

## Neural processes during encoding support durable memory



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### ABSTRACT

The ability to form durable memory is critical for human survival and development, but its underlying cognitive and neural mechanisms have not been well understood. In particular, existing studies have not clearly dissociated the neural processes supporting short- and long-duration memories. The present study addressed this issue with functional MRI and a modified subsequent memory paradigm. Participants were asked to make semantic judgment on a list of 320 words in the scanner. Half of the words were tested after a short delay (i.e., 1 day, T1) and again after a long delay (i.e., 1 week, T12), whereas the other half were tested only once after the long delay (T2). Materials forgotten during T1 were categorized as forgotten trials, and those remembered during T2 were categorized as long-duration trials. In contrast, trials remembered during T1 but not during T12 were categorized as short-duration trials. We found that compared to forgotten trials, short-duration trials showed decreased activation in the posterior cingulate cortex (PCC) and precuneus, which is consistent with many previous observations. Importantly, long-duration trials showed stronger activity in the left inferior frontal gyrus (LIFG) but less deactivation in the PCC relative to short-duration trials. Psychophysiological interactions (PPI) analysis revealed stronger functional connectivity between LIFG and PCC for long-duration trials than for forgotten trials. Our results suggest that strong PCC activity, in combination with strong LIFG activity, supports long-lasting memory.

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### Introduction

It is a common observation that, even with apparently similar learning processes, some items can be remembered after a long delay whereas others are quickly forgotten. This difference can be attributed to many factors during the various stages of memory formation and retention, including encoding, consolidation, and retrieval. Focusing on the encoding stage, early behavioral studies suggested that the “level-of-processing” has a significant impact on memory durability: more durable memory is achieved by deep encoding (e.g., processing based on semantic components) than by shallow encoding (e.g., processing based on phonemic and orthographic components) ( Craik and Lockhart, 1972; Craik and Tulving, 1975). Even more effective than semantic encoding is self-relevant encoding (“Does the word describe you?”) (Rogers et al., 1977; Symons and Johnson, 1997). However, the neural mechanisms underlying these mnemonic benefits have not been clearly elucidated.

Using functional imaging and a subsequent memory paradigm (Brewer et al., 1998; Wagner et al., 1998), studies have examined extensively the neural processes that support lasting memories, by comparing neural activities for the items that were either remembered or

forgotten subsequently (minutes to days after learning) (Kim, 2011; Paller and Wagner, 2002; Uncapher and Wagner, 2009). These studies have consistently revealed that the subsequently remembered items showed greater activation than the subsequently forgotten items in the inferior frontal gyrus (IFG), fusiform cortex, and hippocampus; and greater deactivation in the default network, including the anterior and posterior middle-line.

Because most of the previous studies used a single memory test after a delay, it was not possible for them to directly examine whether the same processes supported both short- and long-duration memories. To address this issue, several studies have compared the subsequent memory effect across different lengths of delay, typically using two different strategies. The first strategy is to test half of the studied material at a short delay and the other half at a long delay. In the first such study, Uncapher and Rugg (2005) asked participants to study a list of words, and half of the words were tested 30 min after learning and the other half 2 days later. Several regions, including the left hippocampus and left dorsal IFG, showed the common subsequent memory effect under both short and long delays. In contrast, whereas the bilateral IFG supported recollection after a 2-day delay, the fusiform gyrus supported recollection after a 30-minute delay. Similar strategies have been used by Ritchey et al. (2008) and Steinmetz et al. (2012) to study how the memory durability effect is modulated by emotion. For example, in Ritchey et al.'s study, emotional and neutral items were tested at 20-minute and 1-week delays. They found that amygdala activation supported the memory of emotional pictures at both short and long delays,

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whereas the amygdala-MTL (medial temporal lobe) connectivity was increasingly important as the delay became longer.

A second strategy, first used by Carr et al. (2009), is to test all studied materials at both short (e.g., 10 min) and long delays (e.g., 1 week). By integrating memory performance in both tests, items could be categorized as consistently recollected items (recollected at both tests), transiently recollected items (recollected at the first but not the second test), consistently familiar items (judged as familiar at both tests), or consistently forgotten items. Using a paired associative learning task and focusing on the MTL, they found that activity in the perirhinal cortex (PRC) showed greater activity for items that were consistently recollected than that for the transiently recollected and consistently familiar items, whereas the parahippocampal cortex showed a subsequent memory effect during encoding of items that were both consistently or transiently recollected (Carr et al., 2009).

Both strategies provide unique and complementary contributions to our understanding of the neural mechanisms of memory durability, but each has its own limitations. For the second strategy, the retrieval process during the first test could enhance subsequent memory performance because all of the items were tested twice (Roediger and Karpicke, 2006). More importantly, it is entirely possible that items with different memory strengths during the short-delay test could benefit differently from this retrieval practice, an idea originally proposed by Ebbinghaus, and experimentally demonstrated by many studies (Anderson et al., 1994). By testing only half of the material at each test, the first strategy avoids the confound of the retrieval effect but at the expense of not being able to clearly isolate items with true transient memory from those with long-lasting memory. That is, some items that were remembered during the first test, thus categorized as short-duration memory, could have been remembered if they were tested one week later, which would have led them to be categorized as long-duration memory.

In all these studies, the short-duration memory was probed within 1 h of the initial study session, whereas the long-duration memory was tested after 24 h to 1 week. Although this design can help to maximize the differences between short and long memory durations, these results can be affected by the differences in consolidation processes. After encoding, memories are consolidated at the cellular level for up to several hours (Dudai, 2004). After that, consolidation continues, with sleep playing an important role in this process (Cartwright, 2004; Gais et al., 2007). It is unclear, therefore, whether the results of previous studies have been confounded by a lack of sleep-facilitated consolidation for the short-duration condition. Research is needed to examine how the encoding process differentially supports short- and long-duration memories when both have had consolidation during sleep (e.g., 1-day vs. 1-week delay).

The present study aimed at examining the neural processes that support long-lasting episodic memory. Participants were asked to make semantic judgment about a list of 320 words in the scanner. Half of the words were tested after a short delay (i.e., 1 day, T1) and again after a long delay (i.e., 1 week, T2); whereas the other half were tested only once after a long delay (T2). This design allowed us to compare memories of different durations with all items having had similar encoding and initial consolidation during sleep. More importantly, it allowed us to clearly isolate short- and long-duration trials while avoiding the contamination of the retrieval practice effect.

