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General and specific brain regions involved in encoding and retrieval of events: What, where, and when

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ABSTRACT Remembering an event involves not only what happened, but also where and when it occurred. We measured regional cerebral blood flow by positron emission tomography during initial encoding and subsequent retrieval of item, location, and time information. Multivariate image analysis showed that left frontal brain regions were always activated during encoding, and right superior frontal regions were always activated at retrieval. Pairwise image subtraction analyses revealed information-specific activations at (i) encoding, item information in left hippocampal, location information in right parietal, and time information in left fusiform regions; and (ii) retrieval, item in right inferior frontal and temporal, location in left frontal, and time in anterior cingulate cortices. These results point to the existence of general encoding and retrieval networks of episodic memory whose operations are augmented by unique brain areas recruited for processing specific aspects of remembered events.

Episodic memory enables people to consciously recollect personally experienced events as such (1). It represents one of the most remarkable capabilities of the human brain/mind. Every one can bring to mind countless previous happenings in which one has participated or that one has witnessed. A great deal has been learned about episodic memory at the behavioral and cognitive levels (1–4). Our understanding of the neural substrates of episodic memory, however, is still rather fragmentary. Neuropsychological studies have provided some useful information about individual brain structures that are necessary for successful remembering of events (5–8), and, more recently, functional neuroimaging studies have begun to fill in the gaps (9–17). Yet, the achievement of one of the major goals of cognitive neuroscience of memory—identification of the neuronal correlates of encoding and retrieval processes of episodic memory—still lies in the future.

Here we report a positron emission tomography (PET) study of regional cerebral blood flow (rCBF) associated with remembering different aspects of experienced events. An event is an occurrence of something at a particular time in a particular place. The major aspects of events, therefore, consist of (i) their “contents” (what?), (ii) their location in space (where?), and (iii) their occurrence in time (when?).

The majority of the previous PET studies of laboratory analogues of episodic memory—remembering of experimentally presented word-events—have been concerned only with remembering of the “what” of the events, the words, although some have been directed at “memory for” spatial information (18, 19). Here we broadened the study of the neuroanatomical correlates of episodic memory to all three major aspects of remembered word-events—what, where, and when. The purpose of the study was to identify brain regions involved in encoding and retrieval of information about these aspects. In line with available evidence concerning widely distributed neuronal memory networks (9, 15), we expected to find certain brain regions to be involved in encoding and retrieval of episodic information regardless of the specifics of the remembered events (“general memory networks”) and others to be associated with the processing of particular individual aspects—what, where, and when—of remembered events (“specific memory networks”).

METHODS

Subjects. Twelve right-handed volunteers (7 females, 5 males; age range, 19–40 years) participated in the study. The participants were screened to ensure that they were free of any significant previous or current medical disorder. The study was approved by the Human Subjects Use Committee of Baycrest Centre, and written informed consent was obtained from all subjects.

PET Scanning. PET scans were conducted with a GEMS-Scanditronix (Uppsala) PC2048-15B head scanner (5–6 mm axial resolution). A laser positioning system was used to obtain images parallel to the orbitomeatal and canthomeatal lines. The head of the subject was restrained using a custom-fit thermoplastic mask attached to the headrest of the scanner bed. A transmission scan with a 68-Ge/68-Ga rotating pin source was used to correct emission scans for photon attenuation. Eight emission scans were then conducted with a bolus injections of 40 mCi (1 Ci = 37 GBq) 15O-H2O for each scan. Injections were administered through an intravenous catheter in the subject’s left arm. Images were acquired over 60 s starting when the bolus tracer arrived in the brain. The interval between scans was 11 min. The cognitive tasks began at the time of bolus injection and ended about 30 s after the data acquisition had been completed. The PET counts accumulated over the 60-s acquisition period were used as an index of rCBF (20). The data from the last (eighth) scan have been reported elsewhere (17), and no further mention will be made of the eighth scan here.

Cognitive Design. The design consisted of seven conditions, each represented by one scan per subject. During all scans subjects (i) saw 15 familiar words presented one at a time at a rate of 4 s per word, and they (ii) responded by pressing a computer-mouse button.

During the first scan (Read), each word appeared either at the left or the right side of a computer screen, the two sides alternating in a random sequence. The subjects were instructed to read the words silently and press either mouse button after reading each word. The purpose of this scan was to provide “nonmemory” rCBF data to serve as a baseline for the remaining six memory scans under otherwise comparable conditions.

Abbreviations: PET, positron emission tomography; rCBF, regional cerebral blood flow; PLS, partial least squares.

