from the house picture set. Similarly, 60 non-famous face-house pairs were created for the non-famous condition. The remainder of the original set of pictures was used in the retrieval task. We also created 72 pairs of scrambled pictures for control trials, by scrambling (in 10 × 10 pixel tiles) randomly selected original face and house pictures. Therefore, one encoding run had 60 face-house trials and 36 scrambled picture trials.

In each face-house encoding trial (Fig. 1B), participants were asked to associate the face and house picture for 3.5 s and then indicate whether it was easy or not for them to make the association by pressing one of two buttons in a 1.5 s response window. The structure of scrambled picture-pair trials was almost identical to that of the face-house trials, except that the presentation duration was reduced to 1.5 s, and that participants were asked to answer whether it was easy or not for them to differentiate the pattern of the two scrambled pictures. A jitter time of 1–4 s, with an exponential distribution across trials and mean time of 1.5 s, was given between trials. The mean contrast and luminance of face/house and scrambled pictures were equalized across trials. Ten encoding practice trials were given before the encoding scan started.

Pre-/post-encoding resting state scans

During each of the three 6-min resting scans, participants were required to relax, keep eyes closed, and remain still. Although participants were allowed to think freely, we stressed that they should relax. To avoid potential contamination on the first resting state scan from the encoding task, the practice block of the encoding task was always given after the first resting scan. Because the order of the two encoding fame conditions was counter-balanced, the order of the famous post-encoding rest and the nonfamous post-encoding rest was also counter-balanced across the participants.

Face/house localizer scan

A block design was used for the face/house localizer task. There were 6 blocks for each of three picture categories, i.e., faces, houses, and objects (all 400 × 350 gray scale pictures). In each picture block, participants were asked to perform a 1-back task in which they needed to press a button whenever they found a repeated picture. Each picture block had 14 pictures and lasted about 16 s, followed by a fixation block of the same time length. The task, lasting about 10 min, was used to localize the FFAs and PPAs.

Unscanned retrieval task

The details of the retrieval task were reported in the separate study focusing on brain activity at encoding (Liu et al., 2017). Briefly, 4 types of face-house retrieval pairs, *intact*, *recombined*, *old-new*, and *new-new* pairs, were constructed for this 3-step retrieval task (Fig. 1C; 24 pairs for each pair type in each fame condition). Both the face and house pictures in the *intact* and *recombined* pairs were old, being encoded by the participants in the encoding phase, but for the *recombined* pairs, the face and house pictures were re-paired. For each retrieval trial, first, a single picture, face *or* house, from a face-house retrieval pair was presented and participants were asked to recognize this single picture using a Recollection/Familiarity paradigm. Then, the other picture of that retrieval pair was added to form a face-house pair and participants needed to respond whether both pictures had been encoded in the encoding phase regardless whether the two pictures had been paired together. At the third step, if participants had indicated that both pictures had been seen in the encoding phase, they were asked to identify whether the pair was intact or recombined. If they had indicated that at least one picture had not been encoded, then they had to respond whether the pair contained one or two new pictures. Face-house pairs from the 4 retrieval pair types and 2 fame conditions were randomly presented. This retrieval task lasted about 30 min.

In the current study, we mainly focused on the associative memory performance derived from the third step of the retrieval task. Specifically, associative memory as indexed by associative identification (Cohn and Moscovitch, 2007), was measured by subtracting the percentage of the recombined trials that were mistaken as intact pairs (false alarm rate) from the percentage of the intact pairs that were correctly identified as intact pairs (hit rate).

Face evaluation

To confirm that participants indeed had prior knowledge about the

famous people whose faces were used in this experiment, after the retrieval task, participants were asked to rate the famous face pictures on *familiarity*, *attractiveness*, *emotion*, and *memory* using 5-point scales. Specifically, we instructed the participants to give a number, from 1 ("none or extremely low") to 5 ("extremely high"), to indicate how familiar they were with the famous people (*familiarity*), how attractive they thought the faces were (*attractiveness*), how strongly the faces evoked emotions or emotional opinions (*emotion*), and how vividly memories of previous experiences (e.g., recall watching these famous people in movies or TV news/advertisement) were triggered by the faces (*memory*). For the first three evaluation tasks, nonfamous faces were also added as fillers. The order of the face pictures was randomized across both the evaluation tasks and participants. The order of these rating tasks was also randomized across participants. The tasks were self-paced, with each about 5 min long. The mean rating score for the famous faces was 3.84 (*SD* = 0.91) for *familiarity*, 3.01 (*SD* = 0.64) for *memory*, 2.65 (*SD* = 0.84) for *emotion*, and 3.24 (*SD* = 0.34) for *attractiveness*. For the nonfamous faces, the mean rating score for *familiarity* was 1.28 (*SD* = 0.45), for *emotion* was 1.63 (*SD* = 0.58), and for *attractiveness* was 1.95 (*SD* = 0.40). Familiarity, emotion, and attractiveness scores were all significantly lower for the nonfamous than famous faces ($t = 7.51$–13.33, $p < 0.0001$). These data showed that participants indeed felt more familiar with these famous faces and had more emotional opinions or stronger emotional responses to them, compared to nonfamous faces, and that they had vivid episodic memories related to these famous people. Therefore, the famous faces used in this study successfully elicited different components of prior knowledge in our participants.

Post-experiment interview

After the experiment, we asked the participants whether they had explicitly thought about the encoding task during each resting scan. Only two participants reported that they had thought very briefly (less than 10% of the total resting time) about something (e.g., objects, people, or events) that was related to the encoding stimuli at the very beginning of the post-encoding rest. Among the two participants, one reported that he/she did this similarly at the beginning of the famous post-encoding rest and the nonfamous post-encoding rest, and the other reported that she/he only did this at the beginning of the famous post-encoding rest. The other 18 participants reported that they had not thought about anything that was related to the encoding task. Importantly, none of the 20 participants reported explicit rehearsal of the face-house association task during the post-encoding rests. Therefore, the current analysis included the data from all 20 participants. The main findings of this study, however, remained the same after excluding the two participants who claimed to have thought briefly about something related to the task material.

To confirm further that participants performed similar mental activity during the 3 rests, we also asked the participants to estimate what percent of their time they spent during each rest thinking about the future, remembering the past, or just mind-wandering. There was no difference on any of the 3 measures among the 3 rests (pre-encoding rest: *Mean* = 38%, 22%, and 40%, *SD* = 31%, 23%, and 32% for future thinking, past thinking, and mind-wondering, respectively; famous post-encoding rest: *Mean* = 35%, 23%, and 42%, *SD* = 30%, 25%, and 32%; nonfamous post-encoding rest: *Mean* = 38%, 22%, and 40%, *SD* = 30%, 22%, and 33%; all $p > 0.16$). There was no correlation between the length of the time that participants spent in active thinking during the rests and the later associative memory performance in the two fame conditions (all $p > 0.45$), providing further confirmation that the participants did not actively rehearse the task material during the rests.