## Material and methods

### Participants

Twenty-four college students (11 males, mean age =  $21.5 \pm 1.22$  years, ranging from 19 to 24 years) were recruited for this study. All participants had normal or corrected-to-normal vision, and were self-reported to be right-handed and to have no previous history of neurological or psychiatric diseases. Informed written

consent was obtained before the experiment. This study was approved by the Institutional Review Board of the National Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University.

### Material

In total, 320 medium to low frequency, two-character Chinese nouns were used as the learning material in an incidental encoding task. Half of the words were tested twice (after both short [1 day] and long [1 week] delays), and the other half were tested only once after the long delay (Fig. 1A). They were counterbalanced across subjects. All words were presented visually in white color on black background. Forty additional words were also included for another purpose (an examination of mental representations of words as affected by linguistic factors). These words were presented in the same way as the words used in the current study, so they should not have affected the results of the current study. Furthermore, these additional words were not tested, and were excluded from this analysis. Another 480 words were used as foils in the two memory tests, so that the ratio of targets to foils was 1:1 at both tests, and none of the foils was used twice. To minimize the primacy and recency effects, three words were added at the beginning and the end of each encoding run, respectively, which were excluded in both behavioral and MRI analyses.

### fMRI procedures

Participants lay supine on the scanner bed, and viewed visual stimuli back-projected onto a screen through a mirror attached onto the head coil. Foam pads were used to minimize head motion. Stimulus presentation and timing were achieved using MATLAB (MathWorks) and Psychtoolbox ([www.psychtoolbox.org](http://www.psychtoolbox.org)) on an IBM-compatible PC. During the scan, participants were explicitly instructed to judge whether each word represented a concrete or abstract concept, by pressing their index fingers. The hand used to indicate an abstract or concrete response was counterbalanced across participants. Participants' responses were collected online using an MRI-compatible button box. Event-related design was used in this study. For each trial, the stimulus was presented up to 2 s until a valid response was received, which was then followed by a cross fixation at the center of the screen until the designated onset time of the next stimulus. Random jitters from 0.5 to 6.5 s (mean: 2 s) were added between words and the sequence was optimized for design efficiency (Dale, 1999) using an in-house program. In total, participants finished two 13-minute runs of the "abstract-concrete" semantic judgment task, each including 186 trials.

### MRI acquisition

Imaging data were acquired on a 3.0 T Siemens MRI scanner in the MRI Center at Beijing Normal University. A single-shot T2-weighted gradient-echo, EPI sequence was used for functional imaging acquisition with the following parameters: TR/TE/ $\theta$  = 2000 ms/25 ms/90°, FOV =  $192 \times 192$  mm, matrix =  $64 \times 64$ , and slice thickness = 3 mm. Forty-one contiguous axial slices parallel to the AC-PC line were obtained to cover the whole cerebrum and partial cerebellum. Anatomical MRI was acquired using a T1-weighted, three-dimensional, gradient-echo pulse-sequence (MPRAGE). The parameters for this sequence were: TR/TE/ $\theta$  = 2530 ms/3.09 ms/10°, FOV =  $256 \times 256$  mm, matrix =  $256 \times 256$ , and slice thickness = 1 mm. In total, 208 sagittal slices were acquired to provide high-resolution structural images of the whole brain.

### Post-scan memory tests

Two recognition memory tests were administered 1 day and 1 week after the scan respectively (Fig. 1A). Half of the words were tested after a short delay (T1) and again after a long delay (T2), whereas the other

half were tested only once after the long delay (T2). As a result, 160 words were probed in the first test and 320 words were probed in the second test. An equal number of new foils were added and randomly mixed with the targets. For each stimulus, the participants were asked to decide whether it had been studied during the MRI scan on a 6-point scale, with 1 indicating “definitely new” and 6 indicating “definitely old.” The stimulus remained on the screen for up to 10 s unless a response was made. The next item appeared after a 1 s delay.

#### Behavioral data analysis

Two indices were used to describe memory performance. The first index was the proportion of correct hits with high confidence (scored 5 and 6 on the 6-point scale). Since this result may be biased by the individuals' response criteria (Snodgrass and Corwin, 1988), another unbiased discriminability index ( $d'$ ) was computed using the following formula:  $d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$ . For discriminability index, repeated measures ANOVA were conducted to examine the effect of the test condition (T1, T12, and T2) on memory performance.

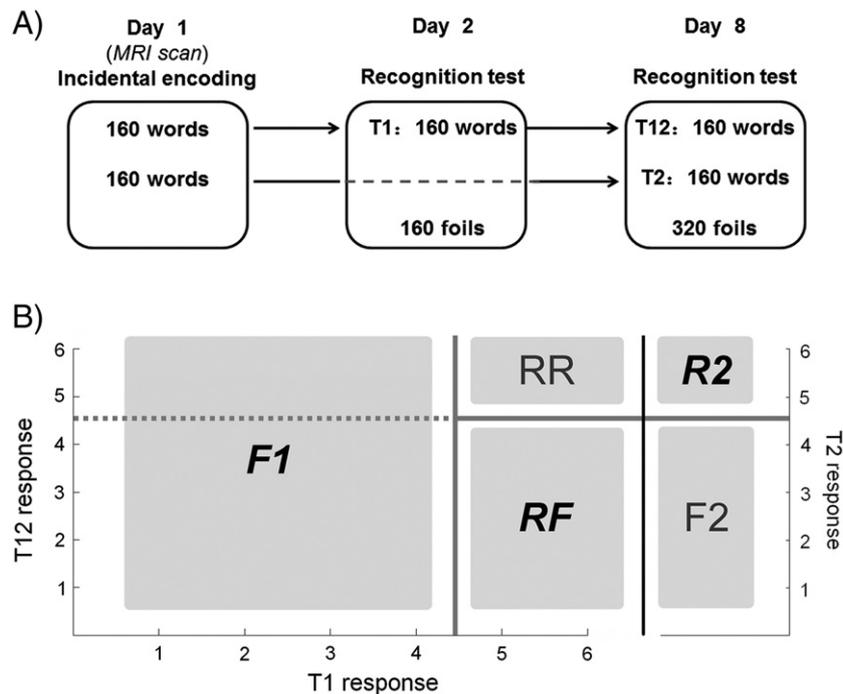
#### MRI data preprocessing and statistical analysis

