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Research report

Neural correlates of semantic associative encoding in episodic memory

Martin Lepage [a,*], Reza Habib [a], Holly Cormier [a], Sylvain Houle [b],
Anthony Randal McIntosh [a]

[a] *Rotman Research Institute of Baycrest Centre for Geriatric Care, 3560 Bathurst Street, University of Toronto, Toronto, ON, Canada, M6A 2E1*
[b] *PET Centre, Clarke Institute of Psychiatry, University of Toronto, Toronto, Canada*

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Abstract

Associations between individual items are the basic building blocks of learning and memory. Functional neuroimaging has now made it possible to study neural correlates of such associations. The present PET study examined three associative encoding conditions differing in the number of words (0, 1, or 2) semantically related to a third word representing the name of a semantic category. A recall task consisting in the presentation of the category names as cues for retrieving the other two members of the triads followed each encoding condition. As expected, retrieval performance increased as the number of semantic exemplars at encoding increased (10%, 43%, 70% items recalled, respectively). A first analysis (partial least squares, PLS) of the PET data identified task-related patterns of activity for associative encoding and cued-recall tasks. A second analysis identified brain regions whose activity was modulated by the number of semantic exemplars at encoding. Some of the task-related brain regions also showed modulated activity by semantic relatedness and consisted in the left inferior prefrontal cortex, right medial temporal lobe, fusiform gyrus and inferior temporal gyrus bilaterally. Some of these regions showed greater activity when words in a triad were unrelated, whereas others did so when the three words were semantically related. These regions have been consistently reported in previous functional neuroimaging studies of associative encoding and may constitute key structures in association formation. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Associative encoding; Relational processing; Cued-recall; PET

1. Introduction

Associations between individual items are the basic building blocks of learning and memory. Association formation consists in the encoding of a relation between events into episodic memory that can be based on many kinds of information such as temporal, categorical, or logical [36,38]. Evidence that associative information in memory is distinct from item memory is cumulating in cognitive psychology [17,20,21,32] and in behavioral neuroscience [4,5,11,56]. In the latter, there is a considerable interest in delineating the brain structures involved in associative or relational memory. In humans, neural correlates of associative memory have been examined using in-depth electrodes [41,57], event-related potentials [9], and functional neuroimaging techniques such as PET, fMRI, and SPECT [8,18,19,25,27,34,35,44,54].

Recent functional neuroimaging studies have specifically investigated the neural correlates of semantic associative encoding of verbal [25,35,44,46,54] and non-verbal stimuli [18,34]. For instance, Henke et al. [18,19] contrasted neural activity induced by an associative semantic encoding task to that of a single-item encoding task for similar materials and reported greater anterior medial temporal lobe activity during the former. These studies have collectively identified brain regions that appear to make a significant contribution to processes involved in association formation. A common observation across these different studies is the activation of the medial temporal lobe including the hippocampal region during semantic associative encoding [6]. Evidence in animal neuroscience also suggests a significant role of the hippocampal region in associative or relational processing [4,11,12,56]. Network models of hippocampal functions [31,45], too, emphasize a role of this brain structure in associative memory.

The approach taken in the present paper to examine neural correlates of association formation firstly involves

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[*] Corresponding author. Fax: +1-416-785-2862; e-mail: mlepage@rotman-baycrest.on.ca

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identifying task-related neural activity induced by an associative encoding task. This has been done successfully in the past, but we wanted to examine if brain structures other than the medial temporal lobe would also make a unique contribution to association formation. In addition, since little is known about the neural correlates of specific processes involved in association formation, we examined the effect on neural activity of manipulating semantic relatedness, a factor known to influence the effectiveness of associative encoding operations, hence, memory retrieval performance [22,42]. This dual approach is modeled after the task-related and item-related process distinction proposed by Düzel et al. [10] in a PET study of memory.

The present experiment was adapted from a study by Mathews [30]. In the Mathews study [30], subjects were presented with word triads in which one word consisted of a semantic category name and the other two were exemplars of that semantic category or from another category. Subjects decided on each trial how many exemplars were semantically related to the category name. Memory performance during a subsequent cued-recall using the category names as retrieval cues for the two other members of the triads increased as a function of the number of exemplars that were semantically related to the category name. Participants in the present PET experiment made judgments about semantic relations among presented triads of words in three encoding conditions in which none, one or two members of the triads (exemplars) were semantically related to the third (category). Each of three encoding conditions was blocked for one kind of semantic decision during the PET scanning period. Task-related activity was examined in a comparison of the three associative encoding conditions to the three cued-recall conditions whereas the modulating effect of semantic relatedness on neural activity was assessed using a parametric analysis examining linear trends across the three encoding conditions.

