

Prefrontal and hippocampal contributions to the generation and binding of semantic associations during successful encoding

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The ability to form and bind associations between items is an important aspect of successful memory formation. We hypothesize that, during encoding, the left inferior frontal gyrus (IFG) supports generation of associations between items and the hippocampus then binds these associations. This study examined the parametric responses of these regions to varying amounts of generative and relational processing during successful encoding (i.e., for subsequently recognized items). Encoding involved presentation of word triads varying in the number of semantic associations among them (none, one or all); participants judged how many associations were present in each triad. Thus, triads with fewer associations had higher generative load while triads with more associations had higher relational load. Participants later completed a forced-choice recognition test for encoding triads. Successful encoding relative to a control task resulted in activation of bilateral IFG and left hippocampus, and the hippocampus also exhibited a significant subsequent memory effect (hits > misses). Linear parametric analyses revealed that generative load modulated activity in bilateral IFG while relational load correlated with activity in left hippocampus. Although univariate analyses distinguished IFG and hippocampal contributions to the generative and relational stages of encoding, respectively, effective connectivity between these regions did not differ according to condition. Furthermore, this analysis revealed that the left IFG played a pivotal role in coordinating associative encoding processes. Our findings illustrate that modulation of components in a memory network can be independent of patterns of mutual connectivity among those components in mediating successful encoding.

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The ability to form and bind associations between items is an important aspect of the successful formation of memories. It has been found consistently that the hippocampus is important in relational processing (Eichenbaum, 2001), such as the binding of associations between items during encoding. In line with this, damage to this region frequently results in impairments in encoding abilities (e.g., Rempel-Clower et al., 1996; Scoville and Milner, 1957; Zola-Morgan et al., 1986). Neuroimaging evidence provides an important complement to lesion evidence in the study of encoding, enabling investigation of the neural correlates of the encoding process independent of retrieval ability. Consistent with lesion evidence, a variety of associative encoding tasks produce robust hippocampal activations, including encoding of word pairs (Henke et al., 1999; Iidaka et al., 2000; Jackson and Schacter, 2004; Meltzer and Constable, 2005; Prince et al., 2005) and triplets (Davachi and Wagner, 2002; Lepage et al., 2000), object pairs (Achim and Lepage, 2005; Eldridge et al., 2005; Kohler et al., 2005), name–face pairs (Sperling et al., 2001, 2003), word–font pairs (Prince et al., 2005), item–source (Davachi et al., 2003) and item–location (Kohler et al., 2005; Sommer et al., 2005) pairs, landscapes and complex scenes (Dickerson et al., 2004; Montaldi et al., 1998). This is in striking contrast to earlier studies that failed to find encoding-related hippocampal engagement (e.g., Baker et al., 2001; Kapur et al., 1994; Mandzia et al., 2004; Otten and Rugg, 2001; Wagner et al., 1998) which may reflect, at least in part, the use of encoding paradigms requiring processing of items rather than relations between items (Schacter and Wagner, 1999).

The binding of items into an integrated trace presumably first requires that some association is generated. The use of frontally-based strategic processes, such as ‘chunking’ information (Bor et al., 2004), forming associations between items (Fletcher et al., 2000) or processing the semantic meaning of information (i.e., “deep” processing, e.g., Kapur et al., 1994; Mandzia et al., 2004), enables the generation of associations that contribute to optimal encoding performance (Bor et al., 2004; Fletcher et al., 2000). Indeed, prefrontal cortex (PFC) is activated reliably by encoding (for reviews see Buckner et al., 1999; Buckner and Koutstaal, 1998), including associative encoding (Cabeza et al., 1997a; Iidaka et al., 2000; Kapur et al., 1994; Lepage et al., 2000; Montaldi et al.,

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1998; Sperling et al., 2001), particularly when elaborative encoding strategies such as deep encoding (e.g., living/non-living judgment vs. “shallow” judgments on surface or perceptual characteristics) are employed (e.g., Baker et al., 2001; Kapur et al., 1994; Mandzia et al., 2004; Otten et al., 2001). It appears that inferior regions of the lateral PFC in particular track encoding success (Blumenfeld and Ranganath, 2006). Findings of subsequent memory effects have even been demonstrated when encoding occurs during the delay period of working memory (Ranganath, 2006; Ranganath et al., 2005a), particularly when the working memory task emphasizes inter-item relations (Blumenfeld and Ranganath, 2006). Whether such encoding-related PFC activity is lateralized to the left PFC (Hemispheric Encoding Retrieval Asymmetry, or HERA model, Tulving et al., 1994) or whether it is lateralized according to stimulus modality (e.g., Kelley et al., 1998; Kirchoff et al., 2000; McDermott et al., 1999; Rugg, 1998) remains a matter of some debate. Regardless of lateralization, it is clear that PFC regions contribute to strategic processing during associative encoding.

The aim of this study was to examine the contributions of PFC and hippocampus to the generation and binding of semantic associations during successful encoding. To do so, we used a semantic-relatedness paradigm, in which triads with varying numbers of semantic relations were presented during encoding (Mathews, 1977, see Lepage et al., 2000 for a neuroimaging adaptation of this task), enabling manipulation of generative and relational load. Specifically, triads with fewer associations had higher generative load, based on the assumption that, if successful associative encoding requires the binding of associations and none are provided, one has to generate associations. Thus, it is likely that a substantial part of the duration of these encoding trials is concerned with the generation of associations, which can then be bound by the hippocampus. Therefore, event-related analysis of these trials using a hemodynamic response function (hrf) should tap the generation of associations rather than binding occurring in the latter part of the trial. In contrast, triads with more semantic associations had higher relational load. Thus, successful encoding would simply require binding of the provided associations for the duration of the encoding trial. As such, event-related analysis of these trials should tap the relational binding of associations.

During this intentional encoding task, participants judged the number of semantic associations in each triad, and in keeping with the use of similar orienting tasks, we predicted that the PFC would be engaged during encoding. We hypothesized that the left inferior frontal gyrus (IFG) would be particularly involved, due to evidence suggesting that this PFC region is involved in semantic generation and judgments (Poldrack et al., 1999; Stebbins et al., 2002), generation of semantic associations between to-be-encoded items (Fletcher et al., 2000) and, more generally, successful verbal encoding (e.g., Baker et al., 2001; Blumenfeld and Ranganath, 2006; Otten and Rugg, 2001; Wagner et al., 1998). Furthermore, we expected to replicate previous findings that this region is increasingly active when fewer associations are provided, as with the high generative load conditions here (Fletcher et al., 2000; Lepage et al., 2000).

We also predicted that the hippocampus would be engaged during successful encoding, primarily on the left given the verbal nature of the task (e.g., Davachi and Wagner, 2002; Strange et al., 2002). More importantly, it was hypothesized that hippocampal engagement would be modulated by relational load. Interestingly, Lepage et al. (2000) reported activation of the hippocampus during

associative encoding (relative to cued-recall) but failed to find any modulation of hippocampal activity with relational load. This is contrary to the hypothesized role of this structure in relational processing and, more specifically, associative encoding. This lack of hippocampal modulation may be due, however, to the block design of this PET study and the inability to remove trials of unsuccessful encoding from the analysis. Inclusion of such trials, which presumably involve inefficient or little hippocampal activation, may ultimately obscure the ability to find a hippocampal effect. Indeed, in an examination of successful relational encoding of triplets, Davachi and Wagner (2002) found that encoding-related hippocampal activity was greatest when all three words were subsequently remembered. Although relational load was not directly manipulated in their paradigm, these data suggest that the amount of relational processing during successful encoding was positively correlated with hippocampal activity. Accordingly, an event-related fMRI design was employed in our study, and only those encoding trials for which triads were subsequently recognized (i.e., successful encoding) were included in analyses.

