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Priming for Novel Object Associations: Neural Differences From Object Item Priming and Equivalent Forms of Recognition

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ABSTRACT: The neural substrates of associative and item priming and recognition were investigated in a functional magnetic resonance imaging study over two separate sessions. In the priming session, participants decided which object of a pair was bigger during both study and test phases. In the recognition session, participants saw different object pairs and performed the same size-judgement task followed by an associative recognition memory task. Associative priming was accompanied by reduced activity in the right middle occipital gyrus as well as in bilateral hippocampus. Object item priming was accompanied by reduced activity in extensive priming-related areas in the bilateral occipitotemporofrontal cortex, as well as in the perirhinal cortex, but not in the hippocampus. Associative recognition was characterized by activity increases in regions linked to recollection, such as the hippocampus, posterior cingulate cortex, anterior medial frontal gyrus and posterior parahippocampal cortex. Item object priming and recognition recruited broadly overlapping regions (e.g., bilateral middle occipital and prefrontal cortices, left fusiform gyrus), even though the BOLD response was in opposite directions. These regions along with the precuneus, where both item priming and recognition were accompanied by activation, have been found to respond to object familiarity. The minimal structural overlap between object associative priming and recollection-based associative recognition suggests that they depend on largely different stimulus-related information and that the different directions of the effects indicate distinct retrieval mechanisms. In contrast, item priming and familiarity-based recognition seemed mainly based on common memory information, although the extent of common processing between priming and familiarity remains unclear. Further implications of these findings are discussed. © 2015 Wiley Periodicals, Inc.

KEY WORDS: repetition priming; novel associations; recognition memory; hippocampus; perirhinal cortex

INTRODUCTION

Recognition memory can be for individual items or for associations between items. Item recognition memory is typically tested by presenting items, some of which were encountered in an earlier study session, and by asking participants which items had actually been presented then. In contrast, associative recognition memory is tested by requiring participants to distinguish items that were encountered together in an earlier study session (intact pairs) from items that were encountered at study but separately in different pairs (recombined pairs). Since both intact and recombined pairs comprise previously studied items, performance cannot be based on item recognition, and so should be driven by recognition of the previously encountered associations.

Some researchers have proposed that the brain structures that support recognition memory for single items are partially distinct from those that support recognition memory for associations, and particularly, associations between previously unrelated items (e.g., Giovanello et al., 2009; Qin et al., 2009). For instance, the relational memory theory holds that the hippocampus is especially important for encoding into memory new, flexible associations between unrelated items, while the adjacent medial temporal lobe (MTL) cortex, comprising entorhinal, perirhinal, and parahippocampal cortex (PHC), is more critical for single item recognition (e.g., Eichenbaum et al., 1994; Cohen et al., 1997; Eichenbaum, 1997; see also Henke, 2010 for a related theory). Neuropsychological (e.g., Giovanello et al., 2009) and neuroimaging (e.g., Yonelinas et al., 2001; Giovanello et al., 2004, 2009) evidence have largely confirmed this view, showing that the hippocampus is involved, to a greater extent, in the recollection of associative than of item information.

Importantly, the relational memory theory proposes that the hippocampus is involved in the processing and representation of relational information regardless of whether retrieval is made with or without conscious awareness. Long-term repetition priming is a kind of stimulus-specific memory for studied items, arguably independent of conscious awareness (e.g., Gomes and Mayes, 2015a; Gomes et al., 2015), in which one or more exposures to a stimulus facilitate or bias performance in memory tasks that do not make reference to these previous encounters (e.g., Schacter, 1987; Richardson-Klavehn and Bjork, 1988). Whereas single item priming is thought to involve mainly occipitofrontal structures (see Buckner and Koutstaal, 1998; Henson, 2003 for reviews) as well as the perirhinal

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cortex (PRC; e.g., Wang et al., 2010, 2014; Dew and Cabeza, 2013), there is an emerging body of evidence linking the hippocampus to the encoding and retrieval of associative unaware memories, where behavioral facilitation is shown when previously encountered pairs of unrelated items are repeated (see Hannula and Greene, 2012 for a review; but see Verfaellie et al., 2012).

Behaviorally, association-specific priming has been observed in tasks such as word-stem completion (e.g., Graf and Schacter, 1985, 1989), lexical decision (e.g., Goshen-Gottstein and Moscovitch, 1995a,b; Goshen-Gottstein et al., 2000), perceptual identification (e.g., Gabrieli et al., 1997; Yang et al., 2008; Kan et al., 2011; Gomes and Mayes, 2015b), classification (e.g., Dew and Giovanello, 2010a,2010b; Gomes and Mayes, 2015b), and category decision (e.g., Verfaellie et al., 2006) tasks. Early studies using an associative word-stem completion task suggested that associative priming required semantic elaboration at study to link previously unrelated words together successfully in memory (e.g., Graf and Schacter, 1985, 1989; Schacter and Graf, 2004). However, it is now generally accepted that other kinds of associative priming do not require semantic study elaboration (e.g., Goshen-Gottstein and Moscovitch, 1995a; Reingold and Goshen-Gottstein, 1996; Gomes and Mayes, 2015b), although they may depend on perceptual information matching between study and test (Gomes and Mayes, 2015b).

The evidence about the neural basis of novel associative priming and particularly the role of the hippocampus is mixed. Some neuropsychological studies indicate that a preserved hippocampus is critical for the emergence of novel associative priming (e.g., Mayes and Gooding, 1989; Paller and Mayes, 1994; Chun and Phelps, 1999; Yang et al., 2003; Carlesimo et al., 2005), whereas other studies have found reliable associative priming despite patients' hippocampal lesions (e.g., Gabrieli et al., 1997; Hamann and Squire, 1997; Goshen-Gottstein et al., 2000; Verfaellie et al., 2012). Several factors may explain the discrepancies across studies (see Gooding et al., 1999 for a discussion). For example, some paradigms may encourage healthy controls to adopt retrieval strategies based on their preserved explicit memory, which is impaired in patients with amnesia. Some associative representations may be more perceptual and inflexible and supported by neocortical structures, whereas more flexible relational memories may depend critically on the hippocampus that is often damaged or dysfunctional in amnesia. Furthermore, some patients may be more impaired than others when their lesions extend into another functional zone essential for associative priming.

Fortunately, functional neuroimaging research can provide good, complementary evidence for what brain regions support novel associative fluency-based priming. In a positron emission tomography study, Badgaiyan et al. (2003) used an associative word-stem completion task and observed that both intact and recombined word pairs significantly reduced the amount of activation observed in the extrastriate area, a brain region commonly associated with perceptual priming (e.g., Schacter et al., 1986, 2007). Reduced neural activity for repeated items is a typical neural signature of priming, and it is often attributed to tuned stimulus-specific cortical representations (e.g., Henson, 2003). Badgaiyan et al. also found increased activation in the left prefrontal cortex as well as in the right MTL, which they interpreted as the involvement of explicit memory during associative priming. Indeed, behavioral evidence suggests that only participants who were aware of the study-test relationship showed associative word-stem completion priming (e.g., Bowers and Schacter, 1990; McKone and Slee, 1997), and severe forms of amnesia disrupted this kind of priming (e.g., Schacter and Graf, 1989; Mayes and Gooding, 1989; Shimamura and Squire, 1989). These data suggest that the associative word-stem completion task may not be suitable to investigate the neural correlates of associative priming due to its possible dependence on residual explicit memory (Gooding et al., 2000).

More recently, Yang et al. (2008) investigated novel associative priming in an functional magnetic resonance imaging (fMRI) study during a word perceptual identification task using Chinese characters. They identified a region in the right posterior PHC that was specific to novel associative priming, which showed less activation for intact relative to recombined pairs. However, behavioral priming performance was not assessed for the scanned participants, which limits confidence in interpreting the fMRI data.

Although both Badgaiyan et al. (2003) and Yang et al. (2008) failed to observe hippocampal activity related to novel associative supraliminal fluency-based priming (where participants are aware of stimuli at study and test), there are some sources of support for the involvement of the hippocampus during subliminal associative priming. These studies have shown enhanced activation in the hippocampus during encoding/retrieval of word-word or face-word associations (e.g., Henke et al., 2003a,2003b; Degonda et al., 2005; Reber et al., 2012; Duss et al., 2014). Explicit memory contamination is extremely unlikely in these studies because the authors used a masked priming paradigm which makes use of subliminally presented items sandwiched between masks at study, so that participants are never conscious of the encoded associations. Duss et al.'s study was particularly impressive because, like the other findings of this group, it not only found that control participants showed hippocampal activation when subliminal associative priming occurred, but that large hippocampal system lesions impaired this kind of priming.

Although subliminal priming effects almost certainly do not involve explicit memory confounds, it is less certain how closely comparable this kind of priming is to supraliminal priming. Whereas increased activity in the hippocampus and also in other structures (such as right thalamus) are seen with associative subliminal priming, neural activity in cortical and subcortical sites is nearly always found to decrease in item-specific supraliminal priming after delays of minutes or longer (see Henson, 2003 for a review). These activity decreases often correlate with enhanced stimulus-related performance (e.g., Dobbins et al., 2004; Orfanidou et al., 2006; Horner and Henson, 2008). In addition, one of the few existing studies examining

supraliminal associative priming only found "decreased" activation in an MTL region (PHC) that correlated with association-specific priming (Yang et al., 2008). The typical difference in direction of activation between subliminal and supraliminal priming remains unexplained, but could arise because of functional/neural differences in the kinds of retrieval involved, the specific kinds of contrast made, or other reasons (see for instance, Henson, 2003; Segaert et al., 2013). At present, it is also unclear whether hippocampal activity is reduced, like activity in other structures, in associative supraliminal priming.

In addition, although some studies have addressed the question of dissociations/similarities between implicit and explicit memory for single items (e.g., Turk-Browne et al., 2006; Voss et al., 2009), a direct comparison between the neural basis of fluency-based associative priming and associative recognition memory for the same stimuli has rarely been attempted (but see Yang et al., 2008, for an exception).

This study aimed to: (1) clarify what the neural correlates of novel associative fluency-based priming are and, in particular, what the role of the hippocampus is in this kind of memory; (2) determine whether the neural correlates of novel associative and item priming can be dissociated from those of associative and item recognition memory, respectively; (3) ascertain what structures contribute independently to associative and item priming; and (4) investigate how well the neural correlates of associative and item priming are related to the behavioral indicators of priming. To achieve these aims, an fMRI experiment was conducted over two sessions. During the first (priming) session, participants decided, at study, which object in a pair was bigger in real life. During the test phase, they performed the same task on intact, recombined, and new item pairs. Immediately following this, in the second (recognition) session, participants performed, at study, the same size-judgement task on new object pairs. At test, they engaged in an associative recognition test, in which they decided whether each presented object pair had been previously paired together during the study phase of the recognition session.