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Three encoding scans provided rCBF data associated with encoding. As in the Read scan, the stimulus words appeared either at the left or the right side of the screen, and they were presented in two immediately successive lists. The beginning of list 1 and the beginning of list 2 were marked visually on the screen. The three encoding scans differed with respect to study instructions, summarized as follows: (i) item encoding—‘‘Study the presented words for a subsequent test; ignore the first/second designation of the list and the left/right location of the words;’’ (ii) location encoding—‘‘Study the words and their left/right placement for a subsequent test; ignore the first/second list designations;’’ (iii) time encoding—‘‘Study the words and their appearance in the first or the second list for a subsequent test; ignore their left/right placement.’’ Subjects pressed one of the two mouse buttons after each presented word.

The remaining three scans were retrieval scans. Each of them matched a corresponding encoding scan. Specifically, information about the word-events studied under specific encoding conditions was retrieved in the immediately following retrieval scan. In all three retrieval scans, subjects saw single test words presented in the center of the screen at the rate of 4 s per word, and, in different conditions, responded to retrieval instructions summarized as follows: (i) item retrieval—‘‘Press the left mouse button if you recognize the word as ‘old’, one that appeared in the study list, and the right mouse button if you think the word is ‘new’, not studied previously;’’ (ii) location retrieval—‘‘All the words you see are ‘old’; press the left-hand or the right-hand mouse button depending on whether you remember seeing the word on the left or on the right side of the screen at study;’’ (iii) time retrieval—‘‘All the words you see are ‘old’; press the left-hand or the right-hand mouse button depending on whether you remember seeing the word in the first or the second list at study.’’ In all three retrieval conditions subjects were instructed to guess when in doubt.

Some other details of the procedure were as follows: (i) Half way through the 11-min interval between a given encoding scan and its following retrieval scan, subjects were given a second exposure to the same word-events that they had already seen during the encoding scan. The purpose of this additional study trial was to enhance the behavioral performance. (ii) To familiarize the subjects with the procedure, they were given one practice trial during the transmission scan, under the conditions identical with those of the Read scan. (iii) In the Item Retrieval condition, five of the seven words presented before and after the 60-s acquisition phase were new. (iv) All 15 words presented during the 60-s data-acquisition phase of each of the three retrieval scans were ‘‘old,’’ thereby holding constant their experimental familiarity (21). (v) Stimulus materials and sequential orders of encoding/retrieval scans were counterbalanced across subjects.

**Image Analysis.** Before examination of rCBF as related to the experiment, all subjects’ images were spatially transformed to facilitate intersubject averaging and identification of common areas of change using Statistical Parametric Mapping software (SPM94, Wellcome Department of Cognitive Neurology, London). Each rCBF scan was reconstructed into 15 transverse planes which were interpolated into 43 planes. The images from each subject were realigned to the subjects’ first scan, transformed into a standard space (22), and smoothed using an (10 mm full width at half-maximum) isotropic Gaussian kernel.

Analyses were performed to specifically address the experimental questions: (i) Is there a common neuroanatomical basis underlying episodic encoding and retrieval regardless of specific processing demands? and (ii) Are there additional unique brain areas recruited into a common system depending on specific processing demands? As we expected that both general and specific networks would be comprised of several regions across the brain, we chose the analytic methods with a view to optimizing the ability to detect a distributed pattern of activity across the entire image volume.

Our primary tool was a recently introduced partial least squares (PLS) analysis of data from all conditions (23, 24). The PLS analysis describes the relation between some exogenous source, such as the experimental design, and the functional brain images. It does so by first computing the cross-covariance between (i) a matrix containing contrast vectors that code the experimental design and (ii) all the voxels in each image for all subjects in all tasks. (Images are ratio corrected for global flow.) The cross-covariance matrix is then decomposed using singular value decomposition, yielding pairs of latent variables. The first element of the pair represents a linear combination of contrasts that has the largest relation to (is most covariant with) the brain images, and the other element of the pair is a weighted linear combination of voxels that is most related to that combination of contrasts. (Because this image is derived from a singular value decomposition, it is called a singular image.) Put another way, the first pair extracted represents the largest effect in the experiment, and identifies the contrast, or combination of contrasts, representing the effect and the pattern of voxels showing the effect. The brain image extracted can thus be interpreted as nodes of a distributed system that is most affected by the manipulation. Successive extractions of latent variables will account for other less strong experimental effects until all cross-covariance is accounted for.