An additional aim of this study was to examine the effective connectivity of the IFG and hippocampus during associative encoding. Previous studies have suggested that the IFG may influence the hippocampus during encoding (e.g., Reber et al., 2002), and there has been some examination of the functional connectivity of the IFG and hippocampus during encoding (e.g., Grady et al., 2003; Habib et al., 2003; Ranganath et al., 2005a,b). However, to our knowledge, this is the first study to examine effective connections, and the directionality of such connections, between these regions during successful encoding. We hypothesized that, if the IFG generates associations which are then bound by the hippocampus, this sequence of processes should result in stronger effective connectivity from IFG to hippocampus. Furthermore, we anticipated that this pattern of connectivity would be most evident under conditions of high generative load.

Materials and methods

Participants

Twelve healthy right-handed adults (five male, seven female; mean age, 26.25 years; range, 21 to 34 years), with no history of neurological or psychiatric impairment, participated in this study. The average number of years spent in formal education was 19.90 years (range, 16 to 26 years). All participants gave written informed consent for the study, approved by the University Health Network Research Ethics Board.

Encoding task

The semantic-relatedness encoding task (Mathews, 1977) involves the presentation of triads consisting of a category name and two category exemplars (see Fig. 1a). Fifty-four of the triads used in this study were identical to those used by Lepage et al. (2000), and an additional fifty-one triads were constructed for the present study. These triads were constructed using the Battig and Montague (1969) and Murdock (1976), such that only exemplars frequently associated with a category were used. Over the duration of scanning, 105 encoding triads were shown, 35 of each of three trial types: (1) triads in which no exemplars relate to the category name (“zero-link” trials; high in generative load, low in relational load); (2) triads in which only one exemplar relates to the category

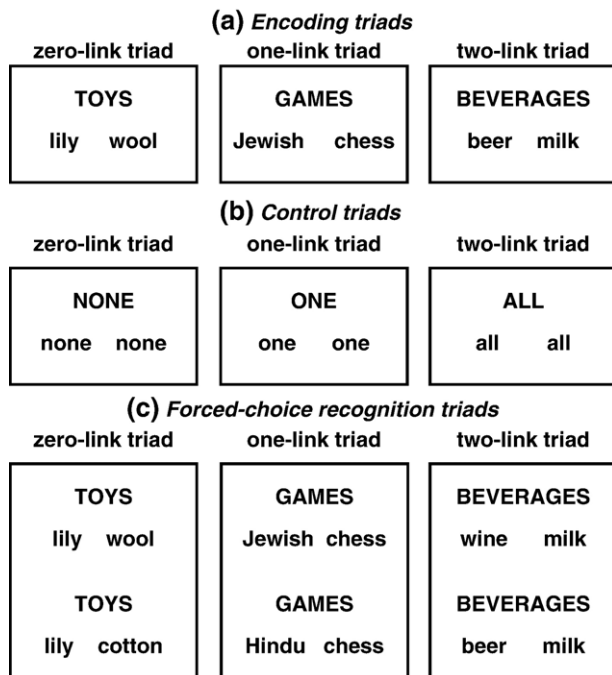


Fig. 1. (a) Examples of in-scanner stimuli presentation for zero-, one- and two-link triad conditions. Each triad consists of a category name (top) and two category exemplars (bottom) which are either semantically related or unrelated to the category, depending on the condition. (b) In-scanner presentation of the control triads for each trial type. (c) Examples of forced-choice recognition trials, in which one previously seen triad and one foil triad were presented.

name (“one-link” trials); and (3) triads in which both exemplars relate semantically to the category name (“two-link” trials; low in generative load; high in relational load). Control trials, consisting of triads of one word corresponding to a response option (i.e., either “none”, “one” or “all”; Fig. 1b), were randomly interspersed through scanning.

Forced-choice recognition task

Identification of successfully encoded triads was based on subsequent recognition of triads during forced-choice recognition. Each of 105 trials consisting of an old triad presented during scanning and a new triad (see Fig. 1c) was presented. New triads were identical to the old triad, except for one exemplar being replaced with a semantically related foil which was taken from the same category in the category norms (Battig and Montague, 1969; Murdock, 1976). The position of the old and new triads (i.e., top or bottom half of the screen) was assigned randomly. Furthermore, the position of the foil (i.e., whether the left or right exemplar is replaced) and whether the foil replaced a related or non-related exemplar in one-link triads was also assigned randomly to triads.

Procedure

Prior to scanning, participants were familiarized with the encoding task by presenting four practice trials. The instructions emphasized that memory for the encoding triads would be tested subsequently. During scanning, all stimuli were presented in black text on a white background and back-projected onto a white screen

viewed by the participants through a mirror incorporated into the head coil. E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) was used for the presentation and timing of stimuli and collection of reaction times and response data. Responses were made on an MR-compatible five-button response box (Rowland Institute of Harvard, Cambridge, MA).

The scanning session was divided into 3 runs, each a duration of 9 min 20 s. During each run, 46 trials (control, zero-link, one-link and two-link triads) were presented in a random order, with trials averaging 12 s in duration. Each trial consisted of the triad presentation for 6 s, and a fixation cross for an average of 6 s (the duration of fixation cross was jittered, ranging between 4 and 8 s). Six seconds was considered sufficient for triad encoding, based on the results of Lepage et al. (2000), in which triads were presented for 5.5 s. For each encoding triad presentation, participants were required to decide how many of the words in the lower portion of the triad could be considered exemplars of the category named in the top portion of the triad. The buttons on the response box assigned to each response were as follows: “none” (right index finger); “one” (right middle finger); or “all” (right ring finger). Thus, the three encoding trial types (zero, one and two link) are identical in terms of the cognitive task to be performed and vary only in terms of the number of semantic associations provided. During presentation of control triads (i.e., a triad consisting of either the word “none”, “one” or “all”), participants were required to respond according to the word shown (i.e., to select the response key corresponding to “none”, “one” or “all”).

Immediately following scanning, individuals completed the forced-choice recognition task. Each old–new triad presentation was displayed for 6 s, during which time the participant indicated which triad was seen previously during scanning with a mouse button press. Each old–new display was followed by a 1-second fixation cross. Note that, if a response was made while the old–new triad was still being presented (i.e., within 6 s), the display moved ahead to the fixation cross. On the basis of these data, only those trials which were subsequently recognized (and thus successfully encoded) were entered into analyses.

Data acquisition

Data were acquired on a 1.5 T GE magnet, using standard single-shot spiral acquisition (TE=40 ms, TR=2000 ms, FOV=220 mm). Twenty-five slices, each 5 mm thick with a 1 mm gap, were collected, covering the entire brain. These were acquired in a coronal-oblique orientation, with each slice being perpendicular to the long axis of the hippocampus to avoid partial volumes of this structure. The first three frames were dropped to allow for signal equilibrium. To acquire anatomical images, a standard three-dimensional T₁-weighted sequence (FOV=200) was used to generate 60 axial slices (2.2 mm thick).