2. Methods

2.1. Subjects

Fifteen right-handed subjects (eight females; mean age 25.4, range 22–29 years) participated in the study. None had previous nor current neurological or psychiatric disorders. The study was approved by the Human Subjects Use Committee of Baycrest Centre, and written informed consent was obtained from all subjects.

2.2. Materials

The basic unit of material (a ‘triad’) presented at encoding consisted of three words: a name of a category (e.g., FURNITURE) and two exemplars of the category (e.g., BED, SOFA), gleaned from the category norms of Battig and Montague [1] and of Murdock [37]. Fifty-four such triads constituted the pool from which experimental displays were constructed. Depending upon the experimental condition, subjects would encounter (i) triads in which

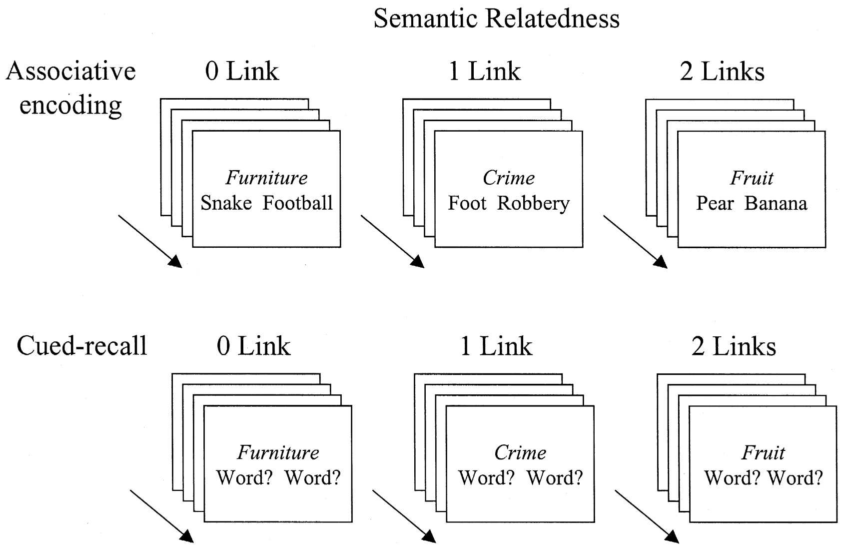

Fig. 1. Illustration of the experimental design. Six conditions were examined during PET, three associative encoding conditions (upper part) and three cued-recall conditions (lower part). At encoding, subjects were presented with word triads in which one word consisted of a semantic category name and the other two were exemplars of that semantic category or from another category. Subjects decided on each trial how many exemplars were semantically related to the category name. The degree of semantic relatedness was manipulated in three encoding conditions in which none (0 link), one (1 link), or two (2 links) members of the triads (exemplars) were semantically related to the third (category). Each of three encoding conditions was blocked for one kind of semantic decision during the PET scanning period. Following each encoding condition, a cued-recall task using the category name (e.g., Furniture) as a cue for retrieving the exemplars was administered.

both exemplars corresponded to the category name (2 'links'), (ii) triads in which only one exemplar belonged to the named category (1 'link'), or (iii) in which neither exemplar did (0 'link'). Examples of the three kinds of triads are shown in Fig. 1.

2.3. Design

The design is illustrated in Fig. 1. Two tasks (associative encoding, cued-recall) were crossed with three kinds of triads (0, 1, or 2 links). Each subject underwent eight scans. The third and sixth scans in the series consisted in low-level control conditions that are not reported here. The other six scans corresponded to the six experimental conditions yielded by the 2×3 design and their order was counterbalanced except for the fact that each encoding condition was followed by the corresponding cued-recall task.

2.4. Procedure

In each encoding task, which lasted 120 s, the subject was shown 18 triads on a monitor. During the 60-s scanning window of the encoding task, the presented triads were all of the same kind (0, 1, or 2 links, corresponding to the experimental condition), whereas in the initial as well as in the final 30 s period four triads of different kinds were shown in a mixed sequence. Individual triad presentations lasted for 5500 ms and were separated by 1500 ms intervals. For each triad, the category name appeared first, followed 1500 ms later by the two exemplars, presented side-by-side below the category names. For each triad shown, the subject decided how many semantically meaningful links were present between the category name and the exemplars: 0, 1, or 2. They expressed their judgement verbally. Thus, all three semantic encoding conditions were identical in terms of the cognitive task to be performed, the novelty of the information and extent of visual display. Only the number of meaningful semantic links differed.