METHODS

Participants

Eighteen right-handed undergraduate students of the University of Manchester were recruited ($M = 20.89$ years, SD = 2.19 years) in exchange for monetary compensation. All participants had normal or corrected-to-normal vision with no history of psychiatric or neurological disorders. All gave informed written consent to take part in this study before the start of the experiment in accordance with the ethical approval that had been obtained from the School of Psychological Sciences Ethics Committee of the University of Manchester and by the National Research Ethics Committee (reference 10/H1014/39).

Materials

Three-hundred and sixty colored high-resolution clip art images of common objects were selected from an Internet clip art database (www.clipart.com). The pictures consisted of everyday objects from a range of different categories (e.g., animals, transports) and the size of all objects in real life was unambiguous. Shadows and other external features were removed from the pictures and each object was rescaled to fit in a box of 400 by 400 pixels, essentially normalizing all images so as not to create a response bias for larger images. Three lists were created, each containing 120 images. Within each list, 10 groups of 12 images were formed, with each group further divided into two subgroups of six pictures, with the restriction that the six objects in the first subgroup had a different size and were unrelated to the six objects in the second subgroup. Two different word association norms (Moss, 1996; Nelson et al., 2004) were used to ensure the absence of any pre-existing relationship between any two subgroups. This was achieved by selecting pairs that, first, did not belong to the same semantic category (e.g., two pictures of animals were never paired together) and, second, were not produced together in the word association norms mentioned above. Three independent native English judges cross-checked whether the objects in each subgroup were indeed unambiguously bigger than the objects in the other subgroup (there was maximal agreement among the judges). For each participant, the pictures in the first subgroup were randomly paired with the pictures of the second subgroup and the resulting unrelated pairs were randomly assigned to the three different conditions (intact, recombined, and new). In half of the associations, the bigger objects were shown on the left side of the screen, whereas, in the other half, they were presented on the right side of the screen; thus, an equal number of right- and left-sided objects were classified "bigger." The position of the pictures on the screen for both intact and recombined pairs remained constant between study and test phases. For each participant, two of the lists were selected to form the intact, recombined and new pairs for the associative priming task, whereas the remaining list was used to form the pairs for the associative recognition task. The lists were counterbalanced across participants and tasks.

To ensure that intact and recombined pairs were matched in every aspect but the associative link, each recombined object maintained its classification status at test. For example, if the pair "cabbage-ant" were presented at study and, at test, "ant" were recombined with a different object, then this object would also be bigger than the "ant" (e.g., "pineapple"), so that the "ant" would be the smaller object at both study and test. This manipulation ensured that any difference between intact and recombined pairs (our measure of associative priming) resulted from differences in associative context (i.e., associative vs. nonassociative pairing at test) and was not the result of changes in classification status of recombined objects (e.g., from bigger at study to smaller at test). Furthermore, to ensure that any detectable associative effects could only be due to the

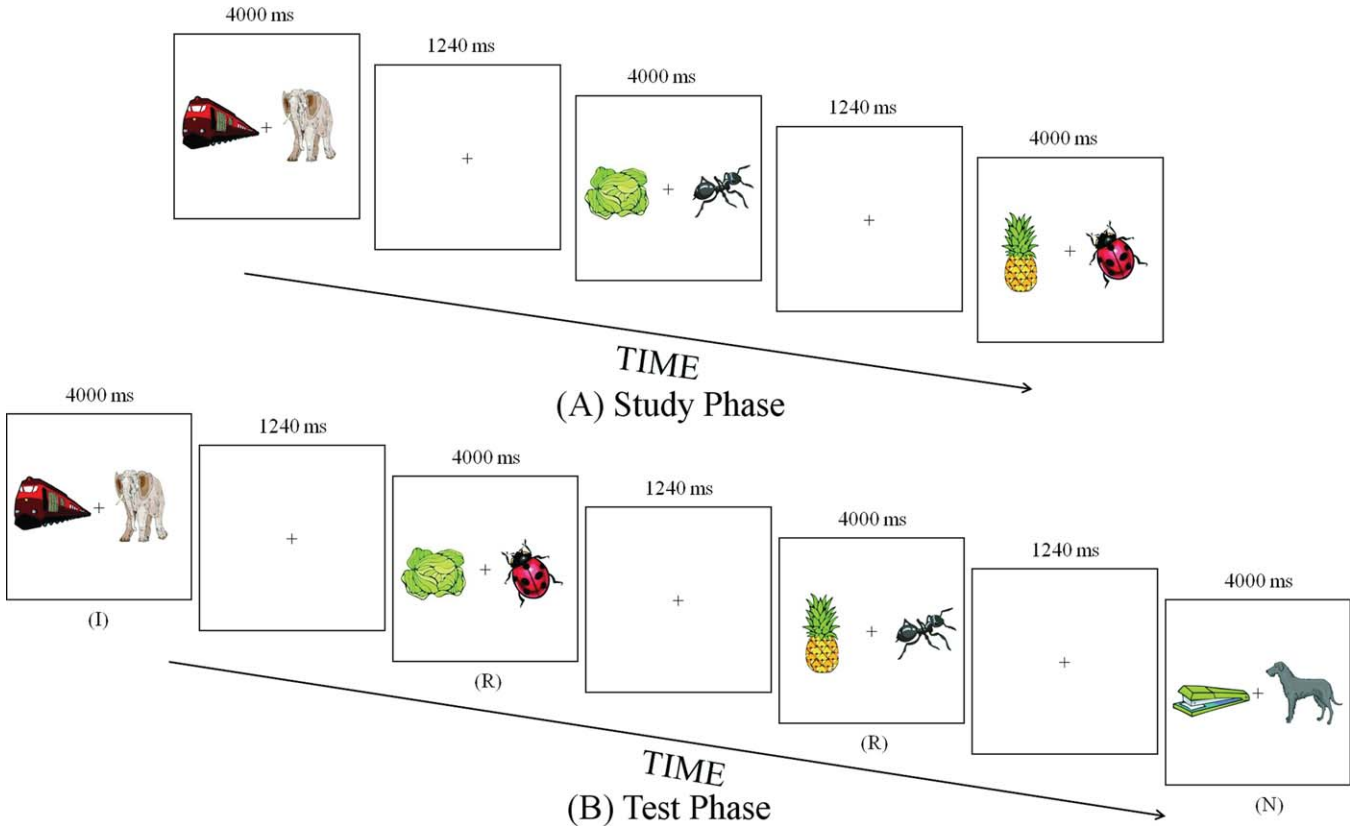

FIGURE 1. Design of the experiment. In the first (priming) session, participants decided which object was bigger in real life at study (A) and, at test (B), they performed the same task on intact (I), recombined (R) and new (N) pairs. In the second (recognition) session, participants saw different object pairs and performed the same study task as in the first session. At test, they were instructed to decide whether the two objects had been presented together in the second study phase. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

associative link between the items and not to difficulty-related artifacts that arise from the fact that intact pairs were easier to judge than recombined pairs, all objects in each subgroup had approximately the same unambiguous size, so that, once a pair was recombined, the difficulty was held constant by recombining the items with similar-size items.

Behavioral Procedure

The whole experiment was run in two separate sessions: the first session comprised the study and test phases of the priming task, whereas the second session comprised the study and test phases of the recognition task (scanning was only performed during the test phases). The priming session always preceded the recognition session to prevent participants from adopting explicit memory strategies during the test phase of the priming session. It is unlikely that any behavioral or neural differences between the two sessions relates to participants' fatigue or greater interference in the associative recognition task due to previous engagement in the priming session. First, the study-test sessions were not long, and reaction times (RTs) during both study phases were very similar (suggesting similar degrees of attentiveness). Second, the behavioral recognition memory data presented here (e.g., Pr scores) were very similar to independent behavioral data acquired in our laboratory in which the same design was used but participants only performed the associative recognition task.

Although scanning took place only during the test phases, participants lay in the scanner throughout the whole experimental session (i.e., study and test phases) in order to allow familiarisation with the scanning environment before engaging in the critical test tasks. During the study phase of the first (priming) session, participants saw 80 pairs of pictures and pressed the left button if they thought the left object was bigger than the right object in real life, or the right button if the opposite was true. Each experimental trial started with a fixation cross displayed for 1240 ms, followed by an object pair for 4000 ms (see Fig. 1). The study phase was divided into three runs (i.e., each pair appeared three times), and for each run the pairs were always presented in a new randomized order.

Immediately after completion of the study phase, participants saw 40 intact pairs, 40 recombined pairs and 40 novel pairs never presented at study (new item pairs), and were again

asked to decide as quickly and accurately as possible which object was bigger in real life (no mention of the 3 possible types of pairs was made). Intact and recombined objects were presented on the same side of the screen as at study. We used an interstimulus-interval (1240 ms) that was not a multiple of the TR (2700 ms), as well as 30 fixation crosses representing implicit baseline (IB) trials, to introduce jitter into the fMRI time series. Each trial consisted of either a pair of objects in one of the conditions (intact, recombined, or new) or the IB, presented in a pseudorandomized fashion for 4000 ms. A different pseudorandomization order was used for each participant, such that, on average, each condition followed each other condition an approximately equal number of times.

After completion of the priming task, participants were once again shown an instruction screen informing them they would now perform the size-judgement task on different pairs of objects from those presented in the previous (priming) session. They were not told that their memory for the pairs would be subsequently tested, which ensured that encoding demands were well matched between the associative priming and recognition sessions. After this second study phase, participants were asked to decide as quickly as possible, without compromising accuracy, whether the two paired objects had been presented together during the second study phase. We opted for a binary response of "previously associated" and "not previously associated" response (the latter of which comprised either a recombined or a new pair), rather than a three-response choice (e.g., "previously associated," "previously encountered but not together" and "new"), because we wanted to equate the number of key presses between the associative priming and recognition tests. Although we acknowledge that this procedure has limitations, such as not being able to objectively measure item recognition memory, it, nonetheless, made the priming and recognition tasks more comparable by avoiding the confound of having a different number of response alternatives. Participants made Yes/No decisions by pressing either the left or right button (counterbalanced across participants). A No decision had to be made regardless of whether objects were recombined or new (unstudied), so, any recognition of single objects was assumed to be incidental. The trial sequence was similar to the one used in the previous session. Participants saw 20 intact pairs, 20 recombined pairs, 20 new item pairs, and 15 fixation crosses representing the IB condition. The reason for the different number of trials between priming and recognition relate to the different amounts of noise often observed for measures of these two kinds of memory. For instance, it is possible to select individual recognition hits that are usually based on true recognition memory. In contrast, one cannot reliably select individual priming "hits," because RTs are determined by many factors other than memory, so the priming memory signal is likely to be noisy, being intermixed with a significant number of unprimed trials. Importantly, we wanted to prevent any semantic, phonological, or associative overlap among objects between the priming and recognition sessions and, for that reason, were restricted with the number of pictures we could select. Thus, for the reasons considered above, we included a larger number of trials in the priming relative to the recognition task in an attempt to reach similar levels of power for detecting fMRI-related signals, under the assumption (which was indeed supported by our data) that recognition effects would be robustly detected even with a comparatively lower number of trials.