Data processing and statistical analyses

All preprocessing and analyses of imaging data were performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). All functional images were co-registered to a structural image, realigned for motion correction, corrected for within-frame time of acquisition, spatially normalized and smoothed using a Gaussian kernel of 7.6 mm full-width half maximum. Data were high-pass filtered to account for low-frequency drifts; a cut-off value of 128 was used. Each stimulus

event was modeled by SPM2's canonical hrf (applied at task onset), and the six head-movement parameters were included as confounds. For contrasts and parametric modulation analyses, each participant's data were analyzed as a fixed-effects model, and the resulting contrast images were taken to the second level and analyzed as a random-effects model.

Univariate contrasts

We examined regions engaged during the encoding of zero-, one- and two-link conditions (for triads which were subsequently recognized) relative to the control task. All maxima reported for the contrast of successful encoding and control trials were significant at a level of $p \leq .005$, corrected for whole-brain false discovery rate (Genovese et al., 2002) and survived an extent threshold of 10 contiguously activated voxels ($2 \times 2 \times 2$ mm). Furthermore, as we had an a priori prediction that the left hippocampus would be active during verbal encoding, a small volume correction was applied to the activation map for this contrast (thresholded at $p < .005$, uncorrected) and only those activations with a threshold of $p \leq .05$ (corrected for false discovery rate across the hippocampal region) were included in the results. The left hippocampal region of interest mask was created in Montreal Neurological Institute (MNI) space using MARINA (Bertram Walter Bender Institute of Neuroimaging, University of Giessen, Germany).

Although direct examination of subsequent memory effects (i.e., activation for hits > misses) was not the main purpose of this encoding analysis, previous studies have found the magnitude of IFG and hippocampal activation to be related to encoding success characterized by that contrast. Therefore, we examined this contrast in three a priori regions of interest (ROIs) found to be significantly active during encoding relative to control trials: (1) left IFG; (2) right IFG; and (3) left hippocampus. Using MarsBar (Brett et al., 2002), percent signal change was extracted from spherical ROIs (radius = 10 mm) centered on the peak voxel in the left and right IFG. Within the left hippocampus, percent signal change was only extracted from the peak voxel given the lateral location of this activation and the fact that a spherical ROI would encompass other structures. Graphs illustrating percent signal change in these ROIs during hits, misses and control trials were constructed.

Parametric modulation analyses

Two random-effects parametric modulation analyses were performed to examine the linear effects of semantic-relatedness (i.e., number of semantic links provided). The first specified a negative linear relationship to identify regions which correlate with generative load (i.e., with lower semantic-relatedness) and the second specified a positive linear trend to identify regions which correlate with relational load (i.e., with higher semantic-relatedness). Furthermore, as recognition performance appeared to demonstrate a non-linear trend, with a significant difference between accuracy for zero- and one-link triads but not one- and two-link triads (i.e., a combination of linear and quadratic components), we performed an additional random-effects analysis to identify regions matching this behavioral pattern by applying the contrast $[-1 \ 0.5 \ 0.5]$ to zero-, one- and two-link conditions, respectively. This would indicate whether the magnitude of activation during encoding in our principal regions of interest, IFG and hippocampus was more reflective of subsequent recognition accuracy than of relational load per se. For all parametric modulation analyses, percent signal change associated with encoding of zero-, one- and two-link triads was extracted using MarsBar (Brett

et al., 2002) from spherical regions of interest (ROIs; radius = 10 mm) centered on the peak voxel in the left and right IFG and left anterior hippocampus/amygdala. Given that the peak voxel of the cluster encompassing the left anterior hippocampus was located in the amygdala, a spherical ROI (radius 10 mm) was used such that signal was extracted from, and averaged across, both structures. The significance threshold for these analyses was set at $p < .005$ (uncorrected), in keeping with other parametric modulation studies (e.g., Addis et al., 2004; Rombouts et al., 1999). An extent threshold of 10 contiguously activated voxels ($2 \times 2 \times 2$ mm) was also applied. Finally, for all analyses, Montreal Neurological Institute co-ordinates were converted to Talairach space, and regions of activations were localized in reference to a standard stereotaxic atlas (Talairach and Tournoux, 1988).

Lateralization index

Our preliminary analyses indicated that the IFG was activated bilaterally, and as there is some debate in the literature over the laterality of verbal semantic encoding in the PFC, we decided to calculate a lateralization index to explore this issue directly. Firstly, masks of the left and right IFG were created in MNI space using MARINA. These were then applied to map of t -scores corresponding to each contrast using the *imcalc* function in SPM, thus creating images containing only those t -scores within the left or right IFG. Counts of voxels whose t -scores exceeded the relevant threshold (i.e., $p < .001$ or $t = 4.02$ for the contrast of encoding and control tasks; $p < .005$ or $t = 3.11$ for the parametric modulation analysis of generative load) were extracted. These counts were converted to proportions of the total number of voxels in each masked region from which signal was collected (i.e., to account for slight differences in the number of voxels within the LIFG and RIFG from which any signal was measured). These data were then used to calculate a lateralization index using the formula $(L - R) / (L + R)$, where L = proportion of left IFG voxels exceeding significance threshold and R = proportion of right IFG voxels exceeding significance threshold. Thus, scores falling around zero indicate little asymmetry in IFG activity; a negative score reflects more activation in the right IFG relative to the left; and a positive score indicates more activation in the left IFG relative to the right.

Effective connectivity analysis

In order to examine the interactions between inferior frontal and MTL regions during encoding, effective connectivity analyses were performed using structural equation modeling (SEM). In contrast to simple correlations between activity in regions of interest, SEM accounts of patterns of correlations activity across all nodes and also provides information about directionality of influences between regions. Two SEM analyses were performed. Firstly, we determined whether patterns of effective connectivity differed between the high generative (i.e., the zero-link condition) and high relational (i.e., two-link condition) conditions. Secondly, we examined the effective connections between regions during associative encoding irrespective of relational and generative load (i.e., successful associative encoding across the zero-, one- and two-link conditions).

Region selection

The selection of regions for these analyses was based upon the theoretical relevance (e.g., Buckner et al., 1999; Schacter and Wagner, 1999) and the findings from our parametric modulation

analyses. Only regions that were (1) significantly active during encoding relative to control trials and (2) significantly modulated by generative or relational load were considered. The peak voxel location for each region was based upon the results of the group parametric modulation analyses. Four regions were selected: left IFG (LIFG, Brodmann area, BA 45; $x=-57$ $y=20$ $z=16$) and right IFG (RIFG; BA 46; $x=-42$ $y=30$ $z=11$), which responded to generative load; and left hippocampus (LHC; $x=-22$ $y=-9$ $z=-16$) and left inferior parietal lobule (LIPL, BA40, $x=-46$ $y=-40$ $z=52$) which modulated with relational load. Note that, although the right inferior parietal lobule met these inclusion criteria, as it was significantly modulated by relational load, the preliminary models were unstable when it was entered and so it was excluded from further consideration.

For each individual, the signal intensity (i.e., the relative difference between neural activity associated with two conditions) was extracted from each voxel in the relevant contrast images. In order to obtain signal intensity data for the high generative and high relational load encoding analysis, two additional contrasts were modeled for each individual: (1) a contrast of zero-link and control tasks to obtain signal intensity data for the high generative load condition; and (2) a contrast of two-link and control tasks to obtain signal intensity data for the high relational load condition. For the associative encoding effective connectivity analysis, data were extracted from individual contrast images corresponding to the comparison of successful encoding (collapsed across zero-, one- and two-link conditions) with the control task.

