

Brain Regions Differentially Involved in Remembering What and When: a PET Study

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Summary

Recollecting a past episode involves remembering not only what happened but also when it happened. We used positron emission tomography (PET) to directly contrast the neural correlates of item and temporal-order memory. Subjects studied a list of words and were then scanned while retrieving information about what words were in the list or when they occurred within the list. Item retrieval was related to increased neural activity in medial temporal and basal forebrain regions, whereas temporal-order retrieval was associated with activations in dorsal prefrontal, cuneus/precuneus, and right posterior parietal regions. The dissociation between temporal and frontal lobe regions confirms and extends previous lesion data. The results show that temporal-order retrieval involves a network of frontal and posterior brain regions.

Introduction

Functional neuroimaging studies have associated remembering past events with increased neural activity in several brain areas, including prefrontal, medial temporal, posterior midline, and parietal regions (reviewed by Cabeza and Nyberg, 1997). Yet, there is little evidence concerning the specific contributions of these regions to different aspects of episodic memory, such as retrieving what the event was or when or where it occurred. Indeed, in typical episodic memory tests, such as free recall, these aspects are mixed in unknown proportions and are difficult to differentiate. One way to delineate the neural correlates of component processes underlying episodic memory is to compare brain activity across tests specifically designed to emphasize different aspects of episodic information. In the current study, we

compare two such tests—a test of item recognition and a test of temporal-order memory.

The frontal lobes have been associated with processes of planning, organization, initiation, monitoring, and inhibition of behavior (reviewed by Stuss et al., 1994b; Fuster, 1997). In the memory domain, they are particularly involved in working memory for object and spatial information, strategic retrieval from long-term memory, metamemory, and memory for temporal information (reviewed by Shimamura, 1995). With regard to memory for temporal information, studies of human and nonhuman primates have shown that damage to prefrontal cortex results in greater memory impairments on tests requiring retrieval of information about when items occurred in a list than on tests requiring only information about what the presented items were (e.g., Milner, 1971; Squire, 1982; Schacter, 1987; Shimamura et al., 1990; Petrides, 1991; McAndrews and Milner, 1991; Milner et al., 1991; Butters et al., 1994; Kesner et al., 1994; Mangels, 1997). For example, in a study by Petrides (1991), monkeys were first shown a series of four objects, one at a time. At the test stage, they were shown two objects from this series (e.g., objects 3 and 4) and were rewarded for choosing the object that appeared earlier (e.g., object 3). Monkeys with mid-dorsal frontal lesions were severely impaired in making these relative recency judgments. Yet, monkeys with frontal lesions are usually unimpaired on memory tests that require only the selection of a previously presented item (reviewed by Petrides, 1994).

These findings point to a specific role of frontal regions in temporal-order memory. However, several issues remain unresolved. First, it is not clear to what extent findings from lesion studies can be generalized to the intact human brain. Although functional neuroimaging studies in healthy humans could answer this question, the two studies that have directly compared item and temporal-order memory failed to find significant differences in dorsolateral frontal activity (Eyler Zorrilla et al., 1996, Soc. Neurosci., abstract; Nyberg et al., 1997). This outcome may be attributable to the type of temporal-order memory task used. Both studies used a list differentiation task, which does not require the kind of precise temporal-order discrimination demanded by the relative recency test typically employed in lesion studies (Milner, 1971; Petrides, 1991; McAndrews and Milner, 1991; Milner et al., 1991; Kesner et al., 1994).

Second, in most previous lesion studies, the temporal-order memory task was more difficult than the item memory task, rendering the findings difficult to interpret. In one condition (Milner et al., 1991), for example, performance in item and temporal-order tasks was 0.96 and 0.70 in control subjects and 0.90 and 0.59 in frontal patients (chance = 0.50). Although the difference was significant in the temporal-order but not in the item task, the dissociation was confounded with performance differences. In this kind of situation, one could argue that the temporal-order task was more sensitive to frontal damage just because it was more difficult. Indeed, there is evidence that frontal lesions produce larger effects