Image preprocessing and statistical analyses were carried out using FEAT (fMRI Expert Analysis Tool) version 5.98, part of the FSL (FMRIB software library, version 4.1, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). The first three volumes before the task were automatically discarded by the scanner to allow for T1 equilibrium. The remaining images were then realigned to correct for head movements (Jenkinson and Smith, 2001). Translational movement parameters never exceeded 1 voxel in any direction for any participant or session. Data were spatially smoothed using a 5-mm full-width-half-maximum (FWHM) Gaussian kernel. The spatially smoothed data were then filtered temporally using a non-linear high-

pass filter with a 60-s cut-off. A two-step registration procedure was used whereby EPI images were first registered to the MPRAGE structural image, and then into the standard MNI space, using affine transformations (Jenkinson and Smith, 2001). Registration from structural images to the standard space was further refined using FNIRT nonlinear registration (Andersson et al., 2007a,b). Statistical analyses were performed in the native image space, with the statistical maps normalized to the standard space prior to higher-level analyses.

The general linear model within the FILM module of FSL was used to model the data. To achieve enough items in each category, words that were recognized with high confidence (scores 5 and 6 on the confidence scale) were considered as Remembered (Otten et al., 2001), and all the rest were considered as Forgotten. According to the memory performance at T1, T12 and T2, items were grouped into the following five categories (Fig. 1B). For the half of the words that were tested twice, there were three categories of items: 1) items forgotten at T1 (F1); 2) items remembered at T1 but forgotten at T12 (RF); and 3) items remembered at both T1 and T12 (RR). For the other half of the items that were tested only once at T2, there were only two categories: items forgotten at T2 (F2) and items remembered at T2 (R2). RF represents short-duration memory and R2 represents long-duration memory. The short- and long-duration subsequent memory effects were assessed by contrasting RF with F1 and R2 with F1, respectively. The other three categories (RR, F2 and R1 [RF + RR]) were used to replicate the findings from previous studies, which used these groups. The 40 words that were not tested together with the 12 filler words were modeled as a single nuisance variable. Null events were not explicitly modeled and thus served as a baseline.

Using a fixed-effects model, cross-run averages for a set of contrast images were created for each participant. These contrast images were then input into a random-effects model for group analysis, using FMRIB's Local Analysis of Mixed Effects (FLAME) estimation. Group images were thresholded using cluster detection statistics, with a height



**Fig. 1.** (A) Experimental procedure. Participants incidentally studied 320 words during fMRI scan. Half of the words were tested after both short delay (T1, i.e. one day) and long delay (T12, i.e. one week), and the other half were tested only once after the long delay (T2). An equal number of foils were added to each memory test. (B) Material grouping according to subsequent memory performance. For the half of the words that were tested twice, there were three categories of items: (1) items forgotten at T1 (F1); (2) items remembered at T1 but forgotten at T12 (RF); and (3) items remembered at both T1 and T12 (RR). For the other half of the items that were tested only once at T2, there were only two categories: (1) items forgotten at T2 (F2) and (2) items remembered at T2 (R2). RF represents short-duration memory and R2 represents long-duration memory. The short- and long-duration subsequent memory effects were assessed by contrasting RF with F1 and R2 with F1, respectively.

threshold of  $Z > 2.3$  and a cluster probability of  $p < 0.05$ , corrected for whole-brain multiple comparisons using Gaussian Random Field Theory (GRFT).

#### Region of Interest (ROI) analysis

To further understand the brain activity involved in memory formation, we selected 11 independent ROIs because Kim's (2011) meta-analysis found significant subsequent memory effects for word items in these regions. The regions included the left inferior frontal gyrus (LIFG, MNI:  $-42, 12, 28$ ) and posterior cingulate cortex (PCC, MNI:  $-2, -26, 38$ ), both of which showed the subsequent memory effect in our whole-brain analysis (see Results section). Additional regions included the left pre-supplementary motor area (pre-SMA, MNI:  $-6, 16, 54$ ), left supplementary motor area (SMA, MNI:  $-4, 0, 58$ ), right inferior frontal cortex (RIFG, MNI:  $50, 26, 28$ ) and right premotor cortex (PMC, MNI:  $50, 6, 30$ ) in the frontal lobe; the left hippocampus (MNI:  $-22, -14, -12$ ) and bilateral fusiform gyrus (MNI: left:  $-44, -48, -22$ ; right:  $50, -52, -16$ ) in the temporo-occipital lobe; and the bilateral intraparietal sulcus (MNI: left:  $-30, -76, 36$ ; right:  $30, -74, 34$ ) in the parietal lobe (Table 3). For each ROI, a 4 mm diameter sphere was grown around the local maxima.

Parameter estimates (betas) of each event type from the fitted model were extracted and averaged across all voxels in each ROI for each participant. Percent signal changes were calculated using the following formula:  $[\text{contrast image} / (\text{mean of run})] \times \text{ppheight} \times 100\%$ , where ppheight is the peak height of the hemodynamic response versus the baseline level of activity (Mumford, 2007).

#### Psychophysiological interaction (PPI) analysis

The whole-brain analysis revealed strong activation in the LIFG and PCC for long-duration memory. We further probed how the functional connectivity between these two regions was associated with memory durability by using psychophysiological interactions (PPI) analysis (Friston et al., 1997). In this analysis, the PCC cluster (from the RF vs. F1 contrast, MNI:  $2, -54, 34$ ) was defined as the seed region. The time course of PCC activity was defined as the physiological variable and its interaction with memory performance (R2 vs. F1) was defined as the psychophysiological interaction variable. We focused on R2 and F1 because the PCC showed similar activity across conditions and our hypothesis was that stronger LIFG-PCC functional connectivity would support long-lasting memory. In this analysis, a relatively liberal threshold ( $p < 0.005$  uncorrected, equal to  $Z > 2.81$  and cluster size  $> 10$  voxels) was used.