The whole experiment was programed and responses recorded using the Matlab (http://www.mathworks.com) toolbox Cogent (www.vislab.ucl.ac.uk).

Design and Behavioral Analysis

The behavioral analysis focused on the proportion of correct responses and RTs as the dependent variables. The experimental design consisted of task (priming, recognition) and type of association (intact, recombined, and new) as within-subject factors. The data were analysed using a repeated-measures Analysis of Variance (ANOVA) and paired *t*-tests. A Huynh-Feldt correction was applied to the degrees of freedom of those tests for which the assumption of sphericity was violated. The alpha level was set, for all statistical tests, at 0.05 and *t*-tests were two-tailed.

fMRI Acquisition

The fMRI data were collected on a Philips Achieva 3 Tesla MRI system (Philips Medical Systems, Andover, MA) using a gradient-echo echo planar imaging sequence, providing Blood Oxygen Level Dependent (BOLD) contrast, with parameters as follows: TR = 2.7 s, TE = 35 ms, flip angle = 75°, FOV = 240 × 240 mm^2, slice thickness = 3.5 mm, and matrix size = 96 × 96, yielding a voxel resolution of 2.5 × 2.5 × 3 mm^3. The whole brain was covered with 40 contiguous axial slices, positioned parallel to the AC-PC axis, and collected in ascending order. A high-resolution structural T1-weighted image was also acquired for each participant (matrix size = 256 × 256; number of slices = 160; voxel resolution = 0.9375 × 1.1733 × 0.90 mm^3).

fMRI Analysis

Imaging data were analysed using the Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/) toolbox. The raw data were first subjected to preprocessing of image volumes, which included, in the following order: realignment to correct for movement; slice timing correction (using the middle slice as the reference slice); coregistration of the structural image to the mean functional image; segmentation of the structural image into gray matter, white matter and cerebrospinal fluid; normalization to the MNI space (voxel size = 2 × 2 × 2); and spatial smoothing of the normalized images using a Gaussian kernel with a full-width at half-maximum (FWHW) of 8 mm. A high-pass-filter of 1/128 Hz was applied to the time-series of each voxel, which was also scaled to a grand mean of 100.

Statistical analysis of the fMRI data was performed in two separate stages. In the first stage (first-level analysis) the BOLD response to each event-type was modeled by convolving a delta function at stimulus onset with a canonical hemodynamic

response function. The events for the priming contrasts consisted of correct responses during the size-judgement task to intact (mean = 36, range = 30–40), recombined (mean = 39.1, range = 37–40) and new (mean = 37.7, range = 33–40) pairs, whereas for the recognition contrasts the events comprised intact pair hits (mean = 17.3, range = 10–20), recombined pair correct rejections (mean = 12.3, range = 6–18) and new item pair correct rejections (mean = 19.5, range = 15–20) during the associative recognition task. A participant-specific fixed-effects general linear model (GLM) was created for each session, including six regressors representing the events (intact, recombined, and new) for each task, as well as the parametric modulation of the RTs for each event using a polynomial expansion of the first order. Additional covariates of no interest included six regressors representing the movement parameters estimated during realignment, session effects, and a global mean. A high-pass filter with a cut-off of 128 seconds was used to remove low-frequency drifts, and temporal autocorrelation across scans was accounted for using an autoregressive AR (1) model. Parameter estimates were obtained for each event of interest by fitting the GLM to the data, and images of contrasts were computed for each parameter estimate.

For the whole-brain analysis, in the second-stage model (second-level analysis) the images of contrasts that resulted from the first-level analysis of each participant's data were entered into a GLM, treating participants as a random effect. SPM's of the *t*-statistic were generated for the contrasts of interest: Intact < Recombined, Recombined < New, Intact > Recombined and Recombined > New. In addition, conjunction analyses were performed to identify common activity between two or more contrasts. Neural associative and item priming were defined as the activity reduction for intact relative to recombined pairs, and reduced activity for recombined relative to new item pairs, respectively. Contrasts performed at the whole-brain level (explicitly masked by the cerebellum, brain stem, and ventricles) were corrected for multiple comparisons with $P < 0.05$ using a voxelwise threshold of $P < 0.001$ and a cluster size of at least 21 contiguous voxels, as determined by Monte Carlo simulations (1000 iterations) via AFNI's AlphaSim program.

Small volume corrections (SVC) using anatomical templates of the hippocampus and the PRC were also performed to test a priori hypotheses, for which some support already exists, about the contribution of these regions in associative and item priming, respectively. These SVCs were corrected for multiple comparisons with $P < 0.05$ using a voxelwise threshold of $P < 0.01$ and a cluster size determined by Monte Carlo simulations (see Results section for the specific cluster-extent of each SVC).

Correlational analyses at the group level were also conducted using the individual mean behavioral and neural priming scores. Two correlations were performed: (1) between behavioral item priming and neural item priming in selected brain regions of the left fusiform gyrus and prefrontal cortex, as suggested by previous research (Dobbins et al., 2004; Horner and Henson, 2008) and (2) between behavioral associative priming and neural associative priming in the hippocampus.

Given the putative link between the hippocampus and associative priming and recognition memory (see Henke, 2010; Hannula and Greene, 2012), a region-of-interest (ROI) analysis was also performed. Anatomical ROIs were defined by binary mask images from the Automated Anatomical Labeling (AAL) database (Tzourio-Mazoyer et al., 2002) for the left and right hippocampus. In addition, recent evidence suggests that the PRC is particularly involved in item priming performance (e.g., Voss et al., 2008; Wang et al., 2010, 2014; Dew and Cabeza, 2013), so we also performed an ROI analysis of this structure using a probabilistic map of bilateral PRC (Devlin and Price, 2007). Parameter estimates associated with each contrast were averaged across the relevant ROI using the SPM toolbox MarsBar (http://marsbar.sourceforge.net/). Association- and item-specific effects were subsequently submitted to an ANOVA. Whenever *t*-tests were performed, the alpha level was set to 0.05.

Finally, we tested for changes in connectivity between a source region (e.g., hippocampus) and other target regions of interest by performing Psychophysiological interactions (PPI) using a generalized form of context-dependent PPI analysis (gPPI; McLaren et al., 2012). PPI analysis characterises the activity in a specific brain region by the interaction between the activity in another brain region and a task-specific effect. At first level, we included (1) the relevant task regressors corresponding to the psychological variables of interest (as in the whole-brain analysis), (2) the time course data of the source region (physiological variable), derived by extracting the first eigenvariate from a sphere of 5 mm radius, centered around the coordinates of the relevant ROI detected at the group level, and (3) the critical cross-products between the psychological variables and physiological variable (the PPI term). For the second level analysis, the PPI contrast images generated at first level were entered into a GLM and one-sample *t*-tests carried out using the same cluster correction for multiple comparisons as in the whole-brain analysis.

RESULTS

Behavioral Results

For intact pairs, only those that had been correctly classified in all three study presentations were included in the behavioral analyses. RTs during the test task that were more than 3 standard deviations above or below the mean value of each condition were considered outliers and removed from subsequent analyses. In addition, incorrect trials during the test phase, defined as either incorrect responses or absence of responses, were also removed from the analyses. These procedures resulted in the elimination of ~6% of all trials.

Table 1 (left) shows the proportion of correct responses and RT data for intact, recombined and new pairs during the priming task. A repeated-measures ANOVA on the proportion data revealed a significant effect of type of association, $F(2,34) = 3.55$, $P < 0.05$, with recombined pairs judged more

TABLE 1.

Proportion of correct responses and RT Data for Intact, Recombined and New Pairs During the Associative Priming Task as well as for Hits (Hs), Misses (Ms), Correct Rejections (CRs) and False Alarms (FAs) During the Associative Recognition Memory Test

	Priming			Recognition					
	Intact	Recombined	New	Hs_{intact}	Ms_{intact}	$CRs_{recombined}$	$FAs_{recombined}$	CRs_{new}	FAs_{new}
Proportion	0.97 (0.01)	0.99 (0.01)	0.96 (0.01)	0.87 (0.03)	0.13 (0.03)	0.62 (0.04)	0.38 (0.04)	0.975 (0.01)	0.025 (0.01)
RTs	1012 (60)	1093 (65)	1403 (73)	1419 (77)	1569 (162)	1754 (110)	1770 (90)	1119 (59)	2376 (435)

The standard error of the mean is given in parentheses.

accurately than new item pairs, $t(17) = 2.35$, $P < 0.05$, but no difference in accuracy between intact and recombined pairs, $t(17) = -1.71$, $P > 0.10$. Regarding RTs, the ANOVA also yielded a significant effect of type of association, $F(1.34,22.73) = 117.87$, $P < 0.001$, with intact pairs judged faster than recombined pairs (associative priming), $t(17) = -6.23$, $P < 0.001$, and recombined pairs judged faster than new item pairs (item priming), $t(17) = -9.26$, $P < 0.001$.

With respect to the recognition memory data, correct answers for intact pairs were Yes, whereas for both recombinations and new item pairs the correct answer was No. Table 1 (right) shows the proportion of responses and RT data for each individual response category.

Associative recognition discrimination scores were computed by subtracting the recombined false alarm rate (i.e., Yes responses to recombined items; $FAs_{recombined}$) from the intact hit rate (Hs_{intact}). A one-sample *t*-test revealed a significant effect, $t(17) = 11.248$, $P < 0.001$, indicating that participants' associative recognition memory was greater than chance.

fMRI Results

Priming whole-brain analysis

Item priming effects: recombined vs. new. Figure 2 and Table 2 show the regions exhibiting less activation for recombined relative to new item pairs. These regions include large areas of the bilateral occipital gyrus, extending into the fusiform gyrus and posterior PHC, as well as an extensive region of the prefrontal cortex (PFC), most notably in the left posterior (BA 9) and inferior (BA 45/47) PFC, as usually observed in classification-based single-item object priming studies (e.g., Dobbins et al., 2004; Horner and Henson, 2008; Race et al., 2009).

