Large Scale Neurocognitive Networks Underlying Episodic Memory

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Abstract

■ Large-scale networks of brain regions are believed to mediate cognitive processes, including episodic memory. Analyses of regional differences in brain activity, measured by functional neuroimaging, have begun to identify putative components of these networks. To more fully characterize neurocognitive networks, however, it is necessary to use analytical methods that quantify neural network interactions. Here, we used positron emission tomography (PET) to measure brain activity during initial encoding and subsequent recognition of sentences and pictures. For each type of material, three recognition conditions were included which varied with respect to target density (0%, 50%, 100%). Analysis of large-scale activity patterns identified a collection of foci whose activity distinguished the processing of sentences vs. pictures. A second pattern, which showed strong prefrontal cortex involvement, distinguished the type of cognitive process (encoding or retrieval). For both pictures and sentences, the manipulation of target density was associated with minor activation changes. Instead, it was found to relate to systematic changes of functional connections between material-specific regions and several other brain regions, including medial temporal, right prefrontal and parietal regions. These findings provide evidence for large-scale neural interactions between material-specific and process-specific neural substrates of episodic encoding and retrieval. ■

INTRODUCTION

Large-scale neural networks are believed to mediate cognitive processes, including memory (Fuster, 1997; Mesulam, 1990). The nature of these networks can be studied with functional neuroimaging techniques that allow the examination of the whole brain simultaneously. For episodic memory (Tulving, 1993), it has been hypothesized that left prefrontal regions work in concert with more posterior regions during encoding to form enduring memory representations (Tulving, Markowitsch, Craik, Habib, & Houle, 1996). Similarly, it has been proposed that right prefrontal brain regions interact with posterior regions when stored information is recovered (Markowitsch, 1995).

There has been little direct evidence to support these proposed neural interactions between prefrontal and posterior regions (cf., Fuster, 1997). A role of prefrontal brain regions in episodic encoding and retrieval is suggested by several studies (for reviews, see Nyberg, Cabeza, & Tulving, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994a), but the neural responses that define actual recovery of event information remain to be defined. Evidence for involvement of posterior regions comes from studies showing regional changes in blood flow correlated with success in retrieval. A few studies have found increased activation of medial temporal lobe (MTL) regions, including the hippocampus, under conditions of higher levels of retrieval (e.g., Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996a; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997; Schacter, Alpert, Savage, Rauch, & Albert, 1996). MTL activation may, however, reflect a conscious recollective process associated with recovery (Schacter et al., 1996). Furthermore, increased activity associated with higher levels of memory performance has been observed in some neocortical brain areas, including superior temporal (Heckers, Rauch, Goff, et al., 1998; Nyberg, Tulving, Habib, et al., 1995; Rugg et al., 1997) and medial parietal (Kapur et al., 1995) regions. In other studies, comparisons between conditions of higher and lower levels of recovery have generated no evidence of differential activation in posterior brain regions (e.g., Buckner et al., 1998; Schacter, Buckner, Koutstaal, Dale, & Rosen, 1997). Thus, activation analyses provide an inconclusive picture regarding recovery-related effects.

Analysis of functional connectivity represents a more direct assessment of the hypothesized neurocognitive interactions between prefrontal and posterior brain regions during episodic memory. Functional connectivity refers to the correlation of activity among brain regions (Friston, 1994), and can be used to explore task-specific changes in the interactions between regions, independently of relative changes in activity. A study of functional connections between prefrontal and medial temporal cortices during episodic retrieval found that a right posterior inferior prefrontal region and a left hippocampal region were bound in a similar pattern of functional connectivity only during conditions of higher, but not lower, levels of retrieval (McIntosh, Nyberg, Bookstein, & Tulving, 1997). The connectivity pattern included bilateral inferior temporal and retrosplenial regions. These results, which were not evident from activation analyses, indicated that functional interactions between frontal and posterior regions is related to level of recovery. However, as level of recovery at retrieval was manipulated by having subjects encode items in a shallow or deep manner, the results could reflect changes related to the way the items were initially processed, rather than recovery-related changes, per se.

The present study was explicitly designed to examine activation changes and changes in functional connectivity associated with level of recovery. Regional brain activity was monitored by positron emission tomography (PET) during encoding and retrieval (yes/no recognition) of verbal (sentences) and nonverbal (pictures) episodic information. Three different retrieval conditions were included for each kind of material, with the conditions varying in terms of target density (0%–50%–100%). We expected that increasing target density would lead to increases in recovery of information, with the understanding that this manipulation also relates to increasing familiarity (Mandler, 1980). It is widely assumed that recognition can have different bases, such as familiarity or recollection, and these may relate to different types of information. In certain paradigms (for example, Yonelinas & Jacoby, 1995), recollection is defined as remembering some criterial feature, whereas familiarity may rely on perceptual characteristics. The present design did not allow separation between responses based on familiarity or recollection, and, hence, any changes in neural responses related to the manipulation of target density can reflect either, or a mixture, of these.

