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ORIGINAL ARTICLE

Effects of Prior-Knowledge on Brain Activation and Connectivity During Associative Memory Encoding

Zhong-Xu Liu[1,2], Cheryl Grady[1,3,4], and Morris Moscovitch[1,3]

[1]Rotman Research Institute, Baycrest Center, [2]Applied Psychology and Human Development, OISE, [3]Department of Psychology and [4]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Address correspondence to Zhong-Xu Liu, Rotman Research Institute, Baycrest Center, University of Toronto, 3560 Bathurst Street, Toronto, ON, Canada M6A 2E1. Email: zhongxuliu@gmail.com

Abstract

Forming new associations is a fundamental process of building our knowledge system. At the brain level, how prior-knowledge influences acquisition of novel associations has not been thoroughly investigated. Based on recent cognitive neuroscience literature on multiple-component memory processing, we hypothesize that prior-knowledge triggers additional evaluative, semantic, or episodic-binding processes, mainly supported by the ventromedial prefrontal cortex (vmPFC), anterior temporal pole (aTPL), and hippocampus (HPC), to facilitate new memory encoding. To test this hypothesis, we scanned 20 human participants with functional magnetic resonance imaging (fMRI) while they associated novel houses with famous or nonfamous faces. Behaviorally, we found beneficial effects of prior-knowledge on associative memory. At the brain level, we found that the vmPFC and HPC, as well as the parahippocampal place area (PPA) and fusiform face area, showed stronger activation when famous faces were involved. The vmPFC, aTPL, HPC, and PPA also exhibited stronger activation when famous faces elicited stronger emotions and memories, and when associations were later recollected. Connectivity analyses also suggested that HPC connectivity with the vmPFC plays a more important role in the famous than nonfamous condition. Taken together, our results suggest that prior-knowledge facilitates new associative encoding by recruiting additional perceptual, evaluative, or associative binding processes.

Key words: associative memory, encoding, fMRI, memory, prior-knowledge

Introduction

In acquiring new information, we frequently benefit from associating it with information we already possess. Investigating this type of prior-knowledge effects at the brain level may help us understand better how new and old memories interact with each other. In a recent influential animal study, Tse et al. (2007) found that after rats learned several spatial locations associated with different food scents, newly added location–scent associations could be learned much more quickly, compared with the initial learning. Moreover, the newly formed associative memory, which originally depended on the hippocampus (HPC), could become HPC independent more quickly. They inferred that the initially learned location–scent associations formed a schema, which refers to adaptable associative networks of knowledge extracted over multiple similar experiences (Ghosh and Gilboa 2014), to facilitate the new learning. Importantly, in a follow-up study (Tse et al. 2011), they found that the ventromedial prefrontal cortex (vmPFC) was crucial for the schema facilitative effects, suggesting that neocortical regions such as the vmPFC are implicated in prior-knowledge effects.

Extending these animal studies to humans, van Kesteren, Fernández, et al. (2010), van Kesteren, Rijpkema, et al. (2010), and van Kesteren et al. (2013) conducted a series of functional magnetic resonance imaging (fMRI) studies to investigate how schemas can affect new memory encoding and retrieval. For example, in one study (van Kesteren, Fernández, et al. 2010), the authors manipulated schema congruency of their memory task by presenting 2 groups of participants intact or reshuffled video

clips of the first half of a movie. One day later, the 2 groups were asked to watch the second half of the movie while their brain activity was measured using fMRI. It was assumed that only the participants who watched the intact video clips on the first day could form a consistent schema for the movie. This study found that the connectivity between the HPC and vmPFC during encoding was stronger for the inconsistent-schema, compared with the consistent-schema, group. They also found that the HPC–vmPFC connectivity in the inconsistent-schema group was negatively correlated with participants' memory of the gist of the movie. In another study, van Kesteren et al. (2013) designed a paired-associate incidental encoding task in which object and scene images were paired in either a schema-congruent (e.g., classroom–chalk) or -incongruent (e.g., tennis court–soup ladle) way. They found that in successful encoding trials, the medial PFC activation increased, but the HPC activation decreased, with increases in schema congruency, consistent with observations in animal studies (Tse et al. 2007, 2011). On the basis of some of these findings, van Kesteren et al. (2012) proposed that the vmPFC activation or vmPFC–HPC interactions play an important role in assimilating new information into existing knowledge, whereas the HPC is more important for encoding novel or schema-incongruent information.

Although these previous studies have discovered that the vmPFC may play an important role in schema-related memory processing, they raise issues that deserve our attention. A current prominent proposal is that the vmPFC or vmPFC–HPC interactions may support the assimilation of new information into existing knowledge system. The vmPFC, however, may contribute in other ways. Considering evidence that the vmPFC can support a wide range of social, affective, or evaluative processes (Barrett and Bar 2009; Binder et al. 2009; Luo et al. 2010; O'Reilly 2010; Etkin et al. 2011; Grabenhorst and Rolls 2011; Roy et al. 2012), it is also likely that the vmPFC may play a similar evaluative role in schema-related processes (Burin et al. 2014). For example, in Tse et al. (2007, 2011), associative learning performance was always related to food rewards. Thus, the medial PFC's involvement in schema-related learning may reflect strong evaluative processes that can enhance associative memory. Similar evaluative processes may also account for the vmPFC's involvement in the studies by van Kesteren, Fernández, et al. (2010) and van Kesteren et al. (2013). This interpretation is supported by recent neuroimaging studies that discovered a social evaluative role of the vmPFC in memory-related processes (Kumaran and Maguire 2005; Kumaran et al. 2009, 2012; Kim and Johnson 2012, 2014; Shenhav et al. 2013; Lin et al. 2015). For example, objects (e.g., water) that satisfy imaged physical need (e.g., thirsty) can activate the vmPFC to a larger extent and be remembered better than objects that do not (Lin et al. 2015). The vmPFC has also been found to respond to both objects' positive affective value and their associations (Shenhav et al. 2013), and support affective simulation of future events (Benoit et al. 2014). Associative inference tasks using both social and nonsocial stimuli also engage both the HPC and the vmPFC (Kumaran and Maguire 2005; Kumaran et al. 2009, 2012; Zeithamova and Preston 2010; Zeithamova et al. 2012).

The seminal studies by van Kesteren and her colleagues succeeded in relating schema effects in human memory to brain function and drew our attention to their importance. The complexity of schemas and their interaction with memory tasks (Alba and Hasher 1983; Bayen and Kuhlmann 2011), however, can lead to findings that are difficult to interpret. For example, in one study, van Kesteren, Fernández, et al. (2010) found that the vmPFC–HPC connectivity was stronger in the schema-incongruent than schema-congruent condition, but in a later study they did not find schema effects on the vmPFC–HPC connectivity (van Kesteren et al. 2013). Instead, they found that the vmPFC connectivity with a parahippocampal region increased with schema congruency. In an associative memory task that was analogous to the one used in the above-mentioned animal studies (Tse et al. 2007, 2011), van Buuren et al. (2014) did not find significant schema modulation effects on vmPFC activation or vmPFC–HPC connectivity during memory retrieval. Instead, they found that vmPFC connectivity was stronger to some posterior medial regions when a schema was involved. Moreover, Bein et al. (2014) found that both the vmPFC connectivity with the HPC and with posterior visual perceptual regions mediated subsequent memory of "schema-inconsistent" events. Thus, the functional dichotomy between the HPC and vmPFC in schema effects proposed by previous studies (e.g., van Kesteren et al. 2012) may be oversimplified and present difficulties in accounting for a variety of findings.

The focus on vmPFC and HPC has diverted our attention from the role that other brain regions may also play in prior-knowledge effects. For example, the anterior temporal pole (aTPL) regions have been proposed to be a hub that supports semantic knowledge (Patterson et al. 2007). Studies have found that degeneration or lesion of aTPL is related to impairments in semantic knowledge or semantic learning in dementia and brain lesion patients (Snowden et al. 2004; Gainotti et al. 2010; Lambon Ralph, Cipolotti, et al. 2010; Lambon Ralph, Sage, et al. 2010; Hsieh et al. 2011; Sharon et al. 2011). Electrically stimulating these regions can improve retrieval of semantic memories associated with previous knowledge or experiences such as the names of famous people or well-known places (Ross et al. 2010, 2011). Lesions of these regions also reduced prior-knowledge facilitation effects on new learning (Kan et al. 2009; Sharon et al. 2011). Consideration of these regions is needed if we are to gain a better understanding of prior-knowledge effects on new memory.

Methodologically, using schema-congruency manipulations to study the brain basis of prior-knowledge effects poses challenges that may be difficult to meet. More often than not schemas are complex mental structures whose neural representations are difficult to specify, in part because they vary from one schema to another. To understand better the effects of prior-knowledge at the brain level, it may be best to use stimuli that can elicit many of the same components of prior-knowledge as do schemas, such as semantics, social emotions, perceptions, or episodic memories, but whose neural representations are well known. It is for this reason that we turned to faces to investigate prior-knowledge effects. There is an extensive literature on human face processing research (Haxby et al. 2000; Johnston and Edmonds 2009; Park et al. 2009; Atkinson and Adolphs 2011; Yovel and Belin 2013), which can inform us about how different components of information related to faces can be processed in different brain regions. For example, face images are preferably processed in the lateral occipital complex and fusiform gyrus, especially the fusiform face area (FFA; Kanwisher 2010). Episodic memories related to familiar or famous faces can be supported by the medial temporal lobe (MTL) or HPC (Douville et al. 2005; Denkova et al. 2006; Elfgren et al. 2006; Trinkler et al. 2009). The aTPL may also support semantic information related to the face, such as the person's name, vocation, or social relationship (Tsukiura et al. 2002; Ross et al. 2010; Ross and Olson 2012; Abel et al. 2015). Also, affective or social evaluative information related to the faces can be supported by the vmPFC or amygdala (Gobbini and Haxby 2007; Rolls 2007; Ishai 2008; Trinkler et al. 2009). Thus, using famous and nonfamous faces as stimuli can be an effective way to

manipulate different aspects of prior-knowledge, and examine their influence on memory at the brain level.

In a recently completed behavioral study (Liu and Moscovitch, under revision), we paired novel pictures of houses with famous and nonfamous faces and asked participants to commit these paired associates to memory. We found that fame enhanced recollection-based associative recognition, as well as recollection of single faces, but it had no effect on familiarity-based associative recognition. Because prior-knowledge exerted its influence on associative recollection, but not on familiarity, and because it is known that the HPC is strongly implicated in recollection, we predicted that prior-knowledge effects would be reflected in increased hippocampal activation. It is also possible that enhanced encoding caused by multiple-component prior-knowledge can be related to greater activation in regions associated with processing faces and houses, as well as regions implicated in semantic and evaluative processes.