Structural and functional MRI scan

All MRI images were acquired in a 3T Siemens MRI scanner with a standard 12 channels head coil at the Baycrest Hospital (University of Toronto). T1-weighted images were obtained using a standard 3-

dimensional MPRAGE (magnetization-prepared rapid-acquisition gradient echo) pulse sequence (160 slices; field of view (FOV) = 256 × 256 mm; 192 × 256 matrix; 1 mm isotropic resolution, TE/TR = 2.63/2000 ms, flip angle = 9°, and scan time = 386 s). Functional T2-weighted images were obtained using an EPI procedure with TE = 24 ms, TR = 2000 ms, 3.5 mm slices (with 0.5 mm gap and a bottom-up interleaved order), and flip angle = 70° (FOV = 200 × 200 mm; 64 × 64 matrix, 3.5 × 3.5 mm in-plane resolution). All images were acquired in an oblique orientation (30° clockwise to the anterior-posterior commisssure axis) to reduce the fMRI signal drop in the ventral medial prefrontal regions. Visual stimuli and instructions, presented by E-Prime software (version 2, Psychology Software Tools, Inc.), were back-projected to a screen and viewed with a mirror mounted on the head coil. Head movements were minimized by inserting a soft cushion into the head coil.

Data analysis

fMRI resting data spatial preprocessing

SPM8 (Statistical Parametric Mapping, Welcome Trust Center for Neuroimaging, University College London, UK; www.fil.ion.ucl.ac.uk/spm/, version 4661) in MATLAB environment (MathWorks, Natick, MA) was used to preprocess the T2-weighted functional images. First, slice timing was corrected using sinc-interpolation with the midpoint slice as the reference. Then, all functional images were aligned using a 6-parameter linear transformation. Next, anatomical images were co-registered to the aligned functional images, and segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) using SPM8 default tissue probability maps. These segmented images were then used to calculate the transformation parameters, including both the Affine and warping regularization matrix, mapping from the individuals' native space to the MNI template space. This procedure was completed using SPM8 *Segment* module with default settings. The resulting transformation parameters were used to transform all functional images to the MNI template. The functional images were then re-sampled at 2 × 2 × 2 mm resolution and smoothed using a Gaussian kernel with the FWHM (full-width at half maximum) of 8 mm. The first 3 fMRI volumes from each run were discarded.

fMRI resting data temporal preprocessing

Several sources of potential confounding variances were deleted from the spatially preprocessed functional time-series using the functional connectivity toolbox *conn* (Whitfield-Gabrieli and Nieto-Castanon, 2012). First, signals from the white matter (WM) and cerebrospinal fluid (CSF) were regressed from the functional time-series using a principal component based noise correction method (Behzadi et al., 2007); the first five principal components were removed. The 6 motion parameters obtained from the re-alignment procedure and their first derivatives also were used as regressors to remove potential confounding effects from the head motion. Then, the resulting time-series were band-filtered (0.008–0.1 Hz) to further reduce potential confounding effects from low frequency drifts and high frequency physiological noise. Finally, a hypobolic tangent function was used to suppress (i.e., despike) extreme values in the fMRI time series to reduce effects of potential outlier volumes (Whitfield-Gabrieli and Nieto-Castanon, 2012).

ROI definition

As mentioned earlier, we focused on 5 pre-defined brain regions, i.e., the vmPFC, aTPL, HPC, PPA, and FFA. We considered these brain regions in both hemispheres, i.e., a total 10 ROIs were included. First, to make sure that the ROIs used in the current post-encoding connectivity analysis were the regions that played a functional role during encoding, we defined the vmPFC, aTPL, and HPC ROIs using the face-house associative encoding task analysis. Specifically, we conducted a first-level SPM general linear model (GLM) analysis, in which the face-house encoding trials were contrasted with the scrambled picture trials. Then, at the
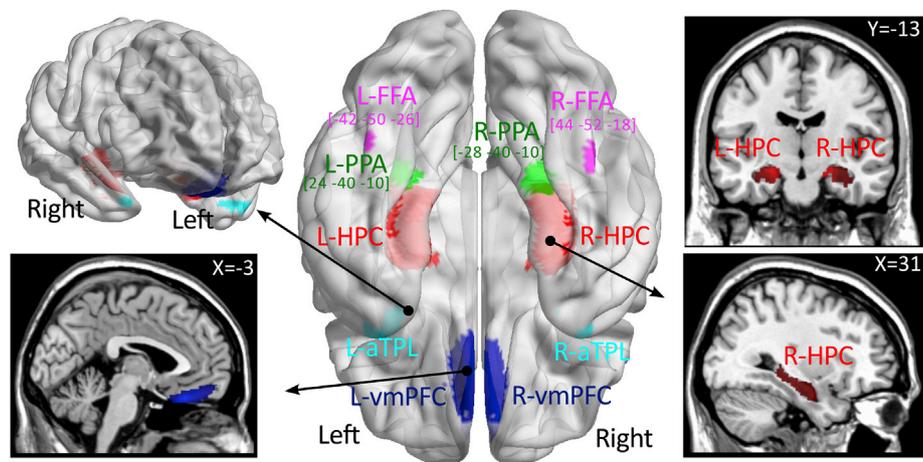
Fig. 2. The 5 bilateral ROIs used in this study, including the left and right ventral medial prefrontal cortex (i.e., L-vmPFC and R-vmPFC), the left and right anterior temporal pole (i.e., L-aTPL and R-aTPL), the left and right hippocampus (i.e., L-HPC and R-HPC), the left and right parahippocampal place area (i.e., L-PPA and R-PPA), and the left and right fusifum face area (i.e., L-FFA and R-FFA). The vmPFC, aTPL, and HPC ROIs were obtained from the encoding task using the face-house trial vs. scrambled trial contrast. The PPA and FFA ROIs were obtained from the face-house localizer task. The MNI coordinates of the FFAs and PPAs (at the peak activation locations) are also indicated.

second level analysis, we obtained voxels within the anatomical mask of vmPFC, aTPL, and HPC that also showed the face-house encoding effect to be the final ROIs. The anatomical masks were generated using the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002) and the WFU-Pickaltas toolbox (Maldjian et al., 2003). The vmPFC mask consisted of the gyrus rectus and the orbital and medio-orbital section of the superior frontal gyrus. The aTPL mask consisted of the temporal pole region of the superior and middle temporal gyrus. The HPC mask was directly obtained from the AAL atlas. For aTPL and HPC, we used $p = 0.0001$ with 10 voxel extension (no corrections) to threshold the encoding effect image. Because the vmPFC anatomical masks were relatively large and contained more heterogeneous functional areas, a slightly more lenient threshold of $p = 0.005$ with 10 voxel extension (no corrections) was used to include more voxels for this ROI (Fig. 2).

Next, we defined the PPA and FFA functional ROIs using our localizer task. First, we conducted a block-design first-level GLM analysis and used the contrast of *face - house* and *house - 0.5face - 0.5object* to localize the FFAs and PPAs, respectively. The first level contrast images were then used in the second level one-sample *t*-test, in which both the FFAs and PPAs were easily identified in the fusiform and parahippocampal gyri using the threshold of $p = 0.005$, with 10-voxel extension.[1] Since aTPL and vmPFC were defined at the group level in the MNI space, we also defined FFA and PPA at the group level, which is also consistent with our previous report (Liu et al., 2017). To make the final functional ROI masks, we first found the voxel with maximum activation in the FFA and PPA cluster (left FFA: [-42 -50 -26], right FFA: [44–52 -18], left PPA: [-28, -40 -10], and right PPA: [24, -40 -10]), then included all voxels within an 8-mm radius sphere that survived the threshold of $p = 0.005$ (see Fig. 2).

