Novelty and Familiarity Activations in PET Studies of Memory Encoding and Retrieval

Endel Tulving,[1] Hans J. Markowitsch,[2] Fergus I. M. Craik,[1,3] Reza Habib,[1,3] and Sylvain Houle[4]

[1]Rotman Research Institute, Baycrest Centre for Geriatric Care, North York, Ontario M6A 2E1, Canada, [2]Physiological Psychology, University of Bielefeld, Bielefeld, Germany, [3]Department of Psychology, University of Toronto, Toronto, Ontario, M5S 1A1, Canada, and [4]Positron Emission Tomography Centre, Clarke Institute of Psychiatry, University of Toronto, Toronto, Ontario M5T 1R8, Canada

Nine young right-handed men viewed colored pictures of people, scenes, and landscapes. Then, 24 hr later while undergoing PET scanning, they viewed previously studied (OLD) pictures in one type of scan, and previously not seen (NEW) pictures in another. The OLD-NEW subtraction of PET images indicates familiarity, and the NEW-OLD indicates novelty. Familiarity activations, signalling aspects of retrieval, were observed in the left and right frontal areas, and posterior regions bilaterally. Novelty activations were in the right limbic regions, and bilaterally in temporal and parietal regions, including area 37. These latter activations were located similarly to novelty activations in previous PET studies using visual words and auditory sentences, suggesting the existence of brain regions specializing in transmodal novelty assessment. The effects of novelty are seen both behaviorally and in replicable patterns of cortical and subcortical activation. We propose a "novelty/encoding hypothesis": (1) novelty assessment represents an early stage of long-term memory encoding; (2) elaborate, meaning-based encoding processes operate on the incoming information to the extent of its novelty, and therefore (3) the probability of long-term storage of information varies directly with the novelty of the information.

Functional neuroimaging techniques are transforming the study of the brain/mind, promising to revolutionize research on neural bases of cognitive processes very much in the way in which the telescope changed the study of the heavens and the microscope the investigation of the infinitesimal world: they bring into view parts of the universe that were not accessible to the senses without these devices. Nowhere is the change more apparent than in the study of human memory. By showing the involvement of specific, widely distributed neocortical regions in various component processes of memory (e.g., Squire et al., 1992; Haxby et al., 1993, in press; Kapur et al., 1994a, 1995; Shallice et al., 1994; Tulving et al., 1994a; Andreasen et al., 1995a; Buckner and Tulving, 1995; Fletcher et al., 1995; Moscovitch et al., 1995), the findings of PET studies of memory complement and supplement the extensive evidence garnered from lesion-based neuropsychological analyses of "localization" of memory functions (Markowitsch and Pritzel, 1985; Squire, 1987; Weiskrantz, 1987; Markowitsch, 1995).

Especially gratifying is the realization that PET studies of memory do not only allow the testing of existing ideas but can generate genuinely novel conceptual insights into the nature and workings of memory. One example is a consistent pattern of PET findings that converges on the hypothesis that encoding and retrieval processes in episodic and semantic memory engage the frontal lobes asymmetrically in a distinctive pattern. This pattern has been interpreted as the HERA (hemispheric encoding/retrieval asymmetry) model of the involvement of the frontal lobes in encoding and retrieval (Tulving et al., 1994b; Buckner et al., in press; Nyberg et al., in press a). According to HERA, (1) left frontal lobes are differentially more involved than right frontal lobes in retrieval of general knowledge (semantic memory information); (2) left frontal lobes are more involved than the right frontal lobes in the encoding of novel aspects of incoming information into episodic memory, including information retrieved from semantic memory; and (3) right frontal lobes are more involved than left frontal lobes in episodic memory retrieval. More recent studies have extended the hypothesis by suggesting that the right-frontal blood-flow changes do not signify the actual recovery of stored information as such, but rather a general "stage setting" for such recovery. This frontal "stage setting" has been characterized as "retrieval attempt" (Kapur et al., 1995; Schacter et al., in press) or "retrieval mode" (Nyberg et al., in press b), processes that involve other brain regions as well.

The main purpose of this article is to illustrate how neuroimaging studies can change the conceptual foundations of the science of memory. We describe a PET activation study involving recognition of complex colored pictures whose results, together with the results of other PET studies, suggest the existence of novelty assessment circuits in the brain that are separate from the circuits subserving memory-based familiarity.

