

## Hippocampal–neocortical networks differ during encoding and retrieval of relational memory: Functional and effective connectivity analyses

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### ABSTRACT

Encoding and retrieval of relational information requires interaction between the hippocampus and various neocortical regions, but it is unknown whether the connectivity of hippocampal–neocortical networks is different at input and output stages. To examine this, we conducted a network analysis of event-related fMRI data collected during a face-recognition, remember/know paradigm. Directed analyses in the medial temporal lobe identified a small region in the left hippocampus that showed differential activation for encoding and retrieval of recollected versus familiar items. Multivariate seed partial least squares (PLS) analysis was used to identify brain regions that were functionally connected to this hippocampal region at encoding and retrieval of ‘remembered’ items. Anatomically based structural equation modeling (SEM) was then used to test for differences in effective connectivity of network nodes between these two memory stages. The SEM analysis revealed a reversal of directionality between the left hippocampus (LHC) and left inferior parietal cortex (LIPC) at encoding and retrieval. During encoding, activation of the LHC had a positive influence on the LIPC, whereas during retrieval the reverse pattern was found, i.e., the LIPC activation positively influenced LHC activation. These findings emphasize the importance of hippocampal–parietal connections and underscore the complexity of their interactions in initial binding and retrieval/reintegration of relational memory. We also found that, during encoding, the right hippocampus had a positive influence on the right retrosplenial cortex, whereas during retrieval this influence was significantly weaker. We submit that examining patterns of connectivity can be important both to elaborate and constrain models of memory involving hippocampal–neocortical interactions.

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### 1. Introduction

The encoding specificity principle (Tulving & Thomson, 1973) and transfer-appropriate processing concepts (Morris & Franks, 1977) were proposed to account for the typical memory advantage shown when retrieval conditions and processes reinstate those present during encoding. The extent to which an event’s rich content, often operationalized as context in laboratory experiments, is recovered during retrieval influences the likelihood that it will be experienced by the individual as a genuine part of the personal past and thus remembered or recollected (Yonelinas, 2002). From a cognitive neuroscience perspective, this would suggest that specific neural networks engaged during encoding of information may be reinstated during retrieval, an argument recently advanced by

Rugg et al. who focussed particularly on hippocampal–neocortical interactions (Rugg, Johnson, Park, & Uncapher, 2008). The aim of our study was to identify the networks implicated in recollective processes associated with episodic memory at encoding and retrieval.

There is now substantial evidence demonstrating the central role played by the hippocampus in both relational memory processing and recollection. In neuroimaging studies, hippocampal activation is greatest during encoding and retrieval of items and their context (e.g., other paired stimuli, spatial location, other details of the encoding event) in comparison to single items and also when individuals experience recollection of a study event rather than mere familiarity regarding an item’s prior occurrence (for reviews, see Davachi, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007; Mayes, Montaldi, & Migo, 2007). Furthermore, several neuroimaging studies have demonstrated that overlapping patterns of neocortical activation can be seen during encoding and retrieval when content is easily differentiated such as pictures versus words (Cansino, Maquet, Dolan, & Rugg, 2002; Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Johnson, McDuff,

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Rugg, & Norman, 2009; Johnson & Rugg, 2007; Kirwan & Stark, 2004; Prince, Daselaar, & Cabeza, 2005). Although the foregoing studies provide evidence for plausible interactions between the hippocampus and various neocortical regions during encoding and retrieval, none of them directly examined patterns of connectivity that could help to further characterize those interactions.

Studies on human and non-human primate neuroanatomy strengthen the idea of a close dialogue between hippocampus and neocortical areas (Buzsaki, 1996; Eichenbaum et al., 2007; Suzuki & Amaral, 1994a, 1994b). As the hippocampus receives a convergence of neocortical inputs from perirhinal and lateral entorhinal cortex (representing object features) as well as parahippocampal and medial entorhinal cortices (conveying information about location), reverse projections follow the same pathways back to the surrounding MTL areas and then neocortical regions, establishing a circuit that could support both encoding and retrieval of 'bound' elements of experiences. One instance of such a model is provided by Teyler and colleagues (Teyler & DiScenna, 1986; Teyler & Rudy, 2007) who proposed that the hippocampus stores an "index" of the neocortical activation pattern during encoding and, by reactivation of this index during retrieval, the hippocampus reinstates that pattern. In agreement with this, it has been hypothesized that the presentation of a stimulus activates a specific pattern of neocortical regions which is then encoded by the hippocampus. Subsequent presentation of the same stimulus leads to partial reinstatement of the original pattern of activity which is recognized by the hippocampus. Overlap between the activities elicited again by the cue and the stored pattern of activity causes the hippocampus to re-activate this memory which in turns leads to full reinstatement at the cortical level (Marr, 1971; McNaughton, 1991; Rugg et al., 2008). These models assume that there are crucial similarities between encoding and retrieval such that some of the same circuitry of hippocampal–neocortical connections underlies both operations, but with differences in the flow of information between the components at input and output. To the best of our knowledge, however, the strength and directionality of these interactions have not yet been tested.

In the present study, we explored the connectivity of hippocampal and neocortical regions at encoding and recognition, focusing on those regions that were differentially engaged during processing of relational information in a face memory paradigm. Specifically, we were interested in whether differences would emerge in the patterns of effective connectivity, using anatomically based structural equation modeling (SEM), between processes involved in initial

binding of relational information and its subsequent retrieval. This method was chosen because it allows not only a description of regional activities that correlate with one another, it also allowed us to determine which region influences the activity of the other. The nodes included in the current SEM analysis were selected from a correlation-based seed partial least squares (PLS) analysis which indicated functional connectivity between a hippocampal seed voxel and various neocortical areas. To enhance our ability to detect hippocampal involvement at encoding and at retrieval, we adapted a face-recognition paradigm from a previous study in which we showed that recollection was differentially impaired in patients with medial temporal lobe epilepsy or excision (Moscovitch & McAndrews, 2002). We asked participants to judge the "personality" of faces at encoding which encouraged them to generate unique multifaceted relational information for each face. At recognition, we asked the participants to make 'remember/know' responses because we assumed the former depend primarily on recollection which reflects recovery of the relational information generated at encoding.

## 2. Methods

### 2.1. Participants

Nineteen right-handed healthy participants with an average age of 26 years (3.4 SD) were scanned. Due to technical problems during scanning, four subjects were excluded, whereas for two subjects only the retrieval data were recorded. Another subject was excluded because she did not have any familiarity responses. The following study, therefore, includes 12 subjects (5 females) at encoding and 14 (6 females) at retrieval. Every participant gave informed consent to the study. The study was approved from the University Health Network Research Ethics Board.