Given seven scans, the contrasts used in the PLS analysis represented the six possible effects: (i) differences between the six Memory conditions and the single Read baseline, (ii and iii) processing demands (item, location, and time), (iv) encoding versus retrieval, and (v and vi) the interactions of processing demands and encoding or retrieval.

A second analytic product of PLS is the scores on each singular image. Since the singular image is a set of numerical weights, they can be applied to each subject’s original image. This is achieved through multiplication of the subject image by the singular image and summing the product, yielding a single number for each subject in each condition. Plotting these scores by scan (task) gives a visual indication of which effect is being expressed in the singular image. Distribution of scores with respect to scan condition was tested for significance by using multiple linear regression of the scores on scan contrasts with the probabilities assigned using permutation tests (25).

The interaction effects obtained with the PLS were evaluated further on a voxel-by-voxel basis using pairwise comparisons in SPM94. This step tested the hypotheses concerning regionally specific condition effects at encoding and retrieval (26). In effect, the PLS analysis acted as an omnibus test of the question, ‘‘Is there an interesting pattern of activity across the whole brain?’’ whereas SPM94 served as a post-hoc test of the subordinate question, ‘‘How does a particular voxel contribute to this pattern?’’

Data from each subject were normalized to his or her own global mean flow (analysis of covariance correction). The contrasts were evaluated by t tests, and then converted to z scores for ease of evaluation [threshold = 3.09 (P = 0.001)]. Since the pairwise comparison were performed only in light of a significant interaction (as indicated by PLS), this threshold of significance is conservative (26).

**RESULTS**

The proportion of correct responses were 86% (SD = 14%) in the item retrieval condition, 62% (SD = 9%) in the location condition, and 71% (SD = 19%) in the time condition. These differences suggest caution in interpreting the rCBF data: the data may reflect not only cognitive components of tasks but also the level of performance.
POSITIVE SALIENCES
NEGATIVE SALIENCES

FIG. 1. Subject scores and horizontal singular images showing associated patterns for dominant latent variables. (a) The first variable distinguished between the read and memory (encoding and retrieval) conditions ($R^2 = 0.52, P = 0.0001$). Positive saliences are regions of relatively higher blood flow in read versus the memory conditions, including bilateral middle temporal gyrus [Talairach (22) $x, y, z = 56, -62, 8; -48, -54, 8$], bilateral Sylvian fissure ($52, 20, 0; -46, -6, 12$), and in right inferior frontal gyrus ($48, 34, 12$). Negative saliences are regions of relatively higher blood flow in memory versus the read condition, including bilateral frontal regions ($20, 50, 0; 36, 22, 24; -48, 18, 32$) bilateral insula ($28, 20, 0; -32, 16, 0$), and anterior cingulate gyrus ($-6, 20, 36; -8, 32, 28$). (b) The second variable distinguished between the encoding and retrieval conditions ($R^2 = 0.51, P = 0.0001$). Positive saliences are regions of relatively higher blood flow in the encoding conditions, including left frontal regions ($-38, 34, 24; -54, 26, 8; -22, 38, 16$) and left fusiform gyrus ($-24, -98, -16$). Negative saliences are regions of relatively higher blood flow in the retrieval conditions, including right frontal regions ($6, 38, 28; 12, 60, 0; 30, 28, 4; 30, 56, 4$) and midbrain ($8, -28, 8$). (c) The third variable distinguished the item from the location and time conditions ($R^2 = 0.34, P = 0.005$). Positive saliences are regions of relatively higher blood flow in the item conditions, including right frontal ($26, 28, 4$) and left anteromedial temporal ($-34, -12, -16$) regions. Negative saliences are regions of relatively
Four latent variables identified by the PLS analysis are graphically depicted in Fig. 1. The first latent variable distinguished between (i) the "nonmemory" reading condition and (ii) "memory" (encoding and retrieval) conditions. Relative to the memory conditions, reading showed increased rCBF in bilateral temporal regions and decreased rCBF in prefrontal regions. The second latent variable distinguished between (i) the encoding and (ii) the retrieval conditions. This distinction was common for all three kinds of information—item, location, and time. Compared with retrieval, encoding conditions showed increased rCBF in left frontal regions and reduced rCBF in right frontal regions. The third latent variable distinguished between (i) the item condition, with relatively higher rCBF in right frontal and left anterior medial temporal regions near the amygdala and uncus, and (ii) the location and time conditions. The fourth variable involved encoding/retrieval interactions across type of information, and was associated with increased activity in the left posterior medial temporal lobe (hippocampus and retrosplenic cortex).

