

## Neuroanatomical correlates of retrieval in episodic memory: Auditory sentence recognition

(positron emission tomography/prefrontal cortex/parietal lobes/consciousness/auditory priming)

ENDEL TULVING\*†, SHITIJ KAPUR‡, HANS J. MARKOWITSCH\*, FERGUS I. M. CRAIK\*†, REZA HABIB†,  
AND SYLVAIN HOULE‡

\*Rotman Research Institute of Baycrest Centre, 3560 Bathurst Street, North York, ON Canada M6A 2E1; †Department of Psychology, University of Toronto, Toronto, ON Canada M5S 1A1; and ‡Positron Emission Tomography Centre, Clarke Institute of Psychiatry, University of Toronto, 250 College Street, Toronto, ON Canada M5T 1R8

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**ABSTRACT** This study used positron emission tomography (PET) to investigate the neuroanatomical correlates of remembering previously experienced events. Twelve young healthy adults listened to “old” meaningful sentences which they had studied 24 hr previously. As a control task the subjects listened to comparable “new” sentences that they had never heard before. Regional cerebral blood flow associated with each task was measured by PET scans using <sup>15</sup>O-labeled water. Comparison (old-sentence task minus new-sentence task) of the PET images revealed an extended strip of increased blood flow in the right dorsolateral prefrontal cortex (Brodmann’s areas 10, 46, and 9) and the anterior portion of area 6. Other principal regions of increased blood flow were situated around the left anterior cingulate sulcus and bilaterally in the parietal lobes (areas 7 and 40). Major decreases in blood flow were situated bilaterally in the temporal lobes (areas 21, 22, 41, and 42). A high proportion of activity changes seemed to be located in the depths of cortical sulci. Increases in blood flow are seen as reflecting the operations of a widely distributed neuronal network involving prefrontal and parietal cortical regions that subserves the conscious recollection of previously experienced events. Decreases in blood flow in the temporal auditory areas are interpreted as reflecting auditory priming. The prevalence of sulcal blood-flow changes may reflect extensive cortical gyrification; it may also indicate that memory-related processes rely on the densely packed neuropil of sulcal regions.

A current theory of organization of human memory holds that there are five major forms or systems of human memory (1, 2). One of these, episodic memory, enables people to remember previously experienced events. That is, it makes it possible for a person to be consciously aware at time 2 of a personal happening in a certain situation at an earlier time 1 (3). Episodic memory is closely related to semantic memory, which registers, stores, and makes accessible for retrieval impersonal shared knowledge of the world in the broadest sense. Thus, knowing that the Eiffel tower is in Paris or that “assassin” is a person who kills for fanatical or monetary reasons is an example of semantic memory capabilities. Recollecting a visit to Paris or remembering that a sentence was presented among other to-be-remembered sentences in a memory experiment is an example of what episodic memory allows one to do. Retrieval from episodic memory is “explicit”—it occurs with conscious recollection of the relevant event—whereas retrieval from semantic memory is “implicit”—it can occur in the absence of conscious awareness of any particular past happening (2, 4).

Episodic remembering depends on how events are originally experienced (encoding processes) and on the conditions under

which their recollection is attempted (retrieval processes). The many effects of encoding and retrieval processes, and their interaction, in both normal and pathological memory, are reasonably well known at the level of cognitive analysis, but our understanding of the brain mechanisms and processes that subserves episodic memory is still fragmentary (1, 5). Such understanding can be enhanced through the use of the technique of positron emission tomography (PET) (6, 7).

In the preceding article (8), we reported a PET study of episodic memory encoding processes. The purpose of the PET experiment reported here was to identify some of the brain regions that are involved in retrieval of previously studied verbal information.