Our strategy for data analysis was as follows: First, we used a partial-least-squares (PLS) analysis (McIntosh, Bookstein, Haxby, & Grady, 1996) to identify task-related activation changes. PLS identifies spatial patterns of brain activity that represent the optimal association between brain images and a block of contrast vectors coding for the experimental design. Of particular interest here was whether significant activation changes relating to type of cognitive process (encoding vs. retrieval) and to level of recovery (low–medium–high) would be observed. Second, we used PLS to explore changes in functional connectivity related to level of recovery. This usage of PLS can be seen as an extension of analyses of pairwise regional interrelations in which a region is selected and it is analyzed how activity in this region correlates, across subjects, with activity in the rest of the brain (for example, Horwitz, 1989). PLS can sort the correlations into what is similar and different across tasks, hence, facilitating comparisons of correlation maps across experimental conditions. Here, we were interested in whether correlations between activity in regions involved in encoding and retrieval of sentences and pictures (as determined by the initial task PLS analysis) and activity in the rest of the brain would change systematically as a function of level of recovery (low–medium–high).

RESULTS

Behavioral Results

Increasingly more items were recovered across retrieval conditions for both sentences and pictures (Table 1). The effect of target density was significant, but not the effect of materials or the target density by materials interaction. The similar behavioral pattern across stimuli suggests that any differences in activity between sentences and pictures do not result from performance differences.

Activation Changes

The PLS analysis of task-dependent activations identified two highly significant activity patterns (permutation test $p < .001$). PLS is a multivariate analysis of activation changes that serves to identify distributed systems that, *as a whole,* relate to some aspect of the experimental design. These systems can nevertheless be characterized by their most salient components (peak voxels), as assessed by reliability assessment (see Grady, McIntosh, Rajah, & Craik, 1998). Table 2 lists coordinates for the peak voxels of the two patterns. A more complete appreciation of the spatial distribution of the different neural systems can be obtained from Figure 1.

The first pattern related to processing of pictures vs. sentences independent of the type of cognitive process (Figure 1A). Compared with sentence processing, picture processing resulted in increased activity in posterior

Table 1. Mean Number of Yes-Responses (SD's) as a Function of Condition and Material

Condition	*Sentences*	*Pictures*
Low (0 targets)	1.27 (1.68)	1.36 (1.36)
Medium (10 targets)	8.64 (1.36)	9.45 (2.88)
High (20 targets)	15.64 (2.77)	16.00 (2.57)

The scores in the low condition represent false alarms (average false alarm rate=7%). The false alarm rate in the medium condition averaged 9%. An ANOVA on number of yes-responses was used to analyze the effect of target density. The results showed a significant effect of condition [$F(2,20)=208.8$, $p<.001$]. The effect of material and the condition×material interaction were non-significant ($p>.20$).

visual and medial temporal regions, especially in the right hemisphere, and sentence processing strongly activated left temporal and frontal regions relative to picture processing. The second pattern distinguished the type of cognitive process (encoding vs. retrieval) across materials and level of recovery (Figure 1B). Compared to retrieval, encoding was most strongly associated with increased activity in bilateral temporal regions, and also in a left dorsolateral prefrontal region. Retrieval, compared to encoding, was most strongly associated with increased activity in left lateral parietal cortex and in right anterior prefrontal cortex.

The PLS analysis of activation changes showed no significant effects relating to the manipulation of target density. Similarly, in univariate statistical analyses (Friston et al., 1995), which explicitly tested for activation changes related to the manipulation of target density, no effect was significant after correction for multiple comparisons. The response in some regions was, however, significant at an uncorrected $p<.001$. These regions are listed in Table 3. For both pictures and sentences ("overall"), the response in several prefrontal regions tended to be related to target density. Importantly, the location of these prefrontal regions did not overlap with the location of the right anterior prefrontal region which was associated with retrieval independently of level of recovery (see Table 2 and Figure 1B). For pictures, a tendency to a recovery-related effect in posterior regions was seen in medial occipito-parietal cortex, whereas the only corresponding effect for sentences was observed in the right insular cortex.

Changes in Functional Connectivity

We next used PLS to identify systematic changes in functional connections as a direct test of whether neural network interactions change in relation to the manipulation of target density/level of recovery (McIntosh et al., 1997). The material-specific regions identified by the first pattern from the task PLS analysis were used as starting points (seed voxels). As determined by the task PLS analysis, these regions were activated during encoding as well as retrieval. If recovery of information engages brain regions challenged during acquisition of the same information (e.g., Squire, Knowlton, & Musen, 1993), we reasoned that these material-specific regions would be good candidates to show recovery-related effects. The specific goal of the analyses was to see whether the image-wide functional connections of the seed voxels changed in a systematic way as a function of target density. That is, we examined whether the correlations between activity in the seed regions and activity in any other brain regions changed such that, across conditions, they became increasingly more positive or increasingly more negative. For example, we expected to find a data pattern showing that the correlation between activity in a seed voxel and activity in a set of distributed brain regions would be negative in the 0%-target condi-

Table 2. Material-Specific and Process-Specific Brain Regions

Effect	*Region (x, y, z)*
Picture processing>Sentence processing	L occipital (−4, −98, −8) R occipital (6, −86, −12) R medial temporal (28, −36, −20)
Sentence processing>Picture processing	L temporal (−56, −38, 0; −52, −6, −8; −44, 0, −12) Left frontal (−52, 12, 16; −42, 26, 4; −44, −8, 40)
Encoding>Retrieval	L temporal (−56, −26, −28) R temporal (50, −60, 4; 36, −20, −24) L frontal (−20, 26, 48)
Retrieval>Encoding	R frontal (36, 46, 12; 20, 46, 0) L parietal (−40, −38, 36)

