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Pre-stimulus Neural Activity Predicts Successful Encoding of Inter-Item Associations

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Abstract

fMRI was employed to investigate the relationship between pre-stimulus neural activity and associative encoding of words and pictures in humans. While undergoing scanning, subjects studied randomly interleaved word or picture pairs. A pre-stimulus cue preceded the presentation of each study pair, and signaled whether it would comprise words or pictures. Memory for the study pairs was later tested with an associative recognition test, which comprised word or picture pairs presented either in the same (intact) or a different (rearranged) pairing as at study, along with pairs of new items. The critical fMRI contrast was between study activity associated with pairs later correctly judged intact and pairs incorrectly judged as rearranged. A key question was whether material-selective pre-stimulus encoding effects could be identified which overlapped regions selectively activated by the respective study material. Picture-selective pre-stimulus effects were identified in bilateral fusiform and the intraparietal sulcus (IPS), whereas wordselective effects could not be identified. Material-invariant pre-stimulus subsequent memory effects were also identified in several neocortical regions, as well as in the hippocampus. Whereas the loci of the neocortical effects suggest that they reflect the benefit to encoding that accrues from engagement of cognitive control processes, their magnitude was negatively correlated acrosssubjects with associative recognition performance, and positively related to false alarm rate. Conversely, the hippocampal effects also predicted unique variance in associative memory, and were negatively related to hit rate. It is suggested that the neocortical pre-stimulus effects may reflect encoding processes that increase familiarity of single items, whereas the hippocampal prestimulus effects are proposed to reflect either the encoding of task-irrelevant features or the retrieval of task-relevant information associated with the pre-stimulus cues. Overall, the results provide evidence that pre-stimulus processes may be deleterious, rather than beneficial, to associative encoding.

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Keywords

Pre-stimulus; Associative Memory; fMRI; Neocortex; Hippocampus

1.1 Introduction

Beginning with Brewer et al. (1998) and Wagner et al. (1998), the subsequent memory procedure has proven an effective approach to investigating the neural correlates of memory encoding with functional magnetic resonance imaging (fMRI; for a review see Kim, 2011). Most studies employing the procedure have investigated encoding effects that reflect processes engaged following the onset of a study item. A few studies, however, have employed the procedure to investigate whether neural activity occurring *before* the onset of a study item differs according to later memory performance (e.g. Fernandez et al., 1999; Adcock et al., 2006; Park and Rugg, 2010). Each of these studies identified 'pre-stimulus memory effects' in the hippocampus or adjacent regions of the medial temporal lobe. Along with convergent evidence from event-related potential (ERP) studies (e.g. Otten et al., 2006; Gruber and Otten, 2010), these findings indicate that neural activity preceding a study event can be predictive of later memory performance and, perhaps, causally related to it (Yoo et al, 2012). They also raise the possibility that, on occasion, pre-stimulus effects (Otten et al., 2006, Park and Rugg, 2010).

To date, studies of pre-stimulus subsequent memory effects have been limited to encoding of single study items. Here, we investigated the encoding of item-item associations. We employed a design that allowed us to ask whether an important principle emerging from studies of post-stimulus encoding generalizes to the pre-stimulus domain. There are several reports that successful encoding of different classes of study materials or contextual features is associated with material- or feature-selective subsequent memory effects that overlap regions engaged during the on-line processing of the same information, and this is consistent with a prediction derived from a widely accepted theoretical framework (reviewed in Rugg et al., 2008) - namely, that subsequent memory effects should be evident in neural regions engaged during the on-line processing of the study items -. Of particular relevance to the present experiment is the study of Park and Rugg (2011), in which subsequent memory effects for word-word and picture-picture associations were contrasted. Whereas effects common to both classes of material were evident in the left inferior frontal gyrus (LIFG) and hippocampus, picture-selective effects were identified in bilateral fusiform regions preferentially activated by pictures, while word-selective effects were identified in a wordsensitive left lateral temporal region. Thus, as with the encoding of single items, successful associative encoding is linked to enhanced activity in material-selective cortical regions¹.

Here, we employed the same approach as in Park and Rugg (2011), but with a design that permitted investigation of pre- as well as post-stimulus encoding effects. Based on prior findings (see above) we expected that the hippocampus would demonstrate material-

 $^{^{1}}$ While regions comprising the MTL (such as the hippocampus) are indeed cortical tissue, for the purposes of the current study we use the terms 'hippocampal' and 'cortical' as shorthand to refer to effects in the hippocampus and neocortex, respectively,

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independent pre-stimulus effects. A key question was whether material-selective prestimulus subsequent memory effects could also be identified, and whether they overlapped regions selectively activated by the respective study material. Furthermore, if these effects overlap with the analogous post-stimulus effects, it would suggest that memory encoding benefits from 'pre-activation' of domain-selective cortical regions, as has been reported for attentionally-cued perceptual judgments (e.g. Ferrera et al., 1994; Luck et al., 1997; Chawla et al., 1999).

In addition to investigating material-selective pre-stimulus associative subsequent memory effects, we also aimed to extend prior studies of pre-stimulus encoding effects more generally by characterizing material-invariant effects. Prior studies have focused on pre-stimulus effects localized to the medial temporal lobe (MTL) and sub-cortical structures (Adcock et al., 2006; Park & Rugg, 2010; Fernandez et al., 1999; Yoo et al., 2012), with little or no mention of any effects localized to regions outside the MTL. In the present study, we characterize both MTL and neocortical material-invariant subsequent associative memory effects, and shed light on their possible functional significance by relating the effects to subsequent memory performance.