We adapted the associative recollection procedure used in the behavioral study to fMRI to investigate the brain basis of prior-knowledge effects on memory. Based on our predictions, and the literature reviewed above, we chose the bilateral HPC, aTPL, and vmPFC as our main regions of interest (ROIs), because the activation of these regions may reflect different aspects of associative processing. We also included FFA and parahippocampal place area (PPA) ROIs because these 2 regions differentially process face- and house-related information (Kanwisher 2010; Yovel and Freiwald 2013; Axelrod and Yovel 2015), respectively. Studies have shown that familiar faces may be processed differently in the FFA, compared with unfamiliar faces (Gobbini and Haxby 2006; Liu et al. 2014). It has also been found that contextual information associated with familiar people, likely supported by the parahippocampal regions, can be evoked automatically by familiar faces (Bar et al. 2008). Thus, by comparing brain activity in these 5 ROIs, and their connectivity, between the famous and nonfamous condition, we can examine how prior-knowledge related to famous faces affected the different components of associative processing. In general, we hypothesize that prior-knowledge may trigger additional evaluative, semantic, or episodic-binding processes, mainly supported by the vmPFC, aTPL, and HPC, to facilitate new memory encoding.

Our specific hypothesis was that during face–house associative encoding, the vmPFC, aTPL, and HPC should show stronger activation when famous faces were involved, reflecting the facilitation effects from the components of prior-knowledge supported by these brain regions. Within the famous condition, we also examined how participants' prior-knowledge with famous faces, such as emotions, vivid memories, general familiarity, and attractiveness, could modulate brain activation in these ROIs. We expected that the HPC, aTPL, and vmPFC should show stronger activation for the trials in which famous faces elicited stronger prior memories and emotions, and for trials in which the face–house associations were later remembered, compared with the later forgotten trials.

Prior-knowledge effects on the connectivity of the HPC with other ROIs were also investigated. Because the vmPFC, aTPL, and HPC may support social evaluative, semantic, and episodic aspect of prior-knowledge, we hypothesized that the HPC should show stronger connectivity with the aTPL and vmPFC when prior-knowledge is involved, especially for the successful encoding trials. The HPC connectivity with the posterior perceptual regions may be stronger in the nonfamous condition because, without prior-knowledge, face–house associative encoding would rely primarily on perceptual binding processes (Eichenbaum et al. 2007).

Method

Participants

Twenty healthy young adults (12 females), between 18–24 years of age (mean = 21.3, SD = 1.9), all right-handed and native English speakers, were recruited from the University of Toronto's St. George campus. All participants were free of current, and past, psychiatric/neurological conditions. The participants were paid $76 and gave their informed consent. The study was approved by the Research Ethic Board at Baycrest Centre for Geriatric Care (University of Toronto).

Procedure

Overview of fMRI Tasks

The scanned session consisted of several components (Fig. 1A): Following a structural MRI scan, there was a 6-min rest period in which participants were asked to relax with their eyes closed. Participants then performed the face–house associative encoding task, for one of the fame conditions, twice, in each of 2 consecutive runs. Following this encoding task, there was another 6-min rest period. Participants then similarly performed the associative encoding task for the other fame condition twice in 2 consecutive runs, following which there was a third 6-min rest period. After this, a face/house localizer task was administered. Total time for the scanned session was about 1.5 h (which included 2 final resting tasks. All resting tasks were not part of this study). After the MRI session, participants were asked to perform a multistep 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).

Stimuli

For the associative encoding task, 192 color 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 actors, whose names were obtained from a list of top actors (ranked by a website based on averaged domestic box office gross http://www.the-movie-times.com/thrsdir/actors.mv?actors+ByAG), and the other half, of nonfamous people. Gender was balanced for both famous and nonfamous faces. Among the 96 famous face pictures, 60 (30 females) were used in the scanned encoding task and each was paired with a house picture randomly chosen from the house picture set. Similarly, 60 nonfamous face–house picture pairs were created for the nonfamous condition. The remaining pictures were used as foils 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, each scrambled pair consisted of one scrambled picture that was the same size as the face picture (210 × 300 pixels) and the other the same size as the house picture (350 × 300 pixels). In 20 (out of the 72) scrambled pairs, the scrambled pattern of one picture was obtained by rescrambling the pattern of the other picture to make the patterns of the 2 scrambled pictures in these pairs similar and difficult to distinguish. This was to make some control trials difficult (see the next section). The luminance and contrast of pictures of the same size (e.g., the face and face-size scrambled pictures) were set to be equal using the SHINE toolbox (Willenbockel et al. 2010) and custom scripts in Matlab (MathWorks, Natick, MA, USA).

For the retrieval task, there were 4 types of face–house pairs: "intact," "recombined," "old/new," and "new–new" pairs. Each

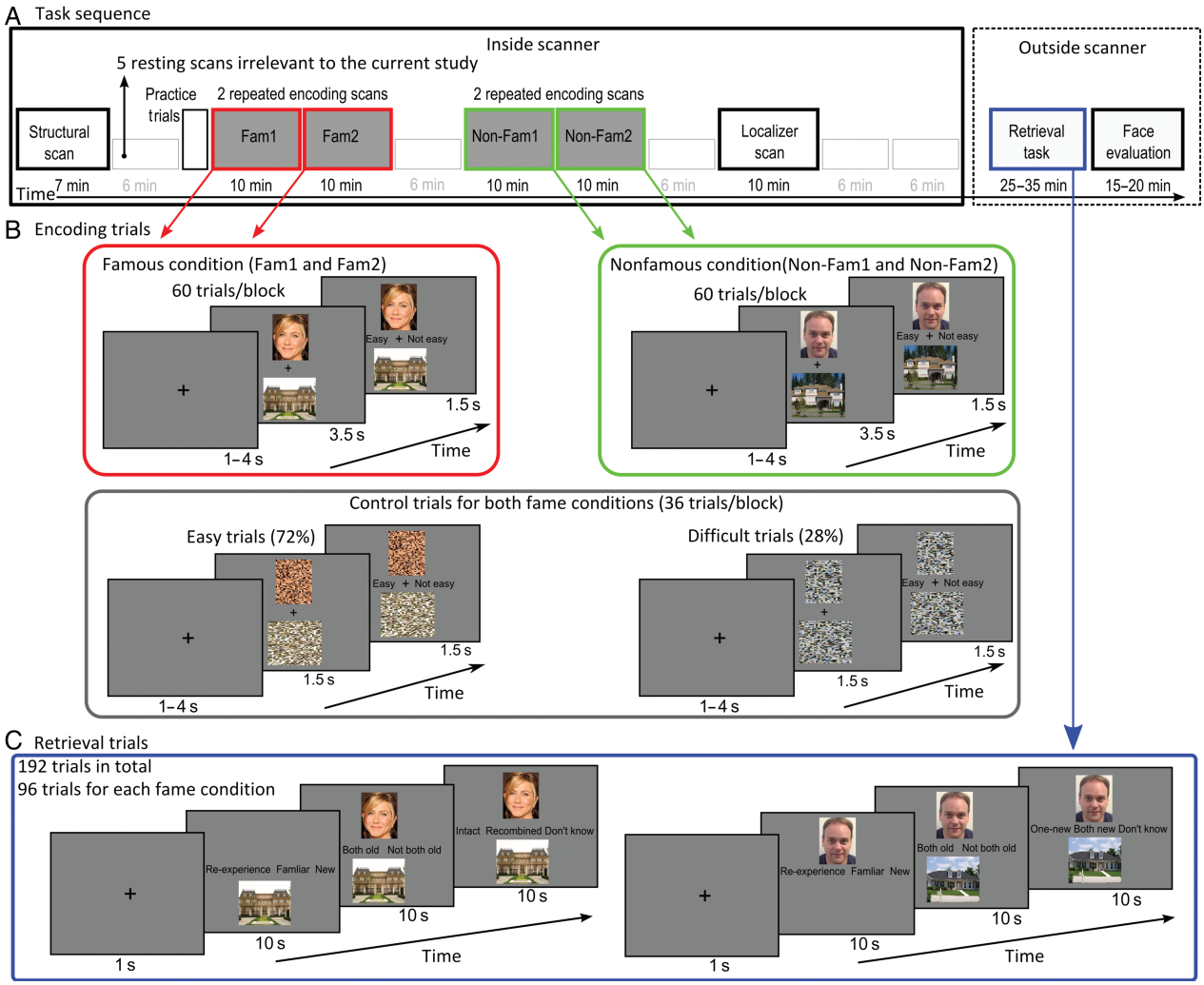

Figure 1. Schematic of experimental design. (*A*) The sequence and approximate time length of the tasks in this experiment. (*B*) Representative face–house encoding trials for the famous and nonfamous condition (upper) and control trials, that is, scrambled pictures trials (lower). For the face–house trials, participants needed to imagine and memorize the 2 pictures together and indicate whether it was easy or not to do so. For the scrambled picture trials in both famous and nonfamous conditions, participant needed to distinguish the pattern of the 2 pictures and indicate whether it was easy or not to do so (for details see the Methods section). (*C*) Typical retrieval trials for the famous and nonfamous condition. Note that images used in this figure are mainly for illustration purposes. Image sources: Jennifer Aniston's face image was downloaded and resized from http://www.justjared.com/photo-gallery/1696871/jennifer-aniston-hes-just-not-that-into-you-premiere-04/fullsize/. The house image paired with Jennifer Aniston was downloaded and resized from http://www.dichan.com/case-show-96727.html. The face image shown in the nonfamous condition was used with the person's written consent. The house image shown in the nonfamous encoding trial was downloaded and resized from http://bbb123.biz/ja/node/6943. The house image shown in the nonfamous retrieval trial was downloaded and resized from http://abhomedesigns.com/3-bedroom-house/3-bedroom-house-with-comtemporary-design-on-decor-design-ideas/.

type had 24 pairs for each fame condition. The intact pairs were randomly selected from the encoding pairs in each fame condition, with gender balanced. The recombined pairs were made by cross-pairing the face and house (i.e., the face of pair A paired with the house of pair B, and vice versa) in another set of 24 pairs that were randomly selected from the rest of the encoding pairs. To make the 24 old/new pairs, the remaining 12 encoding pairs were split and then paired with new house and face pictures, respectively. This produced 12 "old face"–"new house" and 12 "new face"–"old house" pairs (all called "old/new" pairs). The first and last 2 encoding pairs (4 in total) in each fame condition were always chosen to make the old/new pairs in order to exclude these pairs from the final associative memory performance calculation. The 24 new–new pairs were made by pairing the rest of the face and house pictures in the original picture set (i.e., those not used during encoding). In total, there were 192 face–house pairs in the retrieval task. All pictures were randomized across participants.

fMRI Face–House Associative Encoding Task

There were 4 encoding runs in total, with 2 consecutive repeated runs (with same picture pairs) for each fame condition. Each run had 60 face–house trials and 36 scrambled picture trials.

In each face–house trial of this intentional encoding task (Fig. 1*B*), first, a face–house picture pair was presented for 3.5 s, with the face on the top of the screen, the house at the bottom, and a cross "+" in between. Participants were required to look at the face–house pictures, and imagine and memorize as vividly as possible that the person (of the face) was standing in front of the house. Then, while the pictures were still on the screen, the words "Easy" and "Not easy" appeared for 1.5 s. Participants needed to press 1 of 2 buttons to indicate whether it was easy

(or not easy) for them to imagine the associated pair. Finally, before the onset of the next trial, a jitter time of 1–4 s (with an exponential distribution across trials and mean time of 1.5 s) elapsed with only the "+" on the screen.