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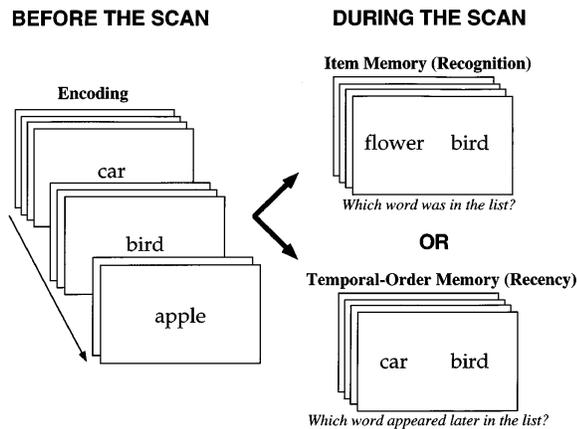


Figure 1. Paradigm of the PET Study
Subjects studied a list of words before each scan and then performed a recognition test or a recency test during the scan.

on demanding memory tests than on simpler ones (e.g., Wheeler et al., 1995).

Third, despite evidence for the anatomical (e.g., Petrides and Pandya, 1994) and functional (e.g., Stuss et al., 1994b) heterogeneity of the frontal cortex, lesion studies with humans have not conclusively answered the question of what particular regions within the frontal lobes are associated with temporal-order memory. Experimental lesions in monkeys suggest that the dorsal regions of the frontal cortex are particularly involved in temporal-order memory (e.g., Petrides, 1991), but brain lesions in humans are usually not circumscribed enough to test this idea.

Finally, it is likely that nonfrontal brain regions are involved in temporal-order memory as well, but lesion studies provide no evidence on this issue. In other aspects of information processing, such as spatial and object working memory, the frontal cortex is only one part of a functional network that also includes posterior sensory and association areas (e.g., Goldman-Rakic et al., 1993; Petrides, 1994). Specifically, regions in frontal cortex appear to be actively involved in the maintenance, monitoring, and organization of information represented in posterior areas (e.g., Fuster et al., 1985; Yajeya et al., 1988). This is likely to be equally true for temporal-order information (Mangels, 1997). Certain aspects of temporal processing are spared in patients with frontal lobe lesions and may rely on other brain structures (Mangels, 1997). As of yet, these other regions have not been identified.

We designed our positron emission tomography (PET) study to identify the brain regions differentially involved in item and temporal-order memory, using more tightly controlled conditions than in previous studies. In addition to using a recency discrimination task, we explicitly manipulated the difficulty of item and temporal-order memory tasks. Young healthy subjects studied a list of words and were then scanned in two kinds of tests while seeing pairs of words (see Figure 1). In the item memory test, one word of each pair was previously studied and the other was not, and the subject's task was to identify the studied word by clicking the left or the right mouse

key. In the temporal-order memory test, both words were studied, and the subject's task was to indicate, by clicking a mouse key, which of the two words had appeared more recently in the study list. Chance probability of a correct response in both of these two-alternative forced-choice tasks is 0.50. These tests resemble everyday memory retrieval situations, where recognition of an event requires a distinction between those events that occurred and those that did not, whereas memory for when the event happened involves a decision about whether a past event took place before or after another. Encoding conditions were manipulated so that each test would have two significantly different levels of performance, high and low, and so that performance in the low item and high temporal-order conditions was similar. Given these behavioral outcomes, it was possible to control for differences in task difficulty by using accuracy as a covariate and by comparing directly the low item and the high order conditions.

On the basis of the aforementioned lesion evidence, we hypothesized that frontal regions would be more activated in the temporal-order than in the item condition. Some preliminary lesion data (Milner, 1971) also suggests that temporal lobe regions will show the opposite pattern. Finally, we anticipated that PET would also reveal other regions involved in temporal-order memory beyond the frontal lobes.

Results

Behavioral Data

The averaged proportions of correct responses in the high item, low item, high temporal-order, and low temporal-order conditions were 0.90, 0.73, 0.72, and 0.61, respectively. The performance differences between the high and low conditions were significant for both tests ($p < 0.0001$), while performance in the low item and high temporal-order conditions was statistically indistinguishable ($F < 1$).

PET Data

The regional cerebral blood flow (rCBF) data of interest in this study were obtained by a contrast between item and temporal-order conditions. Subtracting the temporal-order from the item data indicated what brain regions were differentially related to remembering what the studied items were. Subtracting the item from the temporal-order data indicated what brain regions were differentially related to remembering when the studied items appeared in the list.