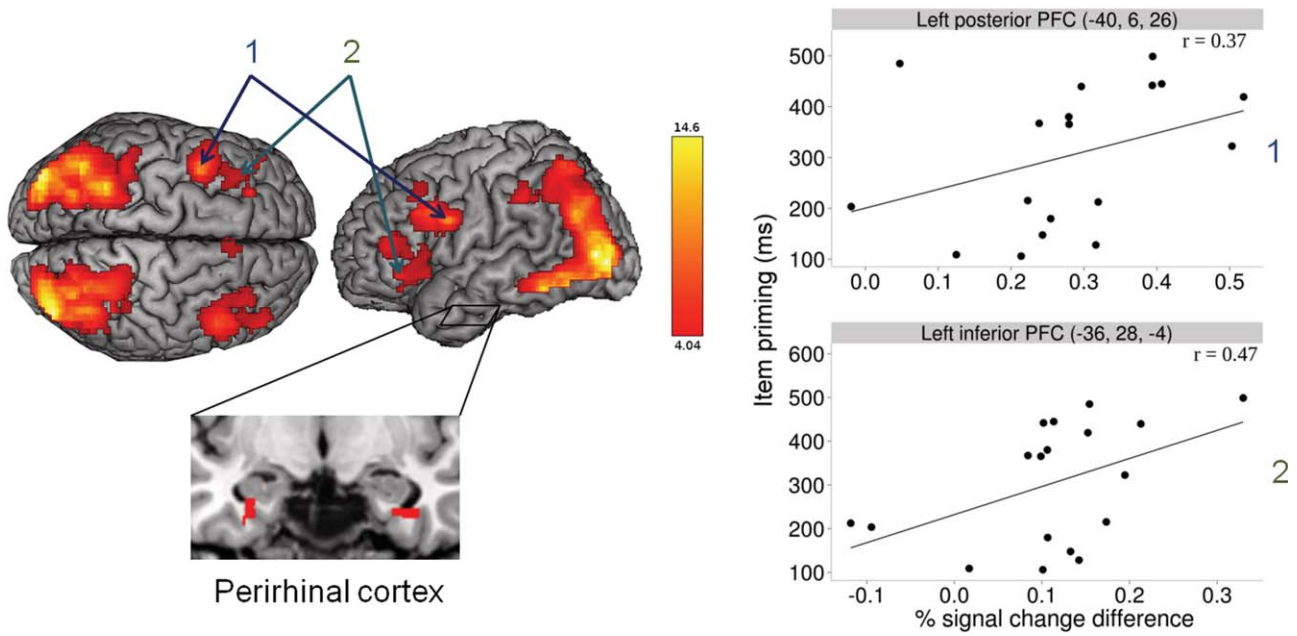

FIGURE 2. Left: Surface rendering of fMRI maps during item priming showing regions of reduced activation for recombined relative to new item pairs. Colorbar indicates range of T-values. Below, the location of perirhinal cortex deactivation observed in the SVC analysis (see text; results are thresholded at $P < 0.001$, uncorrected, for displaying purposes). Right: Correlation between behavioral item priming (new - recombined) and percent (%) signal change difference in the left inferior PFC (top) and left posterior PFC (bottom). The value *r* indicates the Pearson's correlation coefficient. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 2.

Brain Regions Exhibiting Reduced (Top) And Increased (Bottom) Activation for Recombined Pairs Relative to New Item Pairs During the Size-Judgement Task

Contrast	Region	Voxels	MNI coordinates			Z-scores
			x	*y*	*z*	
Recombined < New						
	R middle/inferior occipital gyrus (BA 19,37)	3325	44	−80	6	6.58
	L middle/inferior occipital gyrus (BA 19,37)	3123	−30	−86	2	6.44
	L posterior prefrontal cortex (BA 9)	432	−40	6	26	5.24
	R posterior prefrontal cortex (BA 9)	520	48	14	32	4.83
	L inferior prefrontal cortex (BA 47)	34	−26	34	−6	4.40
	L inferior parietal lobule (BA 40)	212	−40	−38	40	4.22
	R mid-lateral prefrontal cortex (BA 46)	170	48	40	10	3.90
	R inferior prefrontal cortex (BA 45,47)	145	36	30	−6	3.87
	L inferior prefrontal cortex (BA 47)	164	−36	28	−4	3.64
	R anterior cingulate cortex (BA 32)	58	8	24	38	3.54
	L mid-lateral prefrontal cortex (BA 46)	21	−42	38	6	3.42
	R inferior parietal lobule (BA 40)	30	40	−38	46	3.33
Recombined > New						
	L/R precuneus (BA 7,31)	2378	2	−64	36	5.07
	R angular gyrus (BA 39,40)	427	48	−68	36	4.64
	L angular gyrus (BA 39)	303	−52	−58	30	4.21
	L orbitofrontal cortex (BA 10)	21	−28	50	−4	3.50

Approximate Brodmann areas (BA) are given in parentheses. L = Left, R = Right.

Interestingly, the left fusiform gyrus (−30, −56, −20), left posterior (−40, 6, 26) and inferior (−36, 28, −4) PFC maxima observed in the present experiment were very near the maxima identified in other object priming studies that have also used a size-classification task but on single objects (e.g., fusiform: −24, −57, −15, Dobbins et al., 2004; posterior PFC: −42, 6, 27, inferior PFC: −36, 33, −12, Horner and Henson, 2008). These studies have also reported striking positive correlations between object priming-related neural effects in the left fusiform (Dobbins et al., 2004) and left PFC (Dobbins et al., 2004; Horner and Henson, 2008) and the performance levels of participants. We, therefore, performed correlational analysis using peak voxel coordinates close to those reported in both studies (left fusiform: −30, −56, −20; left posterior PFC: −40, 6, 26; left inferior PFC: −36, 28, −4). Although the correlation between behavioral priming and neural priming in the fusiform gyrus was nonsignificant ($r = -0.03$, $P > 0.10$), both the inferior and posterior PFC showed positive correlations with behavioral item priming, $P < 0.05$ (see Fig. 2), suggesting that a similar mechanism may be driving both kinds of object item priming, despite the use of different priming tasks.

Some recent studies have also related reductions in activity in the PRC to priming for individual items (e.g., Wang et al., 2010, 2014; Dew and Cabeza, 2013). We decided to test the possibility that PRC activity would be detected in item priming, as measured in our associative task, by conducting an SVC (20 voxel-extent) using a probabilistic map of the bilateral PRC (Devlin and Price, 2007). Consistent with previous single item priming studies, we observed reduced activity for recombined relative to new pairs in the right PRC (34, −12, −30; 48 voxels; see Fig. 2), whereas the left PRC fell short of significance (−38, −48, −22; 19 voxels).

A few regions also exhibited greater activation for recombined relative to new item pairs, particularly in the precuneus (BA 7) and angular gyrus (BA 39; see Table 2).

Associative priming effects: intact vs. recombined. Figure 3 shows that the regions exhibiting less activation for intact relative to recombined pairs included the right middle occipital gyrus (mOg; BA 39; 36, −70, 22; 179 voxels) and bilateral hippocampus (right: 34, −24, −8; 27 voxels; left: −36, −26, −6; 24 voxels). However, none of these deactivations correlated with the size of behavioral associative priming. Lowering our cluster-correction extent (5 voxel-extent, $P < 0.001$) we also observed reduced activity in the left fusiform gyrus (BA 37; −28, −64, −8; 9 voxels) as well as in the left mid-posterior PFC (BA 45; −42, 26, 24; 6 voxels), as typically observed in priming studies using binary classification tasks. Importantly, when the item priming contrast was used as an exclusive mask for the associative priming contrast, the reduced activity in the bilateral hippocampus was uniquely associated with novel associative priming (see Fig. 3, red).

The only region in which intact pairs exhibited greater activation than recombined pairs was in the right superior temporal gyrus (BA 41; 36, −52, 10).

Hippocampus

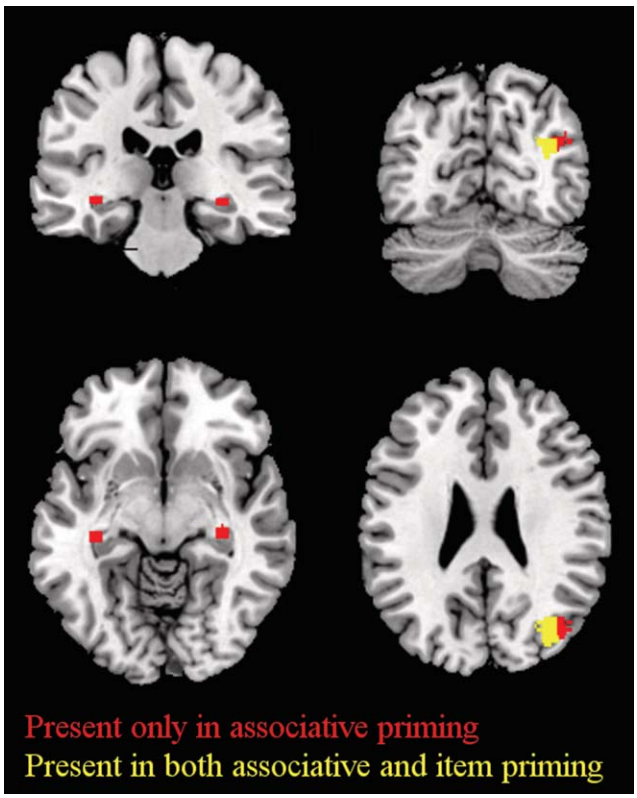

FIGURE 3. Reduced activation for intact relative to recombined pairs (associative priming) in the bilateral hippocampus (left side) and right middle occipital gyrus (right side), overlaid on the MNI space structural image. Red indicates areas where associative priming dissociate from item priming effects, whereas yellow indicates where associative and item priming effects overlap. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Recognition whole-brain analysis

Item recognition effects: recombined vs. new. Table 3 shows the results for the contrast that identified regions showing reduced activation for recombined relative to new item pairs during the associative recognition memory task, which included medial frontotemporal regions as well as the left hippocampus [Because participants' task only required them to differentiate intact pairs from either recombined or new item pairs, it is not possible to obtain a true index of item memory. Although it is likely that differences in activity between recombined and new item pairs reflect incidental item memory (e.g., participants were informed they would see recombinations; postexperimental debriefing indicated that participants recognised most of the recombined objects) we acknowledge that other factors, such as increased processing fluency, may differentially affect the neural response to recombined pairs].