All these ROIs showed stronger activation during the face-house encoding task than the perceptual, i.e., scrambled picture-pair, task (Liu et al., 2017).

fMRI connectivity analysis

Functional connectivity analyses were conducted using the *conn* toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) and custom Matlab scripts. First, fMRI signals were extracted from each of the 10 ROIs, and the average signal across all activated voxels was calculated. Then, for each participant, Pearson correlations (*r*) between each ROI

time-series with all other ROI time-serious were calculated and transformed to Fisher's Z scores ($0.5 \frac{\ln(r+1)}{\ln(r-1)}$). To test the prior knowledge effects on post-encoding brain connectivity, we directly compared the correlation Z scores among these predefined ROIs between the famous post-encoding and nonfamous post-encoding rests using paired t tests. To investigate the relationship between the post-encoding brain connectivity and associative memory performance, we conducted regression analyses in which connectivity measures among these pre-defined functional ROIs (the Z score) were used to predict associative memory performance. These regression analyses were conducted separately for the two fame conditions.

Statistical thresholding. We used false detection rate (*FDR*; Benjamini and Hochberg, 1995) of 0.05 to control for multiple testing in both connectivity condition difference analyses (i.e., paired *t* tests) and connectivity-memory performance regression analyses. This *FDR* correction was conducted at the seed level as implemented in the *conn* toolbox, i.e., *p* values for all connectivity measures related to a specific ROI were corrected with *FDR*. Effects with original $p < 0.05$, but $FDR > 0.05$ and < 0.1, were reported as marginally significant (i.e., trend level) effects and interpreted with caution. When testing specific hypothesized directional effects, one-tailed test with threshold of $p = 0.05$ was used without *FDR* correction. For reporting effect size, Cohen's d was used for *t* tests and explained variance R^2 was used for regressions. We acknowledge that with the sample size of 20, alpha level of 0.05, and statistical power of 0.80, the current study can only detect an effect size of Cohen's d > 0.67 and $R^2 > 0.31$.

Results

Behavioral results

First, we found that associative memory performance (hit rate - false alarm rate) was better for the famous ($M = 0.36$, $SD = 0.21$) than the nonfamous ($M = 0.19$, $SD = 0.14$) condition ($t(19) = 4.60$, $p < 0.0002$, Cohen's $d = 1.03$). The correlation between associative memory performance in the two conditions was also significant ($r = 0.47$, $p = 0.035$). Interestingly, participants' age predicted associative memory performance in the famous ($r = 0.60$, $p = 0.005$), but not the nonfamous condition ($r = 0.11$, $p = 0.63$). To further test whether age specifically predicted memory performance in the famous condition, we conducted a partial correlation analysis with the associative memory performance in the nonfamous condition as a control variable. This analysis confirmed that age predicted associative memory specifically in the famous

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[1] Using a contrast of face vs. house and object localized the same FFA cluster, but the face-specific activity was less robust (threshold would need to be lowered to $p = 0.05$), so we used the face – house contrast to identify the FFA.

condition ($r_{partial} = 0.62$, $p = 0.004$). Because there was no age-memory relationship for the nonfamous condition, the age effect on the associative memory of the famous condition is not likely to be a general developmental effect. Instead, it may reflect a between-participant prior

knowledge facilitation effect, most likely because older participants had gained more knowledge about the famous people and, thereby, benefited more from their prior knowledge when forming associations between novel houses with famous faces.
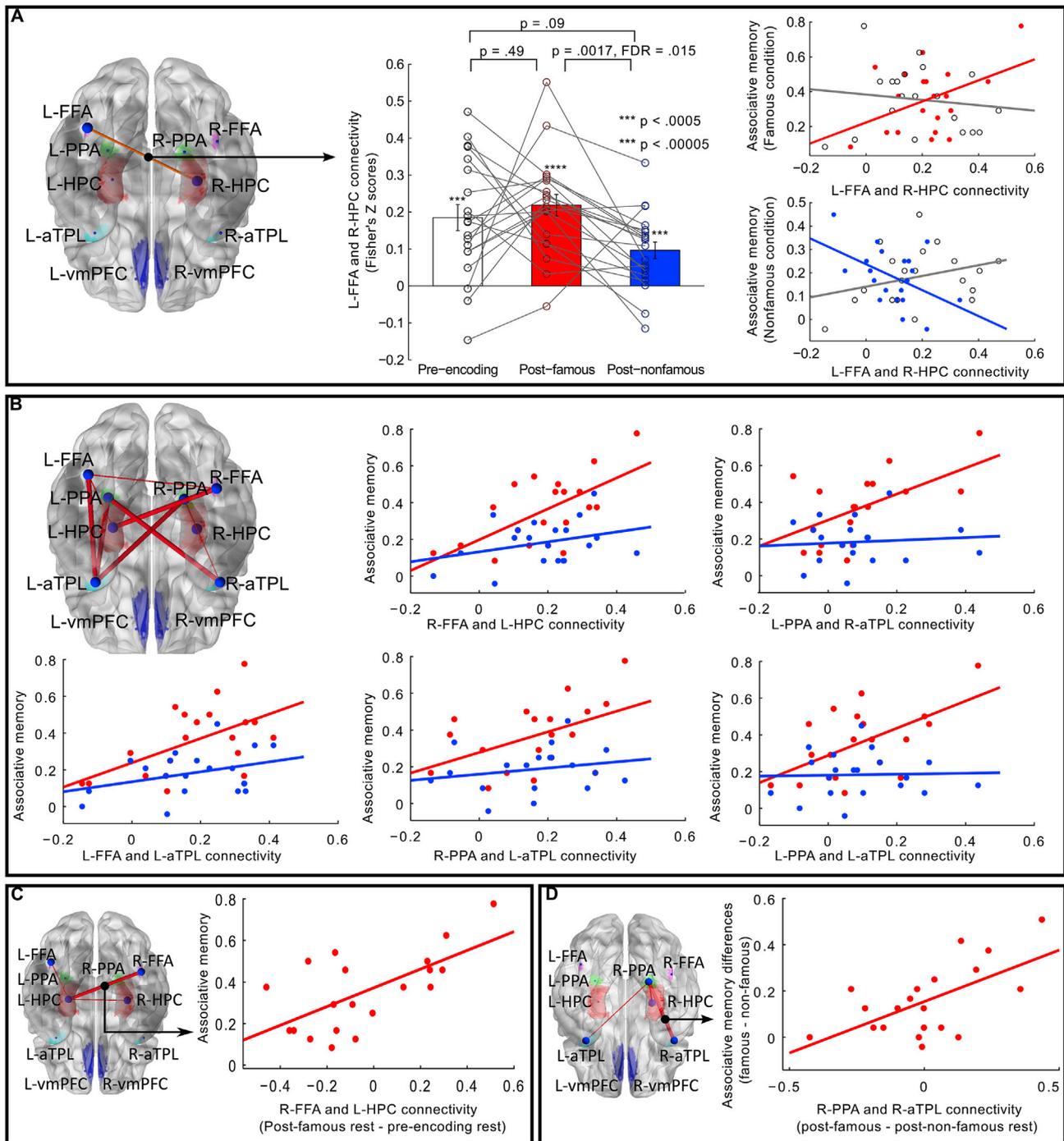