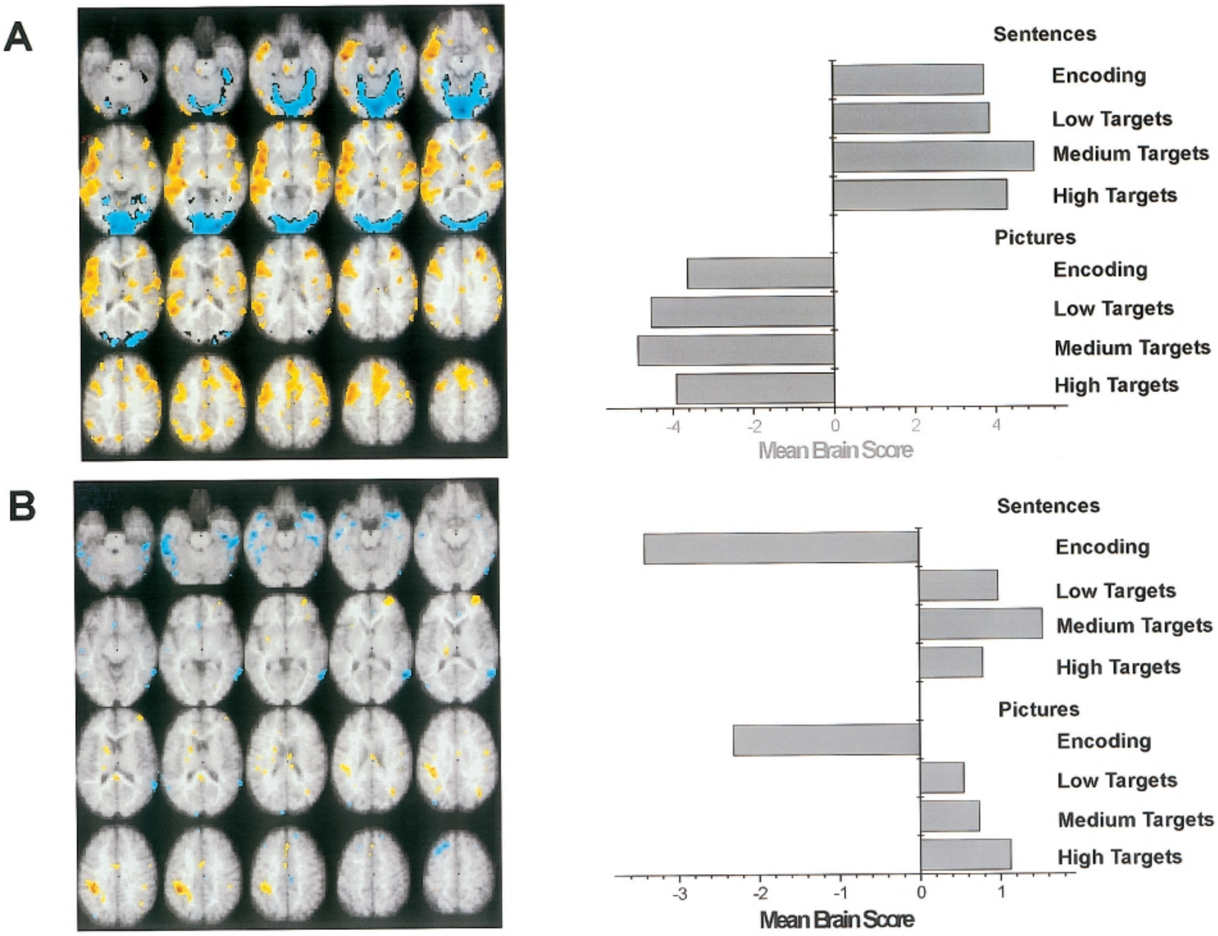

Figure 1. (A) Mean brain scores and associated singular image from PLS for the first pattern that distinguished between sentence and picture processing. Regions in blue were relatively more active during picture processing; regions in yellow were relatively more active during sentence processing. (B) Mean brain scores and associated singular image from PLS for the second pattern that distinguished between encoding and retrieval. Regions in blue were more active during encoding and regions in yellow were more active during retrieval.
Note: Areas are displayed on a standard magnetic resonance image from −28 mm to +48 mm relative to the anterior–posterior commissure (AC–PC) line (in 4-mm increments). The right side of the image corresponds to the right side of the brain. A brain score is the sum of the cross-product of the raw voxel value and the salience for that voxel. Salience is a weight associated with each voxel which express its relation to a specific contrast (for example, encoding vs. retrieval). The brain scores are analogous to factor scores derived from factor analysis.

tion; weakly to moderately positive in the 50%-target condition; and strongly positive in the 100%-target condition. We also expected to observe the reversed pattern—more negative correlations as a function of condition. These two sets of outcomes will be considered equivalent—taken as evidence for recovery-related changes in functional connections—no attempt will be made to interpret the sign of correlations.