In identifying these regions, we adopted a conservative stance. We only accepted as significant those regions that were statistically reliable in each of the three following contrasts: (1) a standard (main effect) contrast between item and temporal-order conditions, (2) a contrast between item and temporal-order conditions in which linear differences in performance were statistically removed by using a behavioral performance measure as a covariate, and (3) a contrast between the two conditions with equivalent performance levels (low item versus high temporal-order). The regions meeting these

Table 1. Blood Flow Increases in Critical Comparisons

Contrast	BA	x	y	z	Z
<u>Item Minus Temporal-Order</u>					
Left anterior medial temporal	28	-14	2	-24	4.7
Left temporal pole	20	-44	-8	-24	4.8
Right anterior medial temporal	28	20	0	-20	3.4
Right temporal pole	38/28	36	8	-20	3.8
Basal forebrain	25	12	8	-8	3.6
<u>Temporal-Order Minus Item</u>					
Right dorsal prefrontal	6	18	-6	44	5.4
Right dorsal prefrontal	9	40	18	32	5.0
Left dorsal prefrontal	6	-22	-6	44	5.1
Right inferior posterior parietal	39/19	38	-70	32	5.1
Posterior midline (cuneus/precuneus)	19	-4	-78	32	5.1
Posterior midline (cuneus)	31	2	-68	8	4.7

Regions showing significant increases in blood flow ($Z > 3.09$, $p < 0.001$, uncorrected) in each of the three following contrasts: (1) a standard contrast between item and temporal order conditions, (2) a contrast between these conditions in which performance differences were covaried out, and (3) a contrast between the two conditions with equivalent performance levels (low item versus high temporal-order). The coordinates and Brodmann's areas (BA) are from the brain atlas of Talairach and Tournoux (1988).

criteria, which are listed in Table 1, can be considered to be independent of task difficulty.

Compared to temporal-order retrieval, item retrieval was related to increased neural activity in temporal and basal forebrain areas. Temporal activations were bilateral and included the anterior part of the parahippocampal gyrus. The peak of the basal forebrain activity was in the vicinity of the nucleus accumbens. Compared to item retrieval, temporal-order retrieval was associated with differential activity in frontal, posterior midline, and lateral parietal regions. Frontal activations were bilateral but more pronounced on the right hemisphere, where they extended from Brodmann's area 6 to area 9. Posterior midline activations extended from the lingual gyrus to the medial parietal cortex and included cuneus and precuneus regions. Activity in lateral parietal areas was right-lateralized and highest in the angular gyrus (area 39).

The main effect of performance (high versus low) and the task by performance interaction did not yield significant rCBF differences. This result provides additional support for the idea that the regions listed in Table 1 are basically independent of performance differences.

Discussion

The present study provided four main findings. First, there was a dissociation between frontal and temporal lobe regions: frontal lobe regions were more activated in the temporal-order than in the item retrieval task, whereas the opposite occurred in temporal lobe regions. Second, item retrieval was specifically associated with increased activity in ventromedial temporal and forebrain regions. Third, temporal-order retrieval was particularly related to activations in dorsal frontal regions. Finally, temporal-order retrieval was also associated with activations in posterior brain regions. These four findings are discussed in separate sections below.

Dissociation between Temporal and Frontal Lobe Regions for Remembering What and When

This dissociation in brain activity is consistent with a double dissociation found in patients with focal lesions.

In a classic study by Corsi (reported by Milner, 1971), patients with frontal or temporal lobe lesions were presented lists of items for which they periodically made recognition or recency judgments. Frontal lobe patients were impaired in recency but not in recognition memory, whereas temporal lobe patients were mildly impaired in recognition but had no difficulty with recency discrimination as such. Furthermore, there was an interaction between lesion laterality and stimulus type. Patients with lesions in the left hemisphere showed deficits with words but not with abstract pictures, whereas those with right hemisphere damage showed impairments with abstract pictures but not with words.

Although historically important, these results leave some gaps. First, the double dissociation between temporal lobe and frontal lobe patients has been difficult to replicate. In a follow-up study (Milner et al., 1991), frontal patients were more impaired in recency than on recognition judgments, but the opposite pattern in temporal lobe patients was not clearly observed. Patients with temporal lobe lesions were surprisingly unimpaired in recognition memory for words or representational drawings; and although temporal lobe patients were significantly impaired on recognition of abstract pictures compared to control subjects (0.78 versus 0.92), they also showed a decrement in recency memory for these items (0.66 versus 0.77). Second, it is unclear from studies with lesion groups whether the differential sensitivity of item and temporal-order memory to temporal and frontal lobe lesions occurs at encoding, retrieval, or both. This is a general limitation of lesion data, since memory impairments due to brain lesions may reflect deficits at any one of these processing stages or their combinations (e.g., Gershberg and Shimamura, 1995). Finally, lesion evidence does not imply that temporal lobe and frontal lobe regions are independently involved in item and temporal-order memory in the normal brain. A certain region can be similarly involved in two tasks but be more necessary for one than for the other (e.g., Cabeza et al., 1997).