Fig. 3. A. Brain connectivity differences between the famous post-encoding rest and nonfamous post-encoding rest. On the left brain surface plot, the connectivity that showed significant effects after FDR = 0.05 correction is indicated in red lines. *Middle*: The bar graph with individual data points showing that the L-FFA and R-HPC connectivity was stronger in the famous post-encoding rest than the nonfamous post-encoding rest after FDR correction. Pre-encoding connectivity data are also added for comparison. *Right*: The scatter plots depict the relationship between connectivity measures and associative memory performance in the two fame conditions (upper: famous condition; bottom: nonfamous condition; gray - pre-encoding; red – famous post-encoding rest; blue - -nonfamous post-encoding rest). **B**. Brain connectivity during famous post-encoding rest positively predicted associative memory of the famous condition. On the brain surface plot, the connectivity that showed significant effects after FDR = 0.05 correction is indicated in thicker red lines. The connectivity whose effects did not survive the FDR correction but reached the uncorrected threshold of $p = 0.05$ is also indicated in thinner red lines (similar notations for the brain surface plots in **C** and **D**). Scatter plots with regression lines shows that the famous post-encoding rest connectivity only predicted the associative memory performance of the famous (in red, FDR < 0.05), not the nonfamous (in blue) condition. **C**. Brain connectivity between the R-FFA and L-HPC during the famous post-encoding rest positively predicted the associative memory of the famous condition at FDR < 0.05, after controlling for the pre-encoding brain connectivity. **D**. The R-PPA and R-aTPL connectivity difference between the famous post-encoding and nonfamous post-encoding rest positively predicted the associative memory difference between the two fame conditions at FDR < 0.05.

Prior knowledge effects on post-encoding brain connectivity

Before testing the main hypotheses of this study, we determined whether the face-house associative encoding task significantly modified resting state brain connectivity. To this end, we contrasted functional connectivity among the 10 ROIs during post-encoding rest with pre-encoding rest. The analysis was conducted separately for the two fame conditions. For the famous condition, we found that the connectivity between the right aTPL and left FFA increased during post-encoding, compared to pre-encoding, rest ($t(19) = 3.43$, $p = 0.0028$, $FDR = 0.025$, Cohen's $d = 0.77$). For the nonfamous condition, the connectivity between the right HPC and right FFA was found to decrease after the nonfamous encoding task ($t(19) = -3.71$, $p = 0.0015$, $FDR = 0.014$, Cohen's $d = 0.83$). No other significant results were found from these analyses.

Next, to test whether prior knowledge differentially affected post-encoding brain activity, we directly compared brain connectivity among the 10 pre-defined ROIs between the two post-encoding rests. The results showed that only the connectivity between the left FFA and right HPC was different between the two post-encoding rests, being stronger in the famous post-encoding rest than the nonfamous post-encoding rest ($t(19) = 3.67$, $p = 0.0017$, $FDR = 0.015$, Cohen's $d = 0.82$). As can be seen in the bar graphs in Fig. 3A, this post-encoding connectivity difference was likely driven by the reduced connectivity in the nonfamous post-encoding rest. Next, using regression analyses, we tested whether the connectivity between the left FFA and right HPC could predict associative memory performance in the two fame conditions. As can be seen in the scatter plots in Fig. 3A, the FFA-HPC connectivity during the famous post-encoding rest positively predicted the associative memory of the famous condition at a trend level ($t(18) = 2.04$, $p = 0.056$, explained variance $R^2 = 0.19$), but the connectivity between the same regions during the nonfamous post-encoding rest negatively predicted the associative memory in the non-famous condition ($t(18) = -2.30$, $p = 0.03$, $R^2 = 0.23$). The brain-behavior correlation for the two fame conditions were statistically different using Z test (Raghunathan et al., 1996), $Z = 3.50$, $p < 0.0005$, Cohen's $d = 0.78$. Critically, the connectivity between the left FFA and right HPC during the pre-encoding rest did not predict the associative memory performance in either of the two fame conditions ($ps > 0.34$; Fig. 3A).

Post-encoding connectivity (mean and standard deviation) among all ROIs in the two fame conditions, as well as differences between the two conditions, are presented in Supplementary Fig. 1.

Famous post-encoding brain connectivity predicting associative memory

As can be seen from Fig. 3A, although post-encoding connectivity between the left FFA and the right HPC was not different from that in the pre-encoding rest at the group mean level ($t(19) = 0.70$ and -1.80, $p = 0.49$ and 0.087, $FDR = 0.64$ and 0.39 for the famous and nonfamous condition, respectively), individual participants' connectivity strength during the post-encoding rest still predicted later associative memory. This result indicated that post-encoding brain connectivity can still be important for memory processing even if it did not differ at the group level from the pre-encoding rest. Thus, it is important to test whether ROI connectivity that did not differ between the two post-encoding rests could still differentially predict associative memory of the two fame conditions.

To test this possibility, we conducted regression analyses using the post-encoding brain connectivity measures that did not show fame effects, i.e., all connectivity measures except the one between the left FFA and right PHC (which has been tested in the previous section), to predict associative memory performance. For the famous condition, we found that the connectivity between the left PPA and the bilateral aTPL, between the right PPA and left aTPL, between the left aTPL and left FFA, and between the left HPC and right FFA (see the thick lines in Fig. 3B) during the famous post-encoding rest positively predicted associative

memory performance in the famous condition ($t(18) = 3.14$, 2.97, 2.72, 2.80, and 3.49, $p = 0.006$, 0.009, 0.014, 0.012, and 0.003, respectively. $FDR = 0.023$–0.043, $R^2 = 0.29$–0.40)[2]. None of the connectivity measures from the famous post-encoding rest significantly predicted associative memory from the non-famous condition ($p = 0.27$ –0.86. See the blue data points and lines in Fig. 3B). Because associative memory performance in the famous condition shared significant variance with that in the nonfamous condition ($r = 0.49$, $p = 0.035$), to further test whether the famous post-encoding connectivity tested above was specifically related to memory processing in the famous condition, we calculated partial correlations between each of the 5 connectivity measures with the associative memory performance in the famous condition while controlling for the associative memory performance in the nonfamous condition. Results showed that all these connectivity measures were still correlated with the associative memory performance in the famous condition ($r_{partial} = 0.47$–0.64, $p = 0.04$–0.0035). These results, therefore, suggest that rather than having a general role in post-encoding memory processing, the famous post-encoding connectivity examined above had a specific role in supporting post-encoding processing of associative memory in the famous condition. Regression coefficients for post-encoding connectivity among all ROIs predicting associative memory in the famous condition are presented in Supplementary Fig. 2.