Model construction

An anatomical model of multi-synaptic connections between the LIFG, RIFG, LHC and LIPL was based upon known primate neuroanatomy (Clower et al., 2001; Felleman and van Essen, 1991; Insausti et al., 1987; Insausti and Munoz, 2001; Mesulam et al., 1977; Petrides and Pandya, 1984, 1999; Rockland and Van Hoesen, 1999; Schall et al., 1995; Suzuki and Amaral, 1994). This model pre-specifies where connections may exist and the potential direction of these connections based on anatomy and ensures that any significant connections found between regions are anatomically viable (Gilboa et al., 2004; McIntosh, 1999). The anatomical model is illustrated in Fig. 2. A functional model for each condition (high generative load, high relational load, associative encoding) was constructed using the signal intensity data from the relevant contrast images of each participant. The extracted signal intensities for all regions were correlated, and the resulting correlation matrix constituted the functional model for that condition.

Path analysis

All structural equation modeling calculations were performed using Lisrel 8.30 (Joreskog and Sorbom, 1993). For all path analyses, the matrix of correlations of beta values among regions in the anatomical model was decomposed, and structural equations were solved to derive estimates of path coefficients (for a detailed explanation, please refer to McIntosh and Gonzalez-Lima, 1994). The resulting coefficients can range from -1 to 1 , with values closer to either end of the range being the maximum strength of a negative or positive connection, respectively. Unlike simple correlations, path coefficients are asymmetric (e.g., the path coefficient for the influence of region A upon B can be different from the path coefficient for the influence of region B upon A), thus providing information about the directionality of inter-regional interactions. Significant differences across between the

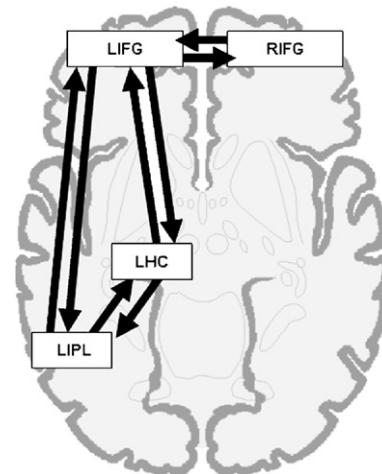


Fig. 2. Anatomical model for the effective connectivity analyses. Arrows represent the anatomical connections that were included in the model, based on known primate neuroanatomy. Note that the connections included in the model do not necessarily reflect monosynaptic connections (i.e., neuron to neuron) but rather multi-synaptic relays. The locations of the structures on the brain schematic are not accurate and are placed to maintain clarity. LIFG=left inferior frontal gyrus (BA 45; $x=-57$ $y=20$ $z=16$); RIFG=right inferior frontal gyrus (BA 46; $x=42$ $y=30$ $z=11$); LHC=left hippocampus ($x=-22$ $y=-9$ $z=-16$); LIPL=left inferior parietal lobule (BA40, $x=-46$ $y=-40$ $z=52$).

high generative and high relational encoding conditions were then assessed using the stacked-model approach (McIntosh and Gonzalez-Lima, 1994). A null model was first constructed in which the path coefficients were set to be equal across groups. This was compared with a second, alternative model in which the path coefficients were allowed to vary. The differences between the models were then assessed by subtracting their goodness-of-fit χ^2 values to obtain a χ^2_{diff} . Significant differences between the conditions are indicated by a significantly lower χ^2 value for the alternative model (i.e., a greater χ^2_{diff} between the models). Thus, statistical significance of the χ^2_{diff} was determined by the difference of degrees of freedom between the null and alternative models. Upon finding no significant difference between these conditions, we then sought to examine the pattern of effective connectivity associated with successful associative encoding from all conditions. In this analysis, only one model was constructed in which the path coefficients were free to vary, and the fit of this model to the data was assessed.

Results

Behavioral results

The average accuracy and reaction times for the encoding judgments (i.e., how many exemplar words fit within the category) are presented in Table 1. These encoding data were collected from all but one participant, for whom data did not record successfully due to a technical failure. A univariate analysis of variance (ANOVA) confirmed that there was no main effect of condition (zero-, one- and two-link) for either accuracy, $F(2,32)=.412$, $p=.666$, or reaction times, $F(2,32)=.529$, $p=.594$.

Average forced-choice recognition accuracy and reaction time data from all participants are also presented in Table 1. A

Table 1
Mean accuracy and reaction time data from the encoding judgment task and forced-choice recognition

	Encoding task			Recognition task		
	0-link	1-link	2-link	0-link	1-link	2-link
Accuracy—mean	95.32	94.55	93.51	68.81*	81.43	85.71
Accuracy—SD	5.89	4.51	3.40	14.49	9.71	8.79
Reaction time—mean	2674.77	2523.66	2417.21	3218.84	2939.85	2607.24
Reaction time—SD	619.17	623.23	521.66	676.37	647.68	530.15

SD=standard deviation.

* Significantly different from all other conditions, $p < .01$.

univariate ANOVA revealed a main effect of condition, $F(2,35) = 7.29$, $p < .010$. Post hoc Bonferroni tests showed that recognition accuracy was significantly reduced for the zero-link condition, relative to both the one-link ($p < .010$) and the two-link ($p < .010$) conditions. There was no difference between the one- and two-link conditions ($p = 1.000$). A univariate ANOVA on reaction time data from the recognition task indicated that there was no main effect of condition, $F(2,35) = 2.915$, $p = .068$, though there was a trend towards significantly faster reaction times when more links were given at encoding.

Successful encoding

To determine which neural regions were differentially active during successful encoding relative to the control task, a univariate contrast of these conditions was conducted (see Table 2 and Fig. 3a). Successful encoding engaged the IFG bilaterally (left BA 44 and right BA 44/45/46), though activation in the peak left IFG voxel was higher in signal intensity (though note,

across the 10 mm ROI activity in the right IFG was higher; see Fig. 3a) and more spatially extensive (as indicated by a positive laterality index, .584). Furthermore, as hypothesized, the left hippocampus was also significantly activated. Additional regions were also engaged by successful encoding, including left medial (BA 6/8) and right middle (BA 46) frontal gyri, bilateral anterior cingulate (BA 32), ventrolateral thalamus and inferior parietal lobule (BA 40), and left fusiform and inferior/middle occipital (BA 19) gyri.

Subsequent memory analyses in regions of interest

Three regions of interest were significantly engaged during encoding relative to the control task: left and right IFG and left hippocampus. To determine whether activity associated with successful encoding was significantly different from that associated with the encoding of subsequently forgotten triads, a subsequent memory analysis was performed. Percent signal change corresponding to hits and misses was contrasted using a paired t -test (see Fig. 3a). This revealed that activity in the left hippocampus did in fact track encoding success relative to encoding failure ($t = 1.753$, $p = .054$). However, neither the left ($t = 0.908$, $p = .192$) nor right ($t = -0.117$, $p = .454$) IFG exhibited a subsequent memory effect.

Parametric modulation analyses

Three analyses were undertaken to investigate whether the BOLD signal varied systematically with generative load, relational load or recognition accuracy. Only items that were subsequently recognized were included in these analyses.