Previous studies have implicated frontal regions of the brain as involved in episodic memory retrieval. An early blood-flow study, using xenon as tracer and measuring lateral cortical activation of a small number of loci, reported that episodic memory recognition of pictures was associated with increased blood flow in the frontal regions, more prominent in the right than in the left hemisphere (9). In another preliminary study, with radioactive gold as tracer (10), blood flow data were recorded from the lateral cortex by 254 detectors. Blood flow was greater in anterior cortical regions while subjects were silently thinking about their past personal happenings (episodic memory retrieval) and was greater in posterior cortical regions when subjects were engaged in silent thinking about impersonal news events or historical events (semantic memory retrieval). In more recent PET studies at Washington University (11, 12) stem-cued recall of words from previously studied lists (episodic memory retrieval) has been found to be associated with changes in the blood flow in the prefrontal cortical regions, especially on the right, as well as in several posterior regions (11, 12).

In light of these previous findings we were especially interested in the extent to which episodic retrieval processes of a somewhat different kind than those explored previously would be correlated with changes in blood flow in prefrontal cortical regions. We designed the experiment in such a way that any observed changes in the blood flow would reflect only the recognition of the presented materials as familiar from a particular study episode. A special feature of our experiment was that the materials during study and test were presented auditorily. Another feature was that subjects, as in some previous studies (10, 13), made no overt responses of any kind during scanning. All measured changes in the blood flow therefore were assumed to reflect mental activity only.

Specifically, healthy young male university students underwent PET scanning while they were silently listening to (i) “new” meaningful sentences which they had never encountered previously or (ii) comparable “old” meaningful sentences which they had heard in a study session in the PET

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Abbreviation: PET, positron emission tomography.

laboratory 24 hr earlier. All other variables and features were held constant between these two conditions. The differences in the blood flow patterns associated with these two listening tasks were expected to provide information relevant to episodic remembering of the old sentences.

Because our experiment varied in several respects from previous comparable experiments—we used the auditory modality, complex semantic information, a 24-hr retention interval between study and test, and large amounts of studied and tested material—the question of the role of prefrontal cortical regions was deemed to be especially interesting, because positive results would add considerably to the generality of the conditions under which prefrontal regions are implicated in retrieval processes.

## METHODS

**Subjects.** Twelve male right-handed (14) university students aged 19–30 years participated in this study approved by the University of Toronto Review Committee on the Use of Human Subjects. Subjects were screened to ensure that none suffered from a current or past medical, neurological, or psychiatric disorder (15). Subjects were also screened for any prior history of serious head injury, prolonged loss of consciousness, or active use of medications or recreational drugs. There were no exclusions. Data for all subjects are presented here.

**Task Design.** A unit of cognitive material consisted of a sentence frame and a semantically related word, the total making a novel definition of the word (e.g., a form of recreation for the jumpy—trampoline; a servant in name only—bridesmaid). We will refer to these units of material as “sentences.” They are meaningful, are initially novel, require deep semantic processing, and are highly memorable (16). Two hundred and forty different sentences were used. Half were presented to subjects in an initial study session, and all 240 were presented in a recognition test in the PET scanning session 24 hr later.

In the initial pre-scan session, while the subjects were reclining on the scanner bed, they heard 120 sentences played on audio tape at the rate of 3–4 sec per sentence. The sentences were presented in three blocks of 40, separated by 5-min intervals, and the sequence was repeated after the third block. Thus subjects heard every sentence twice. Subjects rated the meaningfulness of each presented sentence orally on a 3-point scale. No PET scans were taken in this first session.

In the second session, 24 hr later, each subject underwent six scans. During three of these they heard predominantly old sentences, those that they had already encountered in the first session, and during the other three scans they heard predominantly comparable new sentences, which they had never encountered before. The order of alternation of these two types of scan was counterbalanced among subjects.

During each scan, 40 sentences were presented on audio tape, at the rate of 4 sec per sentence. The first 10 sentences and the last 10 sentences constituted a mixed sequence, in that approximately half were new and half were old; the middle 20 sentences, whose presentation coincided with the 60-sec scan window, were either all new or all old. Indeed, before each scan the subject was told whether the majority of the sentences to be heard during that scan were old or new. They were asked to listen to the sentences silently, with their eyes closed, without making any overt responses. They were also asked to make a mental note every time an “oddball” sentence appeared, one of the type other than the majority, to keep a mental running total of the frequency of these oddball test items, and to tell the experimenter what the total was after each scan. After the final, sixth scan, the subjects were additionally tested for “performance verification.”