The seed voxel PLS analysis identified a significant effect ($p=0.014$) relating to target density during picture recovery when activity in a left occipital region ($x,y,z = -4, -98, -8$) was used as seed (Figure 2A). As revealed by the task PLS analysis, this occipital region was significantly more activated during picture than sentence processing. The peak salient voxels from the images in Figure 2A are listed in Table 4, and, as an aid for interpretation, the univariate correlations of these peak voxels are given as well. (For all listed peaks, there was an orderly change in correlations from low–medium–high.) Increasingly more positive correlations across scans were observed between the occipital seed voxel and regions in bilateral frontal cortex and in left cuneus/precuneus (displayed in white color). Increasingly more negative correlations were observed between the seed voxel and regions in bilateral medial temporal cortex, bilateral occipital cortex, and in left middle temporal cortex (displayed in black).

Table 3. Brain Regions Showing Increased Activity as a Function of Target Density

Material	*Region*
Overall (sentences & pictures)	L frontal (−42, 46, 20; −20, 64, 8) R frontal (30, 28, −8) R insula (32, 6, 12)
Pictures	L precuneus (−16, −74, 36) L posterior cingulate (−24, −62, 8)
Sentences	L frontal (−22, 62, 0) R insula (32, −8, 4)

Regional effects as determined by univariate analyses (Friston et al., 1995). The analyses included all retrieval scans, with a contrast of [−1 0 1 −1 0 1] testing for an overall effect and [−1 0 1 0 0 0] vs. [0 0 0 −1 0 1] testing for material−specific effects. All listed peaks were significant at an uncorrected $p<.001$ ($Z>3.09$) and had a spatial extent of>10 voxels when plotted at a threshold of $Z=2.58$.

For sentences, a corresponding effect ($p=.014$) was observed when a voxel in the left-frontal cortex ($x,y,z=-52$, 12, 16) was used as seed (Figure 2B). This region showed increased activity during sentence processing compared to picture processing (e.g., Figure 1A). The peak voxels from the images in Figure 2B are listed in Table 4, along with the univariate correlations of each peak. (All listed peaks showed an orderly change in correlations from low–medium–high.) Increasingly more positive correlations across scans were found between the seed voxel and regions in bilateral cuneus, bilateral middle temporal gyrus, and right frontal cortex (displayed in white color). Increasingly more negative correlations were observed between the seed voxel and regions in left medial-temporal cortex (displayed in black).

Despite the fact that the location of the seed voxels differed markedly (left occipital cortex for pictures; left frontal cortex for sentences), inspection of the images in Figure 2A and b suggested considerable overlap in the patterns of functional connections. To more formally assess overlap, the reliable peak voxels from each image were cross-multiplied (see Methods). The crossproduct is indicated in red in Figure 2A and B, and the peaks along with corresponding univariate correlations are presented in Table 4. Salient regions of both spatial patterns were located in cuneus/precuneus, thalamus, bilateral temporal cortex, anterior right prefrontal cortex, and in the anterior cingulate. As detailed above, salient regions were also identified near left hippocampus in both analyses, but the locations did not overlap.

Similar, but less strong, trends to recovery-related changes in functional connectivity were observed when other regions from the first pattern of the task PLS analysis were used as seeds, such as the right medial-temporal region ($x,y,z=28$, −36, −20) for pictures, and the left lateral-temporal region ($x,y,z=-56$, −38, 0) for sentences. By contrast, when peak voxels from the second pattern of the task PLS were used as seeds, none of these showed a reliable change in functional connectivity that related to target density. Collectively, these observations indicate that recovery-related changes in functional connectivity involve material-specific regions activated during both encoding and retrieval, rather than material-general regions activated during encoding or retrieval.

DISCUSSION

The present results provide clear evidence for large-scale networks related to episodic recognition memory. We begin by discussing the results which can be characterized as ''recovery-independent'', and then turn to discuss brain responses, which seem sensitive to level of recovery.

Recovery-Independent Effects

Systems-level patterns of co-activation were observed that related to the two dominant dimensions of this experiment. One represented activity that discriminated between the type of material processed (pictures vs. sentences) and was comprised of occipito-temporal cortices (more active for pictures) and left prefrontal and temporal cortices (more active for sentences) (e.g., Grady et al., 1998). The second pattern was associated with the cognitive process (encoding vs. retrieval) and consisted of bilateral, temporal, and left dorsolateral prefrontal cortices during encoding, and right prefrontal and left parietal cortices that were more active during retrieval. There were no large-scale activity patterns to suggest that there was an interaction of material-type and cognitive process, which indicates that encoding and retrieval were superimposed on material-specific activity. This is in line with previous findings that cognitive operations can operate within the same material-specific networks (Köhler, Moscovitch, Winocur, Houle, & McIntosh, 1998a). Thus, although we do not refute the possibility of top-down modulation of material-specific neural responses, our data show that processing of pictures (or sentences) tends to activate the same neural system, regardless of whether subjects perform encoding or retrieval operations.