2.1 Materials and Methods

2.2 Subjects

Twenty-seven right-handed English speakers (mean age: 23 years; range: 18-28; 14 males) were recruited from the University of Texas at Dallas (UTD) and surrounding communities. All subjects were free from neurological or psychiatric disorder. They gave informed consent prior to participating, and were renumerated for their participation in accordance with the human subjects procedures approved by the University of Texas Southwestern Medical Center and the University of Texas at Dallas. Six subjects were excluded from the analyses described below because of insufficient trial numbers for one or more events of interest. One additional subject was excluded due to excessive signal dropout in the temporal lobes.

2.3 Materials

Experimental items were drawn from the same pool that was employed by Park & Rugg (2011) in their study of material-selective subsequent associative memory effects (see section 1.1 Introduction). The critical item pairs were created from pools of 360 concrete words and 360 pictures of nameable objects. The pool was used to form 360 pairs of items, 180 of which comprised two words (word-word pairs), and 180 two pictures (picture-picture pairs). For each subject, 120 pairs of each format served as study items. These pairs were intermixed with the remaining 60 pairs of each format to form a corresponding test list. Item pairs were rotated across subjects such that each pair served equally frequently as a studied or an unstudied (new) pair.

2.3.1 Study Procedure—The 240 study pairs were visually presented during fMRI scanning of an intentional study phase that was divided into 4 consecutive blocks separated by intervals of approximately one to two minutes. The pairs were presented at the center of a

display monitor above and below a central fixation character. The position of the items in each pairing (top or bottom) was counterbalanced across participants. Subjects were required to judge 'which item would fit inside of the other?' and to signal their judgment with one of two button presses that corresponded to the top or the bottom item respectively. Instructions were to make the judgment as quickly as possible without sacrificing accuracy, and subjects were also informed that their memory for the study pairs would later be tested. Practice on the study task was provided outside the scanner using items additional to those described above, and which were not included at test.

As is illustrated in Figure 1, each study trial began with a cue ('x' or 'o') that signaled (with 100% validity) whether the upcoming study pair comprised pictures or words. Instructions were to attend to each cue and use it to prepare for the upcoming size judgment. A reminder was given that memory for the study items would be tested later. Each cue was presented for a duration of 1s, and was replaced by a central fixation cross that remained present until the onset of the study pair. The interval from cue offset to study pair onset varied pseudorandomly between 1s, 3s, and 5s, giving cue-item intervals of 2, 4, and 6 s respectively. Study pairs were presented for 1.3s, and were followed by another fixation period that varied pseudo-randomly between intervals of 2.5s, 4s and 5.5s. The variables of pair format (word or picture), cue-pair interval, and inter-trial interval were each constrained so that repeats of any of these variables did not occur more than three times in a row, and equal numbers of the different possible cue-item and item-cue intervals occurred in each study block. Two buffer trials were presented at the beginning of each of the four study blocks, each of which lasted for approximately 10 minutes. After completion of the study phase, subjects were escorted from the scanner, given a ten minute rest break, and then commenced the retrieval test.

2.3.2 Test Procedure—Subjects were tested outside of the scanner. Test items comprised the 240 pairs of studied items (120 in each format), intermixed with 120 new pairs (60 in each format). Of the 240 pairs of studied items, 160 (80 in each format) remained in the same pairing as at study ('intact' items) while the items belonging to the remaining 80 pairs (40 in each format) were rearranged such that each was paired with an item presented on a study different trial ('rearranged' items). Presentation location (above or below fixation) of the items comprising both intact and rearranged pairs was maintained between study and test. The 360 test trials were separated into four blocks. No pair type was presented more than three times in a row.

Each test trial began with the presentation of a central fixation character for 1s. This was followed by the presentation of the test pair, which remained on the screen until a response had been given. The instructions were to judge whether the items had been paired together at study (intact judgment), had been presented at study but on separate trials (rearranged judgment), or had not been presented at study (new judgment). The test was self-paced, with a 2.5s interval inserted between each response and the onset of the subsequent trial. Subjects were instructed to respond as quickly as possible without sacrificing accuracy. They were also instructed to respond conservatively when unsure of the correct judgment, that is, to respond 'rearranged' when uncertain if a test pair was intact, and 'new' if uncertain about the study status of one or both items.

2.4 MRI data acquisition

T1-weighted anatomical images (240×240 matrix, 1 mm isotropic voxels) and blood oxygenation level-dependent (BOLD), T2*-weighted echoplanar functional images (SENSE factor of 1.5, flip angle 70°, 80 × 80 matrix, FOV = 24 cm, TR = 2000 ms, TE = 30 ms) were acquired with a 3T Philips Achieva MRI (Philips Medical Systems) scanner equipped with a 32 channel receiver head coil. Two hundred and ninety three functional volumes were acquired during each of the four study blocks, for a total of 1172 volumes. Each volume comprised 33 slices oriented parallel to the AC-PC (anterior/ posterior commissure) line (thickness 3 mm, 1mm interslice gap, 3mm isotropic voxels) acquired in an ascending sequence. The first 5 volumes of each scanning session were discarded to allow equilibration of tissue magnetization.

2.5 MRI data processing

Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK), run under Matlab R2011a (MathWorks) was used for fMRI data analysis. Functional images were subjected to realignment (to the mean image), slice timing correction (using the middle slice as the reference), reorientation, spatial normalization to a standard echoplanar template [based on the Montreal Neurological Institute (MNI) reference brain; (Cocosco, 1997)] and smoothing with an 8 mm full-width half-maximum Gaussian kernel. Each subject's structural volume was normalized to the MNI T1 template before averaging to create an across-subjects (N = 20) mean image. The time series in each voxel was high-pass filtered to 128 Hz to remove low-frequency noise and scaled within-session to a grand mean of 100 across voxels and scans. Results are reported in MNI coordinate space.