We also investigated to what extent the connectivity among these ROIs predicted face-house associative memory vs. face/house item memory. To this end, we first calculated the face and house item memory performance using the hit rate minus false alarm rate obtained from all 3 steps of the retrieval procedure and conducted similar regression analyses to examine how the five connectivity measures that predicted face-house associative memory also predicted face/house item memory. We found that these post-encoding connectivity measures did not predict house and face item memory of the famous condition with $FDR \leq 0.05$ (Supplementary Fig. 3). Next, we calculated partial correlations between each connectivity measure and face-house associative memory while controlling for face and house item memory. Although face and house item memory shared a considerable amount of variance with face-house associative memory ($r = 0.47$ and 0.50, $p = 0.035$ and 0.025, respectively), after controlling for item memory, four of the 5 connectivity measures (except for the connectivity between the left aTPL and right PPA) were still correlated, significantly or at a trend level, with face-house associative memory performance ($r_{partial} = 0.44$–0.62, $p = 0.06$–0.006). Therefore, the connectivity among these regions during the famous post-encoding rest was more related to associative, rather than item, memory processing in the famous condition.

Because age positively predicted associative memory performance in the famous condition, which may reflect a between-subject prior knowledge facilitation effect, we also tested whether age could positively predict those 5 pair-wise connectivity measures with specific relationships to associative memory in the famous condition. Our regression analyses confirmed that age positively predicted the connectivity between the right FFA and left HPC, between the left PPA and left aTPL, and between the left PPA and right aTPL during the famous post-encoding rest ($p = 0.031$, 0.044, and 0.033, $R^2 = 0.18$, 0.15, and 0.17, respectively, using a one-tailed test. Supplementary Fig. 4). Age also positively predicted the left HPC-right FFA connectivity increase from pre-encoding to the famous post-encoding rest ($p = 0.024$, one-tailed, $R^2 = 0.20$). Interestingly, these three connectivity measures also showed the strongest (numerically) prediction effects among the five connectivity measures that predicted subsequent associative memory of the famous condition. We also confirmed that the famous post-encoding connectivity measures that were positively predicted by age were stronger for the

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[2] We also found that the connectivity between the left HPC and left FFA, between the right aTPL and PPA, and between the left and right FFA positively predicted associative memory in the famous condition ($t(18) = 2.64$, 2.21, and 2.22, $p = 0.017$, 0.041 and 0.04) without FDR correction ($FDR = 0.07$ - 0.18, $R^2 = 0.21$ - 0.28; see the thin lines in Fig. 3B).

participants who reported more vivid prior memories elicited by the famous faces ($p = 0.005$–0.08; One-tailed, $R^2 = 0.10$–0.31. Supplementary Fig. 4). Although some of the effects were weak (i.e., at trend levels) and should be interpreted with caution, they collectively formed a pattern showing that the strength of the famous post-encoding connectivity that predicted later memory was also positively related to the strength of individuals' prior knowledge.

We also conducted a multiple linear regression analysis with the 5 famous post-encoding connectivity measures as predictors to quantify the predictive effect of these post-encoding connectivity measures on subsequent associative memory in the famous condition. We found that these 5 connectivity measures together explained 71% of the variance of the associative memory performance in the famous condition ($F(5, 14) = 6.89$, $p = 0.002$, $R^2 = 0.71$). To further examine whether post-encoding connectivity among these ROIs had a *unique* contribution to the later associative memory performance, in addition to the contribution of brain activity during the encoding phase, we extracted brain activation scores in the bilateral PPA, FFA, aTPL, and the left HPC from our previous publication (Liu et al., 2017). We also obtained corresponding connectivity among these ROIs *during* the encoding task using identical methods as used in this post-encoding connectivity analysis (for details, please see Supplementary Analysis). This resulted in 12 encoding brain activity variables. We then conducted a principal component analysis on these variables and selected the first six components to represent encoding brain activity, which accounted for 99.1% of the total covariance in the 12 encoding brain activity variables. Finally, we entered these 6 principal component scores into a multiple regression model as controlled variables at the first step and entered the 5 famous post-encoding connectivity measures as predictors of interest at the second step in SPSS (version 22. IBM Corp.). This multiple regression analysis revealed that the encoding brain activity alone accounted for 38.4% of the total variance in the associative memory performance, but the model was not statistically significant ($R^2 = 0.384$, $F(6, 13) = 1.35$, $p = 0.30$). The 5 famous post-encoding connectivity measures accounted for an additional 45.1% of variance in associative memory (R^2 change = 0.451, $F(5, 8) = 4.38$, $p = 0.032$). These results showed that post-encoding connectivity predicted a large proportion of unique variance in subsequent associative memory when prior knowledge was involved in the preceding encoding task.

Finally, we examined whether post-encoding connectivity predicting subsequent associative memory in the famous condition was indeed related to the associative encoding process. If this was the case, we expected that pre-encoding connectivity should not predict associative memory performance in the same way that post-encoding connectivity did. With *FDR* of 0.05, we found no pre-encoding connectivity that predicted associative memory in the famous condition. Without FDR correction, only connectivity between the bilateral PPA during pre-encoding rest positively predicted associative memory in the famous condition ($p = 0.02$). However, as shown earlier, the connectivity between the bilateral PPA during famous post-encoding rest did not predict associative memory in the famous condition. Next, following Tambini et al. (2010), we also subtracted pre-encoding connectivity from famous post-encoding connectivity and used connectivity changes to predict subsequent associative memory in the famous condition. We found that the left HPC and right FFA connectivity changes due to the encoding task also positively predicted associative memory in the famous condition ($t(18) = 3.56$, $p = 0.002$, *FDR* = 0.02, $R^2 = 0.41$; Fig. 3C). Regression coefficients for post-pre encoding connectivity changes among all ROIs predicting associative memory in the famous condition are presented in Supplementary Fig. 5. These results confirmed the specificity of the relationship between post-encoding connectivity and associative memory in the famous condition.

Nonfamous post-encoding brain connectivity predicting associative memory

We conducted similar analyses to test whether nonfamous post-

encoding connectivity predicted associative memory in the nonfamous condition. Results showed no significant relations between the post-encoding connectivity among these pre-defined ROIs and the associative memory of the nonfamous condition, except that, as mentioned earlier, the connectivity between the left FFA and right HPC negatively predicted associative memory performance in the non-famous condition ($p = 0.03$ without *FDR* correction). Regression coefficients for post-encoding connectivity among all ROIs predicting associative memory in the nonfamous condition are presented in Supplementary Fig. 6.