### 2.2. Stimuli and experimental procedure

We used 117 black and white photographs of faces (58 female; age ranges between 25 and 35 years) shown in a frontal view with hair cropped from the image (see Fig. 1). In the experiment, 60 faces were used as targets and 32 as lures. Prior to scanning, participants performed a practice test with 15 study faces and 25 (15 old, 10 new) faces for recognition testing.

During face encoding, participants were instructed to decide whether the person depicted was more likely to be a "sporty-type", "party-goer", "homebody" or "intellectual". This procedure, adapted from our earlier study (Moscovitch & McAndrews, 2002), was designed to provide an opportunity to generate specific contexts for the faces that might comprise relations of perceptual and ideational features. Recognition testing involved a two-stage process. Subjects first made an 'old' versus 'new' response to indicate whether the face was presented during study. For each 'old' response, they had to report whether they could recall something about the encoding context such as the 'personality type' or any other information that accompanied their initial exposure to that face (i.e., a Remember response) or whether they had no recall of any of those aspects (i.e., a Know response). This paradigm for assessing recollection and familiarity was first described by Tulving (1985). The two-step process has been argued to minimize the likelihood that subjects are discriminating Remember and Know solely on the basis of confidence (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000). Testing in the scanner began only when subjects could describe appropriate examples of Remember (R) and Know (K) decisions to the experimenter.

The fMRI experiment consisted of two encoding and two retrieval scans interleaved. During encoding, subjects saw 30 faces per scan for 5 s each. The inter stimulus intervals (ISI) were randomised between 6, 8 and 10 s (average of 8 s) showing a black fixation cross on a white screen. For each face, participants communicated their 'personality type' decision by raising one finger for each category so that the experimenter in the MRI room could record their response. After a short delay, the recognition test began. Per scan, 30 old and 16 new faces were shown for 3 s each in a randomised order. For each face, participants made old versus new decisions followed by (for items judged to be 'old') Remember versus Know decisions; responses were made using an optical mouse. There was a 3 s response time limit for each question. Before the next face appeared on the screen there was a fixation cross for 3 s.

### 2.3. Data acquisition

Anatomical and functional data were acquired on a 3-T Signa MR System (GE Medical Systems, Milwaukee WI). The anatomical scans were taken first (T1-weighted sequence, 120 slices, 220 mm FOV, 256 × 256 matrix). Functional data were acquired in an interleaved order (25 slices, 240 mm FOV, 64 × 64 matrix, TR = 2000). These were taken in an oblique orientation, with each slice being perpen-



**Fig. 1.** Experimental procedure. During encoding, participants studied a sequence of 30 faces and were asked to judge the personalities of the faces. During retrieval, 30 old and 15 new faces were presented. Participants were asked to first indicate by mouse click whether they had studied the face before (Old/New response) and second, if they remembered any associations with the face or not (Remember/Know response). A second encoding/retrieval block with a different set of faces followed the first. Participants were scanned during both encoding and retrieval.

dicular to the long axis of the hippocampus. For each encoding phase we acquired 199 frames and 302 frames were acquired for each recognition phase. The first three frames were dropped to allow signal equilibrium.

#### 2.4. Data processing and statistical analyses

All pre-processing and analyses of imaging data were performed using Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London). Functional data were co-registered to a structural image, slice-time corrected, realigned for motion, spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed using a Gaussian kernel of 7.6 mm full-width half maximum. Each stimulus event was modelled by SPM2's canonical hrf. This was applied at the onset of the face stimulus as reaction time analyses (see below) indicated that processing relevant to the Remember/Know decision was undertaken during the initial yes/no recognition decision. For contrasts, each subject's data were analysed as a fixed-effects model, and the resulting contrast images were taken to the second level and analysed as a random-effects model.

#### 2.5. Medial temporal lobe region of interest analyses

The behavioural measures of subsequent recognition responses were used to back-sort the fMRI encoding events into three conditions: (1) subsequent Remember (sR), (2) subsequent Know (sK) and (3) subsequent Forgotten/Misses (sM). We defined four conditions for the recognition data: (1) Remember (R), (2) Know (K), (3) Correct rejections (CR), and (4) Forgotten/Misses (M). At encoding, the contrast of interest was  $sR > sK$  and at retrieval it was  $R > K$ . As we were specifically interested in the hippocampal contribution to relational processing, we performed region-of-interest (ROI) analyses with bilateral hippocampal masks which included the hippocampus proper, subiculum, and dentate gyrus. They were created with the SPM Anatomy Toolbox (<http://www.fz-juelich.de/inb/inb-3//spm.anatomy.toolbox>). We used these hippocampal masks to extract the averaged signal intensity magnitude (beta values) across the ROI for each subject (i.e., one value per subject) and conducted a one-way ANOVA on signal magnitudes relative to baseline for the conditions of interest. Using the same hippocampal masks, we visualized peak activity for the contrast  $sR > sK$  and  $R > K$  and selected the peak voxel of the overlapping area as the seed for the PLS analysis. As previous research has demonstrated familiarity effects within the entorhinal cortex (ERC) at both encoding and retrieval, we also evaluated the beta values within this area; this anatomic mask was also created in the SPM Anatomy Toolbox.

#### 2.6. Functional connectivity: seed partial least squares analysis

Seed partial least squares (PLS) analysis was conducted to identify candidate brain voxels to be used for structural equation modeling (SEM). PLS is a covariance based multivariate technique that examines the relationship between brain activity in a target region (seed voxel) and brain activity across the whole brain as a function of the different experimental conditions over time (McIntosh, Bookstein, Haxby, & Grady, 1996; McIntosh, Chau, & Protzner, 2004; McIntosh & Lobaugh, 2004). This technique was chosen because PLS provides not only characterization of the unique neural patterns within distinct conditions, but also indicates where conditions are similar to one another. This latter point was particularly important for us because we expected some coherence in brain activity between encoding and retrieval of relational information. Based on the results of the ROI analyses that the same region within the left hippocampus ( $-18, -32, -6$ , MNI overlap coordinate) was activated during both encoding ( $sR > sK$ ) and retrieval ( $R > K$ ) of relational information, we conducted a seed PLS analysis to identify brain regions that were functionally connected to this hippocampal region for sR and R items.

Detailed applications and limitations of PLS to neuroimaging data has been discussed previously (McIntosh et al., 1996, 2004; McIntosh & Lobaugh, 2004). In short, the seed PLS procedure consists of three steps: 1. The computation of correlation maps (one per condition) which contain all correlation coefficients between brain activity in the seed voxel and every other brain voxel across subjects. 2. Decomposition of the stacked correlation maps using singular value decomposition (SVD) identifies a new set of orthogonal variables (latent variables; LVs). Each LV consists of three new matrices: the singular image of voxel saliences, singular values, and task saliences. The voxel saliences give the spatiotemporal activity pattern for the LV. 3. Multiplying the BOLD signal value in each brain voxel for each subject by the salience for that voxel, and summing across all voxels, gives a "brain score" for each subject on a given LV. Brain scores indicate the degree to which each subject shows the spatial pattern of voxels expressed in the LV. The task saliences indicate the degree to which each task is related to the identified pattern of brain-seed correlations. Task saliences can be interpreted as the optimal contrast that codes the effect depicted by the voxel saliences.