2.6.1 MRI data analysis—The model used for the principal first level analysis was very similar to that employed by Park & Rugg (2010). It comprised a General Linear Model (GLM) in which cue-related activity was modeled with a variable boxcar function that onset concurrently with the cue. The boxcar tracked the duration of the cue-item interval (2, 4, or 6 s), and was convolved with a canonical hemodynamic response function (HRF) to model the predicted BOLD response (Friston et al., 1998). Stimulus-related activity was modeled as a delta function onsetting synchronously with the onset of each study pair. It too was convolved with a canonical HRF. Because this model included both pre- and post-stimulus regressors we refer to it as the 'cue and stimulus' model. To allow comparison of our data with the findings of the study that motivated the present experiment (Park and Rugg, 2011) (see 1.1 Introduction), we also employed a second analysis model in which only stimulus-related activity was modeled (hereafter the 'stimulus-only' model) (see Park & Rugg (2010) for a similar approach). Finite impulse response (FIR) models were employed to estimate the time-courses of effects identified by the two GLMs (see below).

Two events of interest were included in the cue-and-stimulus model for each of the regressors (pre-stimulus and stimulus-related) and pair formats (words and pictures). The events were associative hits (intact test items later judged correctly to be intact) and associative misses (intact test items later judged incorrectly to have been rearranged). Included as additional events were intact items and rearranged pairs that were incorrectly judged 'new', and an amalgam of other events of no interest, such as buffer trials and trials

containing omitted or multiple responses (these various trial types were collapsed into a single category because there were no, or very few, trials of any given type for most subjects). The model also included as covariates six regressors representing motion-related variance (three for rigid-body translation and three for rotation), and regressors modeling the separate scan sessions and the across-session mean. As described above, both the cue-item and the inter-trial intervals were jittered across trials (Figure 1). The jitters served to reduce, but not eliminate, colinearity between the cue and item regressors was 0.71). The choice of jitters, and consequentially the degree of colinearity between the two regressors for cue-and item-related activity, reflects the need to effect a compromise between a design that permits optimal deconvolution of pre- and post-stimulus activity and the need to employ cue-stimulus intervals that allow the cue to retain its psychological meaning as a signal to prepare for the upcoming study event. Nonsphericity of the error covariance was accommodated by an AR(1) model, in which the temporal autocorrelation was estimated by pooling over suprathreshold voxels (Friston et al., 2002).

For the stimulus-only model, the same events of interest were modeled, but using the stimulus-related regressor only. Thus, a total of eight events were defined. The model also included the same covariates as in the cue-and-stimulus model. The model included temporal and dispersion derivatives as additional basis functions so as to maintain consistency with the approach employed by Park & Rugg (2011).

2.6.2 Contrast thresholds—Subject-specific parameter estimates of the study activity elicited by item pairs that went on to become associative hits and misses were taken forward to second-level, across-subject analyses. Unless otherwise noted, contrasts were heightthresholded at p < 0.005 one-tailed, and combined with a 45 voxel extent threshold. As estimated using Monte Carlo simulations implemented with the 3dClustSim function in AFNI (http://afni.nimh.nih.gov/afni/afni_help/alphasim.html), this extent threshold gave a whole brain corrected cluster-wise significance level of p < 0.05. Contrasts employed as exclusive masks were thresholded at p < 0.05, one-tailed (note that the more liberal the threshold of an exclusive mask, the more conservative is the outcome). Material effects that were used as inclusive masks to identify regions sensitive to material-specific effects (picture > word and word > picture, respectively) were thresholded at p < .0025, to give a two-sided threshold of p < .005. When inclusive masks were used to identify materialinvariant effects common to both word and picture stimuli (hence ensuring inclusion only of voxels that exhibited simple effects of subsequent memory for each material type), the masks were thresholded at p < .05. Results are displayed either by rendering onto the PALS-B12 atlas (Van Essen, 2005) of the visualization program Caret (Van Essen et al., 2001) with mean fiducial mapping, or by projection onto sections of the across-subjects mean normalized structural image.

2.6.3 Time course estimation—In addition to the previously described GLMs, we created another GLM in which a finite impulse response (FIR) model was used to estimate the time courses of activity for events of interest. The FIR analysis was performed to estimate the time courses of effects identified with the cue-and-stimulus and stimulus only

models. Time courses were separately estimated for the 2, 4, and 6 s cue-pair intervals across 13 time points (sampling interval of 2s) that began with the volume acquired 8 s prior to study pair onset and continued until 16 s post-onset. Plotted time courses display across-subject mean parameter values after averaging, within-subjects, across each of the pre-stimulus intervals contributing data to the different time-points: thus, one third of trials were used to estimate activity for the 6 s cue-study onset interval, two thirds of the trials contributed to the estimate of the 4s pre-stimulus interval, and the first time-point at which all three cue-stimulus intervals contributed to the model was 2 s prior to the onset of the study pair.

2.7 Contrasts

As described below, we performed a series of contrasts to identify material selective and material-invariant pre-stimulus subsequent memory effects during the interval between the cue and the study pair onset and, separately, created an additional GLM to identify effects related to and following the onset of the study pairs.

2.7.1 Pre-stimulus Material-Invariant Memory Effects—Using the cue-and-stimulus GLM, we identified pre-stimulus subsequent associative memory effects that were shared by both classes of material by exclusively masking the subsequent memory contrast (intact > rearranged) for the cue-related regressor with the subsequent memory × material interaction (p < .05, two-sided), thereby removing any voxels where there was a significant difference in the magnitude of the two classes of subsequent memory effect. To ensure that the resulting effects were not driven by only one class of study material, we inclusively masked the resulting SPM with the simple subsequent memory effect (thresholded at p < .05 one-sided) for each class.