In addition to the 60 face–house picture trials, there were 36 scrambled picture-pair control trials with the same picture sizes, locations, contrast, and luminance (as the face–house trials). The presentation duration of the scrambled picture pairs was reduced to 1.5 s, and participants responded whether it was easy (or not easy) for them to differentiate the patterns of the 2 scrambled pictures when the words "Easy" and "Not easy" appeared. Except for these differences, the scrambled picture-pair trials were identical to the face–house pair trials.

To make an efficient event-related experimental design, the 36 scrambled pairs were pseudorandomly dispersed into the 60 face–house pairs using an optimization method (Dale 1999; Birn et al. 2002). Specifically, 50 000 sequences were randomly generated with the first and last 2 positions of the sequences always given to face–house pairs as fillers. Then, the sequence that most efficiently detected the contrast effect between the face–house versus scrambled trials was chosen.

Both fame conditions used the same event-related design with identical presentation sequence. The 2 repeated encoding runs within each fame condition also used the same sequence, but for each encoding run the face–house and scrambled picture pairs were randomly assigned to the sequence, so that the order of the picture pairs was different across the 2 repeated runs. The first and last 2 face–house pairs were used as fillers and were not changed across the repeated encoding runs. To keep approximately the same time interval during which a specific picture pair was re-encoded, the random assignment of the face–house picture pairs to the presentation sequence was conducted within small groups of pictures. Specifically, first, the 56 face–house picture pairs (60 – 4 fillers = 56) in each fame condition were divided into 6 groups, with pairs 1–9 being assigned to group 1, pairs 10–18 to group 2, . . . , and pairs 46–56 to group 6. Then, for each repeated encoding run, the 9 pairs in group 1 were randomly reassigned to the first 9 face–house trials in the presentation sequence, the 9 pictures in group 2 were randomly assigned to the next 9 face–house trials, and so on, until the last 11 pictures in the last group, which were randomly assigned to the last 11 trials in the sequence. The same method was used for the scrambled pairs with 6 pairs per group.

Half of the participants performed the famous condition first, in 2 consecutive fMRI runs, and then performed the nonfamous condition twice (AA–BB order). The order was reversed (BB–AA order) for the other half of the participants. This counterbalanced design can significantly reduce potential confounding effects caused by the sequence of the tasks in the whole fMRI session or eliminate them entirely. It should be noted that the use of repeated encoding was to boost memory performance because a behavioral pilot study showed that the encoding task was difficult. The total time needed for each run was about 10 min. There was a 1-min interval between the repeated encoding runs in each fame condition and a 6-min rest interval between the 2 fame conditions. Participants were given 10 practice trials in the scanner with additional pictures before the first scanned encoding run started.

Localizer Scan Task

A block design was used for the face/house localizer scan, with 6 blocks for each of 3 picture categories: faces, houses, and objects. To reduce potential interference effects from the localizer task on the later memory retrieval of the main encoding task, a different set of face and house pictures was used. Specifically, 72 computer-generated face pictures, 72 multifloor building pictures, and 72 common objects (such as furniture, toys, utensils, etc.) were used. All pictures were black-and-white with a gray background and the size of 400 × 350 pixels. The luminance and contrast were also balanced across all pictures. In each picture-category block, 14 pictures were presented sequentially, with onset duration of 650 ms followed by a 550-ms fixation time per picture. Among the 14 pictures, 2 pictures were repeated and the participants were asked to perform a 1-back task in which they needed to press a button whenever they saw the repeated pictures. Each picture block was also followed by a fixation (baseline) block of the same duration (i.e., 16 s). The order of the face, house, and object blocks was pseudorandomized with the condition that the same category block would not repeat consecutively. This task lasted about 10 min.

Unscanned Retrieval Task

After the fMRI scan, participants completed a retrieval task in another testing room. There were 3 steps in each retrieval trial (Fig. 1C). First, a single picture (face or house) of a face–house retrieval pair was presented, with faces being presented first in half of the trials for each pair type. Participants were asked to indicate whether they could recognize the single picture by pressing 1 of 3 number keys on the keyboard using a Recollection/Familiarity paradigm (1: Re-experience, 2: Familiar, and 3: New). Then, the other picture of the retrieval pair was added to form a face–house pair. This time participants needed to respond whether both pictures had been presented in the encoding phase by pressing 1 of 2 number keys (1: Both old and 2: Not both old). If they answered "Both old," at the next step they would be asked whether the pair was intact or recombined, by pressing 1 of the 3 number keys (1: Intact, 2: Recombined, and 3: Don't know). If at the second step participants responded "Not both old," they needed at the third step to answer whether one or both pictures in the pair were new, by pressing 1 of the 3 number keys (1: One new, 2: Both new, and 3: Don't know). Similar to the encoding task, face pictures were always presented on the top of the screen. The pairs from the 4 retrieval pair types and 2 fame conditions were randomly presented. This retrieval task lasted about 30 min.

It should be mentioned that this study mainly focused on the associative memory measures derived from the last step of the retrieval task. Other measures obtained from the first 2 steps of the task were used for other purposes and not reported here.

Face Evaluation

After the retrieval task, participants were asked to evaluate the famous face pictures that had been used in the associative encoding task on "familiarity," "attractiveness," "emotion," and "memory" using 5-point scales. Specifically, we instructed the participants to give a number, from 1 to 5, to indicate how familiar they were with those faces (familiarity), how attractive they thought the faces were (attractiveness), how strongly the faces evoked emotions or emotional opinions (emotion), and how vividly memory of previous experiences were triggered by the faces (memory). For the first 3 evaluation tasks, nonfamous faces were also added as fillers. Face pictures were randomized across both the evaluation tasks and participants. The order of these tasks was also randomized across participants. The tasks were self-paced, with each about 5 min long.

Structural and Functional MRI Scan

A 3T Siemens MRI scanner with a standard 12-channel head coil at the Baycrest Hospital (University of Toronto) was used to

acquire MRI images. Head movements were minimized by inserting soft cushions into the head coil. In the structural MRI scan, T_1-weighted high-resolution MRI volumes were obtained using a standard 3-dimensional magnetization-prepared rapid-acquisition gradient echo (MPRAGE) pulse sequence [160 slices; field of view (FOV) = 256 × 256 mm; 192 × 256 matrix; 1 mm isotropic resolution, echo time (TE)/repetition time (TR) = 2.63/2000 ms, flip angle = 9°, and scan time = 386 s]. For the functional MRI scan, blood oxygenation level-dependent signal was assessed using a T_2-weighted echo planar imaging acquisition 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). To reduce fMRI signal drop in the ventral medial prefrontal regions, the images were acquired in an oblique orientation 30° clockwise to the anterior–posterior commissure axis. T_1-images acquisition used the same slice orientation. Visual stimuli were presented by E-Prime software (version 2, Psychology Software Tools, Inc.), backprojected to a screen, and viewed with a mirror mounted on the head coil. Responses were collected with an MRI-compatible response box.

fMRI Data Preprocessing

SPM8 (Statistical Parametric Mapping, Welcome Trust Center for Neuroimaging, University College London, UK; www.fil.ion.ucl.ac.uk/spm/, version 4661) in the MATLAB environment (MathWorks) was used to preprocess the T_2-weighted functional images. First, for each participant, several raw images were randomly selected from each run for quality check and no obvious fMRI artifacts were found for any participants. Then, slice timing was corrected using sinc-interpolation with the midpoint slice as the reference and all functional images were aligned using a six-parameter linear transformation. Next, anatomical images were coregistered to the aligned functional images, and segmented into white matter, gray matter, and cerebrospinal fluid using SPM8 default tissue probability maps. These segmented images were then used to calculate the transformation parameters mapping from the individuals' native space to the MNI template space. Next, the resulting transformation parameters were used to transform all functional images to the MNI template. The final functional images were resampled at 2 × 2 × 2 mm resolution and smoothed using a Gaussian kernel with the full-width at half maximum of 8 mm. The first 3 fMRI volumes from each run were discarded to allow the magnetization to stabilize to a steady sate.

fMRI Analysis

Overview

First, SPM8 voxel-wise general linear model (GLM) was used to estimate all the contrasts of interest at the first (i.e., individual)-level analysis. Because we hypothesized that specific brain regions, that is, the vmPFC, aTPL, HPC, PPA, and FFA, should be differentially affected by prior-knowledge, we then conducted ROI analyses (ROI details described in "ROI Definition" section) at the group level to test our hypotheses. Specifically, using the Marsbar toolbox for SPM8 (Brett et al. 2002; http://marsbar.sourceforge.net/), we calculated mean values of the contrast estimates across each ROI from the first-level contrast images and subjected the mean values to the second-level one-sample *t*-tests to test whether these mean contrasts were greater than zero. To provide more data for potential future data synthesis, we also presented the SPM whole-brain voxel-wise results in Supplementary Tables.

As mentioned earlier, repeated encoding was used in this study to boost memory performance. However, the literature has shown that repetition of stimuli may change neural responses (Henson et al. 2000; Grill-Spector et al. 2006; Johnson et al. 2008; Kumaran and Maguire 2009; Yanike et al. 2009; Suzuki et al. 2011; Hargreaves et al. 2012; Manelis et al. 2013; Vannini et al. 2013; Kremers et al. 2014). Therefore, although repetition effects were not the aim of this study and we focused mainly on the results from the 2 encoding runs combined, we also presented results for individual encoding runs and tested repetition effects when the results for 2 encoding runs were significantly different.

It is also worth mentioning that the face–house associative task used in this study was mainly a visual–spatial task, which may recruit the right hemispheric ROIs to a larger extent, compared with tasks using semantic or verbal stimuli (Kelley et al. 1998; de Schotten et al. 2011; Hervé et al. 2013). However, prior-knowledge elicited by famous faces can contain rich social semantic information, which has been found to engage predominantly the left hemisphere (Gainotti 2011; Ross and Olson 2012; Hervé et al. 2013). In the face processing literature, there is also evidence showing that the left and right aTPL may support different types of face-related information, such as names versus familiarity or known versus novel faces (Gainotti 2007; Von Der Heide et al. 2013). Due to the potentially complex laterality effects involved in this task, we treated all the left and right side ROIs separately. However, laterality effect itself was not the aim of the current study.