Figure 4 (top row) and Table 3 show the regions demonstrating greater activation for recombined relative to new item pairs. As expected, many bilateral occipitoparietal and frontal sites previously implicated in item-specific object recognition memory (e.g., Yonelinas et al., 2001) showed increased activity for recombined relative to new item pairs. Interestingly, the location of most of these activations appear to coincide with the brain sites that showed reduced activity during item object priming (see also Conjunction analysis), supporting the idea that this contrast detected activity related to item (and not associative) object memory.

Associative recognition effects: intact vs. recombined. No voxels showed reduced activity for intact relative to recombined pairs in the recognition task.

Figure 4 (bottom row) and Table 4 show the regions that demonstrated greater activation for intact vs. recombined pairs. Of particular interest, some of these activations were located in the medial frontal gyrus (BA 10), posterior cingulate cortex (BA 31), precentral gyrus (BA 6), parietal lobe (BA 40), inferior PFC (BA 44), and left posterior PHC. Activation in these regions has previously been linked to recollection-based memory (e.g., Henson et al., 2005; Yonelinas et al., 2005; Diana et al., 2007; Vilberg and Rugg, 2012), a kind of memory that supports recognition and that is characterized by the retrieval of study-related context-specific information (e.g., Yonelinas, 2002). Similarly, we also observed increased activity in the left putamen (BA 13), a region that has been shown to increase in activity during the encoding of novel face-name associations that led to subsequently successful associative recognition memory (Sperling et al., 2003).

Conjunction analysis

To ascertain whether deactivations in regions involved in priming overlapped with activations in regions involved in recognition memory, we performed a conjunction analysis (1) between item priming (recombined Priming < new Priming) and recognition (recombined Recognition > new Recognition) and (2) between associative priming (intact Priming < recombined Priming) and recognition (intact Recognition > recombined Recognition). Table 5 shows the conjunction for the item-specific contrasts. This revealed several overlapping regions, including the bilateral mOg (BA 19), inferior PFC (BA 47), and left fusiform gyrus (BA 37).

The conjunction analysis for the association-specific contrasts did not reveal any significant clusters. This absence of an overlap was surprising given our expectation of a hippocampal involvement in both conscious and unconscious associative memory (e.g., Henke, 2010; Hannula and Greene, 2012). We decided to perform an SVC within the hippocampi using the anatomical template provided in the AAL atlas (27 voxel-extent). Here, the left (−22, −16, −16; 68 voxels) and right (36, −18, −12; 18 voxels) hippocampus showed an overlap, although only the left cluster survived the cluster correction.

Two further analyses were also performed to investigate possible incidental recognition memory during the priming task, which may reflect a form of post-decision remembering. This was achieved, first, by running a conjunction analysis between recombinations showing greater activation than new item pairs during both the priming and recognition tasks, and, second, by running the same analysis but to see if intact pairs showed

TABLE 3.

Brain Regions Exhibiting Reduced (Top) and Increased (Bottom) Activation for Recombined Pairs Relative to New Item Pairs During the Associative Recognition Memory Task

Contrast	Region	Voxels	MNI coordinates			Z-scores
			x	*y*	*z*	
Recombined < New						
	L/R medial frontal gyrus (BA 10)	918	−10	54	−2	5.29
	L hippocampus	68	−28	−16	−20	4.21
	L middle temporal gyrus (BA 21)	137	−54	−6	−18	4.21
	L/R anterior cingulate cortex (BA 24)	256	−2	−12	42	4.16
	L supramarginal gyrus (BA 40)	108	−62	−26	20	3.79
	L precentral cortex (BA 4)	48	−18	−20	62	3.76
	R supramarginal gyrus (BA 40)	36	60	−50	34	3.74
Recombined > New						
	L lateral prefrontal cortex (BA 9,46)	1406	−46	30	28	5.53
	L precuneus (BA 7,40)	1984	−32	−46	38	4.82
	R inferior prefrontal cortex (BA 47)	456	32	24	−6	4.72
	R precuneus (BA 7,40)	1294	36	−62	46	4.49
	L/R anterior cingulate cortex (BA 6,32)	787	−6	18	42	4.35
	L middle frontal gyrus (BA 6)	48	−40	6	52	4.14
	L middle frontal gyrus (BA 10)	183	−40	46	−2	4.08
	R mid-lateral prefrontal cortex (BA 46)	201	48	36	20	3.77

Approximate Brodmann areas (BA) are given in parentheses. L = Left, R = Right.

greater activation than recombined pairs. The first conjunction yielded increased activity for recombined relative to new item pairs in the left precuneus (BA 7; −6, −66, 44), left medial frontal gyrus (BA 10; −30, 50, −2) and, at a more lenient threshold, left angular gyrus (BA 39; −38, −66, 40; $P < 0.001$, uncorrected). Importantly, no voxel survived the threshold value in the second conjunction (i.e., intact > recombined), even at more lenient thresholds.

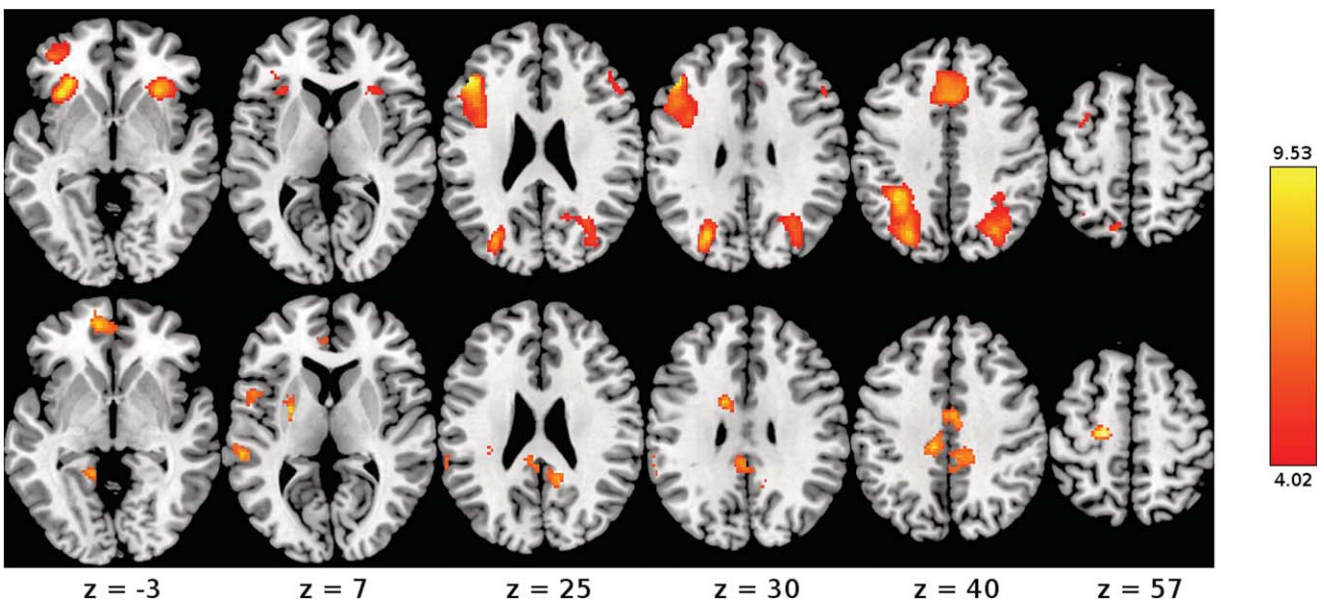

FIGURE 4. Brain regions exhibiting increased activation for recombined relative to new item pairs (top row) and intact relative to recombined pairs (bottom row) during the associative recognition memory task, overlaid on the MNI space structural image (*z* coordinates are shown in mm). Colorbar indicates range of T-values. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 4.

Brain Regions Showing Increased Activation for Intact Relative to Recombined Pairs During the Associative Recognition Memory Task

Contrast	Region	Voxels	MNI coordinates			Z-scores
			x	*y*	*z*	
Intact > Recombined						
	L putamen (BA 13)	179	−24	−4	10	4.96
	L precentral cortex (BA 6)	114	−18	−20	58	4.72
	L posterior cingulate cortex (BA 31)	178	−12	−24	36	4.34
	L superior temporal gyrus (BA 22)	117	−58	−34	8	4.16
	L anterior cingulate cortex (BA 24)	66	−16	2	30	4.15
	L medial frontal gyrus (BA 10)	175	−10	52	−2	3.99
	R posterior cingulate cortex (BA 23,31)	420	12	−50	24	3.83
	L/R posterior cingulate cortex (BA 6,24)	309	−4	−16	50	3.81
	L posterior parahippocampal cortex (BA 34)	46	−14	−46	−2	3.81
	L inferior prefrontal cortex (BA 44)	45	−50	8	6	3.54
	L supramarginal gyrus (BA 40)	33	−60	−34	20	3.33

Approximate Brodmann areas (BA) are given in parentheses. L = Left, R = Right.

ROI analysis

Considering the evidence of an involvement of the hippocampus in both priming for novel associations (e.g., Mayes and Montaldi, 1999; Yang et al., 2003; Carlesimo et al., 2005; Greene et al., 2007; Mayes et al., 2007) and associative recognition memory (e.g., Eichenbaum, 1997; Yonelinas et al., 2001, 2005; Giovanello et al., 2003), separate ROI analyses were performed on the association-specific (intact vs. recombined) and item-specific (recombined vs. new) effects in the bilateral hippocampus using the anatomical template provided in the AAL atlas.

Figure 5 (top) shows the plotted data for both tasks across all conditions. For the association-specific contrast, a 2 Hemisphere (right, left) × 2 Task (priming, recognition) × 2 Condition (intact, recombined) repeated-measures ANOVA only revealed a significant interaction between task and condition, $F(1,16) = 7.415$, $P < 0.05$, indicating that association-specific effects differed between tasks. The three-way interaction, however, showed a trend to significance, $F(1,16) = 3.28$, $P = 0.089$. Separate paired *t*-tests revealed that, for the priming task, hippocampal activity for intact pairs was reduced compared to the activity for recombined pairs in both the left, $t(16) = -3.22$, $P < 0.01$, and right, $t(16) = -2.650$, $P < 0.01$, hemispheres. In contrast, greater activity for intact pairs relative to recombined pairs was found for the recognition task, although this effect was only significant in the left hemisphere (left: $t(16) = 2.55$, $P = 0.01$; right: $t(16) = 0.60$, $P > 0.10$).

For the item priming contrast, a 2 Hemisphere (right, left) × 2 Task (priming, recognition) × 2 Condition (recombined, new) repeated-measures ANOVA only revealed a significant main effect of task, $F(1,16) = 14.853$, $P = 0.001$, with greater

TABLE 5.