2.7.2 Pre-stimulus Material-Selective Memory Effects—Material-selective subsequent memory effects were identified with a two-stage masking procedure. To identify subsequent memory effects that fell within material-sensitive regions (see 1.1 Introduction), word- and picture-only subsequent memory effects were inclusively masked with the corresponding material effect (word > picture and vice-versa) derived from the stimulus-only model (i.e., section 2.6.2). Consistent with our prior study (Park & Rugg, 2011), the material-specific effects (i.e.: I > R, words) were thresholded at p <.01. The conjoint significance of the resulting SPM was p< .001, according to Fisher's procedure (Fisher, 1950; Lazar et al., 2002). To ensure that the resulting memory effects were selective for the given material, each SPM was then exclusively masked with the alternate cue-related subsequent memory effect (p <.05, one-sided). The final SPM was thresholded at 20 contiguous voxels since that was the corresponding extent threshold identified by Monte Carlos simulations (see section 2.6.2) to provide a whole brain corrected cluster-wise significance level of p < 0.05 for the resulting conjoint significance of the contrast (p <.001).

2.7.3 Stimulus-Related Effects—The contrasts for material-invariant and material-selective stimulus-related subsequent memory effects were identified in a manner analogous to those described above for the cue-related effects, but were implemented in the stimulus-only GLM.

2.7.4 Overlap between pre- and post-stimulus subsequent memory effects— Our final analysis addressed whether post-stimulus memory effects in the stimulus-only model were preceded by pre-stimulus memory effects, as identified by the pre-stimulus regressor in the combined model. The question was addressed by inclusively masking the two effects (i.e. pre-and post-stimulus,) for both material-invariant and material-specific contrasts (each thresholded at the same levels as was used to identify them each independently, as detailed in section 2.7.1 for material-invariant effects and in section 2.7.2 for material selective effects). Relatedly, this analysis also addressed the possibility, first raised by Otten et al. (2006), that subsequent memory effects captured by a post-stimulus regressor might in fact reflect pre-stimulus effects that carried over into the post-stimulus period (cf. Park & Rugg, 2010).

2.7.8 Small volume correction for hippocampal effects—There were strong apriori reasons to expect subsequent memory effects in the hippocampus based upon a large prior literature documenting such effects ins studies of post-stimulus subsequent memory effects (for review see Kim, 2011), and the two prior studies that reported pre-stimulus hippocampal effects (Adcock et al., 2006; Park & Rugg, 2010). Small volume corrections (Worsley et al., 1996) were performed within 3 mm spheres centered on the peak coordinates of the post-stimulus hippocampal subsequent memory effects identified in the meta-analysis of Kim (2011) (left: -22, -10, -16; right: 18, -7, -19). Since there only two prior studies have reported pre-stimulus subsequent memory effects in the hippocampus (Adcock et al., 2006, Park and Rugg, 2011), we assessed the present findings with respect to the loci of the anterior hippocampal effects reported in each of those studies (21, -12, -18 and -36, -18, -18, for the earlier and later study respectively).

3.1 Results

3.2 Behavioral Results

Reaction times (RTs) to study pairs presented as intact at test were analyzed with an ANOVA that employed the factors of later memory judgment (intact [intact pairs correctly endorsed as intact], rearranged [intact pairs wrongly endorsed as rearranged]) and study material (word, picture). The ANOVA revealed a main effect of material (F(1,19) =29.11, p < .001), indicating that picture pairs were responded to more quickly than word pairs (Table 1). There was, however, no effect of memory judgment (F(1,19) = <1), and nor was there an interaction between material and memory judgment (F(1,19) = 2.25).

At test, mean associative hit rates (correct 'intact' judgments) were 0.57 (SD =.03) for words and 0.64 (.03) for pictures. Mean associative false alarm rates (incorrect 'intact' judgments) were 0.18 (.03) and 0.24 (.03) for words and pictures respectively. Hit rates were significantly greater for pictures than for words t(19) = 2.67, p = .015, and the difference in false alarm rates approached significance, t(19) = 2.00, p =.06. Associative memory performance (pHit – pFA) was .39 (.03) for words and .40 (.04) for pictures; unsurprisingly, these values did not significantly differ, t(20) = .447, p = .659. Consistent with the findings reported above for hit and false alarm rates, response bias (calculated as pFA/1-(pHit-pFA), Snodgrass & Corwin, 1988) was significantly more liberal for pictures than it was for words (means (SDs) of .39 (.28) and .30 (.19) respectively, t(19)= 2.31, p =.032).

3.3 fMRI Results

Subsequent memory analyses were based upon contrasts between BOLD activity associated with studied word and picture pairs that were later correctly identified as 'intact' (associative hit) and pairs that went on to be incorrectly judged 'rearranged' (associative miss). Across subjects, there was a minimum of 9 trials in each response category [intact word: range = 28-63, (mean = 44); rearranged word: 9-36 (22); intact picture = 24-64 (50); rearranged picture: 10-41 (19)].

3.3.1 Material-invariant Pre-stimulus Subsequent Memory Effects—Pre-stimulus subsequent memory effects common to both classes of study material were identified in bilateral prefrontal cortex, anterior and posterior cingulate cortex, and bilateral posterior parietal cortex (Figure 2, Table 2). The time courses of these effects (see Methods section 2.6.3) are also illustrated in Figure 2, and strongly suggest that the effects do indeed reflect activity occurring pre-stimulus.