Encoding Effects

First, to test brain activation differences between different encoding conditions (i.e., house–face vs. scrambled pictures or famous vs. nonfamous pairs), at the individual-level GLM analysis, we concatenated all 4 encoding runs, that is, the first and second encoding run in the famous and nonfamous conditions. In the event-related design matrix, we added trial onsets of the face–house picture and the scrambled picture trials, convolved with the SPM8 canonical hemodynamic response function (HRF) and its time derivative as separate regressors in each run. Therefore, there were 16 regressors of interest in total, with 4 regressors in each run. We also included 6 motion parameters obtained from the image alignment processing, as well as the linear drift and mean activation for each run, as regressors of no interest. Default high-pass filter with cut-off of 128 s was applied. A first-order autoregressive model AR(1) was used to account for the serial correlation in fMRI time-series in the restricted maximum-likelihood estimation of the GLM. We constructed 2 contrasts using only HRF-convolved regressors at the first-level analysis: First, to identify brain regions that were commonly engaged by our associative encoding task (i.e., the main effect of picture type), we constructed a *t*-contrast to compare the "face–house encoding trials" with the "scrambled picture trials" while collapsing the 2 fame conditions. Second, for our main hypothesis testing of prior-knowledge (i.e., the face fame) effects during the associative encoding, we constructed a "fame" by "picture type" interaction *t*-contrast to compare the face–house encoding trials in the 2 fame conditions while controlling for the scrambled picture trials in each condition. For these analyses, the 2 repeated runs were included and given the same weight. The contrast images obtained from the first-level analyses were then used in group-level ROI and voxel-wise one-sample *t*-tests (with participants as a random factor).

Prior-Knowledge Modulation Effects Within the Famous Condition

Second, we conducted SPM8 parametric modulation analyses to examine whether the brain regions that showed stronger activation in the above-mentioned famous versus nonfamous contrast

analysis also showed stronger activation for the encoding trials in the "famous condition" where famous faces were reported to elicit more/stronger prior-knowledge. These analyses could help us to confirm whether the fame effects obtained from the famous versus nonfamous contrast were indeed related to participants' prior-knowledge even within the famous condition. Specifically, because the 4 face ratings (i.e., emotion, memory, familiarity, and attractiveness rating) were correlated with each other (Table 1), we first conducted a principal component analysis (PCA) to extract the principal component that accounted for the largest portion of the total variance (57%) among the 4 original variables and used it as a continuous parametric modulator. The loadings of the 4 original ratings on this component were 0.78 for emotion, 0.87 for memory, 0.76 for familiarity, and 0.54 for attractiveness. All other principal components each accounted for <20% of the total variance. In each individual-level parametric modulation analysis, we first concatenated the 4 encoding runs as we did in the previous analysis. Then, we included 8 HRF-convolved regressors, with one regressor for the face–house encoding trials and one for the scrambled picture trials for each encoding run in each fame condition. For the famous condition, we then included the PCA parametric modulation regressor for each run using trial-by-trial famous face PCA scores. Regressors of no interest were identical to those in the previous analysis. A *t*-contrast that averaged the 2 parametric modulation regressor estimates (for the 2 repeated runs in the famous condition) was used to investigate the prior-knowledge modulation effects. The parameter modulation contrast images at the first level were then used in the second-level ROI and voxel-wise one-sample *t*-tests.

Subsequent Memory Effects

Third, to examine whether the brain regions showing stronger activation in the famous encoding condition indeed played a role in the associative memory formation, we conducted another parametric modulation analysis to examine the subsequent memory effects in the famous condition. The design matrix was similar to the above-mentioned face evaluation parametric analysis, except that the parametric modulators were constructed from memory performance data and 2 more parametric modulator regressors were added for the nonfamous condition. Specifically, the encoding trials that were used as "intact pairs" in the retrieval condition, and were indeed correctly identified as intact pairs by the participants, were coded as 1 (i.e., remembered). For the encoding trials that were used as "recombined pairs" in the retrieval, if both the cross-recombined pairs were correctly identified as recombined pairs, indicating a high likelihood that the participant remembered both of the 2 original pairs, these recombined pairs were also coded as 1 (i.e., remembered). All other pairs were coded as −1 (i.e., forgotten). This resulted in an average of 16.1 trials/run × 2 runs = 32.2 remembered trials, ranging from 6 to 66 trials, and 43.9 trials/run × 2 runs = 87.8 forgotten trials, ranging from 54 to 114 trials. Only one participant had <10 remembered trials. Then, *t*-contrast images from the first-level analysis that averaged the 2 parametric modulation regressor estimates (for the 2 repeated runs in the famous condition) were used in the ROI and voxel-wise one-sample *t*-test at the second-level analysis.

It should be noted that this parametric modulation analysis on subsequent memory effects should be equivalent to the analysis in which parameter estimates of β-values are obtained separately for the remembered and forgotten trials at the individual level, and then compared at the group level. Because we were interested in brain activation differences between the 2 types of trials, we chose to obtain directly their contrast values for simplicity of data presentation. However, parameter estimates for the remembered and forgotten trials separately were also given in Supplementary Material (see the Results section).

Table 1 Mean correlations across participants among memory, emotion, familiarity, and attractiveness ratings of famous faces

	Memory	Emotion	Familiarity	Attractiveness
Memory		0.53	0.56	0.32
Emotion	(0.18)		0.42	0.34
Familiarity	(0.28)	(0.25)		0.22
Attractiveness	(0.19)	(0.22)	(0.16)	

Standard deviations are also presented in parentheses. All mean correlations were significantly larger than zero.

Fame Effects on Hippocampal Connectivity

Fifth, to investigate the brain connectivity differences between the famous versus nonfamous encoding condition, we conducted a psychophysiological interaction (PPI) analysis using SPM and the generalized PPI toolbox (Friston et al. 1997; McLaren et al. 2012), with the HPCs as seed regions. For the HPC seeds, only voxels within the structural HPC masks, defined by the automated anatomical labeling (AAL) template (Tzourio-Mazoyer et al. 2002), that survived the threshold of $P = 0.0001$ (no correction) in the "face–house" versus "scrambled" pictures contrast (mentioned in the first analysis) were included. In the PPI analysis procedure, time-series data (i.e., the first eigenvalue) were extracted from the seed region and deconvolved with the HRF to reflect its corresponding neural events (Gitelman et al. 2003). Then, interaction terms were formed between the deconvolved time-series and all other condition regressors (McLaren et al. 2012). Finally, these interaction terms, as well as the seed region time-series data, were added to the original univariate design matrix. Therefore, in each PPI GLM analysis design matrix, in addition to the 8 original HRF-convolved regressors, there were 8 corresponding PPI regressors (one for the face–house encoding trials and one for the scrambled picture trials for each encoding run in each fame condition) and 1 seed (i.e., the HPC) time-series regressor. Other regressors of no interest were identical to those in the univariate analysis. A similar "fame" by "picture type" interaction *t*-contrast was used to detect connectivity differences between the famous and nonfamous encoding conditions while controlling for the scrambled picture trials in each condition. The contrast images from the first-level analysis were then used in the second-level ROI and voxel-wise one-sample *t*-test.

Subsequent Memory Effects on Hippocampal Connectivity

Next, to test our hypothesis that the stronger connectivity of the HPC with anterior brain regions (e.g., aTPL and vmPFC) in the famous condition would facilitate associative memory formation, we conducted another PPI analysis to examine the subsequent memory effects of the HPC's connectivity, that is, to test whether the connectivity of the HPC with the aTPL and vmPFC would be stronger for the later remembered than forgotten face–house pairs during the famous encoding condition. In this analysis, we used the identical design matrix as we did in the previous PPI GLM analysis, except that all the encoding trials (for both the famous and nonfamous condition) were separated into later remembered and forgotten trials. Then, a PPI regressor was formed for each of the 12 condition regressors (one for remembered face–house trials, one for forgotten face–house trials,

and one for scrambled picture trials in each run and fame condition). In this analysis, we focused on the famous condition. Therefore, a contrast that compared the remembered and forgotten trials in the 2 runs of the famous condition was estimated in the first-level GLM analysis. Similar to the previous analysis, these contrast images were then used in the second-level ROI one-sample *t*-test.

Hippocampal Connectivity Predicting Memory Performance Across Participants

Finally, we explored "across participants" how the HPC connectivity was associated with associative memory performance. The motivation of this analysis was based on a previous study that found that the HPC connectivity with the vmPFC was associated with memory performance differently depending on whether prior-knowledge was involved (van Kesteren, Fernández, et al. 2010). In this second-level regression analysis, we used the first-level contrast images from the first PPI GLM analysis, that is, the HPC connectivity contrast between the face–house encoding trials and the scrambled picture trials (for each fame condition separately) as the dependent variable. The associative memory performance, calculated by subtracting the false alarm rate, that is, the percentage of the recombined retrieval pairs that were mistaken as intact pairs, from the hit rate of the intact pairs, was used as the independent variable of interest. Participants' age and the fame order during encoding (i.e., the block order of AABB or BBAA) were included as covariates. Potential fame order effects were also covaried out from the associative memory performance measure. The regression analysis was conducted separately for the famous and nonfamous condition.

ROI Definition

AAL template (Tzourio-Mazoyer et al. 2002) and the WFU-Pickatlas toolbox (Maldjian et al. 2003) were used to generate structural ROI masks for the vmPFC, aTPL, and HPC (Fig. 2A). The vmPFC mask consisted of the gyrus rectus and the medio-orbital section of the frontal gyrus. The aTPL mask consisted of the temporal pole region of the superior and middle temporal gyrus.

For the PPA and FFA regions, we generated bilateral functional ROI masks using the analysis of the localizer task (Fig. 2A). The preprocessing procedure was identical to the main encoding task. In the first-level analysis, a block-design GLM was used. Specifically, a boxcar function (16 s) convolved with the canonical HRF was used for each of the 3 picture blocks (faces, houses, and objects) and all fixation blocks. We also included 6 motion parameters and the total mean as the regressors of no interest. Default high-pass filter with cut-off of 128 s was applied and a default AR(1) was used. We then used the "face" versus "house" contrast and "house" versus "face" and "object" contrast to localize the FFAs and PPAs, respectively. These contrast images were then used in the second-level one-sample *t*-tests. Both the FFAs and PPAs were easily identified in the fusiform and parahippocampal gyrus at the threshold of $P = 0.005$, with 10-voxel extension. To make the final functional ROI masks, we took a spherical volume with 8 mm radius around the maximum activation voxel (left FFA: [−42 −50 −26], right FFA: [44 −52 −18], left PPA: [−28, −40 −10], and right PPA: [24, −40 −10]; Fig. 2A). [It should be noted that using contrast of face vs. house and object can localize the same FFA cluster, but the threshold needs to be lowered to $P = 0.05$.]

Statistical Thresholding

For the ROI analyses that were used to test our hypotheses (i.e., the one-sample *t*-tests), the threshold for statistical significance was set at $P < 0.05$. False detection rate (FDR) of 0.05 was used to correct for multiple comparisons (Benjamini and Hochberg 1995) when they were involved. These *t*-tests, with df = 19 (unless otherwise mentioned), were one-tailed following the SPM convention, which is also appropriate for our a priori directional hypothesis testing.

We also added results from whole-brain voxel-wise analyses in Supplementary Material. These results are thresholded at $P = 0.005$ with 10 voxel extension to facilitate future meta-analysis (Lieberman and Cunningham 2009). To find the anatomical labels for all activated regions in each analysis, we used the AAL toolbox (Tzourio-Mazoyer et al. 2002).