Retrieval was tested by cued recall. In each retrieval condition, the subject was shown 18 successive displays, each for a period of 1.5 s. Each display consisted of a previously studied category name and was followed 1500 ms later by ''WORD? WORD?'' as shown in Fig. 1. The test triads in a given retrieval condition represented one of the three meaningfulness conditions — 0, 1, or 2 links. The subject's task was to say out aloud the two actual words that had appeared with the category name at encoding, or say 'pass' if not able to do so.

Prior to the PET scanning session, subjects were familiarized with the different tasks during a practice session while the subject lied in the PET scanner. Subjects first practiced the encoding task (four trials), then performed a cued-recall task for these items.

2.5. PET data acquisition and analyses

We used the standard PET procedures of our laboratory, which have been described elsewhere [40]. Briefly, we used a GEMS-Scanditronix (Uppsala) PC2048-15B head scanner (5–6 mm axial resolution). Images were acquired over 60 s starting when the bolus tracer arrived in the brain. The eight scans were separated by 11-min intervals. The cognitive task started 30 s before the bolus injection and ended 30 s after scan acquisition. PET images were processed with statistical parametric mapping SPM96 (developed at the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherborn, MA, USA) on a SunUltra1 workstation. All PET scans of an individual subject were realigned to a mean image, transformed into a standard space, then smoothed using a 10-mm isotropic Gaussian kernel [13,14].

Statistical analyses were performed in two steps. First, partial least squares (PLS), a multivariate technique was used in order to show patterns of brain activity that relates to the experimental design. A complete mathematical description of the PLS can be found elsewhere [33]. PLS describes the relation between (i) neural activity across the entire brain and (ii) the experimental design represented by a set of orthonormal contrasts. In PLS, an optimal least-squares fit to the cross-block correlation between the experimental design and dependent measures (PET images) is obtained using singular value decomposition. The cross-block correlation matrix is decomposed into orthogonal pairs of singular vectors or latent variables (LVs), which account for the covariance in the matrix in decreasing order of importance. These vector pairs reflect the relation between components of the experimental design most related to brain activity on the one hand and the optimal pattern of image-wide activity related to the identified design components on the other. This second vector can be displayed in image space, which is referred to as singular images. The numerical weights within an image are called saliences. The singular image from the design-brain PLS identifies the collection of voxels that as a group are most closely related to the design effects expressed in the LV. Another product of the PLS analysis are brain scores, which are conceptually similar to factor scores from factor analysis. They are obtained for each participant's image and indicate how strongly that participant expresses the particular pattern depicted in the singular image. They are created from the dot product of the singular image and each participant's image. The inferential significance of a LV is assessed through permutation tests (500 iterations), and the reliability of a voxel's contribution to the LV is assessed by bootstrap estimation of standard errors (S.E.) for the voxel salience (100 iterations). Voxels were considered reliable if the S.E. ratio exceeded 2.3.

In the second step of the analysis, we used SPM96 and linear contrasts to identify cerebral sites at which blood

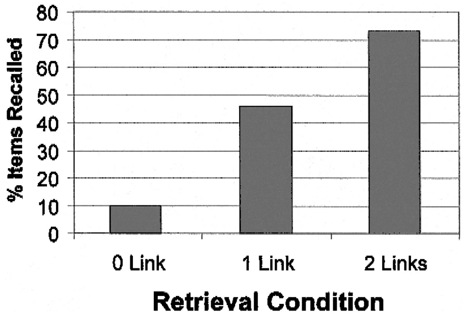

Fig. 2. Behavioral performance in the three cued-recall conditions.

flow changes varied parametrically with the number of semantically related exemplars at encoding (0, 1, 2 links conditions). For this analysis, we adopted the statistical threshold of $P < 0.001$, uncorrected for multiple comparisons, with an extent threshold of 30 contiguous voxels.

3. Results

3.1. *Behavioral performance*

At encoding, all participants could make the semantic judgment task faultlessly. The encoding manipulation of the number of semantic associations had a significant effect on the cued-recall performance. Fig. 2 shows the mean number in percentage of exemplars recalled following each of the three encoding conditions. As expected, memory performance increased monotonically with the number of semantically related exemplars presented at encoding (all t's$(14) > 5.4$, $p < 0.001$). Intrusion rates were 2%, 0%, and 5% for the low, medium and high retrieval condition, respectively. This pattern of performance replicates previous findings using this experimental design [30].