Materials and Methods

Picture Recognition: A PET Study

The study was initially designed to test the generality of the retrieval component of the HERA model (Tulving et al., 1994b). Its design was very similar to that of our earlier study of auditory sentence recognition (Tulving et al., 1994a), except that the materials consisted of complex visual pictures. The main objective of the study was to compare patterns of regional cerebral blood flow (rCBF) for viewed pictures in what we refer to as the OLD/NEW design or paradigm.

In the NEW condition, subjects viewed novel colored pictures of people, scenes, and landscapes that they had not seen before. In the OLD condition, they viewed similar pictures that they had already encountered once before, in a session held in the PET laboratory 24 hr earlier. This cognitive task design isolates the processes having to do with episodic memory ("did you see this picture earlier in this experiment?") from other perceptual, other cognitive, and response variables, which are held constant. It reveals two kinds of changes in rCBF: increases (activations) for novel stimuli relative to familiar ones, and increases for familiar stimuli relative to novel ones.

Subjects

The subjects were 12 young right-handed men who had volunteered to participate in the study, and who had agreed to comply with the protocol approved by the Research Ethics Committee of the Rotman Research Institute of Baycrest Centre for Geriatric Care, affiliated with the University of Toronto. The subjects were screened to ensure that they did not suffer from any medical, neurological, or psychiatric disorder. They were also screened for active use of medications or recreational drugs. All 12 subjects passed the screen. However, because the data from three subjects were contaminated by movement artefact during scanning, the results from only nine subjects are reported here.

Procedure

Subjects participated in two sessions, held 24 hr apart, in which they viewed pictures. The pool of stimuli consisted of 160 pictures, divided randomly into two sets of 80, A and B. The subjects saw the

pictures of set A (or, for half the subjects, set B) in the first session, and pictures of both sets in the second session. This treatment rendered half the pictures in the second session "old" (seen before) and the other half "new" (not seen before).

The first session consisted of "dry" PET runs, during which the subject was exposed to 80 pictures (either set A or set B). The pictures were shown in two blocks of 40 pictures, appearing on the screen of a computer monitor, at the rate of 3 sec per picture, while the subject reclined on the scanner gurney. After the two blocks, the sequence was repeated once more. The subject was instructed to inspect each picture and rate its pleasantness on a three-point scale (1, not pleasant; 2, neutral; 3, pleasant). The purpose of asking subjects to make these decisions was to exercise some control over the encoding processes, and to decrease the likelihood of episodic-memory retrieval, that is, to discourage subjects from processing the pictures in some relation to places that they had personally visited and to scenes personally witnessed. No scanning took place in the first session.

In the second session, 24 hr later, each subject underwent six scan trials. During each trial the subject viewed 40 pictures presented at a rate of 3 sec per picture, and performed a specific cognitive task on the pictures. The trial, and cognitive activity, began approximately 30 sec before the injection of a bolus of $H_2{}^{15}O$, the PET scan occupied the middle 60 sec portion of the cognitive task (the scan "window"), and the cognitive task ended 30 sec after the close of the scan window.

The first two scan trials served as "warm-up," to blunt the effects of the novelty of the actual PET procedure, and to habituate the subjects to the activity of "viewing pictures" under specific task conditions. During each of these scans three pictures, which did not appear in any other part of the study, were presented repeatedly, over and over again, in a random sequence, and the subject's task was to mentally keep track of the number of times that the picture presented first appeared during the total task period. The data from these scans are not reported here.

Scan trials 3–6 comprised the experiment proper and provided the data of interest. They included two scans during which the subjects viewed old pictures, those seen on day 1, and two scans during which the subjects viewed new pictures, those not seen on day 1. The order of these OLD and NEW scans was counterbalanced among subjects. For the first 30 sec subjects saw both old and new pictures, during the 60 sec scan window they saw only old, or only new pictures, and for the last 30 sec they again saw both old and new pictures. The subjects had been informed after scan 2 and before scan 3 that during the rest of the session they would be seeing series of pictures, and that in each series, corresponding to a scan, the pictures would be mostly old (seen on day 1) or mostly new (not seen on day 1). Before each "old" (or "new") scan they were specifically instructed (1) that the majority of the pictures that they would see during the next scan would be old (or new), (2) that there would also be minority of new (or old) pictures, and (3) that their task was to note the appearance of the "minority" ("odd-ball") pictures and keep a mental count of them. At the end of the scan they were asked to report this count. Subjects made no overt responses of any kind during the OLD or NEW tasks; they engaged in mental activity only. Subjects were not apprised of the fact that on any given trial all pictures appearing during the scan window would be homogeneous, all OLD or all NEW. Neither did any subject, on questioning during debriefing, report noticing this fact.