The statistical significance of each LV was assessed by a permutation test. In this procedure, each subject's data were randomly reassigned without replacement to different experimental conditions, and the entire PLS analysis recalculated. Following 500 randomizations, the number of times the singular value from the randomized PLS analysis exceeded the singular value from the original PLS was noted. The reliability of voxel saliences was assessed by means of a bootstrap estimation of the standard error. Bootstrapping is a sampling technique in which subjects are

randomly selected into the analysis with replacement from the entire group of subjects. For each new sample, the entire PLS analysis is re-calculated. In the present study, this sampling and analysis procedure was carried out 100 times, resulting in estimates of the standard error of the salience at each voxel. No corrections for multiple comparisons are necessary because the voxel saliences are calculated in a single mathematical step on the whole brain. We considered clusters of 10 or more voxels in which the bootstrap ratio was greater than 3.00 (roughly equal to a z-score and to a 99.7% confidence interval, or a *p* value less than 0.003) to represent reliable voxels. Local maxima were selected from the bootstrap results and SPM Anatomy toolbox was used to localize these maxima. In the current analyses, we specified a 12-s temporal window for each event (i.e., 6 TRs). The PLS analyses display the results for each lag (i.e., each TR) separately.

#### 2.7. Effective connectivity: structural equation modeling

We were especially interested in whether differences would emerge in the patterns of effective connectivity between regions involved in initial binding of relational information and its subsequent retrieval. Although the same hippocampal area was identified for both encoding and retrieval, we considered it likely that inter-regional connectivity might vary considerably as a function of the nature of the memory process. We, therefore, examined the interactions between the hippocampi and neocortical regions during encoding and retrieval of relational information using structural equation modeling (SEM; LISREL 8.80, Student Edition, Scientific Software Inc., Mooresville, IN). SEM uses inter-regional correlations and anatomical pathways among selected brain areas as the input to compute path coefficients. These path coefficients provide information about the strength and directionality of influences between two regions; in distinction from symmetrical correlation analyses, these path weights can differ between two connected regions. For example, a strong positive connection from A to B in our data would indicate that fluctuations in BOLD signal for A are accompanied by similar fluctuations at B. Even when the anatomic model implies reciprocal connections, the path coefficients are unidirectional, so that changes in B do not need to exert a similar influence on A. Further methodological details, principles, and limitations of the applications of SEM to functional neuroimaging data have been discussed previously (McIntosh & Gonzalez-Lima, 1994; Protzner & McIntosh, 2006).

##### 2.7.1. Region selection

Our selection of regions for the SEM analysis was based on the highest bootstrap ratio and cluster size identified in the PLS results, as well as functional relevance to relational memory (Skinner & Fernandes, 2007; Spaniol et al., 2009). Eight voxels that co-varied with the hippocampal seed were integrated in the SEM analysis (MNI coordinates in brackets): bilateral hippocampi (LHC =  $-18, -32, -6$ ; RHC =  $14, -32, -10$ ), bilateral inferior frontal cortices (LIFG =  $-34, 28, 4$ ; RIFG =  $36, -56, 40$ ), left inferior parietal cortex (LIPC =  $-36, -56, 40$ ), left precuneus (LPC =  $-14, -70, 42$ ), right parahippocampal gyrus (RPHG =  $26, -28, -18$ ) and right retrosplenial cortex (RRSC =  $6, -44, 20$ ). The left posterior cingulate also met these criteria but it was removed from the analysis because the resulting models were unstable. To ensure model stability we also limited our inclusion of prefrontal regions to those with the largest and most stable indices in the seed analysis.

##### 2.7.2. Model construction

An anatomical model of multi-synaptic connections between the chosen regions was derived from the known primate neuroanatomy (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Clower, West, Lynch, & Strick, 2001; Eichenbaum et al., 2007; Suzuki & Amaral, 1994a; Vann, Aggleton, & Maguire, 2009). As we were especially interested in the interactions between the hippocampus and neocortex, we only included connections between these brain structures (i.e., excluding cortico-cortical connections). We then constructed a functional model for relational memory at encoding and retrieval. For each individual, the signal intensities were extracted from each chosen region in the relevant SPM contrast images, i.e., for encoding  $sR > sK$  and for retrieval  $R > K$ . The extracted signal intensities for all regions were then correlated, resulting in a correlation matrix of the differences between  $sR > sK$  and  $R > K$ .

##### 2.7.3. Path analyses

For all path analyses, the matrices of correlations were used to calculate path coefficients, representing the magnitude of the influence of each directional path (McIntosh & Gonzalez-Lima, 1994). Using a stacked-model approach (McIntosh & Gonzalez-Lima, 1994), we tested for differences between encoding and retrieval of relational information. A null model was first constructed in which the path coefficients were set to be equal. This was compared to the fit of an alternative model in which the path coefficients could vary across conditions. The null model indicates that there are no different path coefficients between encoding and retrieval whereas the alternative model indicates that there are differences between both stages. In order to test which model would be the best fit to the data, the goodness-of-fit chi-square values for both models were calculated and directly compared to determine if there was a significant difference in the fit of one model compared to the other. In the event that the alternative model fit better than the null model, individual paths were allowed to vary in a step-wise manner to determine which connections contributed to the increased fit of the alternative model. Because the order in which



connections vary could influence those which emerged as significant, we allowed connections to vary in four different orders (i.e., from anterior to posterior; from posterior to anterior; from the left hemisphere to the right hemisphere and from the right hemisphere to the left hemisphere). Only those connections which emerged as significant in all four approaches are reported.

### 3. Results

#### 3.1. Behavioural results

##### 3.1.1. Accuracy

The overall proportion of faces correctly categorized as old or new was  $0.81 \pm 0.6$ . The mean rates for R (23.4, range 11–31 of 60 old faces) and K (21.2, range 11–27 of 60 old faces) were similar,  $t(26) = 0.94$ ,  $p > 0.05$ . Of all 72 false positive responses, there were 12 false R and 60 false K responses (see Table 1 for all memory measurements). Recognition accuracy did not differ between the first and second test ( $t(26) = 1.17$ ,  $p > 0.05$ ). We therefore collapsed data into one analysis.