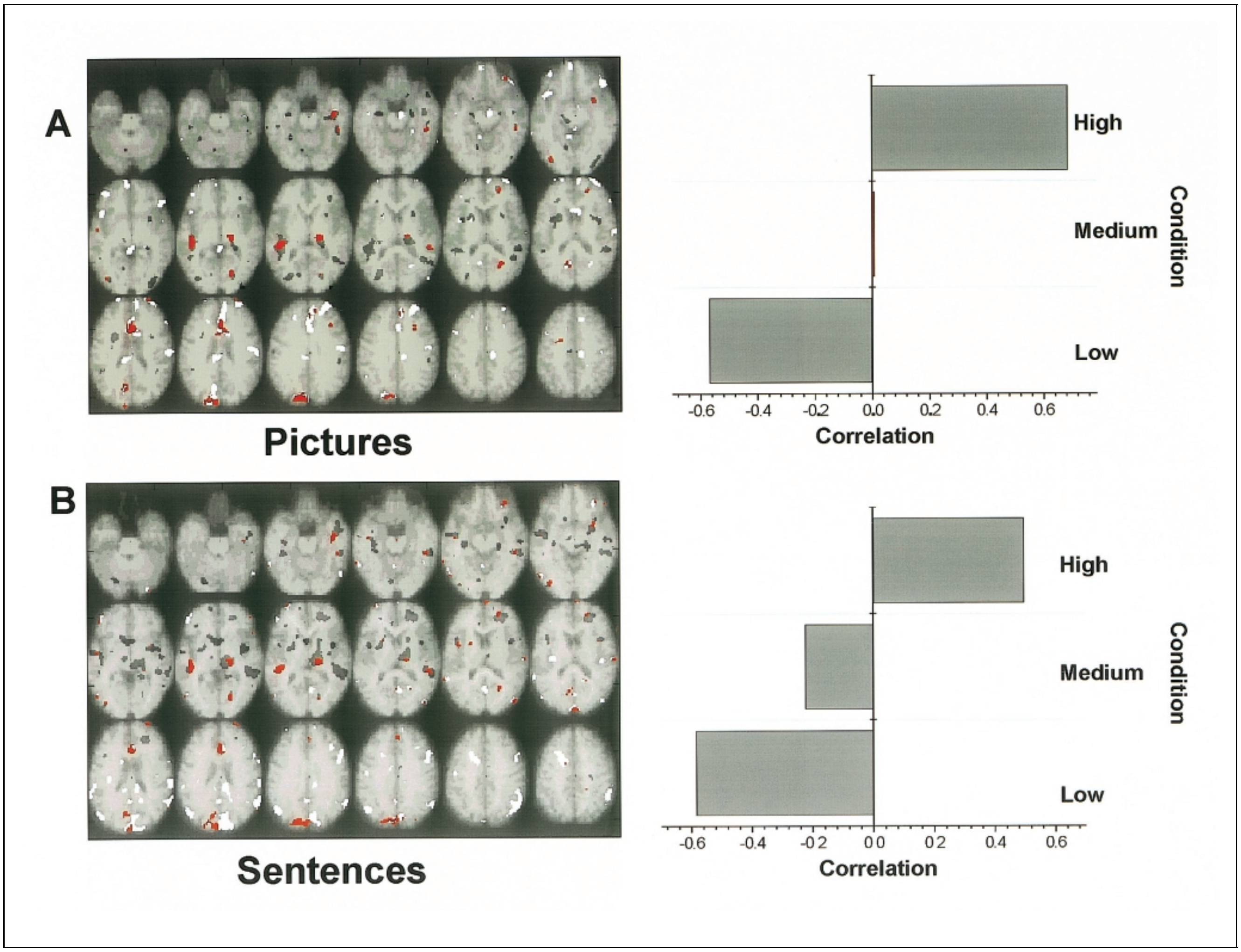

Figure 2. (A) Results from the analysis of seed voxel correlations for left occipital area 18. The plot of correlation of brain scores with the occipital voxel by condition shows a roughly linear change in the covariance of this voxel across picture retrieval conditions with the singular image displayed on the left. Peak salient voxels with a positive loading (correlations becoming more positive across scans) are displayed in white. Peak salient voxels with a negative loading (correlations becoming more negative across scans) are shown in black. Regions shown in red are those for which a similar pattern of functional connections were observed for both seed voxels (that is, left area 18 for pictures and left area 44 for sentences). (B) Results from the analysis of seed voxel correlations for left frontal area 44. The plot of correlation of brain scores with the frontal voxel by condition shows a roughly linear change in the covariance of this voxel across sentence retrieval conditions with the singular image displayed on the left. Peak salient voxels with positive loading are shown in white, and peak salient voxels with negative loading are shown in black. Regions shown in red are those for which a similar pattern of functional connections were observed for both seed voxels.
Note: Areas are displayed on a standard magnetic resonance image from −28 mm to +48 mm relative to the anterior–posterior commissure (AC–PC) line (in 4-mm increments). The right side of the image corresponds to the right side of the brain.