Brain Regions Showing an Overlap Between the Item Priming Contrast (Recombined Priming < New Priming) and the Item Recognition Contrast (Recombined Recognition > New Recognition)

Contrast	Region	Voxels	MNI coordinates			Z-scores
			x	*y*	*z*	
Conjunction (item priming and recognition)						
	L middle occipital gyrus/precuneus (BA 7,19)	1021	−26	−72	28	5.99
	R middle occipital gyrus/precuneus (BA 7,19)	1000	32	−68	32	5.55
	L posterior prefrontal cortex (BA 46)	309	−44	12	28	4.66
	L inferior prefrontal cortex (BA 47)	281	−34	24	0	4.47
	R lateral prefrontal cortex (BA 46)	136	46	36	16	4.27
	R inferior prefrontal cortex (BA 47)	122	34	24	−6	3.95
	L fusiform gyrus (BA 37)	40	−48	−54	−12	3.69
	R anterior cingulate cortex (BA 32)	30	8	20	42	3.50

Approximate Brodmann areas (BA) are given in parentheses. L = Left, R = Right.

Hippocampus

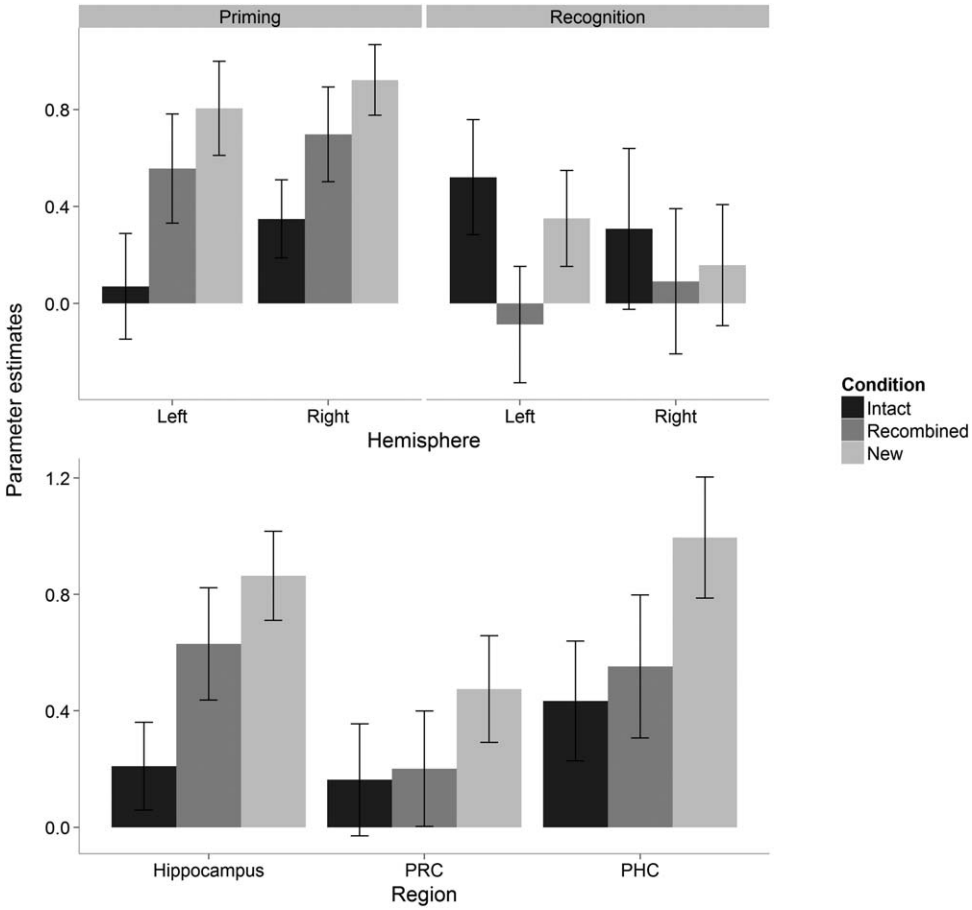

FIGURE 5. Top: Mean parameter estimates in the hippocampus for each task (Priming, Recognition) and condition (Intact, Recombined, New) separated by hemisphere. Bottom: Mean parameter estimates in the hippocampus, perirhinal cortex (PRC) and parahippocampal cortex (PHC) during the priming task for each condition (Intact, Recombined, New). Error bars represent the standard error of the mean.

activation of the hippocampus for the priming task (0.74) than for the recognition task (0.13).

We also wondered whether the neural associative priming effect in the MTLs would be specific to the hippocampus using this more sensitive ROI approach. As mentioned in the Introduction, a growing body of research has linked reduced activity in the PRC to item priming performance (e.g., Voss et al., 2008; Dew and Cabeza, 2013; Wang et al., 2014), so we questioned whether we could dissociate activity in the PRC from activity in the hippocampus relating to associative priming [we also included the PHC in this analysis since Yang et al. (2008) linked this region to associative priming]. Although the difference in activity between intact and recombined pairs in either the PRC, $t(16) = -0.222$, $P > 0.10$, or PHC, $t(16) = -0.652$, $P > 0.10$, failed to reach significance, activity in the hippocampus for intact pairs was substantially reduced compared with activity for recombined pairs, $t(16) = -3.402$, $P < 0.01$, indicating that only the hippocampus was sensitive to associative priming (see Fig. 5, bottom). Interestingly, reduced activity in both the PRC and PHC was observed for both intact and recombined pairs when contrasted to new pairs (all $ts > 1.672$), which suggests that these two structures were sensitive to the repetition of individual but not previously associated objects (i.e., only responded to item priming).

Functional connectivity anaylsis

Lastly, we performed functional connectivity analysis with key structures that were previously reported to be involved in item and associative priming and were also detected in this study. With respect to item priming, Dew and Cabeza (2013) recently reported connectivity between the right PRC and right PFC/cuneus that was increased for primed relative to unprimed items in a masked priming paradigm. Thus, we analysed connectivity using the right PRC as a seed. Of note, connectivity increased during recombined relative to new pairs in the left middle/superior temporal gyrus (BA 39), right fusiform gyrus (BA 19), left insula (BA 13), left cingulate gyrus (BA 31), and precuneus/cuneus (see Table 6). Interestingly, decreased activity in these regions has been consistently associated with item recognition based on familiarity (e.g., Montaldi et al., 2006),

TABLE 6.

Brain Regions Showing Connectivity with the Perirhinal Cortex During Item Priming

Contrast	Region	Voxels	MNI coordinates			Z-scores
			x	*y*	*z*	
PPI (item priming)						
	L middle/superior temporal gyrus (BA 39)	495	−56	−54	14	4.27
	L middle temporal gyrus (BA 21)	38	−60	−16	−8	4.22
	R fusiform gyrus (BA 19)	64	38	−48	−6	4.02
	R putamen	50	32	10	4	4.00
	L posterior cingulate gyrus (BA 31)	37	−20	−46	24	3.99
	L insula (BA 13)	52	−46	−26	20	3.55
	R precuneus/cuneus (BA 31)	168	4	−76	30	3.55

Approximate Brodmann areas (BA) are given in parentheses. L = Left, R = Right

again suggesting that item priming and item recognition may involve similar structures.

For associative priming we used the left hippocampal cluster detected in the conjunction analysis (−22, −16, −16; 68 voxels) as a seed, since we could look at connectivity during both associative priming and recognition using the same seed region. For associative priming, there was greater connectivity for intact relative to recombined pairs in the right caudate (16, −6, 24; 31 voxels), a region important for the establishment of stimulus-response (S-R) associations during associative learning tasks (Winocur and Eskes, 1998), whereas for associative recognition, we observed functional connectivity between the left hippocampus and the left superior frontal gyrus (BA 10; −12, 56, 22; 52 voxels).

Given that the whole-brain analysis revealed a cluster in the mOg that is associated with perceptual processing, whereas associative recognition involved regions involved in semantic memory (e.g., left inferior frontal cortex), we decided to apply a more lenient threshold ($P < 0.005$, uncorrected) to ascertain whether connectivity in associative priming and recognition would be increased in mainly perceptual and semantic regions, respectively. Indeed, associative priming involved regions mostly linked with perceptual processing, such as the right middle/superior occipital gyrus (24, −70, 48) and left PHC (−18, −32, −8; see Fig. 6, red). It is interesting to note that the PHC has been previously associated with associative priming based on perceptual processing (Yang et al., 2008), and our whole-brain analysis also suggested a role of the right mOg in associative priming (see Fig. 3). For associative recognition we further observed a cluster in the left ventral lateral PFC (BA 45; −42, 28, 2; see Fig. 6, green), a region that has been previously implicated in the retrieval of semantic relational memory (e.g., Prince et al., 2005).

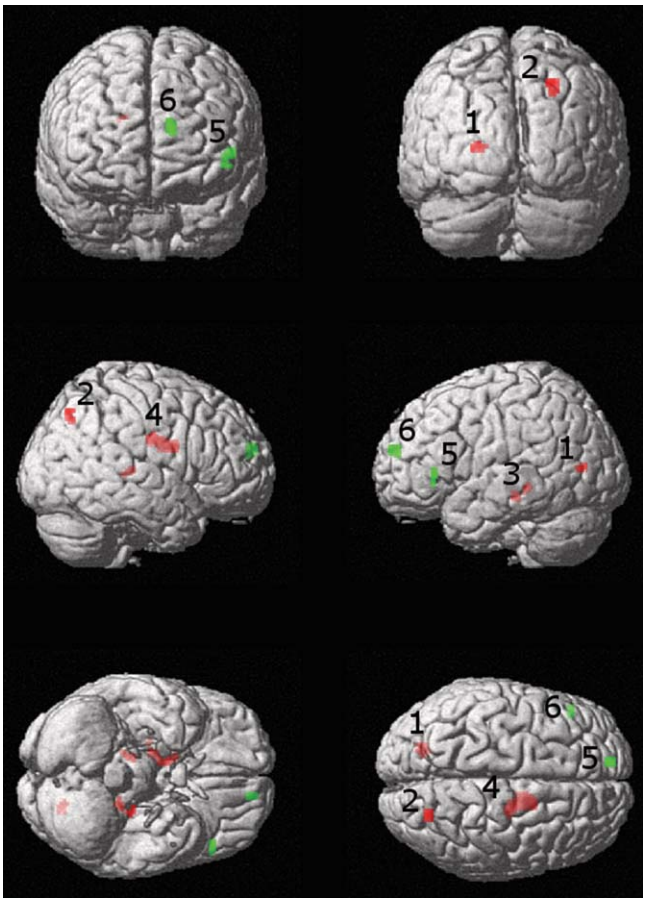

FIGURE 6. Surface rendering of brain regions showing connectivity with the left hippocampus (seed region) that was greater for the intact relative to the recombined condition during associative priming (red) and associative recognition (green). 1: left middle occipital gyrus/cuneus; 2: right middle/superior occipital gyrus; 3: left parahippocampal cortex; 4: right caudate; 5: left ventrolateral prefrontal cortex; 6: left superior frontal gyrus. Note: values are shown at $P < 0.005$, uncorrected, for displaying purposes; only clusters 4 and 6 survived correction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DISCUSSION