## Results

#### Behavioral performance during encoding

To examine whether there were systematic biases in material selection, we compared the accuracy rates and reaction time during semantic encoding between the words that were tested 1 day later and those that were tested 1 week later. Results showed no differences in accuracy during the study/encoding session (96.38% vs. 96.15%;  $F(1,23) = 0.58$ ,  $p = 0.45$ ), and a small but statistically significant difference in reaction time (median: 792 ms vs. 782 ms;  $F(1,23) = 4.47$ ,  $p = 0.05$ ). As we have systematically counterbalanced the materials across subjects, this difference was probably caused by chance or an unexpected material-by-subjects interaction. Because the words with different memory durations (R2, RF and F1) did not differ in either reaction time ( $F(2,46) = 0.76$ ;  $p = 0.47$ ) or accuracy ( $F(2,46) = 0.64$ ;  $p = 0.53$ ) during encoding (Table 1), this small difference in RT was not likely to have confounded our results.

Previous studies have suggested that concrete words enjoy a mnemonic advantage due to specific brain processes (Fließbach et al., 2006). To examine whether this advantage is modulated by the delay

of the memory test, we first calculated the proportion of concrete and abstract words in F1, RF and F2 (Table 1). Repeated measures ANOVA showed a significant interaction ( $F(2,46) = 5.76$ ;  $p = 0.006$ ). Further analysis showed significantly fewer concrete words than abstract words in F1 ( $F(1,23) = 4.54$ ,  $p = 0.04$ ), but no difference in either RF ( $F(1,23) = 2.39$ ,  $p = 0.14$ ) or R2 ( $F(1,23) = 0.008$ ,  $p = 0.93$ ). These results suggested that the concreteness effect on memory might not be very durable.

#### Recognition memory: test enhanced memory performance

We then examined whether T1 testing enhanced memory performance at T12, a critical issue in order to clearly separate short- from long-duration memories. Because the number of correct hits with high confidence (or hit ratio) depends crucially on subjects' judgment criteria, it is important to ensure that the criteria were comparable at T1 and T12/T2. Although bias (C) is a good index for decision bias, it is determined by both hit ratio (which is largely affected by memory strength and decision criteria) and false alarm rate (which is largely affected by decision criteria). Moreover, the memory strength differed significantly between tests at short and long delays. As a result, false alarm rate was used here to index the decision criteria. We found that the false alarm rate was very similar across both test sessions (17.24% vs. 15.03%,  $F(1,23) = 1.18$ ,  $p = 0.29$ ), providing good evidence that subjects used similar judgment criteria in both test sessions.

There was also a potential confound between test delay and list length in our study: the recognition test was twice as long in the long delay condition as the short delay condition. During the long delay test, all words (i.e., words tested at T1, those that were not tested at T1, and foils) were randomly mixed and equally divided between two runs. Using false alarm rate as the index of decision criteria, we found no differences between the two runs ( $F(1,23) = 0.033$ ,  $p = 0.86$ ), suggesting that no systematic biases were associated with list length.

The average hit ratios (hits with high confidence) were 60.68%, 49.81%, and 30.94% for T1, T12, and T2, respectively (Fig. 2A). As expected, memory performance at a short delay (T1) was significantly better than that at a long delay (T2), as indexed by the discrimination index ( $d'$ , 1.29 vs. 0.64,  $F(1,23) = 162.35$ ,  $p < 0.001$ ). Moreover, we found that T1 testing significantly enhanced the memory performance at T12 (Fig. 2B). Specifically, items that were tested at T1 had significantly higher  $d'$  score at T12 than those that were not tested at T1 (i.e., only T2) (1.18 vs. 0.64,  $F(1,23) = 117.96$ ,  $p < 0.001$ ). T12 performance was only slightly worse than T1 performance (1.18 vs. 1.29,  $F(1,23) = 5.41$ ,  $p = 0.03$ ), suggesting that testing can effectively slow down or even prevent forgetting over one week.

#### fMRI results: the neural mechanism of memory duration

In the first analysis, we investigated the neural mechanisms during encoding that supported short- and long-duration memories. The short-duration subsequent memory effect was examined by comparing the RF items (i.e., words that were remembered at T1 but forgotten at T12) with F1 items. This analysis revealed a stronger deactivation in the precuneus and posterior cingulate cortex (PCC, MNI:  $2, -54, 34$ ,  $Z = 3.41$ ) for RF than for F1 (Fig. 3A, Table 2). No difference was found at the LIFG even when a liberal threshold of  $p < 0.01$  uncorrected was used.

The long-duration subsequent memory effect was examined by comparing the neural activity associated with the R2 items (i.e., words that were tested only at T2 and were remembered) and F1 items (i.e., words that were forgotten at T1). This analysis revealed stronger activity in the left inferior frontal gyrus (LIFG) that extended ventrally to the lateral orbital frontal cortex (MNI:  $-36, 28, -18$ ,  $Z = 4.34$ ) for R2 than for F1 (Fig. 3B, Table 2).

A direct comparison between long- (R2) and short- (RF) duration memories revealed significantly stronger activity in the PCC

**Table 1**Behavioral performance during semantic judgment as a function of subsequent memory status (mean  $\pm$  Std).

	F1	RF	RR	F2	R2
Percentage among all items	18.95 $\pm$ 6.29	10.53 $\pm$ 3.99	18.62 $\pm$ 7.23	33.20 $\pm$ 8.02	14.75 $\pm$ 7.44
RT (ms)	785 $\pm$ 167	794 $\pm$ 140	793 $\pm$ 125	780 $\pm$ 143	793 $\pm$ 129
Percentage of concrete words	43.81 $\pm$ 13.93	54.03 $\pm$ 12.48	57.30 $\pm$ 14.93	48.86 $\pm$ 7.39	50.79 $\pm$ 14.50
Percentage of abstract words	56.19 $\pm$ 13.93	45.97 $\pm$ 12.48	42.70 $\pm$ 14.93	50.14 $\pm$ 7.39	49.21 $\pm$ 14.50

(MNI:  $-2, -40, 32, Z = 3.51$ ) for R2 than for RF (Fig. 3C, Table 2). When a relatively liberal threshold was used ( $p < 0.005$  uncorrected, equivalent to  $Z > 2.81$ , cluster size  $> 10$  voxels), the LIFG revealed stronger activity for R2 than for RF (MNI:  $-46, 20, 28, Z = 3.43, 36$  voxels).