The results reported so far showed that post-encoding connectivity between the left PPA and bilateral aTPL, between the right PPA and left aTPL, between the left aTPL and left FFA, and between the left HPC and right FFA (Fig. 3B) positively predicted associative memory in the famous condition, but not in the nonfamous condition. However, whether the predictive pattern of these connectivity measures on associative memory was statistically different between the two fame conditions needs to be formally tested. Therefore, we conducted similar Z tests on related correlations (Raghunathan et al., 1996) to investigate whether the brain-behavior relationship was different in the famous than nonfamous condition. Results showed that all these post-encoding connectivity measures, except for the connectivity between the left FFA and aTPL, had a larger correlation, significantly or at a trend level, with subsequent associative memory in the famous than nonfamous condition ($Z = 1.43$–1.83, $p = 0.075$–0.034, Cohen's $d = 0.32$–0.41, one-tailed). These results confirmed that post-encoding connectivity among these ROIs played a different role in post-encoding memory processing depending on whether prior knowledge was involved in the preceding encoding task.

Finally, we also tested whether the brain connectivity differences between the two post-encoding rests (using famous post-encoding minus nonfamous post-encoding) could also predict differences between the two fame conditions in associative memory performance. This analysis was conducted to test whether prior knowledge effects at the brain level can be directly related to those at the behavioral level. Regression analysis showed that the right PPA-aTPL connectivity differences positively predicted differences in associative memory performance ($t(18) = 3.23$, $p = 0.005$, *FDR* = 0.042, $R^2 = 0.37$; Fig. 3D). The right PPA's connectivity with the left aTPL and right HPC also showed similar predictions at a trend level after the *FDR* correction ($t(18) = 2.71$ and 2.59, $p = 0.015$ and 0.019, *FDR* = 0.056, $R^2 = 0.29$ and 0.27). Supplementary Fig. 7 presents regression coefficients for post-encoding connectivity differences between the two famous conditions among all ROIs predicting associative memory differences between the two fame conditions.

Fame order in the current block design cannot explain the main findings reported in this study

We conducted additional analyses to confirm that the prior knowledge effect on post-encoding connectivity and its relationship with later associative memory reported in this study were not biased by the current design in which different fame order was used across participants (for details, please see Supplementary Analysis).

Prior knowledge effects on post-encoding brain connectivity: using whole-brain anatomical ROIs

For completeness, we also explored the prior knowledge effects on post-encoding brain connectivity beyond our pre-defined functional ROIs. Specifically, we used 90 cerebral brain regions, defined by the Automated Anatomical Labeling (AAL) template (Tzourio-Mazoyer et al., 2002), as anatomical ROIs and directly contrasted the famous post-encoding rest with the nonfamous post-encoding rest. Using seed-level *FDR* = 0.05 as the statistical threshold, we found that only the left HPC connectivity with the orbital part of the right superior frontal gyrus and the left aTPL (in the superior temporal gyrus) connectivity with

the right precuneus were stronger during the famous post-encoding than nonfamous post-encoding rest, $t(19) = 4.41$ and 4.60, $p = 0.0003$ and 0.0002, $FDR = 0.027$ and 0.018, Cohen's $d = 0.99$ and 1.03, respectively (Supplementary Fig. 8). No post-encoding connectivity was found to be stronger in the nonfamous than famous condition. The orbital section of the superior frontal gyrus is part of the vmPFC, whose role in supporting prior knowledge effect has been investigated by previous studies (Liu et al., 2017; van Kesteren et al., 2010a). Therefore, although we did not find a fame effect on vmPFC-HPC connectivity using the *a priori* vmPFC and HPC ROIs, the whole brain analysis with anatomical ROIs revealed that part of the right vmPFC connectivity with HPC was stronger in the famous than the nonfamous post-encoding rest.

Discussion

Using an explicit encoding task in which participants associated novel houses with either famous or nonfamous faces, we investigated how associative encoding with or without prior knowledge involvement differentially affected post-encoding brain connectivity. We hypothesized stronger post-encoding connectivity in the famous than non-famous condition among regions whose activation at encoding was found to play a role in associative memory performance. For the most part, our results were consistent with this hypothesis, thereby providing evidence that prior knowledge can also affect post-encoding brain activity. Specifically, we examined prior knowledge effects on post-encoding functional connectivity among pre-defined functional ROIs, i.e., the vmPFC, aTPL, HPC, PPA, and FFA, all of which had been found to play a role in the face-house associative encoding process (Liu et al., 2017). Our results showed that the right HPC connectivity with the left FFA was stronger during the famous post-encoding rest than the nonfamous post-encoding rest. Using whole-brain anatomical ROIs, we also found that the left HPC connectivity with the vmPFC, specifically the orbital part of the right superior frontal region, was stronger in the famous, compared to the nonfamous condition. Moreover, we found that the aTPL connectivity with the PPA and FFA, as well as HPC connectivity with FFA, specifically predicted the associative memory performance in the famous condition. The connectivity between the left aTPL and PPA and between the left HPC and right FFA during famous post-encoding rest was stronger for the participants who were older and reported more vivid memories about the famous people whose faces were used in this study. Collectively, these results indicate that at least some of the post-encoding connectivity measures that predicted later memory performance in the famous condition were indeed related to the strength or amount of participants' prior knowledge. These observations are consistent with our hypotheses that prior knowledge affects how associative encoding tasks can modulate post-encoding brain connectivity. In addition, our results indicate that, during famous post-encoding rest, the aTPL, a region that supports semantic prior knowledge (Patterson et al., 2007), and the HPC, a medial temporal lobe region that supports episodic and associative memory processing (Davachi and Wagner, 2002; Winocur et al., 2010), continue to interact with posterior perceptual regions such as the PPA and FFA to facilitate off-line associative memory processing.

HPC- posterior neocortex connectivity

Our finding that cognitive tasks can modulate post-learning brain connectivity or affect subsequent memory is consistent with a large body of animal literature (Eagleman and Dragoi, 2012; Euston et al., 2007; Girardeau et al., 2009; Han et al., 2008; Hoffman and McNaughton, 2002; Jadhav et al., 2012; Johnson et al., 2010; Knauer et al., 2013; Lansink et al., 2008; Leclair-Visonneau et al., 2010; O'Neill et al., 2010, 2008; Pennartz et al., 2004; Ribeiro et al., 2004; Wilson and McNaughton, 1994; Yao et al., 2007). This finding is also consistent with recent human neuroimaging studies that focused on brain activity during post-encoding rest (Albert et al., 2009; de Voogd et al., 2016; Groen et al., 2011; Hasson et al., 2009; Hermans et al., 2017; Lewis et al., 2009;

Newton et al., 2011; Staresina et al., 2013; Tambini et al., 2010; Tambini and Davachi, 2013; Tompary et al., 2015; Wang et al., 2012) or immediately following offset of different encoding events (Ben-Yakov et al., 2013; Ben-Yakov and Dudai, 2011). For example, in a study using a similar associative encoding task, Tambini and colleagues (Tambini et al., 2010) found that HPC connectivity with the lateral occipital face area was enhanced after a face-object encoding task, compared to pre-encoding rest. The connectivity enhancement was also positively correlated with later memory performance. By extending this line of research to examine the effects of prior knowledge, we found in the current study that post-encoding connectivity between the right HPC and left FFA on an associative face-house memory task was differentially modulated by prior knowledge of the faces. This finding suggests that brain activity during rest can be extraordinarily sensitive to preceding tasks, which may have implications for the current intensive research on resting state brain activity.