The finding that brain regions generally activated during encoding included left inferior temporal and dorsolateral prefrontal areas, and brain regions generally activated during retrieval involved right anterior prefrontal and left parietal areas, is consistent with much prior research (see Cabeza and Nyberg, 1997). Several of these regions have been suggested to form general encoding and retrieval networks, regardless of type of event information (Nyberg et al., 1996b). The asymmetric involvement of left and right prefrontal areas during encoding and retrieval provides support for the HERA model (Nyberg et al., 1996; Tulving et al., 1994a). This model holds that the left prefrontal cortex is differentially more involved in episodic encoding than is the right prefrontal cortex, whereas the right prefrontal cortex is differentially more involved in episodic retrieval than is the left prefrontal cortex. The activation of the right anterior prefrontal cortex during retrieval is hardly controversial, as activation of this region during episodic retrieval has been demonstrated for several different tasks and kinds of material. It is more noteworthy that the left prefrontal cortex was differentially activated during encoding for both verbal and nonverbal material. This is because, although left prefrontal activation has been observed in several other studies of nonverbal episodic encoding (see Nyberg et al., 1998 for a recent summary), it has been argued that the part of the HERA model that predicts left-lateralized prefron-

Table 4. Peak Regions of Functional Connectivity Patterns with Associated Univariate Seed-Correlations

Material	*Region (x, y, z)*	*Correlation (low–medium–high)*					
Pictures (seed=−4, −98, −8)	L frontal (−40, 42, 0)	−0.48	0.13	0.46			
	L frontal (−44, 16, −4)	−0.47	0	0.71			
	L precuneus (−10, −66, 20)	−0.48	0.06	0.85			
	L cuneus (−24, −80, 32)	−0.47	0.03	0.68			
	R frontal (24, 50, 32)	−0.74	−0.19	0.50			
	R frontal (40, 28, −8)	−0.79	−0.10	0.45			
	R occipital (32, −96, 0)	0.29	−0.75	−0.76			
	L occipital (−36, −82, −8)	0.70	0.24	−0.52			
	L temporal (−44, −36, 4)	0.28	−0.27	−0.86			
	R hippocampus (22, −14, −16)	0.04	−0.02	−0.85			
	L hippocampus (−24, −14, −16)	0.09	−0.01	−0.69			
Sentences (seed=−52, 12, 16)	L temporal (−56, −50, 12)	−0.11	0.29	0.73			
	R temporal (52, −60, 24)	−0.42	0.04	0.52			
	R frontal (46, 16, 28)	−0.35	0.25	0.64			
	R cuneus (2, −66, 8)	−0.53	−0.15	0.13			
	L cuneus (−2, −92, 20)	−0.73	−0.35	−0.20			
	L hippocampus (−32, −22, −12)	0.29	−0.10	−0.62			
Overlap			Pictures			Sentences	
	Anterior cingulate (2, 38, 28)	−0.40	−0.39	0.58	0.13	0.55	0.80
	R frontal (26, 58, 24)	−0.53	−0.22	0.55	−0.13	0.13	0.59
	L cuneus/precuneus (−22, −88, 28)	−0.35	0	0.61	−0.32	0.15	0.28
	R thalamus (12, −22, 4)	0.65	−0.12	−0.48	0.50	−0.24	−0.48
	L temporal (−42, −26, 0)	0.34	−0.51	−0.61	0.39	−0.09	−0.14
	R temporal (40, −10, −20)	0.35	0	−0.60	0.22	−0.49	−0.60

tal activation during encoding has low predictability, when applied to encoding studies involving nonverbal materials (Kelley et al., 1998a, 1998b). The peak in the present study (located in area 8) fell outside the area of left prefrontal cortex (areas 45 and 47) most strongly associated with episodic encoding (but see, for example, Haxby et al., 1996), but our results, nevertheless, suggest that the predictability of the model may not be as low as has been argued.

A final point to consider in this section is the consistent activation of the right prefrontal cortex across the different retrieval conditions. As noted above, activation of the right anterior prefrontal cortex during episodic retrieval has been observed in many functional neuroimaging studies, but the interpretation of this response has been the subject of some debate. This is so even if the discussion is limited to episodic recognition. According to one position, the right anterior prefrontal activation is reflecting retrieval attempt/retrieval mode (Kapur et al., 1995; Nyberg et al., 1995). The basis for this suggestion was findings that the level of regional activation, relative to a common baseline, did not vary as a function of target density or level of recognition success (manipulated by varying the level of processing at study). A conflicting position holds that the prefrontal cortex mediates post-retrieval processing (Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996). This position is based on findings of greater prefrontal activation in retrieval conditions involving many targets compared to retrieval conditions involving fewer targets (see also Tulving et al., 1994b). A recent study by Wagner, Desmond, Glover, & Gabrieli (1998) provided support that right prefrontal regions mediate processes associated with retrieval attempt rather than retrieval success. Wagner et al. showed that under standard recognition instructions, level of right prefrontal activation is not affected by target density. They also showed that if subjects are informed about the relative proportion of targets and lures, conditions of high target density tend to be associated with increased right prefrontal activation. Possibly this is because being informed that most items will be new reduces the involvement of retrieval attempt processes, hence, lowering the level of right prefrontal activation. This observation helps to explain some findings of greater right prefrontal activation when recognition of old and new items were directly contrasted (Tulving et al., 1994b—subjects were informed), and to the extent that subjects on-line can discover/guess that most items are nonstudied, it may be possible to account for similar findings when subjects were not informed about the proportion targets and lures (Rugg et al., 1996). By showing that the right anterior prefrontal response did not vary as a function of level of recovery (target density), the present study is in agreement with the conclusion by Wagner et al., and more generally with the retrieval attempt/mode account. Importantly, though, the analyses of activation changes and connectivity changes pointed to an association between prefrontal involvement and level of recovery. Taken together, these observations hint that the retrieval attempt/mode account and the post-retrieval (success) account are not mutually exclusive, but distinct prefrontal regions may mediate each of these processes. Below, we discuss recovery-sensitive responses in more detail.