Thus, the basic comparison in this study was that between NEW (never seen before) and OLD (seen once 24 hr earlier) pictures that the subjects viewed with the objective of detecting and holding in mind the number of the odd-ball pictures, defined in terms of OLD and NEW, in the test set, with other conditions held constant. The plan of this comparison was identical with that in our previous auditory sentence recognition study (Tulving et al., 1994a).

PET Method and Image Analysis

Brain maps of (rCBF) associated with the different task conditions were determined using the ^{15}O-labeled water technique (Herscovitch et al., 1983; Raichle et al., 1983). Measures of blood flow were obtained using the Scanditronix/GEMS PC 2048-15B brain-scanning unit, which allows the detection of 15 isotropic slices simultaneously, 6.5 mm apart, with an in-plane spatial resolution of 5–6 mm (Evans et al., 1991). A custom-fitted thermoplastic face mask was used to stabilize the subject's head during the procedure. A bolus of 40 mCi of ^{15}O-labeled water (5 ml) was infused through an indwelling venous catheter prior to each scan. The image-data were acquired during the 60 sec "scan window" that occupied the middle part of the 120 sec cognitive task. The intervals between successive scans were 11 min.

The scans were reconstructed using a Hanning filter and were corrected for attenuation with a transmission scan obtained using a 67Ge rotating pin-source. The specific neuronal pattern associated with the different tasks were assessed using statistical parametric mapping (SPM; Friston et al., 1991a). The images were preprocessed to reduce errors due to positioning variation in the scanner and individual differences in brain anatomy. Variability in positioning among subjects were removed by a semiautomated method (Friston et al., 1989), which reorients the images to standard reference planes as outlined by Talairach and Tournoux (1988). Variations in brain morphology were compensated for by linear rescaling of size differences and nonlinear resampling to correct for differences in anatomy across subjects (Friston et al., 1991b). Resulting images were smoothed using a Gaussian-filter to increase signal to noise characteristics and to correct for local variations in gyral anatomy. Differences in global activity between scans were partitioned out by analysis of covariance with the global-activity of a scan as a covariate—this process permits the evaluation of regional effects independent of global activity (Friston et al., 1990). Differences between scans were then obtained for each pixel, and the significance of the observed difference at each pixel was assessed by comparing the magnitude of the difference with the error variance at that pixel. A particular difference between scans was considered further only if the number of pixels that showed a significant increase, in the entire scan, significantly exceeded the number expected by chance as evaluated by means of the χ^2 statistic.

Results

Behavioral tests showed that subjects' ability to distinguish between novel and familiar pictures was good. Each scan consisted of a total of 40 items, 28 of which composed the majority type, and the remaining 12 belonging to the minority type. Subjects were required to provide a count of the number of minority items presented during each scan. On scan 3, the mean deviation of the judged number from the correct value of 12 minority items 3 was 3.17. This number decreased to 2.08 on scan 4, 1.67 on scan 5, and 1.17 on scan 6, thus indicating that subjects became more proficient at the task with increasing practice.

Immediately after the last scan trial (scan 6), subjects were given a yes/no recognition test of the 40 test pictures (12 new and 28 old, or 12 old and 28 new) from that trial. The mean hit rate was 0.88, the false positive rate was 0.11.

The PET results are reported in terms of the differences between averaged blood flow patterns yielded by NEW and OLD pictures. We refer to the higher blood flow for new than old pictures (that is, increased blood flow in the NEW-OLD subtraction) as "novelty activations," and to the higher blood flow for old than new pictures (that is, increased blood flow in the OLD-NEW subtraction) as "familiarity activations."

The highlights of the subtractive PET data are summarized in Tables 1–3. Familiarity activations are shown in Table 1, novelty activations in Table 2 (the right limbic system), and Table 3 (temporal and parietal neocortical regions). Table 3 also includes data on novelty activations in two other OLD/NEW PET studies (Tulving et al., 1994a; Kapur et al., 1995).