In Tambini et al. (2010), the enhanced HPC connectivity was observed only after associative encoding of face-object pairs, not face-scene pairs. In the current study, we used face-house pairs as stimuli, which were similar to the face-scene pairs used in Tambini et al. (2010) in that houses activated the PPA. Like them, we did not find HPC connectivity enhancement from pre-to post-encoding in either fame condition. We did find, however, that the connectivity between the right aTPL and left FFA was enhanced by the associative encoding task in the famous condition. This effect may reflect stronger semantic processes related to famous faces in the famous condition.

When directly comparing the two fame conditions, we found that the connectivity between the right HPC and left FFA was stronger during famous post-encoding than nonfamous post-encoding rest. Interestingly, however, this difference was driven by a connectivity decrease in the nonfamous post-encoding rest. As mentioned above, Tambini and colleagues (Tambini et al., 2010) did not find significant changes in HPC-FFA connectivity after face-scene associative encoding. Although low memory performance of the face-scene condition may explain the null finding in that study, this explanation cannot apply to the current study because the connectivity reduction in the nonfamous condition found in the current study was beneficial for memory processing. Specifically, lower HPC-FFA connectivity during the nonfamous post-encoding rest was associated with better memory performance in the nonfamous condition. For the famous condition, however, although the post-encoding connectivity between the HPC and the contralateral FFA at the group level was the same as that in the pre-encoding rest, at the individual level the connectivity changed considerably (Fig. 3A) and only became positively predictive of later memory performance during the post-encoding rest. Although it is still unclear why there was an opposite brain-behavior relationship for the two fame conditions, our results suggest that prior knowledge during the preceding encoding task can affect the strength of the post-encoding HPC connectivity in facilitating subsequent associative memory.

The procedure used in the current study was somewhat different from that used by Tambini et al. (2010). Whereas Tambini et al. used different types of stimulus pairs (i.e., face-object and face-scene) in the two conditions of their within-subject design, the current study employed a similar within-subject design but used the same type of stimulus pairs, face-house, in the two experimental conditions. Thus, associative encoding in both conditions involved the same brain regions such as HPC, PPA, and FFA. Consequently, competition and interference among those associative memory traces can occur. If this is the case, the above-mentioned opposite brain-behavior relationship in the two fame conditions may reflect a mechanism by which the brain can reduce potential interference or optimize neural resources among these similar, but not identical, memories (Chanales et al., 2017). Also, HPC and FFA showed stronger activation during the encoding of the famous than nonfamous condition and exhibited positive subsequent memory effects in the famous condition (Liu et al., 2017), suggesting that these two regions indeed played an important role in processing associative memory

in the famous condition. This may explain why the post-encoding HPC-FFA connectivity *positively* predicted associative memory only in the famous condition. We acknowledge, however, that this is only speculation and should be examined by future investigations.

vmPFC/aTPL – posterior neocortical connectivity

Using pre-defined functional ROIs, we also found that the left aTPL connectivity with the PPAs and left FFA, and the right aTPL connectivity with the left PPA during the famous post-encoding rest, positively predicted later associative memory performance in the famous condition. Importantly, this brain-behavior relationship was specific for the associative memory in the famous condition, not the nonfamous condition. Additionally, we also found that some of the memory-predictive post-encoding connectivity such as the aTPL connectivity with the left PPA, was stronger for older participants and the participants who reported more vivid memories about the famous people, suggesting that these post-encoding connectivity measures were possibly related to the strength or extent of the participants' prior knowledge. Therefore, our results provide evidence that when prior knowledge is involved in the preceding encoding tasks, the semantic hub region aTPL also maintains its communication with posterior perceptual brain regions such as the PPA and FFA to facilitate the formation of new associative memory. These findings are also consistent with previous studies that have shown the importance of the aTPL and related semantic processing regions in prior knowledge facilitation effects on new learning (Groen et al., 2011; Kan et al., 2009; Sharon et al., 2011; Staresina et al., 2009).

The vmPFC has been proposed to support social/evaluative processing (Benoit et al., 2014; Etkin et al., 2011; Roy et al., 2012; Rushworth et al., 2012), remote memory (Frankland and Bontempi, 2005; Nieuwenhuis and Takashima, 2011), and prior knowledge (schemas) (Kroes and Fernández, 2012; van Kesteren et al., 2012). During the encoding phase, we found that the vmPFC showed stronger activation in the famous than nonfamous condition (Liu et al., 2017). Within the famous condition, the vmPFC also showed stronger activation for the encoding trials in which more vivid memories and emotions were evoked by the famous faces, and the trials in which the face-house pairs were subsequently remembered than forgotten (Liu et al., 2017). In another study by Schlichting and Preston (2016), prior knowledge was manipulated by using an AB-BC learning paradigm. Specifically, participants first learned AB (face-object) pairs and then in the scanner learned BC (object-object) pairs and new object-object pairs XY. The authors then compared the post-encoding brain connectivity associated with BC vs. XY learning and evaluated how brain connectivity predicted memory performance in the two conditions. They found that post-encoding HPC-vmPFC connectivity was stronger after BC than XY encoding. The connectivity enhancement after BC encoding was also related to memory integration success. Therefore, in this study, we also hypothesized that the post-encoding vmPFC connectivity with the HPC and the posterior perceptual regions (FFA and PPA) should play a more important role in the off-line processing of the associative memory of the famous, compared to the nonfamous, condition (van Dongen et al., 2011). Our predefined ROI analyses, however, did not find evidence to support this hypothesis: We found that the vmPFC connectivity did not differ between the two post-encoding rests and did not predict the associative memory of either condition.

The functional vmPFC ROI used in this study, however, does not cover all the vmPFC anatomical regions, which leaves open the possibility that prior knowledge may still affect the HPC connectivity with other vmPFC regions. This possibility was supported by our whole-brain connectivity analysis using 90 anatomically defined ROIs, which revealed that the connectivity of the orbital part of the right superior frontal gryrus with the left HPC was stronger during famous post-encoding rest than nonfamous post-encoding rest (Supplementary Fig. 8). The orbital part of the superior frontal gyrus had been included as part of the vmPFC in a previous investigation (van Kesteren et al., 2010a)

that also focused on prior knowledge (e.g., schema) effects on vmPFC-HPC connectivity. Our finding appears to be different from that of (van Kesteren et al., 2010a) who found that the post-encoding vmPFC-HPC connectivity was stronger when inconsistent prior knowledge or schema was involved in the preceding encoding task. It is likely, however, that in terms of the underlying cognitive processing, the encoding condition without a consistent prior schema in van Kesteren et al. (2010a) resembled more closely the famous encoding condition of the current study. In the former study, participants needed to understand the later part of a movie using the information they had obtained from watching the temporally shuffled early part of the movie. In our study, participants were likely to use their prior knowledge about those famous people to help them form face-house associations. Both experiments required effortful incorporation of new information into an existing knowledge system. That this type of cognitive processing may require vmPFC-HPC interaction was also supported by studies using an associative inference paradigm (Preston and Eichenbaum, 2013; Zeithamova et al., 2012).