We used pairwise image comparisons to identify specific regions involved in encoding and retrieval of the three different kinds of information. In each of these analyses, the rCBF pattern of one type of information was compared, one at a time, against that of each of the other two. We regarded brain locations in which rCBF of one type of information (target condition) was higher than that of both others (reference conditions) as indicating a region uniquely involved in processing of that information.

Table 1 and Fig. 2 show the brain locations in which encoding and retrieval of each of the three kinds of information activated a unique region as just defined. Item encoding activated the left hippocampal region, location encoding a right inferior parietal region, and time encoding a left fusiform region. Item retrieval was associated with increased activity in right inferior frontal and temporal regions, location retrieval involved increased activity in the left middle frontal gyrus, and time retrieval activated anterior cingulate regions.

**DISCUSSION**

PLS analyses identified two patterns that were suggestive of general memory operations. The first pattern included a higher rCBF in memory conditions relative to the "nonmemory" reading baseline in prefrontal regions bilaterally. The second pattern revealed an asymmetrical left and right prefrontal activity associated with encoding and retrieval: left middle frontal gyrus was relatively more active during encoding, and right superior frontal gyrus was more active during retrieval. Because the contrast between reading and memory was based on the single Read scan, we do not wish to make much of the first of these two patterns. More interesting is our finding that the second strongest source of covariance involved a separation of encoding and retrieval conditions across type of information. This finding suggests that general encoding and retrieval networks were operating in all conditions (9, 15). The asymmetrical involvement of the left and right frontal lobes in episodic encoding and retrieval of all three aspects of events—item, location, and time information—is consistent with the HERA (hemispheric encoding/retrieval asymmetry) findings from a large number of previous studies on item memory (27, 28).

In line with our finding of a general involvement of left frontal regions during encoding, it has been proposed that episodic encoding involves left frontal control of hippocampal function (13). Face encoding has been shown to involve left frontal and right hippocampal regions (29), but, to our knowledge, this is the first neuroimaging study to demonstrate left hippocampal involvement in encoding of verbal events. It has been suggested that previous failures to differentially activate hippocampus during encoding is attributable to this region's high state of activity even in the absence of any explicit encoding requirements (30). If we assume that the demand to process location or time information results in an attenuated processing of item information, this suggestion becomes consistent with the present finding of differential activation of left hippocampus during item encoding.

Intentional encoding of location or time information was also associated with changes in rCBF in unique regions. In

![Table 1. Brain regions showing significantly increased rCBF during encoding and retrieval of item, location, and time information](image-url)
agreement with previous findings (31, 32), intentional encoding of location information was associated with increased activity in a region in the right parietal lobe. Encoding of time information—whether items were part of the first or the second list—involved a region in left fusiform gyrus. This finding has no clear parallels in published work, and we regard it as tentative for the time being.

With respect to retrieval, our finding of a general involvement of a region in right superior frontal gyrus indicates that this part of the right frontal cortex suberves one or more general functions, including the maintenance of the attentional focus on the temporal features of the acquisition episode. The majority of previous studies of verbal and nonverbal episodic memory retrieval have also found increased activation in Brodmann area 10 (33).

Specific regions that were involved in retrieval presumably reflected particular cognitive task demands. Item retrieval differentially involved a right inferior frontal region. This very region has previously been found to be generally involved during item retrieval, regardless of the retrieval success (15, 34), suggesting that it subserves decision processes concerning the item’s earlier experimental occurrence. Item retrieval also involved the right anterolateral temporal cortex. This part of the right temporal lobe has been suggested to work in concert with the ventro-lateral right frontal cortex in the process of recovering stored item information (6). Location retrieval activated a region in left middle frontal gyrus. The middle frontal gyrus was also associated with retrieval of location information in a functional magnetic resonance imaging study of working memory (35). The left-sided location of the activation in our study may be related to the verbal nature of the stimuli. Time retrieval involved increased activity in midline frontal regions (anterior cingulate). Patients with frontal damage extending into the medial frontal region have been shown to be impaired on time memory (36), but a specific involvement of medial frontal regions in time retrieval has not been established. It is interesting to note, though, that a recent PET study found that a condition involving verification of the temporal order of script events was associated with increased activation in the medial frontal gyrus (37). The peak activation in that study was more anterior than the peak in our study, but the two studies converge in showing that time memory involves medial frontal regions.

In conclusion, the results of the present study indicate that (i) episodic encoding and retrieval of different types of event information share a common neuroanatomical basis, and (ii) processing of individual aspects of to-be-remembered and remembered events—their contents, location, and time of occurrence—recruits additional unique neuronal regions.

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