Using this liberal threshold, the pre-SMA also showed stronger activation for R2 than for both RF (MNI:  $-2, 14, 54, Z = 3.14, 14$  voxels) and F1 (MNI:  $-2, 24, 48, Z = 3.89, 103$  voxels), but no significant differences between RF and F1. These results were similar to those for the LIFG.

It should be noted that although the PCC cluster in the RF vs. F1 contrast was slightly lateralized to the right ( $x = 2$ ), whereas that in the RF vs. R2 contrast was slightly lateralized to the left ( $x = -2$ ), both clusters were close to the middle-line and contained voxels from both hemispheres. To further examine the functional dissociation of these two clusters, we conducted a region-by-condition interaction analysis. This analysis revealed no significant interaction using a quadratic model ( $F(1,23) < 0.001, p = 0.99$ ), suggesting they showed similar V-shaped relationship with memory duration (F1 vs. RF vs. R2).

### ROI results

ROI analyses were conducted to further quantify the various neural activities associated with short- and long-duration memories and to provide a clear comparison between our analyses and those in previous studies.

The independent ROI analysis suggested a positive association between brain activity and memory durability in the LIFG but a V-shaped relationship in the PCC (Fig. 4A, B, Table 3). Specifically, the LIFG showed the strongest activation for the long-duration memory (R2 vs. RF,  $F(1,23) = 7.20, p = 0.013$ ; R2 vs. F1,  $F(1,23) = 10.96, p = 0.003$ ), but the differences between short-duration memory and forgotten words did not reach significance (RF vs. F1,  $F(1,23) = 0.03, p = 0.86$ ).

In contrast, PCC deactivation was largest for RF (RF vs. R2,  $F(1,23) = 4.32, p = 0.05$ ; RF vs. F1,  $F(1,23) = 6.18, p = 0.02$ ), but comparable between R2 and F1 ( $F(1,23) = 0.24, p = 0.63$ ). Together, these results confirmed the whole-brain analysis and suggested that

strong PCC activity, in combination with strong LIFG activity, supported long-lasting memory.

Additional ROI analyses found that the left pre-SMA showed stronger activation for R2 than F1 ( $F(1,23) = 11.49, p = 0.003$ ) (Fig. 5A, Table 3), and the left hippocampus showed marginally stronger activation for R2 than F1 ( $F(1,23) = 3.38, p = 0.08$ ), but no region showed a short-duration subsequent memory effect (Fig. 5E, Table 3). In addition, direct contrast of short- and long-duration memories indicated that R2 had stronger activity than RF in the left pre-SMA ( $F(1,23) = 11.43, p = 0.003$ ) and marginally stronger activity in the left SMA ( $F(1,23) = 3.67, p = 0.07$ ) (Fig. 5A, B, Table 3).

When RR instead of R2 was used to represent long-duration memory, we found a pattern that was very similar to short-duration memory (RF), especially in the PCC (RR vs. RF:  $F(1,23) = 0.013, p = 0.91$ ; RR vs. R2:  $F(1,23) = 5.02, p = 0.035$ ) (Fig. 4B). This suggests that there was a retrieval practice effect from the first test that facilitated memory for T12. On the other hand, when R1 instead of RF was used to represent short-duration memory, we found a pattern that was very similar to R2 but stronger than RF in the LIFG (R1 vs. R2:  $F(1,23) = 1.06, p = 0.31$ ; R1 vs. RF:  $F(1,23) = 9.80, p = 0.005$ ) (Fig. 4A), suggesting that some R1 items could have been remembered if they were tested after the long delay.

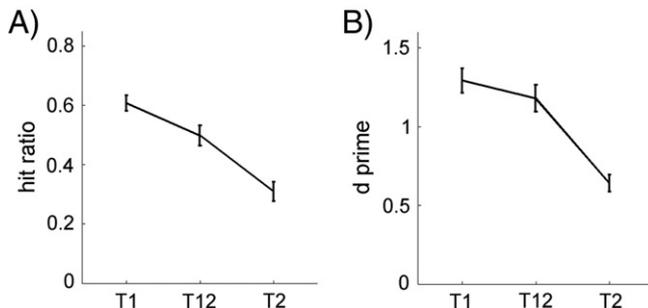
### PPI results

The above analysis suggests that the PCC showed similarly strong deactivation for R2 and F1, and that durable memory could be achieved when it was accompanied by strong activation in the LIFG. To further investigate the role of frontal-PCC functional connectivity in forming durable memory, we conducted a functional connectivity analysis using PPI. This analysis revealed significantly stronger functional connectivity for R2 than F1 in the prefrontal cortex (MNI:  $-46, 38, 12, Z = 3.47, 15$  voxels) (Fig. 4C), as well as the left superior parietal lobule, supramarginal gyrus, and the right superior frontal gyrus (Table 4). This LIFG cluster overlapped with the LIFG cluster identified in the R2–F1 contrast, and the activity in this cluster was significantly stronger for R2 than for F1 ( $F(1,23) = 6.89, p = 0.015$ ). No cluster showed decreased functional connectivity.