3.3.2 Pre-stimulus hippocampal subsequent memory effects—Pre-stimulus hippocampal subsequent memory effects were not identified at the pre-experimentally determined threshold (section 2.6.2). However, in light of prior evidence for such effects (Adcock et al., 2006; Park and Rugg, 2010) we conducted a further, targeted, analysis (section 2.7.8). At a threshold of p < .01, a main effect of subsequent memory was evident in right anterior medial temporal lobe (12, -13, -18, 28 voxels, peak Z = 3.09), extending into the hippocampus (see Fig. 3). The effect survived small volume correction with respect to the coordinates reported by Adcock et al. (2006; see section 2.7.8). Part of this cluster (6 voxels) fell within the anatomical borders of the hippocampus (Insausti et al., 1998), with a peak at 18, -13, -20). A representative time course from the peak of the hippocampal effect (see section 12.6.3) is illustrated in Figure 3, which indicates that it was sustained throughout the pre-stimulus period.

3.3.3 Relationship between pre-stimulus encoding effects and memory

performance—If, as has been proposed (Park and Rugg, 2010), pre-stimulus subsequent memory effects reflect the benefit of adopting an appropriate preparatory set in anticipation of the upcoming study event, one might expect there to be a relationship between the magnitude of such effects and later memory performance. Accordingly, we investigated whether the material-invariant cortical (Figure 2 and Table 2) or hippocampal (Figure 3) effects co-varied across subjects with memory performance (collapsed across the two classes of study material). For the cortical effects, we created a single measure of their magnitude by averaging the parameter estimates representing the effects at each of the peak voxels listed in table 2 (and an additional right parietal sub-peak; see Figure 2). The resulting correlation was significant, albeit indicative of a *negative* relationship between the size of the cortical pre-stimulus effects and performance (r = -.498, p = .025, see Figure 4). When correlations were estimated separately for each peak, the only region where the effect was independently significant was the right IFG (r = -.497, p = .026); right insula: r = .281, p = .230; posterior cingulate r = -.261, p = .266; right inferior frontal sulcus: r = -.350, p = .130; left superior frontal gyrus: r = -.434, p = .056; right parietal: r = -.265, p = .259). The

magnitude of the pre-stimulus effect in the right hippocampus was also negatively correlated with memory performance (r = -.528, p = .017; Figure 4).

The foregoing analyses indicate that both the cortical and hippocampal pre-stimulus subsequent memory effects were correlated with later associative memory performance. We next employed multiple regression to determine whether the two effects accounted for independent proportions of variance in test performance. The regression model was significant (F(2,19) = 6.66, p = .007; R² = .439), as was the contribution of each of the predictor variables (cortical effects: standardized coefficient (β) = -.410, p = .040 hippocampal effects: standardized coefficient (β) = -.415, p = .026). Thus, the two prestimulus effects accounted for independent sources of variance in later associative recognition accuracy.

To gain further insight into the basis for the correlations between the cortical and hippocampal pre-stimulus subsequent memory effects with later associative memory performance, we calculated separate correlations between the effects and the two variables contributing to performance, namely hit and false alarm rate (see Figure 4). The correlation between the magnitude of cortical pre-stimulus effects and hit rate was near-zero (r = -.07, and far from significant) whereas the correlation with false alarm rate was sizeable and statistically significant (r = .54, p =.014). By contrast, the magnitude of the hippocampal pre-stimulus encoding effects was negatively correlated with later hit rate (r = -.630, p = . 002), while demonstrating no relationship with false alarm rate (r= .01).

3.3.4 Pre-stimulus Material-Selective Subsequent Memory Effects—As is

evident from Figure 5 (see also Table 2), picture-selective pre-stimulus subsequent memory effects overlapping picture-responsive cortical regions were identified in bilateral fusiform cortex and bilateral intraparietal sulcus (IPS). Analogous word-selective effects could not be identified; this remained the case even when the threshold for the word-selective subsequent memory effect was lowered to an uncorrected threshold of p < .05. Unlike the material-invariant effects, no relationship with performance was evident for the picture – selective effects described above,

3.3.5 Stimulus-related material-invariant subsequent memory effects—Using the stimulus-only model (see Methods section 2.6.1, section 2.7.3), subsequent memory effects common to the two classes of study material were identified in several regions, including left fusiform cortex, left posterior parietal cortex, and left inferior frontal gyrus (see Figure 6, Table 2).

3.3.6 Post-stimulus hippocampal subsequent memory effects—Post-stimulus hippocampal subsequent memory effects were not identified at the pre-experimentally determined threshold (section 2.6.2). However, since such effects have been reported frequently in other studies of subsequent memory effects (see Kim (2011) for review), we conducted a further, targeted, analysis (section 2.7.8). At a threshold of p < .01, a 77-voxel cluster was identified in left medial temporal lobe (-18, -1, -9, peak Z = 3.06), which included a sub-peak in left hippocampus (-33, -25, -14, peak Z = 3.04) (Figure 3B). This was accompanied by a 31-voxel cluster in the right hippocampus (33, -7,-23, peak Z = 3.06). The

left hippocampal effect survived small volume corrections with respect to the coordinate of the left hippocampal effect identified in the meta-analysis of Kim (2011). The time-course of the effect is illustrated in Figure 3. The right hippocampal effects did not, however, survive small volume correction with respect to the right hippocampal co-ordinates reported by Kim et al. (2011).

3.3.7 Material-Selective Stimulus-related Subsequent Memory Effects-

Material-selective stimulus-related subsequent memory effects are illustrated in Figure 6 and listed in Table 1. Picture-selective effects were evident in the right intraparietal sulcus (IPS) and bilateral fusiform cortex. Word-selective effects were identified in left middle temporal sulcus (Figure 6).

3.3.8 Relationship between post-stimulus subsequent memory effects and

memory performance—In contrast to the findings for pre-stimulus effects, the magnitude of neither the cortical nor the hippocampal material-invariant post-stimulus effects correlated significantly across subjects with later memory performance.