Results

Behavioral Results

Associative memory accuracy was calculated by subtracting the false alarm rate, that is, the percentage of the recombined trials that were mistaken as intact pairs, from the hit rate of the intact pairs. A paired *t*-test showed that associative memory accuracy was higher in the famous (M = 0.36, SD = 0.19) than nonfamous condition (M = 0.18, SD = 0.12), $t = 4.60$, $P < 0.0002$ (Fig. 2B). We also examined whether face–house pairs within the famous condition were remembered better when the famous faces elicited stronger prior-knowledge. To this end, we compared the hit rate for the intact face–house pairs in which the famous faces had higher versus lower face evaluation principal component scores (by median split). The result showed that this associative memory measure was also significantly higher for pairs with strong prior-knowledge (M = 0.55, SD = 0.25) than those with weaker prior-knowledge (M = 0.42, SD = 0.20), $t = 2.81$, $P = 0.011$ (Fig. 2B).

fMRI Results

Encoding Effects: House–Face Pairs Versus Scrambled Pictures

First, to test whether the associative memory encoding task used in this study recruited our predefined ROIs, we contrasted the face–house pairs in the 2 fame conditions with the scrambled picture pairs. After combining the 2 encoding runs, we found that the left vmPFC, bilateral HPC, PPA, and FFA were more strongly activated in the face–house encoding condition than the scrambled picture condition, FDR < 0.05 (see Fig. 2C for detailed statistics). The right vmPFC and bilateral aTPL did not show significant encoding effects, FDR > 0.05.

We also checked the encoding effects in the 2 encoding runs separately to see whether similar patterns occurred. Our results showed that during the first encoding run, all ROIs, except the right aTPL, showed significant encoding effects, all FDR < 0.05 (see Supplementary Fig. 1). During the second encoding run, only the PPA, FFA, and HPC, bilaterally, showed significant encoding effects. In general, these observations were consistent with the literature and indicated that our associative encoding task was effective in recruiting our predefined ROIs. Detailed statistics (*t*- and *P*-values) are presented in Supplementary Figure 1.

Encoding Fame Effects: Famous Versus Nonfamous Face–House Pairs

Second, we tested our main hypothesis to examine which brain regions showed stronger activation when prior-knowledge was involved by comparing the famous with the nonfamous condition. ROI analysis showed that the left and right vmPFC was more strongly activated in the famous than nonfamous condition (FDR < 0.05; for detailed statistics see Fig. 2D). Similar trend level

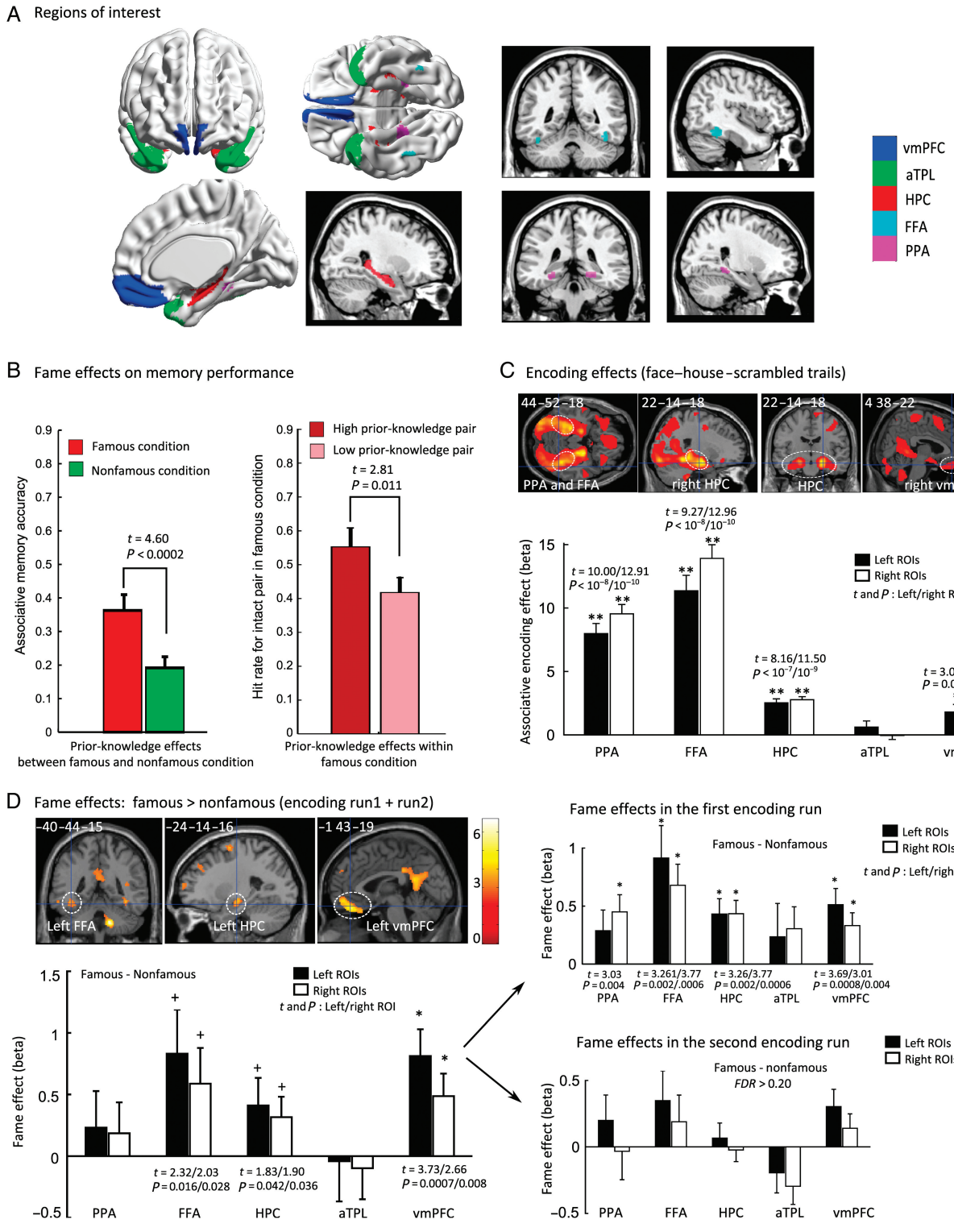

Figure 2. (A) The surface and section views of the 5 ROIs. Note that surface views were generated using BrainNetViewer (http://www.nitrc.org/projects/bnv/). Section views were generated using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). (B) Prior-knowledge (i.e., fame) effects on face–house associative memory between the 2 fame conditions (left) and within the famous condition (right). For within-famous condition results, pairs with high versus low prior-knowledge were categorized by a median split of prior-knowledge principal component scores (for details see Methods and Results sections). (C) Bar graphs showing associative encoding effects (face–house > scrambled pairs) in each predefined ROI. **FDR < 0.00001; *FDR < 0.005. t-statistics and P-values from one-sample t-tests (for ROIs that survived FDR correction) are also indicated. For illustration purposes only, the embedded brain section views (exported from SPM8) show locations of the clusters in these ROIs that survived $P < 0.005$, with 10 voxel extension, no correction. It should be noted that although the bilateral aTPL and right vmPFC did not show significant encoding effects when the 2 encoding runs were combined, the left aTPL and right vmPFC showed significant encoding effects during the first encoding run (FDR < 0.05, see Supplementary Fig. 1). (D) Bar graphs showing the fame effects (famous > nonfamous) in each predefined bilateral ROI after the 2 encoding runs were combined. The embedded brain section views show the locations of the clusters in the left FFA, HPC, and vmPFC that exhibited fame effects at $P < 0.005$, with 10 voxel extension (no correction) only for illustration purposes. Similar bar graphs reflecting fame effects for the first and second encoding run separately are also presented. Significant "encoding run" by "fame" interaction effects were found for the bilateral FFA and HPC and the right PPA and aTPL. +uncorrected $P < 0.05$ and FDR < 0.10; *FDR < 0.05.

effects were found in the bilateral HPC and FFA (FDR = 0.052–0.069). Supplementary Table 1 lists all regions that survived uncorrected threshold of $P = 0.005$ with 10 voxel extension. We did not find significant fame effects in the bilateral aTPL regions although the anterior middle temporal and inferior frontal gyri (see Supplementary Table 1), which also belong to the semantic network (Binder et al. 2009), appeared to be activated more strongly in the famous than nonfamous encoding condition.

We also examined the fame effects separately for the 2 encoding runs and found that the fame effects mentioned above were mainly contributed by the first encoding run. As can seen in Figure 2D, during the first encoding, the bilateral FFA, HPC, vmPFC, and right PPA were activated more strongly in the famous than nonfamous condition (FDR = 0.004–0.0006, for detailed statistics see Fig. 2D). No significant fame effects were found in the second encoding (Fig. 2D). The fame effect differences between encoding runs were confirmed by significant "encoding run" by "fame" interaction effects in the bilateral FFA and HPC, and the right PPA and aTPL ($P = 0.016$–0.0001). β-Values for all ROIs in each fame condition and encoding run are also provided in Supplementary Figure 2, in which ANOVA main effect and interaction P-values are also provided.

Because associative memory performance was different for the 2 fame conditions, it is possible that the fame effects that we found were due merely to the fact that fewer pairs in the nonfamous, compared with the famous, condition were successfully encoded. To exclude this possibility, we compared the 2 encoding conditions using only later successfully remembered pairs. We found that the bilateral HPC and vmPFC, as well as the left FFA, still showed significantly stronger activation in the famous than the nonfamous condition (FDR < 0.05). The left PPA, left aTPL, and right FFA also showed trend level fame effects ($P < 0.05$, FDR = 0.055).

Prior-Knowledge Modulation Effects Within the Famous Condition

Third, we conducted parametric modulation analyses to investigate whether the brain regions that showed stronger activation in the famous, compared with the nonfamous, condition were indeed related to the strength of the participant's prior-knowledge. To test this, we only used the data from the famous condition and examined whether encoding trials in which famous faces elicited stronger prior-knowledge would recruit these ROIs to a larger extent. Specifically, we used participants' face evaluation principal component scores as a continuous parametric modulator. The mean β-value for each ROI from the individual-level analysis was then tested at the group level to reveal whether the ROI was activated more strongly for the encoding trials with higher prior-knowledge scores. The 2 encoding runs were combined because there were no run differences. As can be seen in Figure 3A, our ROI analyses revealed that the bilateral vmPFC, HPC, PPA, and the left aTPL showed stronger activation in the trials in which the famous faces evoked stronger prior-knowledge (FDR < 0.05). Therefore, among the 5 ROIs, the PPA, HPC, and vmPFC not only showed stronger activation during the famous, compared with the nonfamous, condition, but also showed stronger activation within the famous condition for trials in which the famous faces elicited stronger prior-knowledge. The overlap of the fame effects and prior-knowledge modulation effects can be found not only at the ROI level, but also at the single voxel level (Supplementary Fig. 7A). Therefore, these 2 analyses provided consistent evidence that these brain regions played an important role in supporting prior-knowledge effects. The whole-brain analysis results with $P < 0.005$ (10 voxel extension, no correction) are also shown in Supplementary Table 2.