The blood-oxygenation-level-dependent (BOLD) signal examined in this study is an indirect measure of neural activity, unlike animal studies that directly measure neuronal firing rates. Therefore, it is unclear whether the post-encoding brain activity in the current study reflected types of memory replay, or underlying neurophysiological processes, similar to those found in rodents. Because our participants did not report conscious rehearsal of the encoding task, and the validity of subjective reports has been supported by different studies (Groen et al., 2011; Staresina et al., 2013; Tambini et al., 2010), the memory-predictive brain connectivity during the post-encoding rest likely did not reflect conscious voluntary memory replays. Instead, it may reflect continuous coordinated neural-level reactivation of memory traces and related metabolic processes during post-encoding rest from brain regions where the neural/synaptic assemblies were recruited and tagged by the preceding encoding task.

A framework for considering the effects of prior knowledge during encoding and post-encoding rest on subsequent associative memory - post-encoding rest builds on formation of associations at encoding

The results of our study suggest a general framework for the effects of prior knowledge on subsequent memory. As we found before (Liu et al., 2017), prior knowledge also influences the formation of associative memory at encoding. The formation of such associative memories is mediated by sets of brain structures that include posterior neocortical structures, such as the FFA and PPA, that are specialized in higher order perceptual processes, structures such as the HPC and aTPL that represent prior episodic and semantic memory, and anterior structures, such as the vmPFC and amygdala, which are implicated in representing schemas and social/emotional information related to prior knowledge. Because in the encoding phase, we observed stronger activation in these ROIs in the famous than nonfamous condition, and positive subsequent memory effects in the famous condition (Liu et al., 2017), we inferred that new associative processing supported by these brain regions should be more effective and, therefore, may have produced stronger memory traces in the famous condition. During post-encoding rest, when newly formed memory traces started to be stabilized, the stronger associative memory traces formed at encoding in the famous condition, compared to the nonfamous condition, likely triggered more efficient consolidation processes. Thus, the better associative memory performance found in the famous condition could be contributed both by more effective encoding and by post-encoding consolidation processes. However, in the current study post-encoding connectivity between the HPC/aTPL and the posterior perceptual regions FFA/PPA predicted a large proportion of between-subject associative memory variance. Because these ROIs were all localized *a priori* based on our hypotheses and encoding/localizer task analyses, the strong association between post-encoding connectivity and memory performance indicates that when prior knowledge is involved in

memory encoding tasks, memory formation can be significantly affected by early post-encoding brain activity. Thus, focusing only on the encoding phase may not be enough to gain a full understanding of the neural mechanisms of memory formation and consolidation. Instead, brain activity in early post-encoding time windows should be systematically considered in future investigations.

The current finding that the HPC connectivity with posterior perceptual regions predicted later associative memory is consistent with the literature that the HPC is required for early memory consolidation or re-consolidation (Debiec et al., 2002; Kitamura et al., 2017; Tambini et al., 2010; Tse et al., 2011, 2007). Because the aTPL can serve as a semantic hub (Patterson et al., 2007), we suggest that the aTPL connectivity with posterior perceptual regions, which strongly predicted later associative memory, possibly reflected an early stage of the memory transformation process in which gist-like semantic memory related to the specific perceptual associative memory started to build up during post-encoding consolidation (Kitamura et al., 2017; Moscovitch et al., 2005; Winocur et al., 2010; Winocur and Moscovitch, 2011). If this is the case, it is possible that with the facilitating effects of prior knowledge, perceptual associative memory (e.g., face-house associations), which has long been considered as hippocampus-dependent, can also be semanticized and supported by neocortical regions such as the aTPL, by assimilating the new information into an existing semantic network (Gilboa and Marlatte, 2017; Tse et al., 2007). Thus, our study provides an empirical basis for investigating the semanticization of associative memory and its neural underpinnings.

The brain connectivity pattern during post-encoding rest was not identical to the activation pattern seen in the encoding phase. For example, we found that during encoding the vmPFC showed stronger activation when prior knowledge was involved, compared to the no prior knowledge situation, and when associations were successfully encoded, compared to unsuccessful situations. During post-encoding rest, however, although the vmPFC showed stronger connectivity with the HPC in the famous than nonfamous condition, vmPFC-HPC connectivity was not correlated with associative memory performance. On the other hand, during encoding the HPC-PPA/FFA connectivity was not stronger for the famous than nonfamous condition, but during post-encoding the HPC-PPA/FFA connectivity was stronger during post famous, than nonfamous, encoding rest, and predicted differently associative memory for the famous and nonfamous condition. These results also indicate that post-encoding brain connectivity investigated in the current study was not a simple continuation of encoding brain activity, which is consistent with a recent study that also found that resting brain connectivity changes did not always correspond to the tasks that preceded the rest (Tailby et al., 2015). Moreover, our analysis showed that in the famous condition, post-encoding connectivity predicted a large portion of variance in associative memory above and beyond the predictive effect of encoding brain activity. The connectivity among these ROIs also showed a statistically different relationship with subsequent associative memory in the famous vs. the nonfamous condition. Therefore, the current finding that aTPL/HPC connectivity with PPA/FFA during famous post-encoding rest predicted subsequent associative memory is likely not due to a simple continuation effect of the more successful encoding in the famous vs. nonfamous condition. Considering that these ROIs showed a prior knowledge effect during encoding, we think that post-encoding connectivity among these ROIs may reflect a different type of neural processing that is related to memory consolidation and prior knowledge, with its own unique contributions to successful memory formation. Future studies are needed to systematically investigate the relationship between task-evoked brain activity at encoding and its effects on post-task brain activity.

Another issue that should be addressed in future investigations is the laterality of prior knowledge effects on post-encoding connectivity. It has been shown that the face-house associative encoding task recruited more strongly the posterior ROIs such as FFA and PPA in the right vs. left hemisphere and the anterior ROIs such as aTPL and vmPFC on the left vs.

right hemisphere (Liu et al., 2017). Because aTPL is an important brain region that supports prior knowledge related to faces (Gainotti, 2007; Lambon Ralph et al., 2010, 2009), it is possible that the cross-hemisphere connectivity between aTPL and FFA/PPA during post-encoding rest reflected the integration of prior knowledge with perceptual information. However, because we did not experimentally manipulate processing laterality, it is difficult to directly test or interpret laterality effects in the current study. Future investigations of this issue may shed new light on the nature of the information supported by these post-encoding brain activities.

Conclusion

The current findings, consistent with our hypotheses, suggest that when prior knowledge is involved, the HPC, vmPFC, and aTPL, which support prior episodic, social-evaluative/schematic, and semantic memories, respectively, continue to interact with each other and the posterior perceptual brain regions (e.g., the PPA and FFA) during the post-encoding rest to facilitate off-line processing of the newly formed memory and lead to better memory for it. Our findings may also provide preliminary neural evidence that the post-encoding brain not only reflects stabilization of new memory, but may also facilitate the integration of new memory with our vast body of prior knowledge.

Author contributions

Z.-X.L. and M.M. designed research, Z.-X.L. performed research, Z.-X.L. analyzed data with help from M.M., and C.G., Z.-X. L., M.M., and C.G. wrote the paper.

Conflicts of interest

No conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2017.11.032.

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