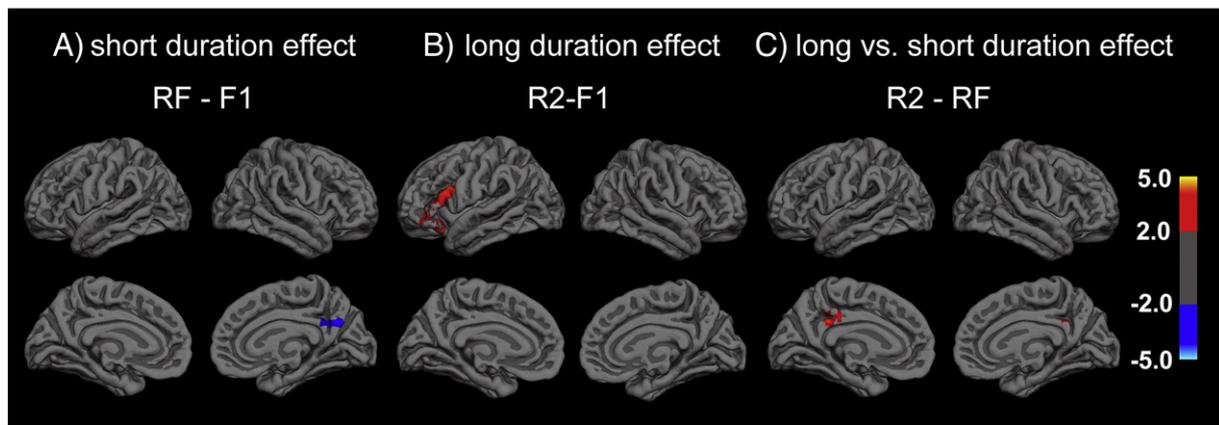
### Discussion

The present study aimed at separating short- from long-duration memories and investigating their respective neural bases. We found that items subsequently remembered for a short duration showed, during encoding, decreased activation in the posterior cingulate cortex (PCC) and precuneus cortex. In contrast, the items with long-duration subsequent memory showed stronger activity in the LIFG but less deactivation in the PCC during encoding. These results provide clear evidence to suggest distinct encoding mechanisms that support short- and long-duration memories.

Consistent with many previous observations, the present study found a significant subsequent memory effect in the left inferior frontal gyrus (LIFG) (Kim, 2011; Wagner et al., 1998; Xue et al., 2010a). One interesting finding in the present study is that although we found a strong



**Fig. 2.** Memory performances as measured by (A) hit ratio and (B) d prime score. The retested words (T12) showed better memory performance than words just tested one week later (T2). Error bars denote standard error of the mean.



**Fig. 3.** The neural activations of (A) the short-duration subsequent memory effect, (B) the long-duration subsequent memory effect, and (C) their direct comparison. All activations were thresholded at  $Z > 2.3$  (whole-brain corrected  $p < 0.05$ ) and rendered onto cortical surface template from the FreeSurfer software (<http://surfer.nmr.mgh.harvard.edu/>).

subsequent memory effect in the LIFG when R1 was compared to F1, we did not find such an effect in this area when items with true long-duration memory were carefully sorted out through experimental design. This result suggests that previous studies might have overestimated the short-duration subsequent memory effect in the LIFG because potential long-duration memory was included in the short-duration memory.

As the LIFG is not involved in memory storage per se, it has been implicated in goal-directed task processing that facilitates input to the MTL (medial temporal lobe) where long-term memory is formed. One such goal-directed process is the selection of specific information for task performance (Badre and Wagner, 2007; Blumenfeld and Ranganath, 2007; Dobbins and Wagner, 2005). This could enhance the cortical representation of item-specific features during encoding (Xue et al., 2013), and thus increase the uniqueness and consistency of cortical input to the MTL.

In line with this proposal, it has been revealed that task manipulations that enhance IFG activation during encoding can lead to better memory. One such manipulation is deep vs. shallow encoding. Relative to shallow encoding (e.g., orthographic or phonological encoding), deep encoding (e.g., semantic encoding) is associated with better memory and stronger IFG activation (Otten et al., 2001; Wagner et al., 1998). Similarly, distributed practice, as compared to massed practice, could reduce repetition suppression in the IFG and lead to superior memory performance (Wagner et al., 2000; Xue et al., 2010b).

With our experimental design, the present study also revealed an important role of the PCC and adjacent precuneus in forming long-lasting memory. In line with several existing studies (Duverne et al.,

2009; Huijbers et al., 2012; Kim, 2011; Otten and Rugg, 2001; Wagner et al., 1998), this study found that items remembered for a short duration showed stronger deactivation in the PCC during encoding than the forgotten items. Notably, this deactivation disappeared for items remembered for a long duration, yielding a V-shaped relationship between PCC activity and memory duration. It should be noted that this pattern did not show up when we tested items under both short and long delays, which might explain why previous studies did not find less PCC deactivation for long-duration memory than for short-duration memory. Interestingly, a previous study on memory retrieval also found a V-shaped relationship between PCC activity and memory delay (Huijbers et al., 2010). That is, PCC activity decreased from short test delay (0 days) to medium delay (3 days), but increased from medium to long delay (31 days).

Our results provide important data about the PCC's function in memory encoding. The PCC is a key part of the default-mode network (DMN) (Biswal et al., 2010; Buckner et al., 2008), which is activated when attention is directed internally to self-related thoughts (Buckner and Carroll, 2007; Northoff et al., 2006). The reduced activity in the DMN during an attention-demanding task indicates less mind-wandering or stronger top-down attention focus, which is associated with better task performance (Buckner et al., 2008). Consistent with this view, memory studies have shown that DMN deactivation during encoding was related to better memory performance (Kim, 2011; Paller and Wagner, 2002; Uncapher and Wagner, 2009).

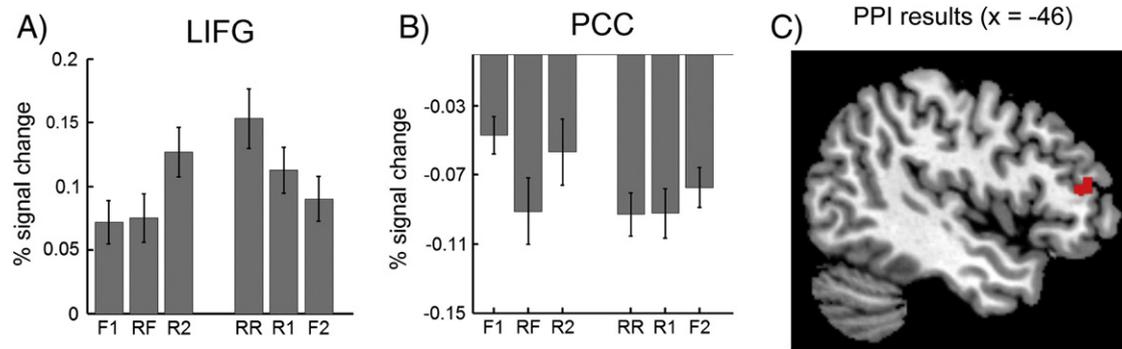
However, as suggested by the present study, high DMN activity might not always be associated with mind-wandering and poor memory encoding. One likely process supported by the DMN that contributes to memory encoding is self-referential processing. Many studies have implicated the PCC in self-related cognition (Johnson et al., 2002; Kelley et al., 2002; Northoff et al., 2006), and behavioral studies suggest that "self-referential" processing could connect the external world with the internal world and result in better memory storage (Rogers et al., 1977; Symons and Johnson, 1997). Nevertheless, because the present study did not explicitly ask subjects to make self-referential encoding, this interpretation is speculative.