Additional analyses are reported in Supplementary Figure 3, including an assessment of prior-knowledge modulation effects for the 4 face ratings separately. These results, consistent with the PCA component modulation effects, showed that the HPC, aTPL, and vmPFC were activated more strongly when the famous faces elicited stronger emotion and memory. We also added these 4 modulators simultaneously in a parametric modulation model to examine their unique contribution to the prior-knowledge modulation effects. The emotion ratings had unique modulation effects on the right vmPFC (FDR < 0.05), and the memory ratings had trend level unique modulation effects on the left HPC and bilateral aTPL ($P < 0.05$, FDR = 0.09). Familiarity and attractive ratings did not show significant unique effects.

Encoding Subsequent Memory Effects

Fourth, to investigate whether the brain regions that showed prior-knowledge effects were indeed important for associative memory formation, we tested subsequent memory effects for the famous encoding condition using parametric modulation analysis. Our ROI analyses showed that both the left and right HPC ($t = 2.72$ and 2.56, $P < 0.007$ and 0.01, respectively) and vmPFC ($t = 2.97$ and 2.50, $P < 0.004$ and 0.011, respectively) exhibited stronger activation for the encoding of the face–house pairs whose associations were later correctly remembered during retrieval than those forgotten pairs. Posterior perceptual regions such as the left and right PPA ($t = 4.24$ and 2.80, $P < 0.0002$ and 0.006, respectively) and FFA ($t = 1.92$ and 4.01, $P < 0.04$ and 0.0004, respectively) also showed significant subsequent memory effects (FDR < 0.05). Estimated β-values for the contrasts between remembered and forgotten trials in each ROI are presented in Figure 3B. Original β-values for the remembered and forgotten trials separately are also given in Supplementary Figure 4. We also noted that after excluding one participant who had fewer than 10 remembered trials, subsequent memory effects in all ROIs remained significant (FDR < 0.05) except for the left FFA ($P = 0.048$, FDR > 0.05). The whole-brain analysis results with $P < 0.005$ (10 voxel extension, no correction) are also shown in Supplementary Table 3.

We also compared subsequent memory effects between the 2 encoding runs and found no significant difference in the bilateral PPA, FFA, HPC, and vmPFC. Only for the aTPL, subsequent memory effects were stronger in the second than the first encoding ($P < 0.03$ for between-run t-test). Further analysis revealed that only in the second encoding, subsequent memory effects of the bilateral aTPL were significant ($t = 2.30$ and 1.99, $P < 0.02$ and 0.03 for the left and right aTPL, respectively, FDR < 0.05. See embedded bar graph in Fig. 3B). These data together indicate that brain regions more strongly activated by the famous, compared with the nonfamous, encoding condition indeed played a role in face–house associative memory formation.

For the nonfamous condition, on average, there were only 8.35 remembered trials per run and 7 participants had no more than 10 remembered trials. Due to the low number of trials, analyses on subsequent memory effects in the nonfamous condition may not be robust. Therefore, we did not include these results in the main text. However, we presented subsequent memory effects of the nonfamous condition and subsequent memory effect differences between the 2 fame conditions in Supplementary Figure 5 for readers who may be curious about the results.

The Relation Between Prior-Knowledge Modulation Effects and Subsequent Memory Effects in the Famous Condition

Our ROI analyses showed that in the famous condition, the PPA, HPC, aTPL, and vmPFC showed stronger activation not only for

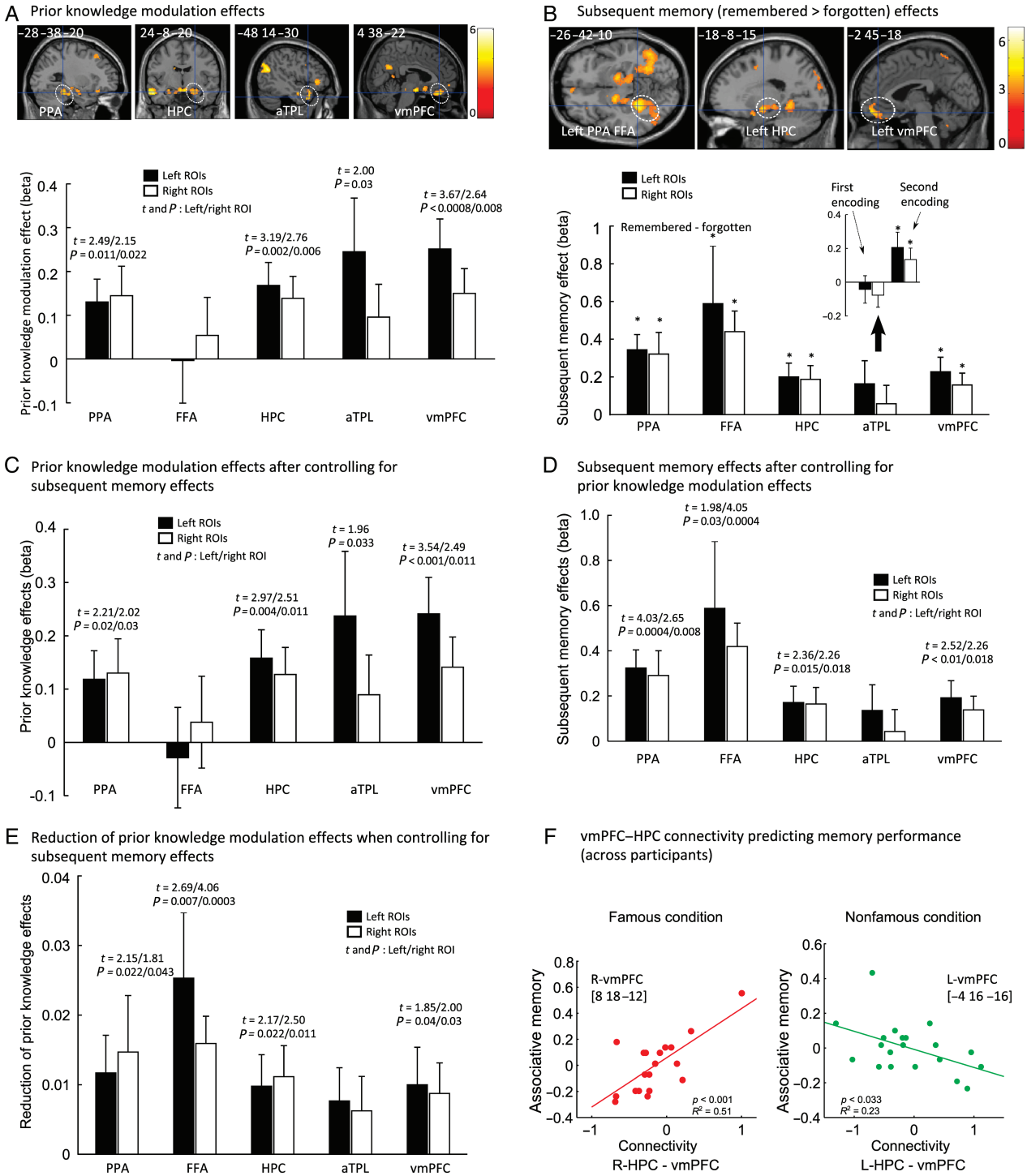

Figure 3. (*A*) Bar graphs showing prior-knowledge modulation effects (i.e., β estimates) in predefined ROIs. Principal component scores derived from the original 4 face ratings (i.e., emotion, memory, familiarity, and attractiveness) were used as the parametric modulator. Positive modulation effects indicate stronger brain activation when prior-knowledge scores were higher. Two encoding runs were combined. The embedded brain section views show the locations of the clusters in these ROIs at $P < 0.005$, with 10 voxel extension (no correction) only for illustration purposes. (*B*) Bar graphs showing subsequent memory effects (i.e., the β estimates for remembered > forgotten contrast) for the famous condition in each predefined ROI. Two encoding runs were combined. Asterisks indicate significant subsequent memory effects (FDR < 0.05). Brain section views show the locations of the clusters in the PPA, FFA, left HPC, and left vmPFC at $P < 0.005$, with 10 voxel extension (no correction) only for illustration purposes. Subsequent memory effects were not statistically different between the first and seconding encoding for all ROIs except the aTPL which showed significant effects only in the second encoding (embedded bar graphs). The original fMRI activation β-values, separately for remembered and forgotten trials, are given in Supplementary Figure 4. (*C*) Prior-knowledge modulation effects after controlling for subsequent memory effects. (*D*) Subsequent memory effects after controlling for prior-knowledge modulation effects. (*E*) Decreases of prior-knowledge modulation effects after controlling for subsequent memory effects. For *A*, *C*, *D*, and *E*, detailed statistics are given for the effects that survived FDR = 0.05 correction. (*F*) Scatter plots that illustrate the opposite relationship between the HPC–vmPFC connectivity and associative memory performance across participants in the 2 fame conditions. The MNI coordinates for the selected clusters (6 mm sphere) in the vmPFC are indicated. Regression analysis *P*-value and explained variance are also indicated.

the trials in which the famous faces elicited stronger, compared with weaker, prior-knowledge, but also for the trial that were later remembered, compared with later forgotten ones. This overlap can also be observed at the single voxel level (see Supplementary Fig. 7) and therefore, is not likely to be an artifact caused by low spatial resolution at the ROI level. Whole-brain voxel-wise overlap between prior-knowledge modulation and subsequent effects, as well as their overlap with fame effects, is presented in Supplementary Table 4.

The results from above-mentioned analyses, however, cannot tell us whether prior-knowledge and subsequent memory independently engaged these ROIs, and/or whether they shared common variance in engaging these ROIs. To understand the precise relationship between prior-knowledge modulation and subsequent memory effects, which is directly related to our research question of how prior-knowledge can facilitate new associative memory formation, we conducted 2 additional analyses. First, we included the prior-knowledge modulator (using the same principal component scores as used in the previous analysis) and the subsequent memory modulator simultaneously in a parametric modulation analysis. We did this to examine whether each factor, that is, prior-knowledge and subsequent memory, can have unique contributions to brain activation during associative encoding. The procedure of this parametric modulation analysis was identical to the ones that we reported earlier in this section (for details, see the Methods section: "Prior-Knowledge Modulation Effects Within the Famous Condition"), except that in this analysis 2 parametric modulators (instead of one) were used in the first-level SPM8 GLM. We should also mention that the SPM default regressor orthogonalization, specifically in the spm_get_ons.m and spm_fMRI_design.m functions, was turned off to ensure that the 2 parametric regressors were treated with equal status (as in a regular multiple regression analysis). [More explanation can be found at http://imaging.mrc-cbu.cam.ac.uk/imaging/ParametricModulations and http://andysbrainblog.blogspot.ca/2014/08/parametric-modulation-with-spm-why.html.] Similarly, ROI analyses were conducted using the Marsbar toolbox for SPM8 at the group level. These ROI analyses showed that activation in the bilateral HPC, PPA, vmPFC, and the left aTPL was still positively modulated by prior-knowledge (FDR < 0.05, for detailed statistics see Fig. 3C) after controlling for the subsequent memory effects. Similarly, subsequent memory effects were still significant in the bilateral HPC, PPA, and vmPFC, and the left aTPL after controlling for the prior-knowledge effects (FDR < 0.05, for detailed statistics see Fig. 3D). These results showed that both prior-knowledge and subsequent memory had unique contributions to these ROIs' activation during associative encoding.