##### 3.1.2. Reaction times (RT)

Although subjects made the old/new and R/K decisions sequentially, preliminary analyses indicated no response time differences for R and K items for that decision,  $F(4,60) = 0.26$ ,  $p > 0.05$ . However, analysis of RT for the old/new decision based on the subsequent R versus K response did reveal significant differences  $F(4,60) = 5.36$ ,  $p < 0.001$ . Specifically, hits with subsequent R responses were faster than those with K responses, Bonferroni's Multiple Comparison test,  $t = 3.39$ ,  $p < 0.05$ , and correct R decisions were also faster than misses,  $t = 3.52$ ,  $p < 0.01$  and FP responses,  $t = 4.15$ ,  $p < 0.001$ .

##### 3.1.3. Item analysis

To examine item-specific effects, we conducted a Kolmogorov–Smirnov test for Gaussian distribution over all responses for the 60 target faces. There was no subset of faces which received more frequent R or K responses than other faces, R, Mean = 5, SD = 3.9, KS distance = 0.19,  $p > 0.1$  and K, Mean = 5.5, SD = 4.5, KS distance = 0.23,  $p > 0.1$ .

#### 3.2. Medial temporal lobe region of interest analyses

##### 3.2.1. Encoding

We conducted ROI analyses, comparing the blood oxygenation level-dependent (BOLD) signal associated with subsequently remembered versus subsequently known faces (sR > sK) within both hippocampi. Peak activation for this contrast was found in both left (–25 –33 –11) and right (25 –27 –14) posterior hippocampus.

Using the anatomical hippocampal masks, we conducted a one-way ANOVA on signal intensity magnitudes (beta values) relative to baseline for the conditions of interest (sR, sK and sM). Values for the left HC were: sR =  $0.25 \pm 0.06$ , sK =  $0.02 \pm 0.06$ , sM =  $-0.11 \pm 0.07$ ; values for the right HC were: sR =  $0.19 \pm 0.05$ , sK =  $-0.02 \pm 0.05$ , sM =  $-0.21 \pm 0.07$  (see Fig. 2). For the left hippocampus, the analysis revealed a main effect of condition,  $F(2,36) = 8.36$ ,  $p < 0.001$ . Post-hoc Newman–Keuls Multiple Comparison test indicated greater activation for sR than sK,  $q = 3.7$ ,  $p < 0.05$  and sR greater than sM,  $q = 5.7$ ,  $p < 0.001$ . For the right hippocampus  $F(2,36) = 11.72$ ,  $p < 0.0001$ , the post-hoc analysis revealed a step-wise activation pattern, showing greater activation for sR than sK,  $q = 3.64$ ,  $p < 0.05$ , sK than sM,  $q = 3.2$ ,  $p < 0.05$ , and sR than sM,  $q = 6.84$ ,  $p < 0.001$ .

To examine encoding activation that might relate to subsequent familiarity effects, we used anatomical masks for the entorhinal cortex for the extraction of beta values for sR, sK and sM (left ERC: sR =  $0.39 \pm 0.11$ , sK =  $0.24 \pm 0.08$ , sM =  $-0.13 \pm 0.06$ ; right ERC: sR =  $0.23 \pm 0.09$ , sK =  $0.11 \pm 0.11$ , sM =  $-0.18 \pm 0.09$ ). The one-

way ANOVA for the left ERC revealed a main effect of condition ( $F(2,36) = 10.18$ ,  $p < 0.001$ ). Newman–Keuls multiple comparison test indicated greater activation for sK than sM ( $q = 4.43$ ,  $p < 0.01$ ) and sR than sM ( $q = 6.23$ ,  $p < 0.001$ ). Activation within the right ERC also revealed a main effect of condition ( $F(2,36) = 4.99$ ,  $p < 0.01$ ), however, only sR versus sM differed significantly ( $q = 4.17$ ,  $p < 0.05$ ).

##### 3.2.2. Retrieval

To identify hippocampal regions associated with successful retrieval of study context, we analysed the contrast R versus K. The ROI analysis revealed greater activation for R than K in the left posterior hippocampus (–22 –34 –5).

Comparison of beta values for R, K, CR and M in the left hippocampus (R =  $0.32 \pm 0.06$ , K =  $0.07 \pm 0.06$ , CR =  $0.12 \pm 0.02$ , M =  $0.06 \pm 0.08$ ) revealed a main effect of response type  $F(3,52) = 3.17$ ,  $p < 0.05$  (see Fig. 2). The activation for R was greater than for all other conditions, K ( $q = 3.66$ ,  $p < 0.05$ ), CR ( $q = 2.99$ ,  $p < 0.05$ ) and M ( $q = 3.8$ ,  $p < 0.05$ ). The ANOVA of beta values for the right hippocampus (R =  $0.16 \pm 0.05$ , K =  $0.05 \pm 0.05$ , CR =  $-0.03 \pm 0.07$ , M =  $-0.11 \pm 0.08$ ) also revealed a main effect of response type ( $F(3,52) = 3.03$ ,  $p < 0.05$ ), however, only activation related with R responses were greater than M ( $q = 4.09$ ,  $p < 0.05$ ).

To examine familiarity effects, we extracted beta values for R, K, CR and M within the ERC (left ERC: R =  $0.27 \pm 0.07$ , K =  $0.12 \pm 0.07$ , M =  $0.18 \pm 0.08$ , CR =  $0.42 \pm 0.09$ ; right ERC: R =  $0.04 \pm 0.04$ , K =  $0.05 \pm 0.21$ , M =  $0.02 \pm 0.19$ , CR =  $0.07 \pm 0.20$ ). The ANOVA for the left ERC revealed a main effect ( $F(2,52) = 2.79$ ,  $p < 0.05$ ), indicating greater activation for CR than K responses ( $q = 3.85$ ,  $p < 0.05$ ). There was no difference in activation within the right ERC (see Fig. 2).

#### 3.3. Functional connectivity: seed PLS analysis

To assess the distributed functional connectivity pattern of the left hippocampus, we conducted a seed PLS. This analysis identified one significant pattern of hippocampal functional connectivity which highlighted similarities between encoding and retrieval of relational information (LV.1,  $p < 0.0001$ , 84% crossblock covariance). The effect was so robust that most of the positive saliences (i.e., regions which correlated positively with the left hippocampus) survived a more conservative threshold of 7.00 (roughly equal to a z-score), whereas even at a low bootstrap ratio of 3.00 no negatively correlated regions emerged. We therefore extracted clusters of 10 or more voxels for lags 2 and 3 in which the bootstrap ratio was greater than 7.00 (see Table 2 and Fig. 3). The pattern of positively correlated brain activity with the hippocampal seed included bilateral hippocampi, bilateral frontal cortices (BA 44, 45, 47, 8, 9), bilateral retrosplenial cortices, left temporal pole, left precuneus, left inferior parietal cortex, left fusiform gyrus, right parahippocampal gyrus, left putamen, left insula lobe and left postcentral gyrus.