Recovery-Dependent Effects

The PLS analysis of task-dependent activations suggested that recovery-related changes in regional activity were weak (no significant activity pattern relating to level of recovery was identified). This suggestion was supported by the outcome of univariate analyses which explicitly tested for recovery-related effects (material-general as well as material-specific effects). None of the identified effects was significant following correction for multiple comparisons, which appears consistent with some previous findings (Buckner et al., 1998; Schacter et al., 1997; Wagner et al., 1998). However, as some of the regional effects which were significant at an uncorrected $p < .001$ were located in brain areas previously associated with level of recovery/target density (prefrontal cortex and precuneus), we will provide some discussion of these effects.

Starting with prefrontal cortex, activity in two left prefrontal areas showed a tendency to recovery-related effects. The peaks fell in the middle frontal gyrus, in or near area 10. Similarly, one of the areas identified by Rugg et al. (1996) to be sensitive to target density was located in left area 10. We also found that activity in a right inferior prefrontal voxel showed a recovery-related trend. In a previous study (Nyberg et al., 1996a), it was observed that activity in this area tended to be greater for subjects who correctly recognized many items than for subjects who recognized few items. Collectively, these studies suggest that activity in specific prefrontal regions is modulated by level of recovery.

Turning now to the precuneus region, as was noted in the Introduction, activity in this area has been related to level of target density in previous studies (Kapur et al., 1995). Kapur et al. argued that their observation of increased activity in posterior cortical regions, including the precuneus, during recognition of studied words could reflect reactivation of stored engrams. Similarly, Roland and Gulyás (1995) presented evidence which led them to suggest that the precuneus area is a storage site for visual patterns, and data obtained by Krause et al. (1999) led these authors to conclude that successful retrieval is dependent on reactivation of engrams in posterior multimodal association cortices, especially the precuneus. These previous proposals are consistent with the present demonstration of a recovery-related effect in precuneus. It is unclear, however, why the effect was only observed for pictures—words were used in both the Kapur et al. and Krause et al. studies. It may be that episodic recognition of the kind of verbal material used in this study differs in significant ways from episodic *word* recognition (and from recognition of nonverbal information). Nonetheless, our findings from the picture conditions provide further evidence that precuneus is a posterior region that shows recovery-related effects.

In addition to testing for activation changes, we explored whether neural network interactions changed in relation to the manipulation of target density/level of recovery. We found that the success of the recovery of information, in terms of the number of items correctly recognized, can be directly related to the interactions among brain regions. That is, using regions showing differential activity related to the type of material, we identified patterns of systems-level covariation across retrieval conditions that changed as the number of items recognized increased. For sentences, activity in a left frontal region showed a change in correlation pattern that mapped on to the increase in old items across recognition scans. For pictures, a corresponding effect was found for a region in left occipital cortex. Thus, through the examination of functional connectivity we provide empirical evidence that the level of recovery can be directly related to the interactions among brain regions. Such an observation is anticipated by theories suggesting that cognition is supported by the operations of large-scale neural systems (Mesulam, 1990).

Interestingly, even though different regions were used as "seeds" for sentences and for pictures, there was significant overlap in the areas identified in the systems-level patterns (indicated in red in Figure 2). Overlapping regions included the anterior cingulate gyrus, thalamus, right prefrontal cortex, and cuneus/precuneus. Moreover, for both seeds, hippocampal regions were implicated, although the specific location of these differed for sentences and pictures. The overlapping areas may be part of a neurocognitive system that interacts with material-specific regions in binding together different components of the episodic experience (John, Easton, & Isenhart, 1997; McIntosh et al., 1997). In light of the activation data discussed above, it is striking that the overlapping areas included regions in right prefrontal cortex and in precuneus. This is so even if the peaks identified in the two sets of analyses did not closely overlap, and taken together, the findings strongly implicate areas in prefrontal cortex and precuneus in aspects of recovery. It is also noteworthy that the connectivity analyses pointed to a role of hippocampal regions in recovery, despite the fact that regional activity did not differ as function of level of recovery. Differential activation of hippocampal regions during episodic retrieval has been related to conscious recollection and/or confidence (see Nyberg et al., 1996a; Schacter et al., 1996). Possibly, the observation here of lack of differential activation of hippocampal regions across retrieval conditions signals equal levels of confidence in the responses—regardless of whether these involve correct recognition or correct rejection. The finding in the connectivity analyses that involvement of hippocampal regions nevertheless relates to level of recovery is in agreement with a recent demonstration that structures in the medial temporal lobe interact with specific posterior neocortical brain regions depending on the type of information retrieved (Köhler, McIntosh, Moscovitch, & Winocur, 1998b). Finally, in addition to the overlapping regions, the patterns for sentences and pictures included unique regions. Notably, for sentences, bilateral posterior temporal regions were involved, whereas for pictures, bilateral lateral occipital regions were implicated. The interactions among material-specific regions may be related to recovery of modality-specific aspects of an experience.