Next, and more importantly, we compared prior-knowledge modulation effects "before" and "after" controlling for subsequent memory effects to test whether prior-knowledge effects can be significantly reduced by subsequent memory. If this is the case, we can use a formal statistical test to confirm that part of the brain activation related to prior-knowledge effects indeed also supported subsequent memory. To this end, we compared the β-values of prior-knowledge modulation effects obtained from the one-parametric modulator model mentioned in Figure 3A and the β-values of the effects after controlling for subsequent memory effects (i.e., from the two-parametric modulator model mentioned in Fig. 3C). The changes in the β-value between the 2 models were tested at the group level with paired t-tests using the Marsbar toolbox for SPM8. This statistical analysis was equivalent to a mediation test (Baron and Kenny 1986; MacKinnon et al. 2007; Wager et al. 2008; Atlas et al. 2010; Edelson et al. 2014) if subsequent memory was considered as a "mediator" that partially mediated prior-knowledge effects on brain activation. These ROI results showed that prior-knowledge modulation effects were significantly reduced (after adding subsequent memory) in the bilateral HPC, FFA, the left PPA, and the right vmPFC (FDR ≤ 0.05, for detailed statistics see Fig. 3E). The decreases in the right PPA and left vmPFC were marginally significant (FDR = 0.054, $P < 0.05$). Therefore, these results confirmed our hypothesis that the same brain regions that supported prior-knowledge also supported new associative memory formation, though the 2 can also contribute independently to the observed effects.

For completeness, we also compared subsequent memory effects with versus without controlling for prior-knowledge modulation effects. Similarly, this can help us to see whether subsequent memory effects on the activation of these ROIs were reduced by prior-knowledge effects. To this end, using the same analysis procedure as mentioned before, we compared β-values of subsequent memory effects obtained from previously mentioned one-parametric modulator model in Figure 3B and the β-values of these effects after controlling for prior-knowledge modulation effects (i.e., from the two-parametric modulator model mentioned in Fig. 3D). The changes in the β-value between the 2 models were tested using group-level paired t-test. Our ROI results showed that subsequent memory effects decreased at a marginally significant level in the bilateral HPC and PPA, and the left vmPFC and aTPL (all $P \leq 0.05$, FDR < 0.094, for detailed statistics, see Supplementary Fig. 6).

Fame Effects on Hippocampal Connectivity

We then conducted a PPI analysis to examine whether the functional connectivity of the HPC, a region that is crucial for associative binding, could be affected by prior-knowledge by comparing the famous versus nonfamous encoding condition. Although our ROI analyses showed that the left HPC connectivity with the right aTPL and right vmPFC, and the right HPC connectivity with the right vmPFC, appeared to be stronger in the famous than nonfamous condition ($t = 1.78$, 1.73, and 2.06, $P = 0.046$, 0.05, and 0.027, respectively), these effects did not survive the FDR correction. Similarly, no significant results were found when the 2 encoding runs were analyzed separately. Supplementary Table 5 lists the whole-brain HPC connectivity analysis results with $P < 0.005$ (10 voxel extension, no correction). The pattern of the results in Supplementary Table 5 is also presented graphically in Supplementary Figure 8.

Analyses on subsequent memory effects showed that although the left HPC connectivity with the left and right aTPL in the famous condition appeared to be stronger for the encoding of the later remembered than forgotten trials ($t = 1.76/1.89$, $P < 0.047/0.037$), the results did not survive the FDR correction and cannot be interpreted with appropriate confidence.

Hippocampal Connectivity Predicting Memory Performance Across Participants

Finally, because a previous study (van Kesteren, Fernández, et al. 2010) found that the HPC connectivity with the vmPFC was associated with memory performance across participants differently depending on whether prior-knowledge was involved, we also examined whether a similar brain–behavior association occurred in this study. To this end, we conducted "across participants" regression analyses to investigate whether the HPC connectivity with the vmPFC in each fame condition could be related to participants' associative memory performance. Using ROI regression analyses, we found that the right HPC connectivity with the right vmPFC was positively predicted by participants' associative

memory performance in the famous condition (regression coefficient $\beta = 0.53$, explained variance $R^2 = 0.18$, $t_{16} = 1.95$, and $P < 0.05$). For the nonfamous condition, the ROI analyses revealed that the associative memory performance negatively predicted the left HPC connectivity with the left vmPFC (regression coefficient $\beta = -0.41$, explained variance $R^2 = 0.16$, $t_{16} = -1.84$, and $P < 0.05$). For illustration purposes, the different brain–behavioral patterns of the 2 fame conditions are presented in Figure 3F using HPC connectivity with selected clusters in the vmPFC ROI.

Discussion

In this study, we found that prior-knowledge about faces facilitated associative memory between these faces and houses. At the neural level, we found that the FFA, PPA, vmPFC, and HPC showed stronger activation in the famous encoding condition. Within the famous condition, activity in the PPA, HPC, aTPL, and vmPFC was also positively related to the strength of prior-knowledge evoked by the famous faces. Moreover, the FFA, PPA, vmPFC, HPC, and aTPL also showed subsequent memory effects in the famous condition, indicating that these regions likely played a causal role in the prior-knowledge enhancement effects. Our connectivity results suggested that the HPC connectivity with anterior ROIs such as the vmPFC was important for the prior-knowledge facilitation effects on new learning. These results support our hypotheses that prior-knowledge may trigger enhanced evaluative, semantic, associative binding, or perceptual processing, each supported by different brain regions, such as the vmPFC, aTPL, HPC, and FFA/PPA, respectively, to facilitate formation of new associative memories.

The Role of the HPC in Prior-Knowledge Effects During Associative Encoding

We found that the HPC was more strongly activated in the famous than nonfamous condition as predicted from our behavioral study that prior-knowledge, which influences associative recollection, but not familiarity (Liu and Moscovitch, under revision), should exert its effect via the HPC. This hippocampal activation may reflect a spontaneous reinstatement of previous memories elicited by the famous faces (Ishai et al. 2002; Ishai 2008; Trinkler et al. 2009) as such memories are elicited by names of famous people and mediated by the HPC (Westmacott and Moscovitch 2003; Westmacott et al. 2004; Renoult et al. 2012, 2014). It may also be indicative of a stronger binding process associated with the famous condition. The 2 possibilities are not mutually exclusive and likely occurred simultaneously (Zeithamova and Preston 2010; Zeithamova et al. 2012). These possibilities can also be supported by our findings that the HPC was recruited to a larger extent by the trials in which famous faces evoked stronger prior-knowledge and the trials in which famous face–house pairs were later remembered, compared with pairs that were forgotten. In either event, our results indicate that modulation of associative recollections by prior-knowledge, like the recollections themselves, is mediated in part by the HPC.

It has been proposed that the HPC may mainly supports encoding of novel information [Tulving and Kroll 1995; Tulving et al. 1996; Kumaran and Maguire 2009; van Kesteren et al. 2013; but see Poppenk et al. (2010)]. Consistently, in this study, we also found that activation in the HPC was reduced during the second, compared with the first, encoding run (see Supplementary Fig. 2). However, we also found that the subsequent memory effects, as well as the prior memory modulation effects of famous faces, in the HPC remained the same during the repeated encoding. Considering that other brain regions such as the PPA, FFA, and vmPFC also showed repetition-related activation reduction, future studies should investigate to what extent the activation reduction in the HPC in repeated encoding is specifically related to the intrinsic functional property of this brain region, or whether it is mainly caused by reduced involvement of other processing systems (such as very early sensory or perceptual systems).

Moreover, we found that the HPC was activated more strongly in the famous encoding condition in which more familiar stimuli were involved, compared with the nonfamous condition, which suggests that novelty alone cannot explain all activity in the HPC. If familiar stimuli elicit strong previous episodic or associative memories, the HPC can be engaged to a larger extent, compared with novel stimuli, not only to support the elicited prior memories, but also to facilitate new memory formation. Consistent with our results, recent neuroimaging and animal studies also found that the HPC was involved in encoding of new associative processing related to prior experience (Preston et al. 2004; Tse et al. 2007; Poppenk et al. 2010).

It is also worth mentioning that both the anterior and posterior HPC were activated during the face–house encoding task, compared with the processing of scrambled pictures (see brain section views in Fig. 2C). According to a recent proposal (Poppenk et al. 2013), this two-loci activation pattern may suggest that the associations between the face and house stimuli can be processed at both a detailed perceptual level, which mainly recruits the posterior HPC, and a gist-like semantic or social emotional level, which mainly recruits the anterior HPC. The former may be driven more strongly by the house stimuli and the latter by the face stimuli. When, however, the 2 fame conditions were compared, only the anterior HPC showed stronger activation during the famous encoding condition (see brain section views in Fig. 2D), in accord with Poppenk et al's proposal. Consistent with previous studies (Sperling et al. 2003; Chua et al. 2007), the anterior HPC and the amygdala activation (see brain section views in Fig. 3B) also showed subsequent memory effects. These results suggest that the types of prior-knowledge involved in the famous condition may make the face–house associations processed at a more semantic or social emotional level, compared with the no prior-knowledge situation (Poppenk et al. 2013). Our finding that stronger involvement of the vmPFC, HPC, amygdala, and aTPL occurred when famous faces elicited stronger prior emotions and memories (Fig. 3A and Supplementary Fig. 3) lends support to this interpretation.

The Role of the vmPFC in Prior-Knowledge Effects During Associative Encoding

In general, the current finding that the vmPFC played an important role in prior-knowledge effects is consistent with previous studies (Tse et al. 2007; Trinkler et al. 2009; van Kesteren, Fernández, et al. 2010; van Kesteren, Rijpkema, et al. 2010; Kroes and Fernández 2012; Zeithamova et al. 2012; Preston and Eichenbaum 2013; van Kesteren et al. 2013, 2014). It has been proposed that the vmPFC interacts with the MTL in supporting the encoding of schema-related information (van Kesteren et al. 2012). Due to its broad anatomical connections (Carmichael and Price 1996; Barbas 2000), the vmPFC can serve as a hub region that integrates memory information from different modalities and domains of knowledge (Nieuwenhuis and Takashima 2011). It is still unclear, however, through what processing mechanisms the vmPFC accomplishes integrative function. Different from the previous studies which used complex schemas (van Kesteren, Rijpkema, et al. 2010), the current study used famous faces to elicit

participants' prior-knowledge. This type of prior-knowledge, which involves rich social emotional, semantic, or episodic information (Ishai et al. 2002; Henson et al. 2003; Ishai 2008), can recruit the vmPFC and exerts its facilitatory effects. This result raises the possibility that merely "using" prior-knowledge, associated with evaluative processing, is an important determinant for vmPFC involvement (Benoit et al. 2014). This interpretation can be supported by our findings that the more strongly the famous faces evoked emotional responses and vivid memories, the more strongly the vmPFC was activated (see Supplementary Fig. 3) and the better the subsequent memory. Moreover, as mentioned in the Results section, when the 4 original face rating variables were entered simultaneously as parametric modulators, emotion ratings still had significant unique contributions to the vmPFC activation during new associative encoding. Thus, from this processing-focused perspective, we suggest a possibility that in previous schema studies (van Kesteren, Rijpkema, et al. 2010), evaluative processes may also be evoked by schema-congruency manipulation and contribute to the schema-related vmPFC engagement. For example, in van Kesteren, Rijpkema, et al. (2010), when participants tried to understand the second half of a movie after watching only a reshuffled version of the first half, they may need to recruit more strongly decision-making, performance monitoring, or emotional processes, compared with the group who watched the intact version of the first half of the movie. Likely, the vmPFC was crucial for supporting these processes.