3.3.9 Overlap between pre- and post-stimulus subsequent memory effects-

To identify regions where pre- and post-stimulus subsequent memory effects overlapped (see 1.1 Introduction) we inclusively masked the respective effects (i.e.: section 2.7.4). No overlap was identified between pre- and post-stimulus material-invariant effects. There was, however, a 27-voxel cluster in the right IPS where pre- and post-stimulus picture-selective memory effects overlapped (Figure 7). The center of mass for the pre- and post-stimulus inclusively-masked effects was maximal at x, y, z coordinate of 26, -58, 39. Inspection of the time-course of this effect (Figure 7) suggests, however, that the overlap may be more apparent than real; the effects are maximal at the early in the post-stimulus epoch, prior to the peak of the HRF response to stimulus onset, and diminish thereafter (because of the roughly 2 sec lag between neural activity and its corresponding BOLD correlate, prestimulus effects can be expected to continue for at least one TR post-stimulus onset). These findings suggest that, as for the post-stimulus effects identified in all other cases, the present effect does not overlap with a pre-stimulus effect (cf. Otten et al., 2006; Park and Rugg, 2011).

4.1 Discussion

The present experiment addressed the question whether pre-stimulus neural activity, as indexed by the fMRI BOLD signal, differentiates successful and unsuccessful associative encoding. It also assessed whether any such pre-stimulus subsequent memory effects vary according to study material (pictures vs. words). Material-selective pre-stimulus effects were identified for pictures only, where they were evident in bilateral fusiform and parietal cortex but did not overlap with analogous post-stimulus effects (see section 4.3.2). Material-independent pre-stimulus effects were identified in both frontal and parietal cortex, and at a reduced threshold, in the hippocampus. The magnitudes of these latter effects were negatively correlated across subjects with later memory performance. Below, we discuss the

implications of these findings for an understanding of the role of pre-stimulus activity in memory encoding.

4.2 Behavioral findings

Study RTs were shorter for picture than for word pairs, but did not differentiate either class of study pair according to later memory performance. Hence it is unlikely that either material-independent or material-dependent fMRI subsequent memory effects merely reflect differences in the efficacy of study processing, at least as this is indexed by RT. In a similar vein, the finding that subsequent memory performance did not significantly vary with material makes it unlikely that the failure to identify word-selective subsequent memory effects can be attributed to weaker memory strength for word than for picture pairs (cf. Wixted, et al., 2010).

4.3 fMRI findings

4.3.1 Post-stimulus effects—Before discussing the findings for pre-stimulus encoding effects we briefly discuss those obtained from the stimulus-only model, an analysis directly paralleling that employed in the study motivating the present experiment (Park & Rugg, 2011). Results from this analysis closely replicated the findings reported in the aforementioned study, and are also consistent with findings reported in other prior experiments on associative encoding (e.g. Chua et al., 2007; de Chastelaine et al., 2011; Sperling et al., 2003; Wong and Rugg, 2013). Left-lateralized material-invariant associative encoding effects were identified in LIFG, and in fusiform and posterior parietal cortex. Also consistent with prior findings (e.g. Chua et al., 2007), associative encoding effects were identified in the hippocampus. More interestingly, perhaps, the present material-selective associative encoding effects - picture-selective in bilateral fusiform cortex and wordselective in left temporal cortex – overlapped with or abutted the corresponding effects reported by Park & Rugg (2011). Thus the present findings add to the evidence that successful associative encoding is associated with differential engagement of materialselective cortical regions (Summerfield et al., 2006; Park and Rugg, 2011), and hence add further support to the theoretical framework motivating the prediction of such effects (Rugg et al., 2008).

4.3.2 Material-selective pre-stimulus effects—For the reasons outlined in the Introduction, we addressed the question whether there was overlap between cortical regions selectively activated by one class of study material relative to the other, and a corresponding material-selective pre-stimulus subsequent memory effect. Such overlap was evident for picture-pairs only, when it was identified in bilateral fusiform cortex and IPS. The reason for the failure to find analogous effects for words is unknown, and limits the strength of the conclusions that can be drawn from this finding. On the face of it, however, it is consistent with the proposal that pre-stimulus subsequent memory effects reflect, in part, the benefit to encoding that results from successful adoption of a material-, task- or reward-specific preparatory set (Adcock et al., 2006; Otten et al., 2006; Park and Rugg, 2010).

Although the above finding for the picture-selective subsequent memory effects is consistent with the idea that 'pre-activation' of material-selective cortical regions can benefit memory

encoding, it is noteworthy that the effects did not overlap with the analogous post-stimulus effects (as we discuss below in section 4.3.2, the one small cluster where overlap was seemingly evident appears to reflect a misattributed post-stimulus effect). This consistent lack of overlap contrasts with findings reported in studies where a pre-stimulus attentional cue resulted in both pre-activation of a domain-selective cortical region, and enhancement of the stimulus-elicited response in the same region (Luck et al., 1997; Chawla et al. 1999; see Driver & Frith, 2000 for discussion). On the basis of those findings, we anticipated that regions demonstrating material-selective pre- and post-stimulus subsequent memory effects would overlap, consistent with the proposal that the post-stimulus effects reflect the benefit to encoding that follows allocation of a relatively large amount of attentional resource to the relevant feature or features of the study event (Uncapher and Rugg, 2009). The present findings do not conflict with this proposal, but they do suggest that the allocation of attention to material-specific attributes of the study items does not depend on a raised prestimulus 'baseline' (cf. Driver and Frith, 2000). Thus, they leave open the question of the functional significance of the present pre-stimulus picture-selective subsequent memory effects.