This was a conventional yes/no recognition test, but with instructions to duplicate the covert performance during the immediately preceding scan. The 28 old sentences and the 12 new sentences (or the 28 new and 12 old) that the subject had heard during the sixth scan were presented on a test sheet, and the subject was asked to indicate how they had classified each sentence, old or new, while they were listening to them.

**PET Scanning.** PET scanning was done as described in the preceding paper (8), except that the task was started 30 sec prior to the 60-sec data acquisition for each scan, and the scans were 11 min apart. The scans were analyzed as described (8).

## RESULTS AND DISCUSSION

As expected, subjects’ recognition performance was uniformly high. On average, their estimated number of “oddball” test items was within one item of the actual number of such items. In the performance verification test, subjects classified correctly as old or new more than 95% of the test sentences.

The PET data, expressed in terms of the subtraction of the new sentence image from the old sentence image, are summarized in Table 1. There were four major regions of activation increases, and three major regions of activation decreases.

Regions of increased blood flow constituted two bandlike activation strips in the frontal lobes. The one in the right dorsolateral prefrontal cortex was quite extended. It began in area 10 at the inferior tip of the frontal lobes and lined up through areas 46 and 9 to end in the anterior portion of area 6. The other one was limited to the left cingulate sulcus anterior to the region of the genu of the corpus callosum. The right dorsolateral prefrontal activity increase and the absence of comparable activity changes in the homotopic left prefrontal cortex is in line with comparable findings of prefrontal lateralization reported in several other PET laboratories (11, 12, 19). We discuss the issue of prefrontal lateralization of episodic memory in the following article (20).

Table 1. The principal cortical areas manifesting significant activation changes in regional cerebral blood flow

Region	Coordinates, mm			Z value
	x	y	z	
Increased activity				
Frontal (lateral)				
Right area 10	30	50	0	3.28
Right area 46	32	44	12	3.84
Right area 44	48	8	32	3.61
Right area 6	32	6	48	4.46
Frontal (medial)/ anterior cingulate				
Left area 24	–16	36	12	3.57
Left area 32	–24	42	4	4.07
Left area 32	–22	32	28	4.02
Parietal				
Right area 40	44	–34	48	6.13
Left area 7	–36	–46	44	5.45
Left medial area 7	–14	–58	32	6.24
Left area 40	–36	–50	40	4.86
Decreased activity				
Temporal/insular				
Right area 42	42	–6	–12	4.71
Left insula	–24	42	4	4.07
Left area 21/22	–50	–50	8	5.36

Areas are named after Brodmann (17), coordinates are according to the atlas of Talairach and Tournoux (18). A Z value above 3.4 is significant at  $P < 0.05$  with Bonferroni correction for multiple comparisons.

The other two major regions of activity increase were found in the parietal lobe bilaterally—namely, in the inferior and posterior portions of area 7 and the dorsal portion of area 40 in the left hemisphere and in the most posterior-medial portion of area 7 and of area 40 in the right hemisphere. In the right hemisphere, area 40 showed the strongest activation in its ventral half.

The major regions of decreased activation (higher blood flow for new than for old sentences) were situated in the temporal lobes of both hemispheres. In the left temporal lobe a zone of strong deactivation was found in the posterior portions of areas 21 and 22. A second zone lay along the ventral lip and fundus region of the sylvian fissure (areas 41 and 42, insular cortex). Deactivation in the right temporal lobe was somewhat less prominent, but a symmetrically situated zone of deactivation was found in the ventral fundus region of the sylvian fissure, extending inferolaterally from the insular cortex.

There were other, more scattered, statistically less significant activation changes. In the left hemisphere there was some activation increase in the posterior part of the left dorsolateral prefrontal cortex (junction region of areas 9 and 6), in the pulvinar, and possibly in the head of the caudate nucleus. Medial area 9 showed decreases. In the right hemisphere, smaller activation increases were seen in the cerebellum, area 19, and area 31. Remarkably, there were no activation changes found in the medial half of the right hemisphere.