Generative load

Activity in the bilateral inferior frontal gyrus (BA 45/46) was correlated with generative load (i.e., negatively correlated with the number of associative links present in triads; see Table 3 and Fig. 3b). Thus, encoding a triad containing fewer semantic associations was associated with increased inferior frontal engagement. Interestingly, the regions of the left and right IFG which were modulated by generative load were fairly similar in spatial extent, though the RIFG activation was slightly more extensive (as indicated by a negative lateralization index, -0.145). Even so, signal intensities in the left IFG regions modulated by generative load were higher than those evident on the right (see plots of percent signal change, Fig. 3b). Additional frontal regions also modulated by generative load included bilateral middle frontal gyrus (BA 9/10) and right superior frontal gyrus (BA 10). Right middle temporal gyrus (BA 39) and left posterior cingulate cortex (BA 23) also exhibited significant parametric responses to generative load.

Table 2
Regions active during successful encoding relative to the control task

Brain region	Co-ordinates			Z-score
	x	y	z	
L. inferior frontal gyrus (BA 44)	-61	9	16	4.61
R. inferior frontal gyrus (BA 44/45/46)	40	26	6	4.16
R. middle frontal gyrus (BA 46)	46	28	19	3.85
L. medial frontal cortex (BA 6/8)	-12	14	44	4.67
L. anterior cingulate cortex (BA 32)	-8	21	38	4.68
R. anterior cingulate cortex (BA 32)	4	20	41	4.69
L. ventral lateral thalamus	-16	-17	5	4.64
R. ventral lateral thalamus	10	-13	3	4.03
L. hippocampus ^{a,b}	-16	-31	-2	3.07
L. inferior parietal lobule (BA 40)	-44	-37	44	5.01
R. inferior parietal lobule (BA 40)	34	-46	45	4.59
L. fusiform gyrus (BA 37)	-42	-53	-18	4.84
L. inferior/middle occipital gyrus (BA 19)	-46	-66	-7	4.94
L. cerebellum	-36	-61	-20	5.16
R. cerebellum	18	-76	-35	5.57

All peak activations (except for left hippocampus) are significant at $p < .005$ (corrected for false discovery rate across the whole brain). For each region of activation, the co-ordinates of the maximally activated focus within each different structure are reported, as indicated by the highest Z-score. BA = Brodmann area.

^a Application of a small volume correction revealed that activation in the left hippocampus was significant at $p = .05$ (corrected for false discovery rate).

^b This region exhibited a significant subsequent memory effect (hits > misses, $p < .05$).

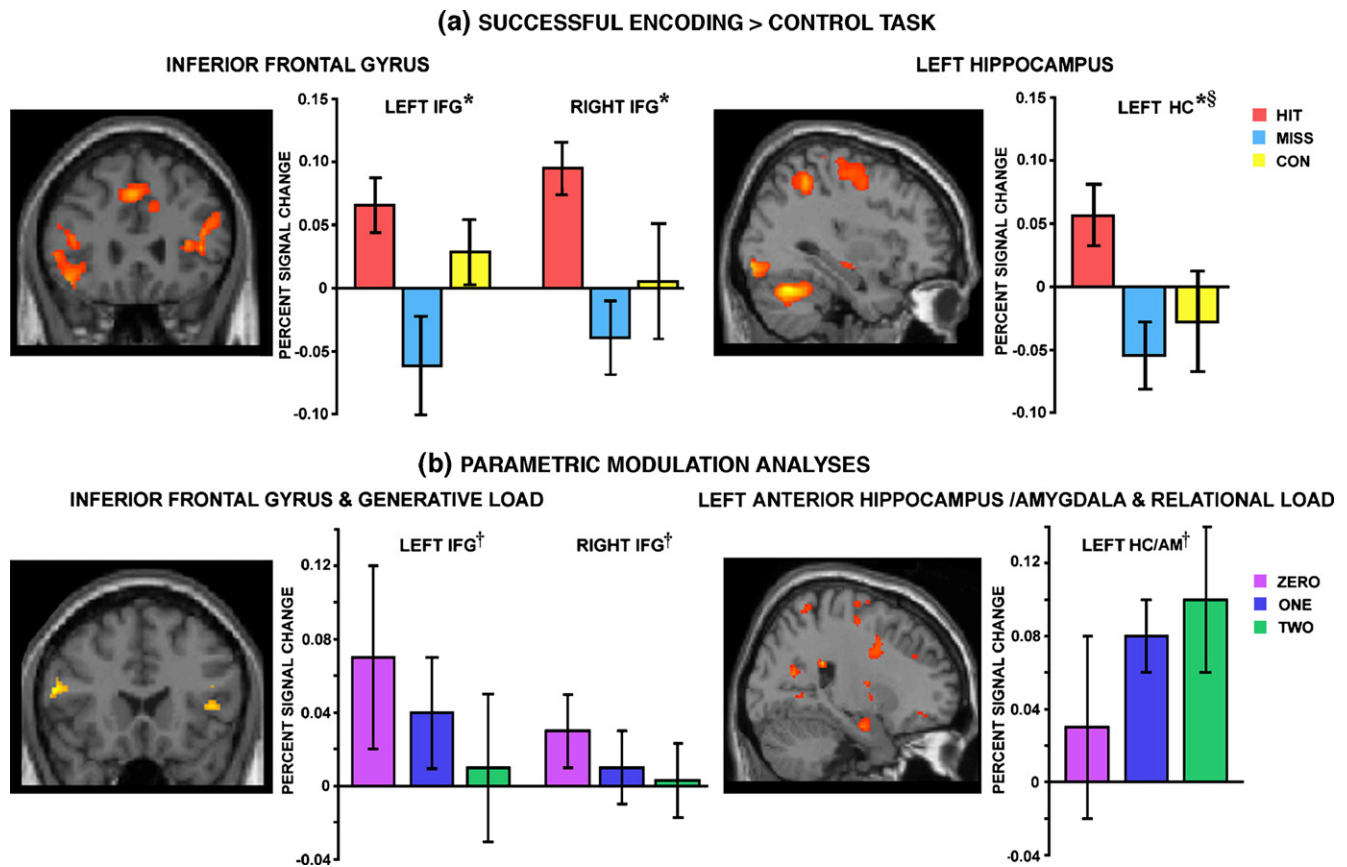


Fig. 3. (a) Regions significantly activated during successful encoding (relative to the control task), including left inferior frontal gyrus (BA 44, $x=-61, y=9, z=16$), right inferior frontal gyrus (BA 44/45/46, $x=40, y=26, z=6$) and left hippocampus ($x=-16, y=-31, z=-2$). Percent signal change associated with the encoding of subsequently recognized (i.e., hits) or forgotten (i.e., misses) triads, as well as control trials are plotted. These data were extracted from left and right inferior frontal ROIs (a sphere with a 10 mm radius, centered on the peak voxel) and a left hippocampal ROI (the peak voxel). Significant differences between hits and misses (i.e., subsequent memory effect; $\$p \leq .05$) or between hits and control trials ($*p < .005$, corrected for false discovery rate) are indicated where applicable. (b) Bilateral inferior frontal regions were modulated by the generative load of the encoding task (left BA 45; $x=-57, y=20, z=16$; right BA 46; $x=42, y=30, z=11$), while the left anterior hippocampus/amygdala ($x=-22, y=-9, z=-16$) was modulated by relational load. Plots illustrating percent signal change during the successful encoding of zero-, one- and two-link triads are included (for all activations, the ROI constituted a sphere with a 10 mm radius, centered on the peak voxel). These linear trends were significant at $p < .005$, uncorrected (as indicated by †). All activations are displayed at $p < .005$ (uncorrected). AM=amygdala; CON=control task; IFG=inferior frontal gyrus; HC=hippocampus; ONE=one-link encoding task; TWO=two-link encoding task; ZERO=zero-link encoding task.