A more likely mechanism might be memory retrieval. The PCC exhibits decreased activity during successful memory encoding, but increased activity during successful memory retrieval, a pattern called the encoding/retrieval flip (E/R-flip) (Daselaar et al., 2009). The E/R-flip has been replicated by many subsequent investigations (Gilbert et al., 2012; Huijbers et al., 2009, 2011). Thus, the increased PCC activity might also reflect retrieval processes triggered by the learning material (Nelson et al., 2013), which might help to integrate the current learning material with existing memories and thus form long-lasting memory. Many behavioral studies have emphasized the role of retrieval practice

**Table 2**

Brain regions showing the short-duration subsequent memory effect (RF vs. F1), the long-duration subsequent memory effect (R2 vs. F1), and the differences between short- and long-duration memories (R2 vs. RF).

Region	Volume (voxels)	Z	MNI coordinates		
			x	y	z
<i>Short duration subsequent memory effect (negative)</i>					
Precuneus/posterior cingulate cortex	334	3.41	2	-54	34
		3.26	10	-50	28
<i>Long duration subsequent memory effect</i>					
Left inferior frontal gyrus/orbital frontal lobe	2229	4.34	-36	28	-18
		3.84	-48	18	24
<i>Long &gt; short</i>					
Posterior cingulate cortex	336	3.51	-2	-40	32



**Fig. 4.** The right two plots show the % signal change in the independent ROIs of the left IFG (A) and PCC (B), which suggest an increased IFG activity but a V-shaped relationship in the PCC as memory retention became longer. Error bars denote standard error of the mean. (C) The left frontal cortex showed stronger connectivity with the PCC for R2 than F1.

in enhancing memory encoding (Carrier and Pashler, 1992; Karpicke and Roediger, 2008). This postulation should be directly examined in future studies.

As both mind-wandering and goal-directed memory retrieval are associated with high PCC activity, its functional connectivity with the prefrontal cortex might help to differentiate them. That is, when strong PCC activity is paired with strong goal-directed processing in the prefrontal cortex, this PCC activity might be directed towards encoding-related processing that leads to durable memory. Indeed, the present study found enhanced functional connectivity between the prefrontal cortex and the PCC when processing items that would be remembered at long delay. Consistent with this observation, anatomical studies have revealed that a portion of the superior longitudinal fasciculus is connected to the medial parietal and lateral frontal lobes in monkey brain (Petrides and Pandya, 1984). Such connections were confirmed by diffusion tensor MRI with human subjects (Makris et al., 2005). Meanwhile, decreased functional connectivity between the prefrontal cortex and the PCC has also been observed on people with mild cognitive impairment such as episodic memory impairment (Wang et al., 2012).

Several studies have found the subsequent memory effect in the left fusiform gyrus using a probe delay of up to a few hours (Cohen et al., 2000; Kim, 2011; Mei et al., 2010; Otten et al., 2001, 2002; Wagner et al., 1998; Xue et al., 2010b, 2011). However, we did not find either

short- or long-delay subsequent memory effect in the left fusiform gyrus, suggesting that this region does not support memory lasting longer than one day. As this region is mainly involved in learning and processing orthography and form-sound association, instead of semantic information (Cohen et al., 2000; Price, 2012; Xue and Poldrack, 2007; Xue et al., 2006), the absence of the subsequent memory effect for durable memory fits very well with the “levels of processing” model.

The MTL is critical for long-term memory formation (Squire and Zola-Morgan, 1991). The present study only found a marginally significant subsequent memory effect in the hippocampus for long-duration memory. This weak involvement of the MTL is consistent with several previous studies that examined the memory of familiar Chinese words (Chen et al., 2013; Mei et al., 2010; Xue et al., 2010a). Future studies should investigate whether the subsequent memory effect is specific to certain types of materials.

The left pre-SMA also showed a subsequent memory effect, with a pattern similar to that at the LIFG. Interestingly, Kim’s meta-analysis also revealed a subsequent memory effect in the pre-SMA. Currently, it is not entirely clear what this region’s role is in memory encoding and whether it causally contributes to subsequent memory. Previous studies have implicated this region in motor action planning and control (Xue et al., 2008), which is unlikely to have accounted for our result, as we found no differences in reaction time between the three conditions. Other studies suggest that the pre-SMA showed stronger activity for recall than repetition (Buckner et al., 1996) and for word generation than word reading or word repetition (Alario et al., 2006; Buckner et al., 1996; Crosson et al., 2001), which suggests that the pre-SMA is involved when the tasks require more effort (recall vs. repetition, word generation vs. word reading or repetition). Therefore, the pre-SMA might have contributed to the effortful and effective encoding involved in our task. Future studies should examine these possibilities.