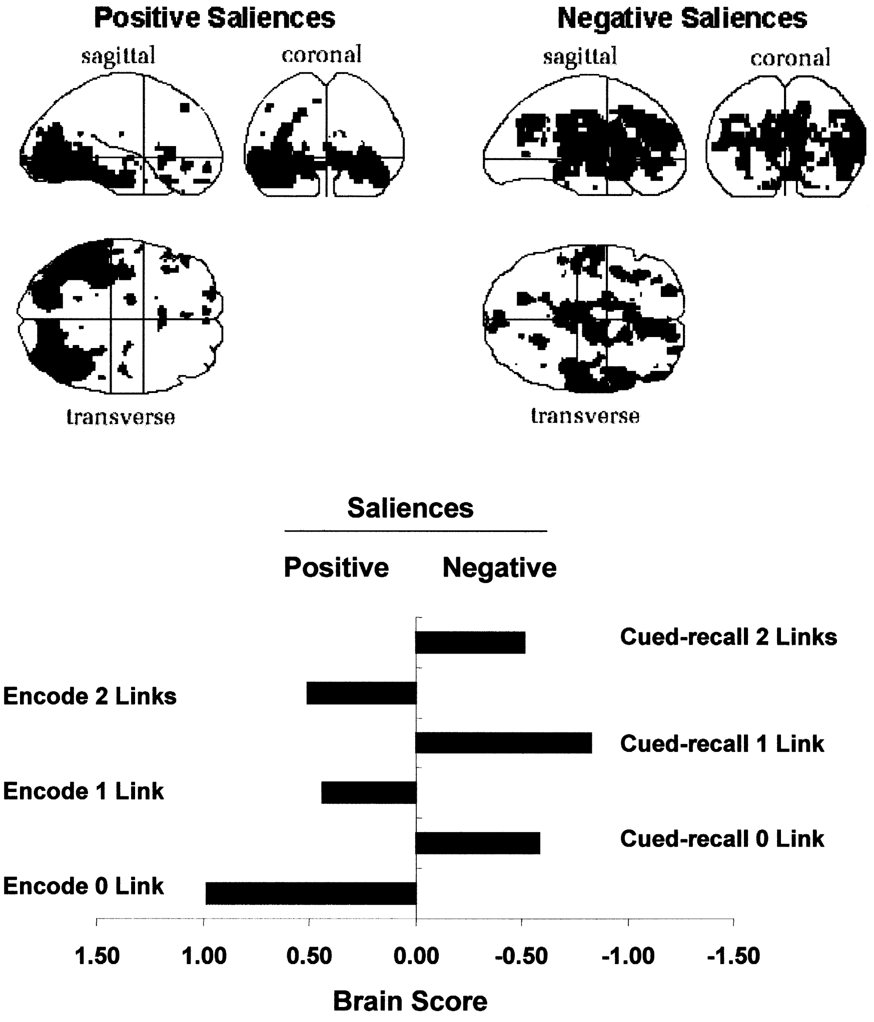

Fig. 3. Singular image 1 from the PLS analysis and corresponding brain scores. (top panel) Positive saliences denote the brain regions in which rCBF is higher during the associative encoding conditions and negative saliences denote the brain regions in which rCBF is higher during the cued-recall conditions. (bottom panel) Standardized brain scores are plotted for each experimental condition. A clear separation between the three associative encoding conditions (negative brain scores) and the three cued-recall conditions (positive brain scores) can be noted.

Table 1
Selected maxima and minima of singular image 1 that distinguishes between the associative encoding conditions and the cued-recall conditions
BA = Brodmann's area; Ratio = stability coefficient in bootstrap analysis; *XYZ* coordinates of representative maxima and minima are listed according to the Talairach and Tournoux system [51].