Brain regions and representative pixels (Talairach and Tournoux, 1988) are given for activations that were either (1) statistically significant at 0.01 level (uncorrected), or (2) significant at 0.05 level (uncorrected) and in close proximity to activations reported in other closely related studies. These thresholds are very lenient, and, consequently, the probability of false positives is not negligible. We have chosen to work with lenient thresholds, however, because we believe that false positives can be identified more readily than misses (false negatives) that are likely to occur when the threshold

Table 1
Brain regions and representative pixels showing "familiarity activations," significant increases in rCBF in the OLD-NEW subtraction

Region	Brodmann areas	Coordinates (mm) x	y	z	Z score
Left frontal medial	10/9/46	−28	52	8	3.3
Left medial and inferior	46/45/10/9	−36	40	12	2.5
		−40	30	20	3.5
		−38	26	24	3.6
		−38	24	28	3.2
Left frontal eye field and Broca's area	8/44	−34	8	28	3.1
		−34	6	32	3.1
		−38	10	36	2.6
Left premotor cortex	6	−20	0	52	2.1
Left anterior cingulate	24/32 and 33	−2	24	24	2.1
		−4	18	32	2.1
		0	12	40	2.4
Right frontopolar and prefrontal	10, 9	18	52	8	2.7
		18	54	12	2.9
		22	52	16	2.5
		22	52	20	2.4
		18	52	24	2.4
		20	48	28	2.0
Right frontal medial	46	28	44	24	2.2
		32	36	16	2.1
Right medial and superior frontal	6/32	14	10	44	3.1
		14	6	48	3.4
Right premotor cortex	6, 44	40	10	24	3.1
		42	4	36	2.9
Right anterior cingulate	24	20	26	20	2.2
Left retrosplenial and medial parietal	31/7	−16	−58	24	3.1
Left striate cortex	17	−12	−76	12	2.5
Right angular gyrus	39	34	−58	24	2.8
Right prestriate/striate cortex	18/17	12	−68	4	2.7
		12	−72	8	2.7

These regions exhibited higher volumes of blood flow during the viewing of familiar pictures, which the subjects had already seen in an experimental session 24 hr previously, in comparison with novel pictures (pictures that the subjects had never seen previously).

Table 2
Brain regions and representative pixels showing "novelty activations," significant increases in the NEW-OLD subtraction in the right "expanded" limbic system

Region	Coordinates (mm) x	y	z	Z score
Right hippocampal formation	26	−12	−20	3.6
	26	−34	−4	2.9
Right parahippocampal gyrus	22	−38	0	2.8
	10	−40	4	3.2
Medial dorsal thalamus	2	−18	16	2.4
Medial prefrontal cortex	2	34	−12	3.7
Medial orbitofrontal cortex	4	12	−16	3.0
Anterior cingulate/medial prefrontal cortex	0	44	−8	3.2
	−2	44	−4	3.5

These regions exhibited higher volumes of blood flow during the viewing of novel pictures, which the subjects had never seen previously, in comparison with familiar pictures, which the subjects had already seen in an experimental session 24 hr previously.

is set high. PET findings are useful only to the extent that they are consistent across studies using similar task comparisons (Roland et al., 1995). Lack of replication of reported data that reflect false positives can be observed, lack of replication of false negatives cannot.

Familiarity activations (OLD-NEW increases in rCBF) were observed in 14 regions, summarized in Table 1. In the left frontal regions they occurred in the medial and inferior gyri, in the anterior cingulate, near the border of the frontal eye field and Broca's area, and the premotor cortex. In the right frontal lobe, the most prominent familiarity activation extended from the frontopolar region through areas 10 and 9 to the medial area 46.

In the posterior cortex, one familiarity activation was observed in the left retrosplenial region, another in the right angular gyrus (area 39), and two more in the occipital lobe, perhaps reflecting the nature of the stimulus materials used in the study.

Prominent novelty activations were found in the right limbic regions (Table 2). They included band-like strips in the right hippocampal formation and the parahippocampal gyrus that extended to the retrosplenial cortex, the posterior end of the right medial dorsal thalamus, another band that stretched from the subcallosal area anterodorsally to the border between areas 32 and 10; as well as the anterior and inferior cingulate cortex. Together, they constitute the "expanded limbic system" (Nauta, 1979). No such extensive limbic activations occurred in the left hemisphere, although a more localized novelty activation was observed in the region of the parahippocampal and fusiform gyri (representative pixels at xyz = −34, −30, and −8, and xyz = −38, −26, and −12).