A potentially interesting, and unexpected, feature of regional activity changes was their specific locus. A high proportion of changes in blood flow was observed in sulcal regions rather than on the lateral or medial surface of the cerebrum. This high proportion may reflect nothing more than the extensive gyrfication of the human cerebral cortex. More intriguing was the finding that the sulcal activations seemed to be localized near the fundus areas of the sulci—i.e., in the transition zones between adjacent cytoarchitecturally diverse areas. The fundus region of the anterior part of the left cingulate sulcus provides a particularly striking example, as the increase in blood flow here coincided with the border region between the limbic juxtallocortex and homotypical prefrontal isocortex. Another relevant example is provided by the aforementioned ventral fundus region of the sylvian fissure. The concentration of peaks of blood flow changes in fundal regions may reflect technical factors relating to image acquisition and image analysis, or it may reflect the particular high density of the neuropil (and consequently enhanced synaptic activity) in the fundus regions. But it is also possible that it reflects a specific involvement of the fundal regions in higher forms of cognition, including episodic memory.

The parietal lobe revealed another quite interesting activity pattern, namely in areas 7 and 40, or area PG in Mesulam's (21) terminology. In the right hemisphere, the activity increase extended to the area homotopical to Wernicke's region (of the left hemisphere), while in the left hemisphere the corresponding more ventrally situated part of area 40 (Wernicke) was inactive. The specific nature of the contribution that the contralateral counterpart of the "language comprehension area" makes to the processing of familiar verbal information remains unclear, although the fact that area 40 represents a late evolutionary development—it is not found in the macaque brain (17)—suggests an advanced function.

The activity decreases in areas 21 and 22 are in line with the assumed involvement of these regions in auditory perception and in language comprehension. Other decreases were observed in the insular and auditory areas 41 and 42. Some of these decreases may reflect auditory priming (22). Because of the subjects' prior exposure to the old sentences, neural

computational requirements for identification and comprehension of these sentences were diminished in comparison with new sentences. Thus, blood flow decreases in bilateral temporal regions may mark neural substrates of auditory priming. The same kind of reasoning has been advanced by Squire *et al.* (11) and Buckner *et al.* (12), who identified bilateral regions in occipitotemporal cortex as involved in visual priming.

The pattern of connectivity suggested by increased blood flow among the bilateral parietal, left cingulate, and right prefrontal cortical regions is suggestive of a complex network of widely distributed brain structures that subserves the attentional, motivational-affective, memory, and other aspects of the auditory sentence recognition task. The activation "strips" in the frontal lobes—the one in the right dorsolateral prefrontal cortex, the other in the left medial prefrontal or anterior cingulate cortex, or both—may be seen as graphically representing some of the local portions of this extended network. Anatomically such a network makes good sense, because there exist extensive connections between prefrontal and cingulate regions and parietal areas (21). Comparable networks have been postulated in support of other forms of higher-order cognitive functioning (21, 23–25), as well as memory (26, 27).

It is not yet possible to delineate the correspondence between specific cortical regions associated with the specific components of the auditory sentence recognition task that we studied. A number of speculative interpretations of the pattern of neuronal activity associated with the task could be offered. We mention only one. It relates the apparent connection between prefrontal and parietal activations to conscious awareness of past events—i.e., subjects' conscious recollection of the episode of first hearing the sentences. The task design of our study excluded overt behavior and assured that the differential neuronal activity that was inferred from changes in blood flow reflected the mental activity of remembering. Remembering includes self-centered mental reference to both time and space. Quintana and Fuster (28) have reported evidence showing that the prefrontal regions are concerned with temporal aspects, and parietal regions with spatial aspects, of visuomotor performance. Other research has suggested that prefrontal lobes are involved in awareness of the flow of time (29–31) and that parietal regions contribute to awareness of space (32–34). When these observations are integrated with our results, it seems reasonable to speculate that prefrontal and parietal regions are among the principal components of the complex neural network from whose interaction emerges conscious awareness of self in subjective space–time. Such awareness is the sine qua non of episodic memory (3).

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