X	*Y*	*Z*	Ratio	Region	BA
Maxima (associative encoding > cued-recall)					
Left hemisphere					
−24	58	32	3.4	Superior frontal gyrus	9
−40	28	−24	2.7	Temporal pole	38
−56	22	0	4.0	Inferior frontal gyrus	45
−18	−10	−16	3.1	Hippocampus	
−44	−34	−24	3.8	Inferior temporal gyrus	20
−32	−36	−20	6.7	Fusiform gyrus	36–37
−30	−78	−16	4.8		
−44	−54	−16	6.6	Inferior temporal gyrus	37
−46	−50	−28	3.3	Cerebellum	
−38	−74	0	7.2	Occipital gyrus	18
Right hemisphere					
2	48	−24	2.7	Orbitofrontal gyrus	11
24	−14	−20	2.8	Hippocampus	
50	−34	−16	2.6	Inferior temporal gyrus	21
40	−46	−8	3.1	Fusiform gyrus	37
50	−68	−20	4.9	Cerebellum	
40	−82	−4	5.9	Occipital gyrus	19
16	−82	−8	5.1	Lingual gyrus	18
Minima (cued-recall > associative encoding)					
Left hemisphere					
−24	52	8	5.0	Middle frontal gyrus	9–10
−30	38	16	2.6	Middle frontal gyrus	46
−38	24	12	2.9	Inferior frontal gyrus	45–47
−14	−2	8	3.8	Putamen	
−10	−22	12	5.4	Thalamus	
−52	−22	4	2.9	Superior temporal gyrus	22
−46	−28	16	3.2	Insula	
−16	−70	28	4.0	Precuneus	7
−2	−94	−28	4.8	Lingual gyrus	18
Right hemisphere					
16	60	36	3.3	Superior frontal gyrus	10
26	58	12	3.0	Superior frontal gyrus	10
52	36	−12	5.5	Inferior frontal gyrus	45
20	20	−12	2.9	Orbital gyrus	11
50	18	−4	4.8	Inferior frontal gyrus	47
50	8	−16	5.5	Superior temporal gyrus	22
62	4	12	3.9	Precentral gyrus	6
36	−10	32	4.4	Precentral gyrus	4
6	−10	4	4.3	Thalamus	
14	−10	−4	5.5	Globus pallidus	
22	−54	−28	3.0	Cerebellum	
60	−68	16	3.7	Inferior parietal lobule	39

3.2. PET data analyses

The first singular image that resulted from the PLS analysis distinguished between the three associative encoding conditions and the three cued-recall conditions and accounted for 40% of the total variance (permutation test probability $P < 0.05$). Fig. 3 depicts this singular image and the corresponding standardized brain scores. Table 1 lists representative local maxima (greater activity during associative encoding) and minima (greater activity during cued-recall) from this image. During associative encoding, significant activity was observed in bilateral occipito-temporal cortices and included occipital, lingual, fusiform and inferior temporal gyrus bilaterally. Bilateral medial temporal lobe activity was also observed while frontal activity was lateralized to the left hemisphere and implicated the inferior convexity and a more dorsolateral prefrontal region.

During cued-recall, significant activity was observed in bilateral frontal regions, subcortical structures (basal ganglia and thalamus), and superior temporal gyrus bilaterally. This pattern of activation is consistent with previous PET studies of cued-recall [2,3,39,47] and will not be discussed here.

The remaining LVs from PLS identified interactions between memory tasks (associative encoding and cued-recall) and the number of semantic associations. Linear contrast analyses based on univariate statistics (SPM) were used to investigate these patterns of brain activity.

Table 2 lists the brain regions showing a positive or negative linear trend across the three encoding conditions. Positive trend reflects brain regions showing increase in activity from the '0 link' to '2 links' encoding conditions whereas negative trend regions show reduction from '0 link' to '2 links', which can also be interpreted as greater activity during the '0 link' condition. Positive trend re-

Table 2
Brain regions showing positive or negative linear trend in activity across the three associative encoding conditions
BA = Brodmann's area; *XYZ* coordinates of local maxima are listed according to the Talairach and Tournoux system [51].

X	*Y*	*Z*	*Z*-value	Region	BA
Regions showing a positive linear trend (0 link < 1 link < 2 links)					
Left hemisphere					
−2	6	−16	3.42	Medial frontal gyrus	25
−24	0	−8	3.35	Putamen / periamygdalar cortex	
Right hemisphere					
44	42	16	3.72	Middle frontal gyrus	46
14	−8	−24	3.47	Parahippocampal gyrus	28
6	−24	12	3.19	Thalamus	
62	−44	−12	4.53	Inferior temporal gyrus	37
18	−94	−20	4.33	Cerebellum	
Regions showing a negative linear trend (0 link > 1 link > 2 links)					
Left hemisphere					
−50	24	−12	3.62	Inferior frontal gyrus	47
−6	18	44	3.42	Medial frontal gyrus	6
−34	−80	−4	3.11	Occipital / fusiform gyrus	19
Right hemisphere					
2	64	16	3.23	Medial frontal gyrus	10
22	52	−16	3.69	Middle frontal gyrus	11
38	14	24	3.65	Inferior frontal gyrus	44
0	−58	−12	3.46	Cerebellum	
24	−80	−8	3.40	Lingual / fusiform gyrus	19

gions included a right medial temporal lobe region, a right dorsolateral prefrontal, right inferior temporal gyrus, right cerebellum, right thalamus, left periamygdalar cortex/putamen, and left medial frontal region. Other