This study compared the neural correlates of novel associative and item priming and equivalent forms of recognition. An

associative size-judgement task was administered at both study and test phases of the priming session, whereas for the recognition session, the size-judgement task was followed by an associative recognition memory task. Significant associative (faster RTs for intact vs. recombined pairs) and item (faster RTs for recombined vs. new pairs) object priming were observed. Associative priming was accompanied by reduced neural activity in the right mOg (BA 19) and the bilateral hippocampus, whereas item-specific priming was accompanied by reduced activity in extensive occipitotemporoparietal regions, including the mOg (BA 19), fusiform gyrus (BA 37), precuneus (BA 7) and PRC (but not hippocampus). Reduced activation was only found with item priming in the left posterior (BA 9) and inferior PFC (BA 46,47) where it correlated with across-participant priming. This partial nonoverlap of the neural correlates of associative and item priming was further supported by the distinct functional connectivity of the hippocampus and PRC found for the two kinds of object priming: whereas associative priming showed functional connectivity between the hippocampus, caudate nucleus and, at a more lenient threshold, PHC, and middle/superior occipital gyrus, item priming showed functional connectivity between the PRC, superior temporal and middle temporal cortices, right fusiform gyrus, right putamen, precuneus/cuneus, and left insula.

Successful associative recognition memory was related to increased activity in several brain regions, such as the left inferior PFC (BA 44), posterior cingulate cortex (BA 6,24) and PHC, where activity typically accompanies recollection. This activity occurred in spatially distinct regions from those showing associative priming. A conjunction analysis, however, did find an overlap in the hippocampus, although the overlap comprised deactivation and activation for associative priming and recognition, respectively. Both item recognition and priming recruited similar brain regions, although, like associative memory, the BOLD response was in opposite directions.

Some of these respective activations and deactivations probably indicate the neural correlates of the information represented in memory. If true, this suggests that associative recognition and priming are supported by largely distinct kinds of stored information derived from the same kinds of recognition and priming stimulus pairs. At present, we can only speculate about the causes of these differences by using reverse inference (Poldrack, 2006). One possibility is that associative recognition depends more on semantic aspects of the object association. This is consistent with our finding that the overlapping hippocampal region functionally connected with a left ventrolateral PFC region (BA 45; −42, 28, 2) only with associative recognition. Activity here has been related to controlled retrieval of semantic relational memory (e.g., Prince et al., 2005, −42, 26, 2). Associative priming may, however, depend more on perceptual aspects of the object association and perhaps, relatedly, on an S-R link to the decision that largely bypasses the need for semantic processing. The tuned/reduced visual processing required is consistent with only associative priming showing a hippocampal functional connection to the middle/superior occipital gyrus, although the absence of this connection with associative recognition may be a power issue because of the lack of an mOg activation found with this kind of memory. The S-R dependence is consistent with the repetition of the stimulus-decision pairing at study and test, the location of a weak PFC deactivation during the whole-brain analysis (e.g., Horner and Henson, 2008; Race et al., 2009), and the observation of a hippocampus-caudate connectivity (Winocur and Eskes, 1998).

In contrast to associative recognition and priming, the results suggest that item recognition and priming depend on much more similar kinds of stored information extracted from item stimuli. Item recognition probably depended on some recollection as well as item familiarity, but the failure to find any significant recognition-related functional connections of the PRC was probably because this region was not affected by item familiarity. The functional connections of this cortex found with item priming broadly corresponded with the regions modulated by different levels of scene familiarity in the study of Montaldi et al. (2006). In that study, scene and object familiarity as well as item object priming in our study were accompanied by PRC deactivation. Given this similarity of the BOLD response's direction and unlike associative recognition and priming, therefore, it is less clear whether item recognition and item priming involve different retrieval mechanisms. However, both this and the other interpretations just outlined can be challenged so they will now be discussed in greater detail with particular emphasis on the possible roles of MTL structures in different kinds of object priming and recognition.

Object Associative Priming and Recognition: The Role of the Hippocampus

It has been disputed whether associative priming critically depends on the hippocampus as does recollection, the form of aware associative memory believed to support both item and associative recognition (Mayes et al., 2007). Strong support for a critical hippocampal role in associative priming requires not only fMRI, but also evidence that relatively selective hippocampal damage disrupts such priming. Currently, the strongest evidence for this is provided by the study of Duss et al. (2014). Following extensive work of this group using fMRI that found hippocampal activity changes when associative priming occurred (e.g., Reber et al., 2012), Duss et al. again performed an associative priming fMRI study, which included a group of patients with variable, but often extensive hippocampal lesions as well as a matched control group. Like this group's other work, a subliminal presentation procedure was used. Unrelated word pairs from different semantic categories were presented at encoding, whereas at test novel semantic neighbors of the subliminally encoded words were used that either retained their semantic relations (e.g., study: violin-lemon; test: cello-mandarin) or were recombined (e.g., study: violin-lemon and table-car; test: harp-truck). Priming was indicated by participants judging new exemplars of each studied category pair to be more semantically related than were novel exemplars from recombined categories; this result must have depended on very

flexible recollection of the subliminally studied pairs. Not only did associative priming change activity in the hippocampus, the patients failed as a group to show reliable associative priming. Interestingly, three patients did succeed in showing relatively normal associative priming but the imaging evidence strongly suggested that these effects were supported by residual functional hippocampal tissue in these mildly impaired patients.

As these three patients' recollection-related memory was very impaired, the authors proposed that associative priming is an unconscious form of the recollection memory that strongly supports associative recognition, but that recollection is a much "stronger" form of relational memory than is associative priming. These strong and weak forms of the same kind of memory are supported by an extended hippocampal system (that minimally includes the anterior thalamus), but successful working of strong relational memory depends on this system working at a much higher level of efficiency than is needed for relational priming. Therefore, whereas recollection is disrupted even by mild hippocampal dysfunction, weak memory is only disrupted by much greater levels of hippocampal dysfunction. This may explain some reports of intact supraliminal associative priming in some amnesiacs if these have insufficient hippocampal damage to disrupt very weak and unconscious associative memory (e.g., Verfaelllie et al., 2012).

Our kind of associative priming differed from that of Duss and coworkers because it, like most priming tasks, depended on supraliminal presentations at study and test, so the associative memory produced should have been somewhat stronger. It is also less clear what, if any, information needed to be recollected to produce the relative size judgement more quickly, because the studied pairs were re-presented at test, although information related to the two objects' relative sizes may have unconsciously cued recollection of the correct decision. This recollection may have involved the retrieval of less information, needing less flexibility than did Duss et al.'s subliminal priming task. Whether related to these two differences or not, associative priming in our task was accompanied by hippocampal deactivation, whereas the subliminal study found hippocampal activation in its control participants (although the three patients who showed associative priming did show a hippocampal deactivation).

It is unclear what this difference in the healthy control direction of hippocampal activation between subliminal and supraliminal associative priming means. A plausible possibility is that, although both involve unconscious forms of associative memory, only subliminal associative priming involves a weak semantically dependent recollection-like memory function. Supraliminal associative priming may involve a different kind of hippocampally dependent retrieval function for weak and unconscious, but supraliminally encoded and tested, associative memory. Some evidence already considered suggests that hippocampal (or at least MTL) lesions disrupt supraliminal forms of associative priming (e.g., Yang et al., 2003; Carlesimo et al., 2005), although these claims can be disputed. Even if the evidence is confirmed however, the currently incomplete understanding of the BOLD effect's neural underpinnings weakens confidence in interpreting changes in opposite directions, particularly given that Duss et al.'s three well-performing patients showed a hippocampal effect opposite in direction to their controls. This surely did not indicate they were using different kinds of retrieval function, although some functional difference must have been indicated by the reversal of the controls' directional change.

In our study, although nonoverlapping left PFC and occipital regions changed their activity with both associative priming and recognition, priming alone showed functional connections between the overlapping hippocampal region and the perceptual processing mOg region as well as the PHC, which was associated with Yang et al.'s (2008) perceptual form of associative priming (see also Prince et al., 2005). The primarily right-sided mOg deactivation fits well with evidence that the right hemisphere is more concerned with processing specifically perceptual representations (e.g., Marsolek, 1995; Marsolek and Hudson, 1999). In contrast, associative recognition alone showed connections to a ventrolateral PFC region associated with semantic relational information (e.g., Prince et al., 2005). This suggests that associative priming drew more on associative perceptual information, whereas associative recognition drew more on semantic information. These different functional connections of associative priming and recognition from a common mid-posterior left hippocampal region correspond well to Prince et al.'s finding that this region is linked to successful semantic as well as perceptual encoding and retrieval (but see Giovanello et al., 2004, for a different proposal). This correspondence, therefore, further supports the argument that our associative priming and recognition tasks involve the retrieval of largely nonoverlapping perceptual and semantic information, respectively.

It is reasonable to suppose, given that the three encoding trials involved making the relative size judgement three times, that, at test, the speeded decision depends on participants using perceptual aspects of the two objects to cue rapid recall of the appropriate decision, largely bypassing the need for semantic processing, consistent with S-R accounts of some forms of item object priming (e.g., Dobbins et al., 2004; Horner and Henson, 2008, 2011; Race et al., 2009). Interestingly, our associative priming task was accompanied by weak left PFC deactivation that was close to the region identified by Dobbins et al. (2004) as relating to an S-R form of item priming (BA 45, *pars triangularis*). However, assuming that the hippocampal effect is driven by recollection with the associative recognition task and an unconscious recollection-like retrieval function with associative priming, it is hard to see how retrieving different information can explain the different direction of the hippocampal response with associative priming and recognition.