Confirming and extending Corsi's findings, the present results showed that temporal lobe regions were more activated in item than in temporal-order memory,

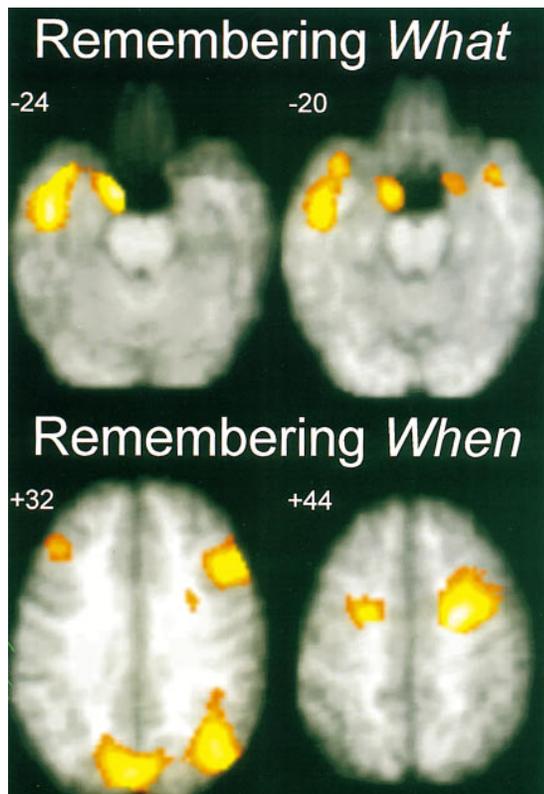


Figure 2. Main Results of the Standard Contrast between Item and Temporal-Order Retrieval Conditions

Z maps ($Z > 3.09$) overlaid on standard MRI templates. The top image shows anterior temporal and medial temporal lobe regions associated with item retrieval. The bottom image shows dorsal frontal and posterior midline and parietal regions associated with temporal-order retrieval. Note that the left prefrontal region at $z = 32$ was not significant in the temporal-high minus item-high subtraction, and hence it is not included in Table 1.

whereas dorsal frontal lobe regions were more activated in temporal-order memory than in item memory (see Figure 2). This dissociation in brain activity existed even when differences in memory performances were controlled by covarying out memory accuracy and by comparing conditions with similar performance levels. Also, the present dissociation shows that temporal and frontal lobe regions are differentially involved in item and temporal-order memory during the retrieval phase. Future research would determine if differences exist also during encoding.

As mentioned previously, the reason why Eyler Zorrilla et al. (1996, Soc. Neurosci., abstract) and Nyberg et al. (1997) did not find frontal regions to be significantly more activated during temporal-order retrieval than during item retrieval is likely to be related to the use of a list differentiation task, which does not demand the type of precise temporal order discrimination required by the relative recency test. Statistical power may also be important; each task was scanned four times in the present study but only once in Nyberg et al. (1997). Conversely, Nyberg et al. (1997) found rCBF differences that were not observed in the present study. These activations

may reflect a confounding with task difficulty. For example, they found the anterior cingulate to be more active during temporal-order than during item retrieval. A similar activation was found in the present study, but it disappeared after performance was covaried out, suggesting it was related to performance differences. On the other hand, it is possible that some differences across studies are related to different aspects of temporal-order memory, which are tapped differently by recency or list discrimination tasks. Further research is necessary to clarify these differences.