#### 3.4. Effective connectivity: SEM

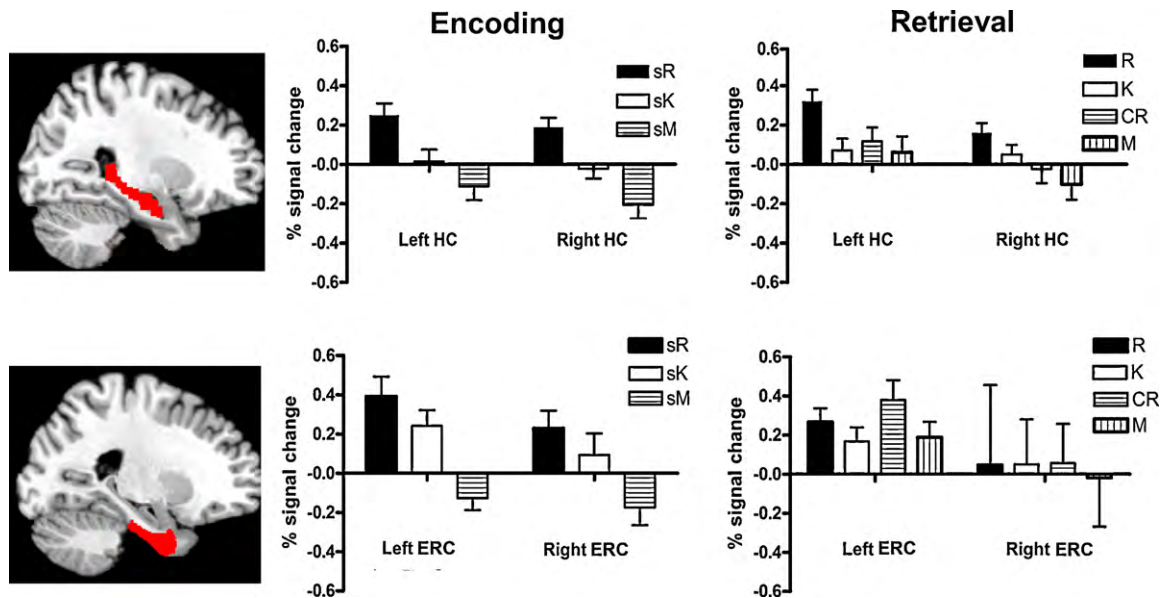
To examine whether the connectivity of hippocampal–neocortical networks differs between encoding and retrieval of relational memory, we conducted an SEM analysis (see Fig. 4). Despite a poor data fit of the null and alternative model (null model:  $\chi^2 = 181.76$ ,  $df = 58$ ,  $p < 0.0001$  and alternative model:  $\chi^2 = 138.54$ ,  $df = 44$ ,  $p < 0.0001$ ), inferences about task-dependent differences are considered valid (Protzner & McIntosh, 2006), particularly with stable models such as ours (both stability indices under 1) (Kline, 2005).

The omnibus SEM analysis revealed that the alternative model was a significantly better fit than the null model ( $p < 0.0001$ ). This finding reflected differences between encoding and retrieval of relational information in three connections (path coefficients

**Table 1**  
Behavioural results.

Item type	Remember	Know	New
Recognition decision			
Old	23.38 (7.04)	21.15 (4.77)	12.00 (5.45)
New	0.78 (0.97)	3.93 (2.76)	25.64 (4.18)
Reaction time (Old/New decision)			
Old	780 (266)	1028 (279)	1007 (562)
New	1016 (349)	1131 (506)	887 (188)
Reaction time (R/K decision)			
Old	958 (280)	934 (351)	1041 (338)
New	991 (518)	1109 (772)	917 (184)

Mean number of each type of recognition decision for old and new items and standard deviations (SD) collapsed over both scans (i.e., 60 old and 32 new faces in total). Mean reaction time and SD for both decisions collapsed over both scans.

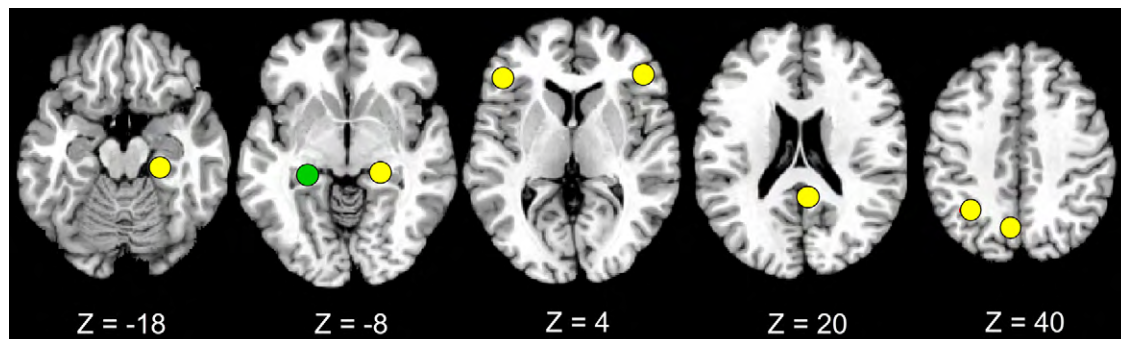


**Fig. 2.** Hippocampal and entorhinal contributions to relational processing. The first row shows % signal changes for all conditions within both hippocampi (HC) and the second row within both entorhinal cortices (ERC). Hippocampal and entorhinal ROIs masks are superimposed on a T1-weighted MRI. The hemodynamic responses for each condition were modeled using the SPM Anatomy Toolbox. Whiskers represent standard errors. sR = subsequent Remember; sK = subsequent Know; sM = subsequent Misses; R = Remember; K = Know; CR = Correct Rejection; M = Misses.

in brackets): 1. During encoding, there was a positive influence from the LHC to LIPC (Encoding: 0.81; Retrieval:  $-0.25$ ) 2. During retrieval the reverse effect was found, i.e., a positive influence from LIPC to LHC (Encoding:  $-0.31$ ; Retrieval: 0.95) and 3. During encoding, there was a positive influence from RHC to RRSC (Encoding: 0.91; Retrieval: 0.15). All other connections were indistinguishable between encoding and retrieval.