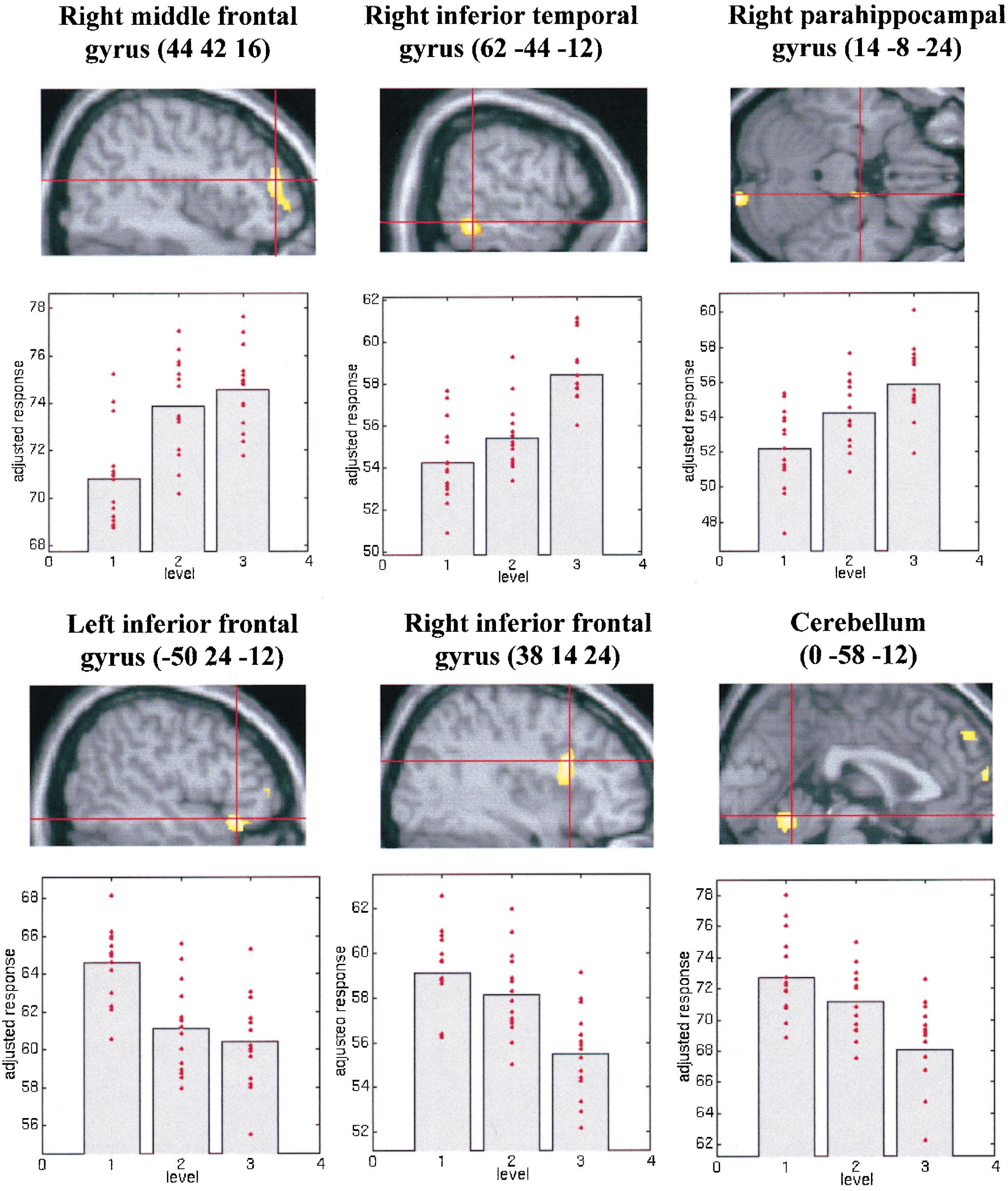

Fig. 4. Examples of positive and negative linear trends at encoding. For each analysis, three activations were selected and displayed (threshold $P < 0.01$) onto a section of a magnetic resonance brain image. A bar graph depicting the ratio-adjusted rCBF value for the three associative semantic encoding conditions is presented for each activation. For each bar graph, the order of the three conditions are 0 link, 1 link and 2 links, respectively.

brain regions showed a negative linear trend and comprised inferior and medial frontal regions bilaterally, fusiform gyrus bilaterally and right cerebellum. Fig. 4 illustrates examples of positive and negative linear trends across the three associative encoding conditions.