Brain Regions Associated with Remembering What

Item retrieval was associated with increased activity in temporal lobe and basal forebrain regions. Temporal lobe activations were bilateral and included anterior medial temporal regions. It is well known that medial temporal lobe regions are critical for episodic memory (e.g., Squire and Zola-Morgan, 1991), and medial temporal activations during episodic memory retrieval have been found in several functional neuroimaging studies (e.g., Buckner et al., 1995; Schacter et al., 1995; Nyberg et al., 1996b; Schacter et al., 1996; Gabrieli et al., 1997; Owen et al., 1997; Rugg et al., 1997). The present results suggest that the involvement of these regions in episodic memory may be more related to the retrieval of item information than to the retrieval of temporal-order information. This conclusion is consistent with evidence that unilateral (Milner, 1971) and bilateral (Sagar et al., 1990) temporal lobectomy tends to produce more severe deficits in recognition than in recency tasks. The lobectomy procedure, however, removes not only medial temporal but most of the anterior half of the temporal lobe. The present findings suggest that item retrieval is particularly associated with the anterior parahippocampal gyrus. The hippocampus proper, in contrast, did not show significant rCBF changes across tasks, suggesting that this structure is not differentially involved in item and temporal-order retrieval.

The basal forebrain is also critical for episodic memory (e.g., Markowitsch, 1995). Lesions in this area impair recognition performance (e.g., Stuss et al., 1994a) and can produce amnesia (e.g., Alexander and Freedman, 1984; Mayes, 1995). Alzheimer's disease, which is characterized by severe memory loss, involves a dysfunction of the basal forebrain cholinergic system (Weinstock, 1995). The basal forebrain is closely linked to medial temporal regions by cholinergic projections (e.g., Dudar, 1975), and it has been suggested that the basal forebrain represents an anterior component of the limbic system rather than a part of the frontal lobes (Stuss et al., 1994a). The finding that the basal forebrain area was coactivated with medial temporal regions in the item retrieval condition suggests that these areas form part of a network that is particularly involved in retrieving item information. However, it is not clear why these two regions are not usually coactivated in PET studies of item memory (Cabeza and Nyberg, 1997).

One region that is typically activated in PET studies of item retrieval, the right prefrontal cortex (Tulving et al., 1994; Nyberg et al., 1996a), was not differentially activated in the item retrieval condition of the present

study. The present results do not imply that the right prefrontal was not involved in the item retrieval condition, but simply that it was less activated than in the temporal order condition.

Brain Regions Involved in Remembering When *Frontal Lobes*

Frontal activations during temporal-order retrieval were bilateral but more pronounced in the right hemisphere. Many PET studies of episodic memory retrieval have reported activations in the right prefrontal cortex (reviewed by Tulving et al., 1994; Nyberg et al., 1996a). Interpretations of these activations have been based primarily on whether they increase (retrieval success, Rugg et al., 1996), decrease (retrieval attempt, Kapur et al., 1995; Schacter et al., 1996), or do not change (retrieval mode, Nyberg et al., 1995) as a function of memory performance. In contrast, there is very little information about the relation of these frontal activations to different aspects of episodic memory retrieval. The present results suggest that at least some of these activations may be more involved in retrieving contextual information regarding when remembered events occurred than in retrieving the content of these events. This idea is consistent with views that emphasize the role of the frontal lobes in memory for contextual information (e.g., Squire, 1982; Schacter, 1987; Squire, 1987).

In PET studies, frontal activations are also commonly found during working memory tasks (reviewed by Awh et al., 1995; Cabeza and Nyberg, 1997). Given that the present frontal rCBF differences were significant even when task difficulty was controlled, it appears that they do not simply reflect quantitative differences in working memory load. Indeed, it seems more reasonable to assume that they reflect qualitative differences in working memory operations. Additionally, the location of the present peaks is more dorsal than the ones typically associated with tests emphasizing item retrieval (reviewed by Cabeza and Nyberg, 1997). In studies with nonhuman primates, the mid-dorsal frontal cortex has been related to high level working memory operations that are critical for temporal-order memory (Petrides, 1994; Petrides, 1995). The present results are consistent with these ideas as well as with those generally linking the frontal cortex with the temporal organization of experience and behavior (e.g., Pribram and Tubbs, 1967; Fuster, 1985; Schacter, 1987).

Posterior Brain Regions

The involvement of posterior midline (cuneus/precuneus) and parietal regions in temporal-order memory has not been noted in lesion studies. Both of these regions are anatomically connected to the dorsal frontal cortex (e.g., Petrides and Pandya, 1984 Goldman-Rakic, 1988) and are typically activated in PET studies of episodic memory retrieval (e.g., Kapur et al., 1995; Fletcher et al., 1995b; Moscovitch et al., 1995; Haxby et al., 1996; Schacter et al., 1996; Owen et al., 1997). The precuneus region was related to imagery (e.g., Fletcher et al., 1995a), but a recent PET study has shown that this area is involved in episodic memory retrieval independent of imagery (Buckner et al., 1996). Consistent with this last study, subjects' introspective reports in the present

study did not reveal a differential use of imagery in the two memory tasks. In addition, it is worth noting that a region close to the precuneus, the retrosplenial cortex, has been previously related to temporal information processing (Bowers et al., 1988).