The discussion of the functional connectivity results has focused on the findings when a left prefrontal seed was used for sentences and a left occipital seed was used for pictures. As noted in Results, similar trends were seen when other material-specific regions from the first pattern of the task PLS analysis were used as seeds (such as a right medial-temporal region for pictures and a left middle temporal region for sentences). Together with the observation that recovery-related changes in functional connections were not seen when seeds from the second pattern of the task PLS analysis (general encoding and retrieval regions) were used, this indicates that recovery-related effects were restricted to material-specific regions commonly involved in encoding and retrieval. While this appears consistent with theoretical proposals (see, for example, Squire, Knowlton, & Musen, 1993), it must be noted that recovery-related effects were not seen for all material-specific regions. Moreover, it is quite possible that recovery-related effects would have been found for other regions. This relates to a general problem with connectivity analyses—selection of regions. Therefore, the present results may best be seen as an empirical demonstration that level of episodic recovery maps on to changes in functional connectivity, rather than as a complete characterization of the involved networks. As such, our findings extend recent observations that other kinds of learning and memory are based on changing interactions between brain regions (Büchel, Coull, & Friston, 1999; McIntosh, Cabeza, & Lobaugh, 1998).

CONCLUSION

In conclusion, the present results show that distinct encoding and retrieval networks operate within common material-specific networks. In line with previous findings, actual recovery of information, manipulated by varying levels of target density, tended to be associated with activation changes in distinct regions. In addition, evidence was provided that level of recovery can be directly related to the interactions among brain regions. Notably, our demonstration that material-specific regions interacted with common regions during recovery show that they were operating within overlapping neural systems (McIntosh, in press). Thus, although the specific events differed (verbal vs. nonverbal), the interactions defining higher levels of recovery involved similar regions. The activation of material-specific regions and their interactions with common areas can be considered a large-scale neural network related to successful retrieval of episodic memories.

METHODS

Cognitive Task

Each encoding condition included 45 items. Subjects were instructed to try to learn as many items as possible for a later test of memory and to press with their right hand any of two mouse buttons after having viewed each item (the items were presented on a computer screen that was placed above the subjects' heads). The verbal materials consisted of a sentence frame and a semantically related word (for example, hairy on the outside but delicious on the inside—coconut). The nonverbal material were scenic pictures of coastlines and water, animals, vegetation, and mountains. Following each encoding condition, subjects were given three memory tests in a counterbalanced order. They were instructed to press with their right hand the left or right mouse button, depending on whether or not they recognized a given item from the study list. Each memory test included four studied and four non-studied items before the scan interval and one studied and one non-studied item after the scan interval. During the scan interval, one test included 20 non-studied items (0%-target condition); another test included 10 studied and 10 non-studied items (50%-target condition); and the third test included 20 studied items (100%-target condition). No studied items were repeated in the same retrieval scan or in different retrieval scans. Half of the subjects were presented the verbal conditions prior to the pictorial conditions; the other half were given the pictorial conditions first. During encoding and retrieval, the presentation rate was 2.5 sec per item (ISI=0.5 sec).

Image Acquisition

Subjects were given eight PET scans (one scan/encoding- and retrieval condition). The scans were obtained with a GEMS-Scanditronix PC 2048-15B head scanner using bolus injections of 40 mCi $H_2{}^{15}O$ and 60-sec data acquisition scans. The study was approved by the Human Subjects Use Committee of Baycrest Center. All subjects gave written, informed consent (four female, seven male; mean age=28.4 years, range=20–39 years). One additional subject was tested but had to be excluded due to software problems during scanning.

Image Analysis

All images were realigned to the subjects' first scan by using AIR (Woods, Mazziotta, & Cherry, 1993), transformed into Talairach space (Talairach & Tournoux, 1988), and smoothed to 10 mm by using SPM-95 (Friston et al., 1996). Partial least squares (PLS) was used to identify patterns of brain activity related to the different tasks (McIntosh et al., 1996). PLS was also used to analyze task-related differences in functional connectivity (McIntosh et al., 1997). Peak voxels used to characterize the singular images from PLS analyses were selected based on their reliability through bootstrap estimation of standard errors (Grady et al., 1998). Two sets of weights are derived for the PLS analysis of functional connectivity: one for the seed voxel within each scan and one for each voxel in the remainder of the image (the singular image). The variation in the weight for the seed voxel across scans indicates whether the pattern of covariances in the singular image represents a task-related difference in functional connectivity. For example, if the seed voxel weights are similar across scans, this would represent a common pattern of functional connectivity. If seed voxel weights follow a linear change from 0% to 50% to 100% targets, then that would represent a change in functional connectivity that maps on to the change in target density. Using a set of linear contrast coding for target density, we statistically evaluated the PLS results for such a pattern by covarying the contrast with the seed voxel weights for each latent variable. The significance of the target-density effect was assigned using permutation tests (McIntosh & Gonzalez-Lima, 1998). The overlapping regions in the two singular images were identified by thresholding (at a ratio of voxel weight to bootstrap standard error greater than 2) the singular images for each seed analysis to include only the reliable peak voxels and computing the cross-product of the two images. Therefore, the overlapping regions are the strongest and most reliable voxels that contributed to the singular image in both seed PLS analyses.

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