4.3.4 Material-invariant pre-stimulus effects—Pre-stimulus subsequent memory effects common to both classes of material were identified in several cortical regions, including bilateral prefrontal and parietal cortex, insula, and posterior cingulate cortex (Figure 2). Material-invariant effects were also evident in the hippocampus (Figure 3), consistent with findings from prior studies that investigated pre-stimulus subsequent memory effects for single study items (Adcock et al., 2006; Park & Rugg, 2010). The cortical regions demonstrating these effects overlap with regions held to comprise one or more large-scale distributed networks supporting cognitive control (see, for example, Dosenbach et al., 2008; Cole et al., 2013), sometimes collectively referred to as the "executive meta-system" (Cocchi et al., 2013; see also Niendam et al., 2012). These networks are thought to support such functions as the adoption and maintenance of task-sets in service of behavioral goals (Braver et al., 2012; Powers & Petersen, 2013; Dosenbach et al., 2008). The finding that members of these networks demonstrate pre-stimulus subsequent memory effects suggests that the effects may reflect, at least partially, differential engagement of one of more control processes in response to the pre-stimulus cue. The negative correlation across subjects between the extent of this differential engagement and associative recognition performance complicates its interpretation, however, as we discuss in the next section.

4.3.5 Relation of pre-stimulus encoding effects to retrieval performance—Both cortical and hippocampal material-invariant pre-stimulus subsequent memory effects were negatively correlated across subjects with associative recognition performance (Figure 4). Furthermore, the two pre-stimulus effects accounted for independent sources of variance in performance. More detailed analyses revealed that whereas cortical pre-stimulus effects were correlated negatively with hit rate. Thus, while the magnitudes of both classes of pre-stimulus effect were predictive of relatively worse associative recognition performance, this was for different reasons in the two cases.

It is commonly held that associative false alarms occur when the aggregate familiarity of the items comprising a rearranged pair is both strong and unopposed by recollection of the true provenance of one or both items (Jones and Jacoby, 2001; Jones and Jacoby, 2005; Lloyd, 2007; Arndt and Jones, 2008; Rhodes et al., 2008; Leding and Lampinen, 2009; Jones & Bartlett, 2009). From this perspective, the positive correlation observed in the present study between cortical pre-stimulus subsequent memory effects and false alarm rate might reflect processes that support encoding at the single item level. These processes strengthen later memory for each item belonging to the study pair, but not for the association between the items. It will be of interest to determine whether these putative item-related processes compete with other encoding operations that do support inter-item associative binding, or whether they operate in parallel with such operations. If there is competition between the two classes of encoding operation, the present finding of a negative relationship between pre-stimulus subsequent memory effects and associative memory performance might be expected to extend to other types of associative encoding, including encoding of item-context associations (such as in source memory).

As noted above, the present hippocampal pre-stimulus subsequent memory effects demonstrated a negative correlation with later hit rate. This finding suggests that larger hippocampal effects were associated with an increased likelihood of ineffective encoding of inter-item associations (item-item 'binding'). To our knowledge, the finding of a negative relationship across subjects between a hippocampal subsequent memory effect and memory performance is unprecedented, and we have no ready explanation for it. However, two speculative possibilities come to mind that might account for the finding, both of which propose that the hippocampal effects reflect engagement of processes that deplete hippocampal resources otherwise available to support associative encoding of the study items. One possibility is that the hippocampal pre-stimulus effects reflect engagement of encoding operations directed toward task-irrelevant features of the study episode such as distracting thoughts or external events (a very similar explanation has been advanced to account for the inverse relationship between post-stimulus encoding-related activity in the temporo-parietal junction and later memory performance; Uncapher and Wagner, 2009, Uncapher et al., 2011). A second possibility is that hippocampal pre-stimulus subsequent memory effects reflect the engagement of *retrieval* rather than encoding operations (there is copious evidence that successful episodic retrieval is associated with enhanced hippocampal activity; e.g. Kim, 2010, Rugg and Vilberg, 2013). By this argument, the effects reflect interference with study pair encoding that arises from retrieval processing initiated during the cue-stimulus interval. Such processing might reflect voluntary or involuntary retrieval of task-irrelevant information or, conceivably, retrieval of task-relevant information (type of upcoming material) associated with the two different pre-stimulus cues.

Current evidence does not allow adjudication between these two aforementioned accounts of the negative relationship between pre-stimulus hippocampal subsequent memory effects and later associative hit rate. One aspect of the present findings that may weigh against both accounts, however, is the lack of a negative relationship between *post-stimulus* hippocampal subsequent memory effects and performance². Such a relationship would be expected according to either account, since both argue that pre-stimulus processing acts to deplete the

hippocampal resources available to encode the study item. It remains to be seen whether the present failure to observe this relationship is a Type I error, or does indeed indicate a dissociation between pre-and post-stimulus hippocampal subsequent memory effects.

In any case, by bringing pre-stimulus encoding and retrieval operations under experimental control, it should be possible to establish which (if either) of the foregoing accounts is the more promising. Importantly, according to both accounts, hippocampal pre-stimulus negative subsequent memory effects should be negatively correlated not only with later associative memory performance, but with performance on tests that depend on retrieval of other kinds of associations, notably, tests of source memory (i.e. Addante et al., 2011).

4.3.6 Overlap between pre- and post-stimulus effects—Strikingly, we were unable to identify any regions demonstrating overlap between pre- and post-stimulus subsequent memory effects. The one small cluster where such effects were identified seems likely to have been the result of a misattribution on the part of the stimulus-only model (see Figure 7). As already noted, the absence of overlap between the two classes of subsequent memory effect suggest that, at least in the present case, post-stimulus effects do not reflect responses potentiated by a raised pre-stimulus baseline (cf. Driver and Frith, 2000). The general absence of overlap also suggests that, while a possibility (Figure 8; Otten et al., 2006), the risk of misidentifying pre-stimulus subsequent memory effects as stimulus-elicited is low.