As for the posterior parietal region, it has been suggested that its close connections to the dorsal prefrontal cortex may be critical not only for spatial responses but also for the representation and manipulation of temporal relations that are necessary for high level planning (Petrides, 1994). In other words, the dorsal stream may have a role not only in processing where (e.g., Ungerleider and Mishkin, 1982) but also in processing when. One possibility is that the brain uses mechanisms specialized for processing spatial information in processing temporal information. Another possibility is that the dorsal parietofrontal circuit subserves a more general role in processing relationships between stimuli and their context, including spatial, temporal, and inter-item associations.

Encoding, Source Memory, and Novelty/Familiarity

Three other issues deserve comment. First, it is reasonable to assume that the frontal regions are involved in temporal-order memory not only during retrieval but also during encoding. In contrast to the suggestions that the encoding of temporal-order information is automatic (Hasher and Zacks, 1979), more recent evidence shows that it is affected by practice, intention to learn, encoding strategies, and individual differences (e.g., Zacks et al., 1984; Naveh-Benjamin, 1990). Moreover, Mangels (1997) reported that control subjects surpass frontal patients in temporal-order memory only when encoding conditions encourage the processing of temporal-order information, suggesting that strategic encoding of temporal information is impaired in these patients, but automatic aspects of temporal encoding are intact. Note that even if frontal regions participate in certain aspects of the encoding of temporal-order information, the specific areas involved are unknown. We are currently investigating this matter using PET.

Second, frontal regions are also assumed to be involved in other forms of context memory, such as memory for the source of information. This makes sense in light of our data, because temporal-order memory and source memory are related phenomena (Schacter, 1987). Moreover, it has been suggested that source memory deficits in frontal patients are a consequence of temporal-order memory deficits (Janowsky et al., 1989). However, it is not clear how the neural correlates of these two forms of context memory overlap or differ in frontal and posterior brain regions. This is another issue we are investigating.

Finally, since in each trial of the tests subjects saw one old word and one new word in the item condition but two old words in the temporal-order condition, it is possible that some of the activations reported in Table 1 were affected by differences in the novelty/familiarity of the words. For example, temporal lobe activations in the item condition—which are close to the transmodal novelty detection regions identified by Tulving et al. (1996)—could have been enhanced by novelty, whereas

frontal activations in the temporal-order condition could have been augmented by familiarity. Yet, these activations did not vary as a function of recognition failure (i.e., increasing novelty) or recognition success (i.e., increasing familiarity), because they remained significant after the effects of performance were covaried out. Although judgments of relative recency are not possible without some level of item retrieval, we believe that the regions differentially activated during the item and temporal-order conditions represent those that are selectively involved when an individual engages in the intentional retrieval of item or temporal-order information from episodic memory.

Conclusions

In summary, the present findings confirm and extend lesion data by demonstrating, in healthy humans and under controlled conditions, that temporal-order retrieval is more dependent on frontal lobe regions, whereas item retrieval is more dependent on temporal lobe regions. Moreover, we provide evidence concerning what specific areas within the frontal and temporal lobes are associated with item and temporal-order retrieval. Furthermore, the present results clearly demonstrate that temporal-order retrieval involves a network of brain regions that includes both frontal and posterior brain regions.

Experimental Procedures

Subjects

The subjects were 12 university students (6 male, 6 female) with a mean age of 25 (range, 20–28 years). All subjects were right handed, and had no history of neurological or psychiatric illness. The study was approved by the joint Baycrest Centre/University of Toronto Research Ethics and Scientific Review Committee.

Materials

The critical stimuli were 560 concrete nouns selected from a database (Quinlan, 1992) with a length between 4 and 8 letters (mean, 5.5) and a frequency between 4 and 100 (mean, 25.8). The nouns were randomly divided into eight lists of 60 words and four lists of 20 words, which did not differ in letter number or frequency ($F_s < 1$). The eight lists were assigned to the eight scans, and the four lists were used as lures in the item retrieval tests. Additionally, other words were selected to be used as buffer items in the study lists and as practice lists. The words were presented in large black letters on a white background on a computer screen suspended 60–75 cm in front of the subjects.