#### 4. Discussion

The purpose of this study was to examine patterns of neural interactions distributed across the brain for encoding and retrieval of relational information. Our analysis focused on the hippocampus as a critical region, as there is considerable experimental evidence suggesting it is strongly responsive to binding and reintegration



**Fig. 3.** Location of SEM nodes. Based on the seed PLS results, we selected eight nodes which were included in the SEM analyses. Here, we show the locations of these nodes, superimposed on a T1-weighted MRI using MRICroN. From left to right: right parahippocampal gyrus (RPHG, 26  $-28 -18$ ), left hippocampus (LHC,  $-18 -32 -6$ ), right hippocampus (RHC, 14  $-32 -10$ ), left inferior frontal gyrus (LIFG,  $-34 28 4$ ), right inferior frontal gyrus (RIFG, 36 26 2), right retrosplenial cortex (RRSC, 6  $-44 20$ ), left inferior parietal cortex (LIPC,  $-36 -56 40$ ), and left precuneus (LPC,  $-14 -70 42$ ). We extracted signal intensities for single voxels, the nodes in the figure are made bigger for display purposes.

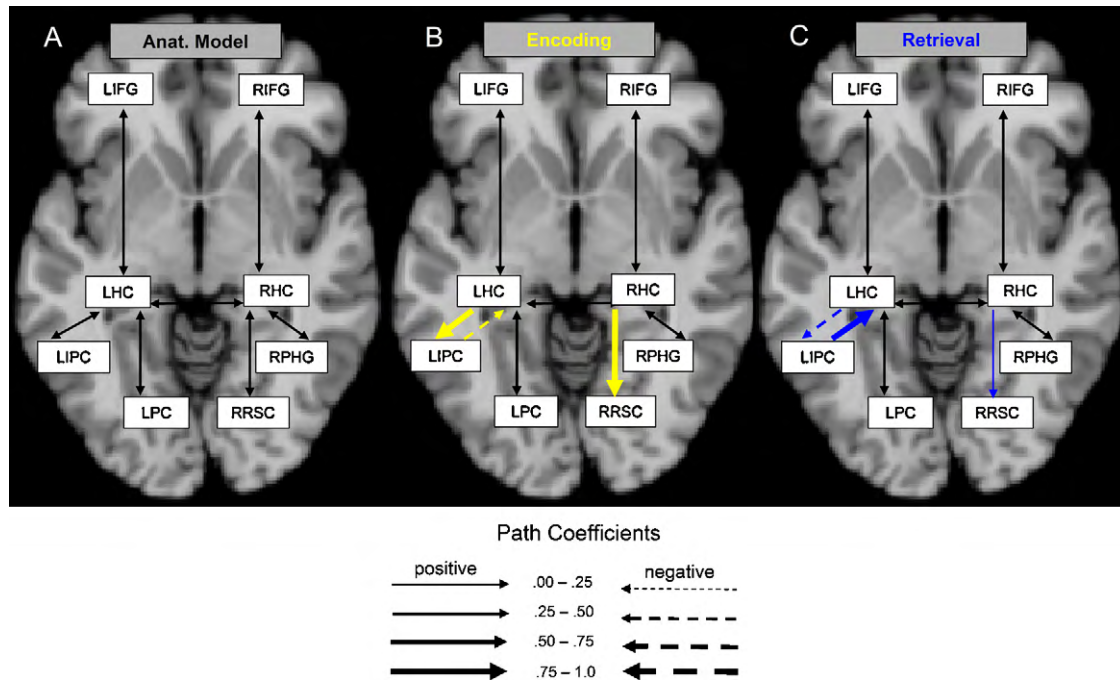
**Table 2**  
Seed PLS results.

Brain regions	BA	Coordinates			BSR	CS	SEM	
		X	Y	Z				
<b>Lag 2</b>								
Left	Hippocampus		-18	-32	-6	71.6	1871	a
Right	Hippocampus		14	-32	-10	16.5	575	b
Left	Precuneus	7	-14	-70	42	12.8	428	b
Right	Inferior frontal gyrus	47	36	26	2	12.4	226	b
Left	Superior frontal gyrus	8	-20	-10	62	11.5	30	
Left	Inferior frontal gyrus	47	-34	28	4	11.4	194	b
Right	Superior frontal gyrus	9	20	42	18	10.9	87	
Left	Middle frontal gyrus	8/9	-26	40	20	10.4	80	
Left	Retrosplenial cortex	29/30	-8	-48	24	8.6	107	
Left	Inferior parietal cortex	39	-36	-56	40	8.0	26	b
Left	Inferior frontal gyrus	45	-52	20	20	7.9	22	
Right	Retrosplenial cortex	29/30	6	-44	20	7.8	11	b
Left	Inferior frontal gyrus	44	-54	10	16	7.7	21	
<b>Lag 3</b>								
Left	Temporal pole	38	-52	16	-6	13.9	86	
Right	Inferior frontal gyrus	47	36	28	2	10.4	186	
Left	Putamen		-32	-2	2	9.8	66	
Left	Postcentral gyrus	2	-24	-50	52	9.7	98	
Left	Superior frontal gyrus	8	-20	-10	62	9.5	27	
Right	Parahippocampal gyrus	35/36	26	-28	-18	8.7	22	b
Left	Fusiform gyrus	37	-30	-71	2	8.3	19	
Left	Insula lobe	13	-44	0	6	8.0	11	
Right	Hippocampus		26	-37	6	8.0	11	
Left	Inferior frontal gyrus	44	-54	10	16	7.9	25	
Right	Retrosplenial cortex	29/30	6	-44	20	7.8	11	
Left	Inferior frontal gyrus	45	-52	20	20	7.5	10	

BA approx. Brodman area, BSR bootstrap ratio; CS cluster size in voxels; coordinates reported in MNI space. For brevity, only clusters for lag 2 and 3 are reported.

<sup>a</sup> Seed voxel.

<sup>b</sup> Included in the SEM analysis.



**Fig. 4.** Effective connectivity differs between encoding and retrieval of relational information. (A) Anatomical model for the effective connectivity analysis. Arrows represent anatomical connections that were included in the model, based on known primate neuroanatomy. (B and C) Representation of positive (solid) and negative (dashed) effective connections that differed between encoding (B, green) and retrieval (C, blue) of relational information. The thickness of the arrow represents the strength of the connection (path coefficient). LHC/RHC left/right hippocampus; LIFG/RIFG left/right inferior frontal cortex; LIPC left inferior parietal cortex; LPC left precuneus; RPHG right parahippocampal gyrus; RRSC right retrosplenial cortex.

of relations at both input and output stages (Eichenbaum, 2006; Eichenbaum et al., 2007; Spaniol et al., 2009). We explored both functional (seed PLS) and effective (SEM) patterns of connectivity between the hippocampus and various neocortical regions to elucidate similarities and differences between encoding and retrieval operations.