Relational load

Notably, activation of the left hippocampus correlated with relational load (see Table 3 and Fig. 3b). In other words, when encoding triads contained more semantic associations, left hippocampal activity was increased. Other regions exhibited similar responses to relational load, including the left ventrolateral thalamus, insula (BA 13), middle temporal gyrus (BA 39) and posterior cingulate (BA 31), right supramarginal (BA 39/40) and lingual (BA 18) gyri and bilateral inferior parietal lobule (BA 40).

Recognition performance

This parametric modulation analysis was conducted to identify those regions exhibiting a positive non-linear trend (two-link and one-link > zero-link) to semantic-relatedness, similar to the effect evident in recognition accuracy. Given that left hippocampal activity followed a positive linear trend (i.e., to relational load), it was expected that this region would also show a response when modeled using a combination of linear and quadratic functions. This was not

the case, indicating that hippocampal activity did not directly track recognition performance in this way. Furthermore, activity within inferior frontal cortex did not appear to follow this non-linear function. However, a number of right hemispheric regions demonstrated such a response, including right middle frontal gyrus (BA 9), right anterior thalamus, superior (BA 39) and middle (BA 22) temporal gyri, as well as the left lingual gyrus (BA 18).

Effective connectivity analyses

The omnibus SEM analysis indicated that the effective connectivity between LIFG, RIFG, LHC and LIPL regions did not differ significantly according to condition (i.e., high generative or high relational load; $\chi^2_{diff} [6] = 1.55, p = .956$). As indicated by this large p -value, the path coefficients for both models were very similar in magnitude and direction. Thus, our hypothesis of an increased influence of left IFG on left HC in the high generative condition relative to the high relational condition was not supported. As expected, given the opposite responses of these

regions in the parametric analysis, the simple correlation between left IFG and left hippocampus were different for the zero-link ($r = -0.12$) and two-link ($r = .36$) conditions, though the correlation was actually stronger in the two-link condition. However, the effective connectivity analyses take into account patterns of correlations among all regions in the model and, despite the simple correlation between left IFG and left hippocampus, none of the path coefficients differed.

Thus, we sought to characterize the pattern of effective connectivity among these regions during associative encoding across all encoding conditions (Fig. 4). The anatomical model constructed for the present path analyses provided a good fit to the data, as indicated by a non-significant minimum fit function chi [$\chi^2(2) = 3.76$, $p = .150$], a high Goodness of Fit Index (GFI = .88) and a low Root Mean Square Residual (RMR = .14, Joreskog and Sorbom, 1993; Kline, 2005). Furthermore, the model was stable (stability index = 1.06, Kline, 2005).

Table 3

Regions exhibiting significant linear parametric responses to generative and relational load and significant positive quadratic responses to semantic-relatedness

Brain region	Co-ordinates			Z-score
	x	y	z	
<i>Generative load (zero-link > one-link > two-link)</i>				
L. inferior frontal gyrus (BA 45/46)	-57	20	16	3.32
R. inferior frontal gyrus (BA 45/46)	42	30	11	4.09
L. middle frontal gyrus (BA 9)	-50	4	40	3.08
R. middle frontal gyrus (BA 10)	30	53	8	3.03
R. superior frontal gyrus (BA 10)	18	55	8	2.72
L. precentral gyrus (BA 6)	-44	4	35	3.70
L. posterior cingulate cortex (BA 23)	-6	-30	27	2.88
R. middle temporal gyrus (BA 39)	36	-69	22	3.92
L. cerebellum	-12	-76	-15	3.07
<i>Relational load (two-link > one-link > zero-link)</i>				
L. medial frontal cortex (BA 9)	-14	37	33	2.78
L. precentral gyrus (BA 4)	-36	-17	51	3.39
L. ventrolateral thalamus	-12	-6	6	3.15
L. hippocampus	-22	-9	-16	3.16
L. insula (BA 13)	-40	11	-7	3.39
L. middle temporal gyrus (BA 39)	-38	-72	28	3.43
L. posterior cingulate (BA 31)	-14	-49	28	3.89
L. paracentral lobule (BA 31)	-4	-31	44	2.99
L. inferior parietal lobule (BA 40)	-46	-36	50	4.23
R. inferior parietal lobule/postcentral gyrus (BA 40)	46	-35	46	4.13
L. supramarginal gyrus (BA 40)	-55	-41	32	2.94
R. supramarginal gyrus (BA 39)	55	-59	31	3.50
R. lingual gyrus (BA 18)	16	-80	-4	3.28
L. cerebellum	-2	-43	-5	3.20
R. cerebellum	10	-49	-11	3.21
<i>Positive quadratic responses (zero-link < one- and two-link)</i>				
R. middle frontal gyrus (BA 9)	42	19	34	3.19
R. thalamus (anterior)	4	-7	17	3.11
R. middle temporal gyrus (BA 21)	59	-6	-10	3.64
R. superior/middle temporal gyrus (BA 39)	32	-53	30	3.24
L. lingual gyrus (BA 18)	-12	-88	-2	2.81

All peak activations are significant at $p < .005$ (uncorrected for multiple comparisons). For each region of activation, the co-ordinates of the maximally activated focus within each different structure are reported, as indicated by the highest Z-score. BA = Brodmann area.

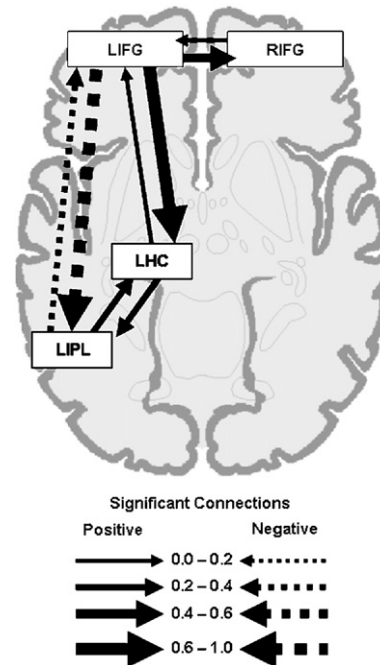


Fig. 4. A diagrammatic representation of positive (solid) and negative (dashed) effective connections during successful encoding of zero-, one- and two-link triads. The thickness of the arrow represents the strength of the connection (path coefficient), as described in the key. LIFG = left inferior frontal gyrus; RIFG = right inferior frontal gyrus; LHC = left hippocampus; LIPL = left inferior parietal lobule.

Of interest here, the strongest effective connection in the model was an excitatory connection from LIFG to LHC (path coefficient = .70). Not only was this influence stronger than the reciprocal connection (i.e., from LHC to LIFG, .16), but it was also the strongest connection in the model. The LIFG also exhibited a strong positive influence on the RIFG (.56), and again, the reciprocal connection was notably weaker (.19). Interestingly, there were strong inhibitory connections between LIFG and LIPL (from LIFG to LIPL, -0.63 ; from LIPL to LIFG, -0.24). Finally, there were moderate excitatory connectivities between LIPL and LHC (from LIPL to LHC, .24; from LHC to LIPL, .30).