Procedure

During the PET scanning session, subjects undertook a block of four scans in the item retrieval condition and a block of four scans in the temporal-order retrieval condition. The scans were 11 min apart, and the two blocks were separated by ~20 min. The order of the two blocks was counterbalanced across subjects. Subjects studied a list of words before each scan and tried to retrieve them during the scan. Subjects were told to study the words for the item or temporal-order tests, which they knew from a short study-test practice at the beginning of each block. During the test, two words were presented in each trial and subjects had to choose—as quickly and as accurately as possible—one of the two words by clicking the left or the right mouse buttons. In the item retrieval test (recognition), one word in the pair was from the study list and one word was new, and subjects had to choose the studied word. In the temporal-order retrieval test (recency), both words in each pair were from the study list (e.g., word 5 and word 15), and subjects had to choose the word that appeared later in the study list (e.g., word 15).

The chance probability of a correct response in both of these two-alternative forced-choice tasks is 0.50. The test lists consisted of 20 word pairs, which were presented for 4 s each with a 1 s interval (total, 100 s). The list started with the injection of the tracer (about 20–25 s before the scan window) and continued for 15–20 s after the end of the 60 s scan window.

In both the item and temporal-order retrieval conditions, high and low levels of performance were produced by manipulating encoding conditions. A series of pilot studies were conducted in order to determine what encoding manipulations would produce significantly different high and low levels of performance in both item and temporal-order retrieval, and what manipulations would also yield an equivalent level of performance in the item-low and temporal-high conditions. The final procedure was based on the combined manipulations of length of study list, presentation rate, and study-test delay. The list length was 65 words in the item condition and 45 words in the temporal-order retrieval condition. In the item condition, the presentation rate was 2 s in the high condition and 0.25 s in the low condition, while in the temporal-order retrieval condition, it was 5 s in the high condition and 2 s in the low condition. The interstimulus interval was always 0.5 s. In the item condition, the approximate interval between the end of study and the start of the test was 3 min in the high condition and 7 min in the low condition, while in the temporal-order retrieval condition, it was 2 min in the high condition and 3 min in the low condition.

In the item condition, 20 words from the middle of the list were tested, paired with lures. In the temporal-order retrieval condition, 40 words from the study list (word 3 to word 42) were used to create 20 test pairs by combining words separated by 8 items (e.g., words 3 and 13, and so on until words 22 and 42). In both the item retrieval and temporal-order retrieval scan blocks, two successive scans corresponded to the high condition and two scans to the low condition, with the order of high and low conditions counterbalanced across subjects.

PET Methods

PET scans were obtained with a GEMS-Scanditronix PC2048–15B head scanner using a bolus injection of 35.5 mCi (1.48 GBq) of ^{15}O - H_2O . The analysis of the PET data involved three steps. First, using the software AIR (Woods et al., 1992), the different images from each subject were realigned to the first image; second, using the software Statistical Parametric Mapping 95 (SPM95, Wellcome Department of Cognitive Neurology, London) implemented in Matlab (Mathworks, Incorporated, Sherborn, MA), the realigned images from each subject were transformed into a standard space (Talairach and Tournoux, 1988) and smoothed using isotropic Gaussian kernel of FWHM of 15 mm. Third, also using SPM 95, the effects of the conditions on the rCBF at each voxel were estimated using a general linear model, wherein the changes in global counts are considered as a covariate (Friston et al., 1995). The effects of each comparison are estimated using linear contrasts, which yield a *t* statistic (expressed as a *Z* score) for a given comparison at each voxel. Contrasts were also performed that included performance in item and temporal-order retrieval tests as a covariate. An activation was considered significant if it had at least 20 voxels above $Z > 3.09$ ($p < 0.001$, uncorrected).

The analysis of PET data followed the 2×2 factorial design and identified brain regions where rCBF showed either a main effect of task (item versus temporal-order retrieval), a main effect of performance (high versus low), or a task by performance interaction. The main effect of task was revealed by contrasting the four item retrieval scans (two high and two low) with the four temporal-order retrieval scans (two high and two low). The main effect of performance was revealed by contrasting the four high performance scans (two item scans and two temporal-order scans) with the four low performance scans (two item scans and two temporal-order scans). The contrast for the task by performance interaction was coded as $1/-1/-1/1$ and $-1/1/1/-1$. Each contrast involved two SPM subtractions (e.g., item minus temporal-order, temporal-order minus item).

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