These findings and interpretations are also consistent with the large body of literature, showing that the vmPFC is a key structure to support social/evaluative/affective processing, including, but not limited to, self-related processing, decision-making, moral judgment, empathy, processing abstract semantic information, or even perceiving preferred everyday objects (Barrett and Bar 2009; Binder et al. 2009; Luo et al. 2010; O'Reilly 2010; Etkin et al. 2011; Grabenhorst and Rolls 2011; Roy et al. 2012). Moreover, the current findings converge with recent studies that discovered a similar evaluative processing role of the vmPFC in memory processes. For example, to understand potential functional roles of the vmPFC in autobiographical memory, Lin et al. (2015) asked participants to imagine situations with different states of physiological needs (e.g., hungry) and items that may or may not satisfy these needs (e.g., hamburger vs. water). They found that when the items can satisfy the imagined physiological need, the vmPFC showed stronger activation and the items were recognized better in a later recognition task. They concluded that the vmPFC may add a value to imagined scenarios, and thus potentially play an evaluative role in autobiographical memory processing. In another study, Shenhav et al. (2013) used an object recognition task and showed that the vmPFC functioned as a shared cortical substrate for processing both objects' affective value and their associations. Along a similar line, Kumaran and Maguire (2005) found that the vmPFC was activated when participants "navigated" through their social relations (e.g., finding a person from their social circle to connect 2 other friends), but the HPC was activated when they navigated through matched spatial relations. In other 2 studies, Kumaran et al. (2009, 2012) also found that decision-making and social inference components in relational processing involved interactions between the HPC and vmPFC. Self-related processing and the monitoring component of memory task were also found to recruit the vmPFC (Gilboa et al. 2006; Kim and Johnson 2012, 2014, 2015; Mitchell et al. 2013). Thus, there seems to be sufficient evidence of an evaluative role of the vmPFC in memory processing to support the idea that this role also emerges when prior-knowledge is involved.

In the current study, this evaluative processing could result in selective or predictive, and likely deeper, encoding of some aspects of the face–house associative information through a top-down process (Summerfield et al. 2006; Bar 2007, 2009; Henson and Gagnepain 2010; Preston and Eichenbaum 2013). Such effects may have contributed to the better associative memory in the famous condition. Therefore, it is likely that this type of evaluative processing, enhanced by prior-knowledge and supported by the vmPFC, enables the vmPFC to act as a hub region to make available the structures that mediate prior-knowledge effects on the one hand, and support the assimilation of new information, on the other. From this perspective, we speculate that in the previous studies that focused on schema effects (e.g., Tse et al. 2007; van Kesteren, Fernández, et al. 2010), the evaluative component of those schemas manipulated by the studies contributed to the involvement of the vmPFC.

The Role of the aTPL in Prior-Knowledge Effects During Associative Encoding

Similarly, as a semantic hub region (Patterson et al. 2007), the aTPL has been found to mediate prior-knowledge effects (Kan et al. 2009) and support face processing (Ross and Olson 2012; Axelrod and Yovel 2013; Von Der Heide et al. 2013). Lesions of the aTPL can lead to impairments in semantic knowledge or learning (Snowden et al. 2004; Gainotti et al. 2010; Lambon Ralph, Cipolotti, et al. 2010; Lambon Ralph, Sage, et al. 2010; Hsieh et al. 2011; Sharon et al. 2011). Stronger activation in this region has also been found in neuroimaging studies when familiar versus unfamiliar faces, names, houses, and voices are processed (Nakamura et al. 2000, 2001; Gorno-Tempini and Price 2001; Tsukiura et al. 2006, 2010). Moreover, the aTPL is functionally and anatomically connected with the vmPFC (Kondo et al. 2003), indicating that the semantic system can work closely with the evaluative or affective system (Zahn et al. 2007; Simmons et al. 2010; Binder and Desai 2011; Skipper et al. 2011; Olson et al. 2013) in supporting prior-knowledge effects, for example, by providing semantic valence and structures. In this study, we found that the aTPL showed stronger activation during trials in which famous faces elicited stronger emotions and memories, suggesting that prior-knowledge related to famous faces may trigger stronger semantic processing, which in turn contributes to better memory performance.

The Role of Posterior Neocortical Regions in Prior-Knowledge Effects During Associative Encoding

We also found that posterior perceptual regions such as the FFA and PPA were activated more strongly during the famous than nonfamous encoding conditions (Fig. 2*D*). These regions were also engaged to a larger extent for later remembered than forgotten famous trials (Fig. 3*B*). With regard to prior-knowledge effects on the FFA activation during face processing, inconsistent findings exist in the literature, with studies reporting no effects (Gorno-Tempini and Price 2001), positive effects (Simon et al. 2011; Liu et al. 2014), or negative effects (Rossion et al. 2001; Gobbini and Haxby 2006). Most of these previous studies, however, employed perceptual, not memory, tasks. In the current study, because the FFA activation was also modulated by participants' prior emotions elicited by the famous faces (see Supplementary Fig. 3), it is likely that social evaluative processes were evoked in the famous condition and led to deeper processing of famous faces even at the level of higher-order visual cortex, which is consistent with results from Chikazoe et al. (2014) who found that

regions of the ventral temporal lobe coded information by emotional valence. This modulation also facilitated the face–house associative processing and consequently strengthened the activation of the PPA in the famous condition. In addition, it has been found that episodic context information related to famous faces, supported by the parahippocampal cortex, can be automatically evoked while processing familiar faces (Bar et al. 2008). Consistently, we also found significant modulation effects of prior memory in the PPA (Fig. 3A). Therefore, it is possible that retrieved context information related to famous faces was involved or was utilized in the new face–house associative processing, which may also explain the stronger PPA activation in the famous condition.

Interactions Between the HPC and Neocortical Structures in Producing Prior-Knowledge Effects on Associative Encoding

We also predicted that the HPC should show stronger connectivity with the vmPFC and aTPL in the famous condition to reflect stronger involvement of rich semantic or social emotional prior-knowledge in new associative binding. Although we observed that the HPC showed numerically stronger connectivity with the aTPL and vmPFC in the famous than nonfamous condition, and that within the famous condition, the HPC–aTPL connectivity was stronger for the remembered than forgotten trials, these results did not survive multiple testing corrections, making it difficult to draw firm conclusions based on these findings. Similarly, we did not find significant HPC–FFA or HPC–PPA connectivity differences between the 2 fame conditions. Future studies with higher statistical power are needed to examine this issue.

Consistent with our hypothesis, however, the finding that the HPC connectivity with the vmPFC was positively associated with participants' memory performance in the famous condition suggests that communication among anterior ROIs is important for prior-knowledge facilitation effects. In a previous study, van Kesteren, Fernández, et al. (2010) showed that there was a positive trend between the HPC–vmPFC connectivity and memory performance in the schema-congruent condition although the relationship was not significant. Moreover, in the current study, the HPC–vmPFC connectivity in the nonfamous condition was negatively related to memory performance, similar to the schema-incongruent condition in van Kesteren, Fernández, et al. (2010). These data suggest that using prior-knowledge to solve new problems, which involves memory retrieval, decision-making, or goal/reward-relatedness monitoring processes, drives vmPFC–HPC connectivity.

Future Directions

In this study, we showed that prior-knowledge can facilitate new associative memory formation by recruiting strongly associative/episodic processing brain regions (e.g., the HPC), perceptual regions (e.g., the PPA), semantic regions (aTPL), and social evaluative brain regions (e.g., the vmPFC). We believe that the involvement of these brain structures reflects additional or deeper associative binding, perceptual, semantic, and social evaluative processes, respectively, in new associative memory processing. Because we did not experimentally manipulate the different components of prior-knowledge and the cognitive processes that we think they may have evoked during new memory processing, the link between our observation of brain activation pattern and hypothesized cognitive processes could be stronger than that observed in our correlational analyses. Also, although all the ROIs used in this study, and their supported cognitive functions, are among the most studied subjects in cognitive neuroscience and numerous studies have supported our hypothesis regarding the functional roles of these brain regions, future studies are needed to assess the causal relationship between the components of prior-knowledge, their triggered different cognitive processes, and the corresponding brain activity. One way to achieve this goal is to experimentally manipulate the content of prior-knowledge, for example, by training participants to associate specific semantic or social emotional information with unknown faces and then using fMRI to trace its specific effects (e.g., Brod et al. 2015). Animal studies that employ similar paradigms but examine their effects on memory component processing at a more causal and biological level (Tse et al. 2007, 2011; Wiltgen et al. 2011) will also significantly advance our understanding of how new and old memories interact in the brain. Moreover, in this study, we only manipulated prior-knowledge related to the face stimuli. It is possible that prior-knowledge related to house pictures, or scene and spatial information in general, may not have identical cognitive and neural effects on new associative encoding. Thus, future studies should also systematically explore effects of different types of prior-knowledge (Poppenk et al. 2010) to gain better understanding of this phenomenon.

Conclusions

In this study, we found that prior-knowledge facilitated new associative encoding by recruiting additional activation in posterior perceptual regions, such as the FFA and PPA, anterior brain regions, such as the vmPFC and aTPL, and the key associative memory processing structure, the HPC. This strengthened brain activation pattern likely reflects additional perceptual, evaluative, semantic, and associative binding processes engaged by prior-knowledge. We also found that these additional processes enhanced specifically later recollection of the encoded face–house associations, indicating that the familiar famous faces used in the current study indeed had profound influences on new associative processing. These observations may reflect a general mechanism by which multiple-component prior-knowledge can affect new learning.

These findings are also consistent with the component processing model of memory (Moscovitch 1992; Cabeza and Moscovitch 2013; Moscovitch et al. 2016), which posits that different processing components, supported by different brain regions, can be dynamically recruited in a memory task. From this perspective, we can propose that the type of prior-knowledge that is invoked and, more importantly, how different aspects of that prior-knowledge influence component memory processes are the key factors that determine prior-knowledge effects. Moreover, our brain-level findings, and the conclusions we drew from them regarding component processes, are also consistent with those drawn from a long history of psychological research on schema (e.g., Alba and Hasher 1983). Therefore, this processing-focused perspective should also benefit the current neuroscientific research on schema (Tse et al. 2007; van Kesteren, Fernández, et al. 2010; Richards et al. 2014), in that directly targeting these processing components would prove to be an effective and efficient means of revealing the neural mechanism mediating schema effects.

Authors' 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.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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