Discussion

Prefrontal contributions to associative encoding

The contrast of successfully encoded (and subsequently recognized) triads with the control task replicated previous findings of PFC engagement. As predicted, this included activation of the IFG, and although bilateral in nature, this activity was more spatially extensive on the left. This is consistent with the idea that semantic encoding, particularly in the context of decisions about word meanings and associations, may rely specifically on the left PFC (Cabeza et al., 1997a; McDermott et al., 1999; Otten et al., 2001; Wagner et al., 1998). The activation of this region even in studies of visual encoding suggests that it may be responsible for a more general amodal set of processes, such as the use of strategies to optimize encoding performance (Bor et al., 2004; Fletcher et al., 2000; Reber et al., 2002; Tulving et al., 1994). Of interest, effective connectivity analyses revealed that the left IFG exerted the

strongest influences, both positive and negative, on other nodes in the network during encoding. Indeed, the positive influences on the left hippocampus were observed even though the two regions were affected in the opposite direction by the manipulated encoding variable—the number of links presented. This suggests that the left IFG plays a pivotal role in co-ordinating associative encoding processes.

Activation in inferior frontal regions did not directly track accuracy, in terms of whether items were subsequently recognized or forgotten. While this is in contrast to previous findings of a subsequent memory effect in these regions (e.g., Otten et al., 2001, 2002; Prince et al., 2005; Reber et al., 2002; Sommer et al., 2005; Sperling et al., 2003; Wagner et al., 1998), others have only found this effect at subthreshold levels (e.g., Jackson and Schacter, 2004) or not at all (e.g., Fernandez et al., 1999; Kirchoff et al., 2000; Ranganath et al., 2005b). In the context of the present study, this finding is not surprising, given that the majority of forgotten triads fell within the zero-link condition, a condition which maximizes generative load and IFG activity. A similar logic obtains for the failure for IFG activity to demonstrate modulation in sync with recognition accuracy (i.e., two-link and one-link > zero-link). Despite strong engagement in encoding (relative to control trials) and a high degree of influence on the hippocampal activity during encoding, the specific processes reflected by IFG activation in this paradigm do not directly correlate with recognition performance. It is possible that activation occurring later in the trial may have a different relationship with encoding success, but our aim here was to maximize the contrast between generation and binding operations and thus focus on the onset of the event.

Our results did confirm the hypothesis that the IFG is particularly responsive to the generative load of the encoding task (Fletcher et al., 2000; Lepage et al., 2000), in that encoding triads which contained fewer semantic associations resulted in increased IFG activity. The left IFG has been previously associated with generation of semantic associations (Fletcher et al., 2000; Poldrack et al., 1999). In the current task, recruitment of this region could be crucial to successful encoding of triads in which no pre-experimental associative links exist. Thus, it is likely that, in trials where no or few links are provided, the IFG is engaged to generate associations which can be recovered at recognition. Despite the fact that our instructions did not require participants to generate links but rather to evaluate relations among words in the triad and that discrimination of targets from foils could be based on item memory, our behavioral data parallel the free-recall findings of Lepage et al. (2000), suggesting that such associations were both formed and retrieved. Reber et al. (2002) also report that the left IFG exhibits increased levels of encoding-related activity when participants are instructed to intentionally encode words and suggest that encoding effort may be key to the engagement of this prefrontal region. This idea could apply to the present results. However, it is likely that increased effort is due to the fact that strategies must be engaged and relations between items must be generated, a factor which could also be present in Reber et al.'s intentional encoding condition. Another alternative explanation of this modulatory response is that it reflects an increased demand for selection between semantic associations when encoding triads are high in generative load (Kan and Thompson-Schill, 2004; Thompson-Schill et al., 1997). Encoding of triads low in generative load, where semantic links are provided and alternative associations are unlikely to be generated, would not require a great deal of selection. Although our data do not speak directly to this

issue, examination of the locations of the peak voxels correlating with generative load suggests that selection demand is not likely to explain our findings. The region of the IFG shown here to be responsive to generative load centers on BA 45 and 46, rather than the more inferior and posterior aspect of the left IFG (BA 44) consistently implicated in selection between alternatives (Kan and Thompson-Schill, 2004; Thompson-Schill et al., 1997).

Of interest, the right PFC was also engaged during our encoding task and showed the same pattern of response to the generative load parameter. Similar activation in the right PFC has been reported in other studies of verbal encoding (Daselaar et al., 2003a,b; Grady et al., 2003; Kirchoff et al., 2000; Stebbins et al., 2002), even in manipulations of generative load (Fletcher et al., 2000; Lepage et al., 2000). It is possible that, in the current context, such activation may reflect use of visual encoding strategies for triads in which semantic associations are not provided, although we have no direct evidence on this point. While the precise processes that right PFC activations reflect remain unclear, the connectivity analysis demonstrated a remarkably weak influence of the right IFG on other nodes in the network. Of interest, Grady et al. (2002) also found a predominance of left PFC and medial temporal connectivity during a visual encoding task.

Hippocampal contributions to associative encoding

While hippocampal activity did not conform to the non-linear trend evident for recognition performance (i.e., two-link and one-link > zero-link), the subsequent memory contrast revealed that hippocampal activity did in fact track accuracy. Specifically, encoding of subsequently recognized triads resulted in significant activation of the left hippocampus when contrasted with either control trials or subsequently forgotten triads, consistent with previous findings (e.g., Davachi and Wagner, 2002; Eldridge et al., 2005; Kirchoff et al., 2000; Otten et al., 2001; Prince et al., 2005; Ranganath et al., 2005a,b; Reber et al., 2002; Sperling et al., 2003; Strange et al., 2002). Encoding-related activity in the right hippocampus, however, did not surpass the statistical threshold, revealing a laterality difference consistent with the verbal nature of the triads. It is interesting that activity in the medial temporal lobe was clustered in the left anterior hippocampus and amygdala and did not extend into the parahippocampal gyrus. Several recent studies have demonstrated that the hippocampus, more so than other medial temporal regions, tracks encoding success. For instance, Strange et al. (2002) examined responses of regions within the medial temporal lobe to primacy and successful encoding and found that activity in the hippocampus tracked encoding success. Recently, Eldridge et al. (2005) reported that medial temporal activity that predicts retrieval success is localized to the left CA2, CA3 and dentate gyrus.

Notably, we report evidence of hippocampal modulation according to the relational load of the encoding task. Specifically, when triads contained more semantic associations, engagement of the left hippocampus increased. This finding substantiates further the role of the hippocampus in the binding of associations during memory formation. Henke et al. (1999, see also Daselaar et al., 2003b) suggest that hippocampal activity reflects the number of associations successfully encoded and that enhanced hippocampal engagement during deep encoding is related to the increased number of associations generated and available for binding when stimuli are processed deeply. In line with this hypothesis, Davachi and Wagner (2002) demonstrated that hippocampal activity predicted the number of words subsequently recognized from a

triplet presented at encoding. Here, we manipulated the number of associations provided within triads to influence the number of associations immediately available to the hippocampus at encoding, and accordingly, this significantly increased the level of hippocampal activity.