4. Discussion

The study reported here produced two sets of findings that are important for the understanding of the neural correlates of semantic associative encoding. First, a pattern of task-related activity distinguishing between the associative encoding task and the cued-recall task was identified. A second pattern identified brain regions whose activity level was modulated by the number of semantic exemplars presented at encoding. Some of these regions exhibited a positive linear trend, others a negative linear trend across the three encoding conditions. Most importantly, it was found that some brain regions that show task-related activity also show modulated activity as a function of semantic relatedness. This finding can be seen as a starting point to define the functional role of these regions during association formation by showing that some brain regions are more active during the encoding of semantically unrelated words, whereas other brain regions show greater activity for semantically related words.

4.1. Task-related neural activity during semantic associative encoding

During the associative encoding task, subjects examined word triads and made semantic judgments concerning the number of semantic exemplars present on each trial. Later, they were presented with a single member of a triad (the category name) and attempted to retrieve from memory the two other members of the triad. At the brain level, a clear separation between brain regions differentially involved in associative encoding and retrieval was revealed by the PLS analysis. As can be seen in Fig. 3, this clear separation between associative encoding and cued-recall tasks encompassed all encoding and cued-recall conditions and cannot be attributed to one single condition driving this effect. Therefore, it is safe to conclude that these patterns of activity reflect task-related activity. This analysis identified several regions whose activity level was greater during the associative encoding conditions compared to the cued recall conditions.

During semantic associative encoding, greater neural activity was observed in left inferior and superior prefrontal cortex. Left inferior prefrontal activation has been reported in previous studies examining semantic encoding of single words [15,23,24,26,55], during semantic associative encoding tasks [19,44,54] and appears to constitute a marker of semantic processing [16,50]. Bilateral anterior medial temporal lobe activation was observed, a finding consistent with previous PET and fMRI studies [28,48]. Multiple posterior brain regions also exhibited greater activity during semantic associative encoding and included the cerebellum bilaterally and the inferior portion of occipital–temporal cortices (occipital, lingual, fusiform and inferior temporal gyrus). Previous functional neuroimaging studies have implicated the posterior temporal regions in the storage of information [7,29,58]. In addition, these posterior regions have been shown to be active to a greater extent during semantic processing compared to episodic memory retrieval [58] and the present results are entirely consistent with this idea.

4.2. Modulating effect of semantic relatedness on neural activity during associative encoding

The major finding of the present study resides in the observation that the semantic relatedness of an association between three words can modulate activity level in specific brain regions. This modulating effect occurred when all other factors, such as the type of processing, were kept constant. This effect was bidirectional, some brain regions showed positive and others negative linear trend in activity across the three encoding conditions. For instance, a right medial temporal lobe and right prefrontal cortex regions showed a positive linear trend, whereas other prefrontal regions and fusiform gyrus bilaterally showed a negative linear trend. Since the understanding of functional brain imaging results relies on a good understanding of the variables that influence patterns of neural activity, the present study by showing a modulating effect on neural activity of semantic relatedness adds to current knowledge on associative memory. This variable has not been systematically manipulated in previous associative encoding studies. For example, some studies did involve semantically related materials [44,54], whereas others involved semantically unrelated materials [18,19].

At the current stage of our understanding, caution must be exercised in interpreting the direction of these effects. An increase in activity from the 0 to 2 links condition may also reflect a deactivation or large-scale reduction in activity affecting the 0 link condition [43,49]. The safest conclusion one might draw is that the number of semantic associations presented at encoding modulates activity in these regions. Further support for that idea is provided by the observation that the level of neural activity for the middle condition (link 1) was often found to be somewhere between the other two conditions (see Fig. 4). Nonetheless, the presence of brain regions showing linear positive or negative trends in activity across encoding conditions varying in semantic relatedness provides evidence at the functional neuroanatomical level that semantically unrelated and related materials are processed differently by the brain. Such a finding can be seen as the starting point to understand the contributions of these different brain regions to associative encoding.