#### 4.1. Hippocampal ROI

Our study identified a region in the left posterior hippocampus that was activated for successful encoding ( $sR > sK$ ) and later retrieval ( $R > K$ ) of relational information. These findings are generally concordant with the current literature examining relational memory during encoding and retrieval (Cansino et al., 2002; Eichenbaum, 2006; Eldridge et al., 2005; Kirwan & Stark, 2004; Knowlton & Eldridge, 2006; Prince et al., 2005). What is particularly striking about our results is that the same region of the hippocampus that supports initial binding of information generated to enable the “personality” decisions with the face also supports retrieval/reintegration of elements of that experience. This high degree of spatial specificity within the hippocampus is compatible with recent electrophysiological recording data from hippocampal units. Gelbard-Sagiv, Mukamel, Harel, Malach, and Fried (2008) found that the same units that fired during encoding of a particular film clip reinstated that activity when subjects were able to retrieve those memories with the aid of cues. That is, successful encoding and retrieval of that rich multifaceted information involved the very same neural element in hippocampus.

These conclusions are strengthened by the use of a paradigm in which medial temporal lobe (MTL) damage is known to disrupt recollection of faces (Moscovitch & McAndrews, 2002). In our study, successful encoding of relational information was associated with bilateral posterior hippocampal activation, whereas for retrieval only left posterior hippocampal activation was above threshold, with right hippocampal activity falling below it. The latter finding is surprising, as face processing typically is associated with the right medial temporal lobe (Bengner et al., 2006; Chiaravalloti & Glosser, 2004; Kelley et al., 1998; Milner, 1968; Moscovitch & McAndrews, 2002; Moscovitch, Scullion, & Christie, 1976; Rizzolatti, Umiltà, & Berlucchi, 1970). It may be that while our encoding task (the ‘personality’ designation) engages both left and right medial temporal regions, initial binding of elements is more dependent on the right hippocampus and thus this step is undermined selectively by right medial temporal damage. Further, whereas our previous lesion study had used a set of faces that varied with respect to physical characteristics such as age, style of hair and dress, and emotional expression (Moscovitch & McAndrews, 2002), the stimuli in the current study were very similar looking faces (grey scale, appearance in the 20–30 year age range, no distinctive clothing, hair or adornment). In the absence of these obvious visual differences, the participants may have created more verbal associations during the personality decision task, which would account for the robust activation in the left hippocampus (Eichenbaum et al., 2007). Nonetheless, the scant literature on face associative memory in patients with medial temporal damage is mixed with respect to laterality and prevalence of deficits (Bird, Shallice, & Cipolotti, 2007; Cipolotti et al., 2006). Despite some small differences in detail, our study provides generally converging evidence from lesion and functional neuroimaging studies on the involvement of the MTL in recollective aspects of face recognition.

Activation in the entorhinal cortex (ERC) is rarely associated with recollection but it is consistently correlated with variations in item familiarity (Eichenbaum et al., 2007). Whereas during encoding, activity in this area is increased for items which are later judged as familiar in comparison to items which are later forgotten ( $sK > sM$ ) (Kensinger & Schacter, 2006; Ranganath et al., 2003),

activity during retrieval is decreased for familiar relative to forgotten or new items ( $M$  or  $CR > K$ ) (Daselaar, Fleck, & Cabeza, 2006; Montaldi, Spencer, Roberts, & Mayes, 2006). We support these findings, reporting greater activation for  $sK$  than  $sM$  within both ERC during encoding. During retrieval, activation within the left ERC was increased for  $CR$  versus  $K$ , but activation for  $M$  and  $K$  were similar. The elevated activation level for  $CR$  support other studies showing that the ERC detects novel information, generally called “novelty effect” (Daselaar et al., 2006; Kohler, Danckert, Gati, & Menon, 2005; Strange, Hurlmann, Duggins, Heinze, & Dolan, 2005).

#### 4.2. Functional connectivity

Based on the ROI results that the same region within the left posterior hippocampus was activated during both encoding ( $sR > sK$ ) and retrieval ( $R > K$ ) of relational information, we used seed PLS analysis to extract brain regions that were functionally connected to this hippocampal region. The seed PLS identified one significant latent variable (LV) of hippocampal functional connectivity, highlighting commonalities between encoding and retrieval of relational information<sup>1</sup> as assessed by remember responses. This result is not surprising, given the huge overlap between brain regions in the current literature on encoding and retrieval of relational memory (Skinner & Fernandes, 2007; Spaniol et al., 2009). Indeed, based on the recent review by Rugg et al. (2008), one would predict that the activation pattern elucidated during encoding should be reinstated during retrieval. As seed PLS is based on correlated patterns of brain activity, it does not permit us to specify the differential interactions between brain regions. However, it provides a powerful tool to detect functional connectivity between the seed voxel and other brain regions. In the current study, we used this information to construct an anatomical model for the effective connectivity analysis.

#### 4.3. Effective connectivity

Given the high overlap in brain regions involved in initial binding of relational information and its subsequent retrieval, we were specifically interested in whether differences would emerge in the patterns of effective connectivity, using anatomically based SEM. The overall SEM analysis revealed three significant differences in connectivity between nodes for encoding ( $sR > sK$ ) and retrieval ( $R > K$ ). We discuss each in turn.

##### 4.3.1. Hippocampal–parietal connections

During encoding, left hippocampal (LHC) activity showed a positive influence on left inferior parietal cortical (LIPC) activation, whereas during retrieval, the reverse occurred. This finding is very interesting as several recent review articles have begun to articulate the role of parietal-mediated contributions to episodic encoding (Uncapher & Wagner, 2009) and retrieval (Cabeza et al., 2008; Ciaramelli, Grady, & Moscovitch, 2008; Olson & Berryhill, 2009; Vilberg & Rugg, 2008; Wagner, Shannon, Kahn, & Buckner, 2005). Although there is no relevant empirical literature regarding the directionality of hippocampal–parietal interactions, some

<sup>1</sup> We cannot infer that all regions that are functionally connected to the seed voxel contribute only to remember–know differences. Given our SEM results that the parietal lobe is differentially involved in encoding and retrieval, and the recent reviews on parietal contributions to relational memory, it was important to check whether the selected parietal voxel supports recollection rather than familiarity. We, therefore, conducted a contrast (univariate analyses) for  $R > K$  and  $K > CR$  ( $p < 0.001$ , uncorrected). This analysis revealed that the parietal voxel we chose for the SEM model showed greater activation for  $R$  than  $K$ , but that it did not show activation for  $K$  versus  $CR$ . Thus, this voxel faithfully expressed the distinction of interest.



recent research using a correlational approach does demonstrate strong functional connectivity between brain activity in the inferior parietal cortex and hippocampus for episodic memory at retrieval (Takahashi, Ohki, & Kim, 2008; Vilberg & Rugg, 2009; Vincent et al., 2006). Our finding of increased effective connectivity between the hippocampus and parietal cortex is consistent with this literature, though we are the first to consider differences in the direction of connectivity between these structures at encoding and retrieval. In interpreting SEM findings with BOLD fMRI, it is important to bear in mind that directionality does not imply timing of signal/information flow. It is possible that the timing of initial events in the information transmission cascade, which could only be revealed by EEG or MEG (Astolfi et al., 2005, 2004), is distinct from the magnitude effects captured by fMRI in our study. Path coefficients here indicate directionality and strength of information flow (i.e., increases in region B cause increases in region A) over the time interval measured (McIntosh & Gonzalez-Lima, 1994).