Given that familiarity, unlike recollection but like priming, is often related to deactivation of potentially mediating structures, including MTL structures, such as the PRC (e.g., Montaldi et al., 2006), it is tempting to argue that associative familiarity exists, depends on the hippocampus, and deactivates it. If so, our associative priming task may have involved a weaker and unconscious (below threshold) associative familiarity-like form of memory (see Berry et al., 2012, for a

similar account of item priming and recognition). There are several problems with this proposal when applied to associative memory. Mayes et al. (2007) and Montaldi and Mayes (2010) have argued that, although some forms of associative familiarity exist, they depend on kinds of input processing that stress similarities of these inputs to other inputs, which only the neocortical components of the MTL can perform. So, provided the components to be associated can be bound in these neocortical regions, then these forms of associative familiarity will be found. If informational components do not converge until they reach the hippocampus, the distinct microstructure of this archicortical structure processes its inputs so as to stress differences rather than similarities and this supports recollection, not associative familiarity (see Montaldi and Mayes, 2010). Therefore, if the relevant components that support faster relative size judgements only converge in the hippocampus, they should support weak and unconscious recollection, not a subthreshold (unconscious) form of associative familiarity-like memory.

Inconsistently with this, Smith et al. (2014) recently postulated that the hippocampus supports both recollection and associative familiarity that links items to their study context. There is, however, no evidence for their view, although it must be admitted that it is very difficult to test for associative familiarity with convincing control procedures and even more difficult to determine which MTL structures are affected by it (see Montaldi and Mayes, 2010). Until good evidence for this is provided, it is otiose to hypothesise that associative priming involves a weak familiarity-like form of memory. In addition, as argued above, our associative priming task probably depends on a speeded response based on perceptual features that link the two studied objects, rapidly cueing unconscious "recall" of the correct relative size judgement.

The mechanism underlying the hippocampal deactivation found with associative priming remains unexplained. However, as the hippocampal activations shown by Duss et al.'s well-performing patients suggest, factors distinct from the kind of retrieval function may change the direction of activation (see also Kafkas and Montaldi, 2014). However, one other kind of explanation can probably be rejected. This is that the hippocampal deactivation is an artefact of incidental recollection. The use of three study trials suggest that some recollection and familiarity would have been present for some of the stimuli, although, given that recollection is usually effortful, its levels should have been considerably below the associative recognition levels found in the intentional recognition task. This recollection would probably not have primed fluency because it took appreciably longer than the primed responses. However, it could have confounded associative priming effects in the hippocampus because this might have happened even if recollection occurred after the primed response was completed. However, this argument simply does not work because associative recognition of the intact vs. recombined stimulus pairs was accompanied by hippocampal activation (indicative of greater recollection in the intact condition). If this had occurred sufficiently in the associative priming condition, it would have reduced hippocampal deactivation, eliminated it altogether or even reversed it, not artefactually caused it.

A more plausible confound is that the recombination priming condition was accompanied by associative novelty detection that triggered enhanced encoding to produce better subsequent recollection for recombined relative to intact pairs. This should have produced more hippocampal activation for recombinations, which would have caused an associative priming hippocampal deactivation. These possibly enhanced encoding effects may have also been amplified by recall-to-reject occurring in the recombined priming condition so as to produce more hippocampal activity than in the intact condition. Although this enhanced subsequent recollection encoding effect was not apparent in the associative recognition contrast, this could have been because the intact pair recollection activation was greater than any recombined pair encoding subsequent recollection memory activation. In our view, this explanation remains as unproved as our interpretation that the hippocampal deactivation reflects true unconscious associative memory. It cannot explain why participants, concentrating on making fast and accurate relative size judgements would have had sufficient time to identify associative (not item!) novelty and, even if they did, pay enough attention to it to enhance their encoding of associative information connected with the tested pair so as to support superior recollection. Nevertheless, we have not eliminated this possibility, so more work is needed to determine which interpretation is correct.

Item Object Priming and Recognition: The Role of the PRC

Item object priming in our task was indicated by how much faster relative size-judgement RTs were for recombined compared to new object pairs. This procedure differs from what is standardly used with priming for individual objects, which involves participants making timed judgements, such as whether previously studied single objects are larger than a shoebox (e.g., Horner and Henson, 2008). The brain activity changes accompanying item object priming in our task did, nevertheless, seem very similar to those found with the typical kind of single-object priming tasks that rely on speeded absolute judgements. First, we found that large occipitotemporal regions (e.g., mOg, fusiform gyrus) showed significant repetition deactivations, as commonly observed in item repetition priming studies involving classification judgements (e.g., Koutstaal et al., 2001; Vuilleumier et al., 2002; Dobbins et al., 2004; Horner and Henson, 2008, 2011). Furthermore, the close correspondence between our neural priming effects and those in the aforementioned studies is noteworthy (e.g., left fusiform in our study: −30, −56, −20; left fusiform in Dobbins et al. study: −24, −57, −15). Deactivation in these regions may relate to facilitation of perceptual processes, as the same pictures of objects were presented at both study and test phases. Moreover, our item object priming task involved deactivations in left PFC regions that play a role in both semantic processing (BA 9,47) as well as S-R learning (BA 45) (e.g.,

Horner and Henson, 2008; Race et al., 2009), so it was notable that activity levels in both regions were the only ones to predict priming levels across participants. These findings suggest that our item priming task involved unconscious memory for not just visuoperceptual aspects of the object stimuli but also semantic and rapid S-R-based retrieval of previously encoded decisions.

Most importantly, with focused analyses, unlike with associative priming, no deactivation was found in the hippocampus, but a region of the PRC was found to deactivate that was close to a region Wang et al. (2014) found to deactivate with a word-based semantic priming task (e.g., right PRC in Wang et al. study: 24, −9, −45; right PRC in our study: 34, −12, −30). Wang et al. (2010) had previously found that semantic word priming was disrupted in patients with lesions extending into the PRC, but not with hippocampal lesions that did not extend this far. The maximal overlap was in the same region that deactivated with priming. This suggests that item-based semantic priming depends on this PRC region but not on the hippocampus. Wang et al. (2014) argued that the PRC may play a key role in mediating item familiarity memory as well as item semantic priming because they found that item priming and familiarity were accompanied by deactivation in an overlapping region of the PRC. PRC deactivation often accompanies word familiarity (but see Yonelinas et al., 2005) as well as object and scene familiarity (e.g., Montaldi et al., 2006). This is consistent with item priming and item familiarity memory depending on overlapping neural mechanisms, at least those mediated by the PRC.

Familiarity depends on a poorly understood connected system of brain structures, central to which is the PRC. This leaves open whether item priming and familiarity either just share PRC process(es) or whether item priming is a weak, subthreshold and hence unconscious form of item familiarity. If the latter is true, then there should be extensive overlapping and correspondingly increased activity in structures functionally connected to the PRC with both item object priming and familiarity in our task. Although we did not measure familiarity directly with our somewhat atypical recognition task, which was not accompanied by significant PRC deactivation, performance on it should have depended strongly on item familiarity. Consistent with this, both our recognition task and object and scene familiarity tasks (e.g., Montaldi et al., 2006; Kafkas and Montaldi, 2014) were accompanied by activations in overlapping extra-MTL sites that included the middle frontal gyrus, left precuneus, bilateral angular gyrus, supramarginal gyrus and anterior cingulate cortex. This overlap indicates the robust contribution of item object familiarity to our task.

We also observed overlapping neural effects between item object priming and recognition in the bilateral mOg (BA 19), bilateral PFC (BA 46/47), left fusiform gyrus (BA 37) and anterior cingulate gyrus (BA 32), although priming was accompanied by deactivations, whereas recognition was accompanied by activations. However, increased activity in overlapping regions of the bilateral precuneus (BA 7), left medial frontal gyrus (BA 10) and the left angular gyrus (BA 39) accompanied both item priming and recognition. Many regions showing effects in our item object priming and recognition tasks overlapped extensively with those affected during object and scene familiarity (e.g., Montaldi et al., 2006; Kafkas and Montaldi, 2014).

Two broad kinds of interpretation are possible. The first assumes that the effects indicate the neural bases of item priming. The second indicates that at least some of the effects are confounds of incidental familiarity memory that accompanied object priming. If the first interpretation is correct, then object familiarity and priming may share similar processing in a number of structures. These may include the PRC, where object information is integrated at a high level and stored in a way suitable for both priming and familiarity. Processing also seems to be shared in several other structures. Some of these may also be concerned with mediating object memory representations, but others may support distinct kinds of essential processing. However, the literature and our data suggest that there must also be processing differences between item familiarity and priming. This is suggested when overlapping effects are in opposite directions and also when priming and familiarity effects occur at different sites (e.g., Donaldson et al., 2001; Voss et al., 2009).

Supraliminal item priming is usually accompanied by deactivations, and activations have often been interpreted as owing to incidental explicit memory (Henson, 2003). Increased activity for recombined pairs relative to new item pairs was also observed during both the item priming and recognition tasks in the bilateral precuneus, left medial frontal gyrus and left angular gyrus - brain structures previously implicated in familiarity memory (e.g., Montaldi et al., 2006). This suggests that incidental familiarity probably occurred during our priming condition, especially considering the supraliminal nature of the three study trials and the minimal effort typically needed for this form of explicit memory. Even if it occurred immediately following the making of the primed response (e.g., Badgaiyan et al., 1999, 2001; Gooding et al., 2000; Henson, 2003) so that it could not have mediated priming, it could still have artefactually produced apparent priming activations because of the poor temporal resolution of fMRI (Henson, 2003). It may also have produced the PRC deactivation because this is sometimes found with familiarity, although the lack of such an effect with our particular recognition task makes this unlikely. When item priming and recognition (and also familiarity) effects overlapped but were in opposite direction, there may have been similar representations being made, but also a suggestion of different memory processes.

Work will be required to determine which broad interpretation is nearer the truth. It seems unlikely that item familiarity can artefactually drive priming task performance such as ours so lesion studies of patients with relatively selective PRC lesions should help resolve this issue.

CONCLUSION

For the first time, we observed a hippocampal deactivation linked to fluency-based supraliminal associative priming, whereas associative recognition was characterized by typical

activations in recollection-related regions, including the hippocampus. If the hippocampal deactivation that accompanied associative priming is not an artefact of incidental recollection in the intact condition, of associative-novelty-detection-triggered enhanced encoding of subsequent recollection in the recombined condition, or even of the incidental and unproved occurrence of hippocampally mediated associative familiarity, then the deactivation reflects a kind of memory retrieval. Whether this is a weak kind of recollection as Duss and coworkers have argued for subliminal associative (relational) priming or a new kind of associative retrieval remains unresolved and will require further investigation. Relatedly, the general directional-difference of BOLD response found with associative recognition and priming (i.e., activations vs. deactivations) is interesting and may suggest different processing roles and/or brain mechanisms underlying these two kinds of memory. Future research will be needed to determine more precisely the source of these differences.

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