Table 3
Summary table for the present experiment and for a selection of published studies on associative encoding in memory. Four brain regions were selected based on the two complementary analyses of the PET data from the present experiment. The four regions consisted of the hippocampal and inferior temporal regions bilaterally, the left fusiform gyrus and left prefrontal cortex. Activation reported in eight previous studies of associative encoding were reviewed and activations in the vicinity of the four regions are indicated by the presence of Talairach and Tournoux coordinates. Unless noted otherwise, all these studies used the PET technique

Study	Task comparison	Material	Medial temporal lobes			Left fusiform gyrus			Left prefrontal cortex			Inferior temporal cortex		
			X	*Y*	*Z*	*X*	*Y*	*Z*	*X*	*Y*	*Z*	*X*	*Y*	*Z*
Present experiment														
Task-related activation														
	Semantic associative encoding — cued recall	Words	−18	−10	−16	−32	−36	−20	−56	22	0	−44	−54	−16
			24	−14	−20	−30	−78	−16				50	−34	−16
Modulated activation by semantic relatedness														
	Positive/negative linear trends in activity	Words	14	−8	−24	−34	−80	−4	−50	24	−12	62	−44	−12
Activation reported in previous studies														
Kapur et al. [25]	Semantic associative encoding — word reading	Words				−38	−34	−4	−48	36	0			
Vandenberghe et al. [54]	Semantic associative encoding — matching task	Words/line drawings of objects	−18	−16	−12	−46	−46	−20	−42	22	20	−44	−10	−28
									−16	30	−12			
Henke et al. [18]	Semantic associative encoding — single item encoding	Pictures of houses and faces	32	−16	−12	−30	−34	−16						
			30	−26	−12									
Montaldi et al. [34][a]	Associative encoding — matching task	Pictures of landscapes	−16	−10	−16							56	−4	−24
			−24	−14	−24									
Ricci et al. [44]	Semantic associative encoding — matching tasks	Line drawings of objects	−26	−24	−20	−24	−46	−16	−36	16	28	−44	−58	−8
									−30	10	24			
Henke et al. [19]	Semantic associative encoding — single item encoding tasks	Words	22	−10	−20	−30	−34	−24	−38	26	−8			
Mottaghy et al. [35][b]	Associative encoding — associative retrieval	Words	−28	−20	−16	−28	−36	−16	−32	32	44	−48	−56	−16
Rombouts et al. [46][c]	Semantic associative encoding — rest	Line drawings	Yes (11/12 subjects)			Yes (12/12 subjects)			Yes (10/12 subjects)			Yes (10/12 subjects)		

[a] This study used SPECT.

[b] This study used fMRI.

[c] No Talairach and Tournoux coordinates were reported in this fMRI study. Instead, the number of subjects that did show activation in the vicinity of one of the four regions is reported; *XYZ* coordinates of local maxima are listed according to the Talairach and Tournoux system [51].

4.3. Convergence of findings from task-related and modulated activity analyses

We examined the overlap between the task-related analysis and the linear trend analyses in order to identify brain regions that would be common to both analyses. We compared local maxima for Tables 1 and 2 and looked for peaks that were within 12 mm on all three Talairach and Tournoux dimensions from one another. Six regions met these criteria. These included left inferior prefrontal, right anterior medial temporal lobe, fusiform and inferior temporal gyrus bilaterally. The left prefrontal and fusiform activity bilaterally showed a negative linear trend, whereas the other three regions showed a positive trend. These could involve the exact cortical site or slightly different neighboring sites.

We used these six regions just described as a starting point to review the functional neuroimaging literature on association encoding. Activation in four of these regions has been consistently reported in previous studies of associative encoding using PET, fMRI, and SPECT. These are the medial temporal lobes, the left fusiform gyrus, the left inferior prefrontal cortex and the inferior temporal gyrus bilaterally. As can be seen in Table 3, these studies have compared neural activity for an associative encoding task to all kinds of control tasks and have used different kinds of materials including words, faces, houses, landscapes and line drawings of objects. The general picture that emerges is that medial temporal lobes and left fusiform gyrus activations constitute the most robust findings, observed in seven out of eight studies selected in addition to the present study. Left inferior prefrontal cortex activation have been reported in six out of eight studies whereas inferior temporal cortex activation has been reported in five studies.

The fact that these four brain regions have been reported consistently in previous functional neuroimaging studies and that they exhibited both task-related activity and modulated activity in the present study is taken as strong evidence of their participation in associative encoding. This finding suggests that in addition to the medial temporal lobe region, other brain regions make a unique contribution to the formation of association in memory. This reiterates the importance of examining the neural correlates of episodic memory in and beyond the hippocampus [52,53]. Of these four regions, the right parahippocampal gyrus and right inferior temporal gyrus showed a positive linear trend in activity whereas the left inferior prefrontal and the left fusiform showed a negative trend in activity. This suggests that left prefrontal and fusiform cortex could be making a contribution to association encoding that is functionally different from that of right parahippocampal and inferior temporal regions. Future studies will be necessary in order to define even more precisely the contribution of these brain regions to association formation.

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