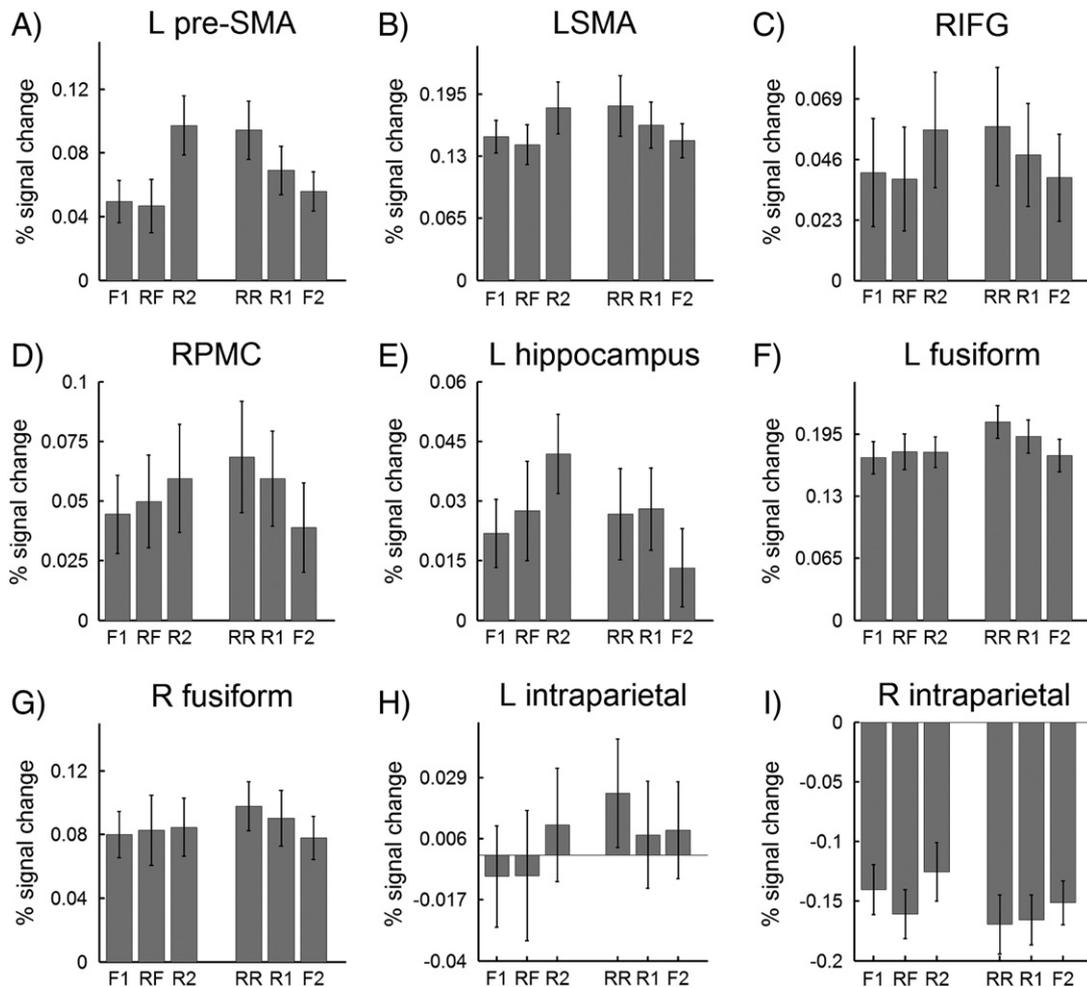
Several other questions need to be addressed in future studies. First, as discussed above, the precise role of the PCC in forming durable memory should be examined. Special attention should be paid to the finer functional dissociations in the posterior medial cortex (Huijbers et al., 2012; Whitfield-Gabrieli et al., 2011) and functional lateralization. Second, future studies should examine how goal-directed processes and memory-specific processes together help to form long-lasting memory, which might provide a mechanistic account of the benefits from semantic encoding and self-referential encoding when forming long-lasting memories. Third, with the rapid development of multi-voxel pattern analysis (MVPA) and its implications for memory research (Rissman and Wagner, 2012), its use might help to uncover the finer neural representations and processes that contribute to durable memories (Kuhl et al., 2012; Visser et al., 2013; Xue et al., 2010a). Finally, although the present study focused on the encoding stage, future studies should also examine how the post-encoding processes such as consolidation and retrieval contribute to memory durability.

**Table 3**

The F-values for the short-duration subsequent memory effect (RF vs. F1), the long-duration subsequent memory effect (R2 vs. F1) and the comparison between short- and long-duration memories (R2 vs. RF) in all independent ROIs.

	MNI	RF vs. F1	R2 vs. F1	R2 vs. RF
LIFG	−42, 12, 28	0.03	10.96**	7.20*
PCC	−2, −26, 38	6.18*	0.24	4.32*
<i>Frontal lobe</i>				
L pre-SMA	−6, 16, 54	0.07	11.49**	11.43**
LSMA	−4, 0, 58	0.28	2.22	3.67
RIFG	50, 26, 28	0.01	1.02	1.14
RPMC	50, 6, 30	0.11	1.32	0.61
<i>Temporo-occipital lobe</i>				
L hippocampus	−22, −14, −12	0.26	3.38	1.94
L fusiform	−44, −48, −22	0.18	0.32	0.00
R fusiform	50, −52, −16	0.04	0.21	0.03
<i>Parietal lobe</i>				
L intraparietal	−30, −76, 36	0.00	1.37	1.59
R intraparietal	30, −74, 34	1.19	0.47	3.95

Notes: \* $p < 0.05$ ; \*\* $p < 0.01$ . Abbreviations: L, left; R, right; IFG: inferior frontal gyrus; PMC: premotor cortex; pre-SMA: pre-supplementary motor area; SMA: supplementary motor area.



**Fig. 5.** Results for additional independent ROIs. Error bars denote standard error of the mean. Abbreviations: L: left; R: right; IFG: inferior frontal gyrus; PMC: premotor cortex; pre-SMA: pre-supplementary motor area; SMA: supplementary motor area.

## Conclusions

In sum, the present study clearly distinguished memories with different durability and revealed distinct neural processes during encoding that were associated with these memory outcomes. These results indicate that long-lasting memory can be achieved when strong PCC activity (or weaker deactivation) is combined with strong goal-directed processing in the IFG during encoding, suggesting that they might be involved in some specific mnemonic processes that support memory encoding. In contrast, short-duration memory can be achieved when there is strong PCC deactivation, suggesting some attentional mechanisms. These results provide a deeper understanding of the neural processes that lead to durable memories.

**Table 4**

Brain regions showing stronger functional connectivity with the posterior cingulate cortex for R2 than for F1 ( $p < 0.005$  uncorrected, cluster size  $> 10$  voxels).

Region	Volume (voxels)	Z	MNI coordinates		
			x	y	z
<i>R2 &gt; F1 in PPI analyses</i>					
Left inferior frontal gyrus	15	3.47	-46	38	12
Right superior frontal gyrus	19	3.36	16	-2	76
Left superior parietal lobule/lateral occipital cortex	27	3.4	-34	-60	60
Left supramarginal gyrus	15	3.05	-64	-28	44
Left superior parietal lobule/supramarginal gyrus	12	3.07	-32	-50	40

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