It is interesting that, despite using a very similar paradigm, [Lepage et al. \(2000\)](#) failed to find an effect of relational load on hippocampal activity. This was likely due to the blocked design (as necessitated by PET) and, consequently, the inclusion of triads for which associations were not successfully bound (i.e., subsequently forgotten items). Given that hippocampal activity tracks encoding success relative to failure, collapsing across subsequently recognized and forgotten items may have very well have obscured the hippocampal response to relational load.

A further advantage of an event-related design is the ability to distinguish the generative and relational aspects of encoding within a trial. The successful encoding of all triads presumably involves the binding of associations, but it is likely that the timing of this differs according to the generative and relational load. Specifically, encoding of zero-link triads should be initially predominated by the generation of associations, and once formed, these can then be bound. In contrast, the encoding of two-link triads would simply require binding the associations provided. This question about the timing of these encoding operations in tasks high in generative or relational load certainly warrants further investigation in studies designed specifically to tap these differences. However, in the present study, the aim was to maximize the difference between generative and relational load. Modeling these data with a canonical hrf at trial onset means that the initial processes engaged during encoding of these triads would be tapped, namely, semantic evaluation and generation in zero-link triads and binding of associations in two-link triads. Indeed, the results of the current parametric analyses demonstrate that this semantic-relatedness task can successfully tease apart the prefrontal and hippocampal contributions to the generative and relational stages of encoding respectively. This paradigm will likely prove fruitful for questions requiring dissociation of these two processes, for instance, the debate surrounding the age-related decline in associative encoding and whether this results from deficient strategy use and/or deficient relational processing (e.g., [Anderson et al., 2000](#); [Cabeza et al., 1997b](#); [Naveh-Benjamin et al., 2003](#)).

Encoding-related activity in lateral parietal regions

Bilateral inferior lateral parietal lobule (BA 40) was significantly engaged by successful encoding relative to the control task, as well as modulated by the relational load of the encoding task. Although it remains unclear what role this region plays during both encoding and retrieval, the consistency of such activations has led to considerable interest in this question (e.g., [Wagner et al., 2005](#)). One hypothesis recently advanced by Wagner and colleagues is that lateral parietal engagement during retrieval may reflect the modulation of attention to internal representations such as memorial content, guiding information processing such that it aids and enhances hippocampally based memorial processes. The lateral parietal cortex may play a similar role during encoding, and a number of findings from the present study suggest this may be the case. Firstly, the left inferior parietal lobule was strongly connected with the left hippocampus during encoding, and, furthermore, this parietal region exhibited a robust parametric response to relational load and the resulting increase memorial

content (i.e., increased numbers of associations to be bound). Inferior parietal cortex may also provide an interface between medial temporal regions and the lateral temporal regions storing the semantic knowledge on which the associations provided within one- and two-link triads are based.

There were also strong reciprocal inhibitory influences between the left IFG and left lateral parietal cortex during successful encoding, which may reflect mutually exclusive roles in attentional modulation during encoding. Thus, it may be that, when associations are provided within triads, the lateral parietal cortex orients attentional resources towards fixed memorial representations, resident and readily accessible in semantic memory, and the enhancement of medial temporal processing and consequently inhibits frontal attentional systems. However, there may be a shift to frontally mediated attentional processes when few or no semantic associations are provided and controlled processing is required to generate associations. Thus, the onset of strategic processing may lead to a suppression of the lateral parietal attentional mechanisms, resulting in negative connectivity.

Prefrontal–hippocampal connectivity

Despite differences in the modulatory responses of prefrontal and hippocampal regions under conditions of high relational and generative load, the effective connectivity between these regions did not significantly differ according to the number of links presented. The network supporting associative encoding in all conditions was dominated by a strong connection from left IFG to the hippocampus. This suggests that, irrespective of the degree to which the left IFG is specifically engaged to generate associations, it still appears to co-ordinate the encoding process in conjunction with the hippocampus. In two-link triads, which do not require generation of associations, this pathway may simply reflect conclusion of an evaluative step which conveys information regarding the presence of semantic associations that require binding. Interestingly, the connection from the left hippocampus to left IFG was weak, suggesting that the information transmission is primarily unidirectional. Once associations have been successfully bound, it is likely that the encoding process terminates and thus further communication between these structures does not occur.

The finding of strong positive connectivity despite opposite patterns of response to the encoding manipulation in the univariate analyses may seem contradictory at first glance. However, there is no necessary relationship between intensity modulation at one region (demonstrating sensitivity to process) or simple correlations between regions and patterns of effective connectivity across an entire network (indicating interactions between regions). This concept is illustrated in a recent paper by [Rajah and McIntosh \(2005\)](#), who investigated the hypothesis that episodic and semantic memory are based on distinct effective networks. Regional differences in positron emission tomography activation were identified for the two types of retrieval and those brain regions showing maximal differentiation were used in constructing separate structural equation models—one for the semantic system and one for the episodic system. They propose that patterns of interactions among the nodes of each network should be different for the two types of retrieval task if they reflect distinct memory systems, but this was not borne out by the effective connectivity analysis. This result, they argue, supports the notion that regional activation differences identified by contrast analyses reflect the degree to which specific processes or modes in a unitary memory

system are engaged by particular retrieval tasks. In applying this argument to our data, IFG and hippocampal regions are differentially engaged depending on the degree of generation or binding operations engaged during the encoding task although interactions among regions in this network are the same during successful associative encoding irrespective of the specific requirements of the encoding task.

We believe this pattern also underscores the importance of evaluating functional and effective connectivity between regions in addition to examining local patterns of response to manipulated variables, and by inference, to cognitive processes. Our hypothesis, which was not supported by the data, was that the prefrontal to hippocampal influence would be enhanced when there was maximal generative load. That it was not suggests a number of other possibilities. For example, it may be that the particular regions inserted in the model are part of a larger coordinated system of strategic or associative encoding operations with a consistent positive influence on medial temporal function. Another possibility is that the timing of operations may differ between encoding link conditions such that the influence is always positive irrespective of when the target node (i.e., hippocampus) reaches its maximal level of activity (e.g., later in the high generative condition relative to the high relational condition). Such possibilities can be explored in subsequent studies directed at testing these ideas. Certainly, the past 15 years of neuroimaging data indicating that prefrontal and hippocampal regions are critically involved in potentially dissociable aspects of successful encoding serves as a strong impetus to begin evaluating how these regions interact with each other and within a broader network. Finally, the use of effective connectivity provides additional information not obtainable by use of simple correlational or functional connectivity analyses, namely the direction of the influence between regions. Others have previously documented functional connectivity between IFG and hippocampus during encoding (e.g., Grady et al., 2002). Here, we further understanding of inferior frontal–hippocampal connectivity during successful associative encoding by demonstrating that this interaction is predominated by the strong positive influence of the IFG upon the hippocampus, supporting the idea that it is the IFG region which directs associative encoding. This result accords well with observations of poor use of encoding strategies observed in patients with prefrontal damage or dysfunction (Craik and Jacoby, 1996; Gershberg and Shimamura, 1995; Stuss et al., 1994).

Overall, the findings from this study confirm that the IFG, particularly the left, is implicated in the generation of semantic associations during verbal encoding and that the level of activation is modulated by the generative load of the task. Furthermore, these data demonstrate that the external provision of semantic associations within the to-be-encoded stimuli enhances the accuracy of encoding and the engagement of the hippocampus during the initial phase of encoding. Finally, the left IFG communicates strongly with the left hippocampus irrespective of the generative or relational load of the encoding task, reflecting the co-ordinating role of the left IFG in the encoding process.

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