4.4 Conclusions

The findings from the present study go beyond prior investigations of pre-stimulus subsequent memory effects in four main ways. First, we demonstrate that pre-stimulus effects, reported previously only for the encoding of individual study items, generalize to the encoding of item-item associations. Second, the study provides evidence that, like post-stimulus effects, pre-stimulus subsequent memory effects reflect both material-invariant and material-selective encoding-related activity. Third, the findings demonstrate that previously-reported pre-stimulus hippocampal subsequent memory effects can be accompanied by effects in midline and lateral cortical regions that have been implicated in a variety of aspects of cognitive control. Finally, the negative relationship between both cortical and hippocampal pre-stimulus effects and later associative memory performance raises the possibility that the effects reflect processes that are deleterious, rather than beneficial, to associative encoding.

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Highlights

fMRI was used to study neural correlates of encoding word and picture pairs

Material-invariant cortical and hippocampal pre-stimulus effects were identified

The material-invariant effects co-varied negatively with later memory performance.



Figure 1. Schematic of the study task



Figure 2. Material-invariant pre-stimulus subsequent memory effects

Left: regions where pre-stimulus activity was greater for study pairs that were later correctly judged intact than for pairs that were later incorrectly judged as re-arranged. Results are rendered onto the PALS-B12 atlas of the visualization program Caret, using mean fiducial mapping (see Methods section 2.6.2). Right: estimated time courses from two representative regions. Y-axis represents mean parameter estimates derived from an FIR analysis of activity from the two indicated loci, and are plotted in 2 s intervals relative to stimulus onset. Error bars represent estimated standard errors of the difference between conditions. The coordinates of the voxels from which timecourses were derived are (A) 42, 14, 22; (B) -3 -31, 25.

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Figure 3. Material-invariant hippocampal subsequent memory effects

Top left: pre-stimulus subsequent memory effects projected onto a section of the acrosssubjects mean normalized structural image. Top right: estimated time courses of activity for the right hippocampus (18, -13, -20); see figure 3 legend for details. Bottom left: stimulusrelated subsequent memory effects; right: estimated time courses of activity the left hippocampus (-33, -25, -14).



Figure 4. Across-subjects correlation between pre-stimulus subsequent memory effects and later associative recognition performance

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Figure 5. Picture-selective pre-stimulus subsequent memory effects

Top: regions where pre-stimulus activity was greater for picture pairs that were later remembered than for picture pairs that were later incorrectly judged as re-arranged. Bottom: estimated time courses from the loci indicated above; see Figure 3 legend for details. The coordinates from which timecourses were derived are (A) -33, -82, 16; (B) -42, -61, -35.



Figure 6. Stimulus-related subsequent memory effects

Top: Material-invariant subsequent memory effects. Middle: picture-selective effects. Bottom: word-selective effects. Right: estimated time courses from representative regions, taken from the indicated regions; see figure 3 legend for details. Coordinates for each time course are (from top to bottom) -39, 8, 28; 54, -55, 14; -51, -37, -8, respectively.



Figure 7. Overlap between pre- and post-stimulus picture-selective subsequent memory effects Post-stimulus picture selective subsequent memory effects masked within regions demonstrating pre-stimulus picture selective subsequent memory effects (see Methods section 2.7.4). Blue: pre-stimulus effects; Yellow: post-stimulus picture effects; Red: Overlap. Right: Estimated time courses of activity for the center of mass of the cluster demonstrating overlap (24,-61, 39); see Figure 3 legend for details. Error bars represent estimated standard errors of the difference between conditions.

Table 1

Reaction times (ms) and standard deviations for each class of study judgment, segregated by later memory performance

Material type	Intact	Rearranged
Word	1406 (104)	1440 (101)
Picture	1231 (80)	1225 (76)

Table 2
Coordinates of results for peak activity of subsequent memory effects

MNI Coordinates (x,y,z)	Z	No. of Voxels	Region	
Cue Related Common Effects – Material Invariant Sub sequent Memory Effects				
36, 56, 13	5.20	165	R. Inferior Frontal Gyrus	
-3, -31, 25	4.75	1185	Posterior Cingulate	
48, 8, 7	4.75	120	R. Insular Sulcus	
-30, -67, -41	4.60	66	L. Cerebellum	
42 35 19	4.41	195	R. Inferior Frontal Sulcus	
-30 56 22	3.76	90	L. Superior Frontal Gyrus	
0, -61, -41	3.33	50	L. Cerebellum	
Cue Related Picture-Sensitive Subsequent Memory Effects				
33, -55, -29	4.18	104	R. Fusiform	
-33, -82, 16	4.14	460	L. Intraparietal Sulcus	
30, -58, 37	3.62	160	R. Intraparietal Sulcus (IPS)	
-42, -61, -35	2.97	86	L. Fusiform	
Stimulus Related Material Invariant Subsequent Memory Effects				
-54, -46, -23	3.71	65	L. Fusiform	
-39, 8, 28	3.64	146	L. Inferior Frontal Sulcus	
-36, -73, 25	3.54	56	L. Intraparietal Sulcus	
Stimulus Related Picture-Sensitive Subsequent Memory Effects				
54, -55, -14	3.73	142	R. Fusiform	
33, -64, 40	3.40	125	R. Intraparietal Sulcus	
-39, -49, -20	2.84	72	L. Fusiform	
Stimulus Related Word-Sensitive Subsequent Memory Effects				
-51, -37, -8	2.93	28	L. Superior Temporal Sulcus	