In recent reviews, the LIPC has been considered in light of internally directed attention on memory processes (Cabeza et al., 2008; Ciaramelli et al., 2008). How might we conceptualize this in terms of our encoding results, where an increase in LHC activation led to an increase in LIPC activation? Recall that our encoding instructions were deliberately open-ended to encourage participants to use any information at their disposal to make the personality assignments. As there was sparse information in the nominal stimulus, this meant participants had to generate and reflect on potentially relevant and likely highly idiosyncratic information (e.g., that looks like my cousin Molly and she is quite the athlete – Sporty Type) which likely recruited attentional mechanisms in parietal cortex to focus on the relevant information that was delivered by this type of memory process. Indeed, it was our intention to encourage this rich internal generation of cues, as we thought it would more appropriately mimic realistic relational processing instead of the more arbitrary and somewhat sterile experimenter-provided associations that are seen frequently in this literature (e.g., the use of color or spatial location in source judgments or words embedded in unrelated scenes).<sup>2</sup> Therefore, success of this ‘internal attention to memory’ during encoding of stimuli, as reflected in subsequent recollection, may be an index of the degree to which hippocampal binding capability drives internal reflection. It is not merely the availability of appropriate associations that produces a memory ‘trace’ that supports recollection but the degree to which the hippocampus is engaged in integrating the product of that internal attention and reflection.

During retrieval, the reverse directionality was found, i.e., the LIPC had a positive influence on the LHC. Considering the relationship of attention and memory processes, this directionality would suggest that heightened internal attention enhances the probability of retrieval of self-generated associations and this in turn influences the likelihood of reintegration of those encoded elements. The path relationships here would seem at first blush to be contrary to predictions from the Attention to Memory model (Cabeza et al., 2008), which postulates a LHC to LIPC information flow in recollection. Indeed, that may well be the initial and critical pattern of signal transmission but precise timing information cannot be derived from fMRI BOLD and it could very well be that the LHC is sending an ‘initial flag’ to the LIPC to trigger reflexive attention but follow-

ing this initial hippocampal signal, the LIPC response exerts a direct influence on hippocampal activity. Even if we accept that the LIPC responds in a more reflexive than directive manner in recollection as asserted by AtoM, those authors were clear that the distinction between ‘top down’ and ‘bottom up’ attentional processes of the dorsal and ventral regions was “graded rather than sharp” (Cabeza et al., 2008) and we contend further that there may be an ongoing dynamic interplay amongst regions that is not easily captured by BOLD fMRI studies. We are currently collecting EEG data on similar paradigms that will allow us to examine these interactions at a higher temporal resolution.

#### 4.3.2. Hippocampal–retrosplenial connections

Relative to retrieval, there was a positive influence from the right hippocampus (RHC) to the right retrosplenial cortex (RRSC) during encoding. As a growing body of neuroimaging data show, the RSC is associated with a core network that underlies episodic memory (Byrne, Becker, & Burgess, 2007; Johnson et al., 2009). Vann et al. (2009) review the functional role of the RSC in a number of different cognitive tasks, such as navigation and episodic memory. They propose that the hippocampus indexes the location that is embodied in an episodic memory, scene or imagined event and the RSC then translates this information to an egocentric representation so that the memory, scene or imagined event can be viewed from a specific viewpoint. During learning, this circuitry is involved in constructing a scene (which need not be spatial per se but rather a coherent combination of elements from an egocentric perspective) that subsequently can be re-constructed or updated (Byrne et al., 2007; Hassabis & Maguire, 2009; Summerfield, Hassabis, & Maguire, 2010). This interpretation is also compatible with our findings. As described above, in our encoding setting, participants were asked to create all sorts of associations which may have involved many elements of scene construction to make a personality attribution. The success of those operations, indexed by increased activation and connectivity, translated into a higher probability of subsequent retrieval of those elements. From this perspective, it makes sense that RHC activity (i.e., imagining scenes or events), influences RSC activity (i.e., translating it to an egocentric viewpoint). At retrieval, the path coefficient for RHC–RRSC was also positive, indicating that retrieving these associations also influence RRSC activity, but this influence was much weaker, perhaps because there is less need for those translational operations if the event is recollected as an integrated whole.

This interaction was found in the right hemisphere, whereas including the left RSC resulted in an unstable model. It is interesting to note that throughout the various analyses, activity in the right hippocampus and its interactions with other cortical regions in the right hemisphere were strong at encoding and much weaker at retrieval. This may be specific to the face recognition task, or to the particular variant of encoding and retrieval conditions used here. Adjudication of these issues requires further systematic studies of encoding and retrieval with various types of materials, instructional sets, and analytic approaches to fMRI data.

#### 4.4. Generalizability of effective connectivity results

While there are several recent proposals for modeling hippocampal–neocortical interactions in memory (Cabeza et al., 2008; Rugg et al., 2008), ours is the first study to evaluate directly the strength and directionality of interactions using an effective connectivity analysis. However, we emphasize that these network models are only approximations that account for some aspects of the present data set. That is, the current connectivity analysis was only meant to explain variance attributable to a direct contrast of encoding and retrieval of relational information and only for those specific regions we elected to interrogate; it was

<sup>2</sup> A concern might be raised that this form of encoding leads to an unintended ‘mixing’ of retrieval with encoding processes, as in this example which illustrates one of many types of relational information our participants could have generated to complete the encoding task. Nonetheless, we are confident that our effects can be attributed to encoding processes given the results of the subsequent memory contrasts which parallel those established in previous studies as well as the different patterns of connectivity for encoding and retrieval in our own study.



not intended to directly test predictions of conceptual models such as AtoM. Furthermore, although we believe the connectivity results reflect regional interactions important to relational memory processing and recollection, this cannot be taken as a claim of exclusivity, in that we did not directly evaluate possible differential connectivity for other memory decisions (e.g., based on familiarity) or cognitive operations. We expect that the present models of hippocampal–neocortical interactions will be reformulated and improved in the light of new empirical outcomes to provide more general accounts of regional interactions in mnemonic processes. We argue that examining patterns and directions of connectivity for a variety of memory tasks and materials is necessary to permit elaboration and validation of biologically plausible models.

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