The remaining novelty activations in the present study were located in neocortical sulcal and opercular areas in temporal and temporoparietal lobes bilaterally. Some of these activations, summarized in Table 3, are especially interesting, because of the remarkable overlap with similar findings from other OLD/NEW PET studies. The data from two such studies (Tulving et al,. 1994a; Kapur et al., 1995) are included in the summary in Table 3. Like the data from the present OLD/NEW picture study, these other sets of data represent decreased activations in the OLD-NEW subtractions, or increased activations in the NEW-OLD subtraction, with either auditory sentences (Tulving et al., 1994a) or common words (Kapur et al., 1995) as stimulus items. In the regions listed in Table 3, the peaks of these novelty activations were within a few millimeters of one another. No familiarity activations, from any study known to us, have been observed at or near these sites.

Discussion

The results of our study broadly confirmed the findings of previous OLD/NEW comparisons by revealing familiarity activations in widely distributed cortical regions. The new findings were in agreement with the hemispheric encoding/retrieval asymmetry (HERA) model (Tulving et al., 1994b; Nyberg, Cabeza, and Tulving, unpublished observations) in the sense that familiarity activations, associated with recognition, were observed in the right prefrontal cortical regions (Brodmann areas 10, 9, and 46). But, not quite in keeping with HERA, recognition of "old" pictures also activated regions in the left frontopolar regions, and left medial and inferior frontal gyri (Brodmann areas 10, 9, 46, and 45). It is possible that episodic retrieval of complex pictorial information engages the prefrontal regions more symmetrically than does retrieval of other kinds of information. It is also conceivable that the left-frontal familiarity activation signifies the presence of a subprocess in retrieval, such as further encoding, that depends on neuronal computations in this region and that has not been present to the same extent in other episodic retrieval. This latter possibility is supported by the finding that more left-frontal activation has been observed during retrieval (recognition) of verbal material encoded on a single study trial than during retrieval of comparable over-learned material (Andreasen et al., 1995a).

Recent work (Kapur et al., 1995; Schacter et al., 1995; Nyberg et al., in press b) has suggested that the right-frontal activation reflects the operation of pre-ecphoric processes ("retrieval mode," or "retrieval attempt") to a larger extent than it reflects ecphory (effective recovery of stored information). In the present study, as in our previous study using

Table 3
Brain regions and representative pixels showing "novelty activations," significant increases in the NEW-OLD subtraction in temporal and parietal cortical regions

	Visual pictures			Visual words			Auditory sentences		
Region	x	y	z	x	y	z	x	y	z
Left opercular, medial, and inferior temporal regions									
	−48	−6	−12 (3.3)	−48	−6	−8 (3.4)	−44	−12	−4 (3.1)
	−44	−8	−16 (3.7)				−50	−12	−8 (2.6)
	−44	−14	−20 (3.7)	−44	−12	−16 (3.4)	−52	−14	−12 (2.6)
Right opercular, medial, and inferior temporal regions									
	46	−6	−8 (2.1)	48	−2	−12 (3.9)	44	−8	−8 (3.4)
	46	−4	−12 (2.4)	48	0	−16 (3.5)	42	−6	−12 (3.6)
Left parietal and temporal opercula									
	−52	−28	20 (3.4)	−44	−38	16 (5.3)	−54	−26	16 (2.7)
	−42	−42	20 (3.5)	−48	−32	20 (4.7)	−56	−28	20 (2.1)
	−48	−28	24 (3.3)	−48	−34	24 (4.8)			
Right parietal and temporal opercula									
	46	−32	20 (2.8)	52	−30	20 (4.9)	NIL		
	48	−24	28 (2.1)	50	−30	16 (5.4)			
Left temporo-occipital junction (Areas 19/37)									
	−32	−66	−12 (3.1)	−36	−64	−8 (4.4)	NIL		
	−28	−66	−8 (2.8)						
Right temporo-occipital junction (Areas 19/37)									
	38	−56	−16 (2.6)	40	−60	−8 (4.2)	44	−58	0 (3.1)
Left medial temporal gyrus									
	NIL			−50	−52	12 (3.7)	−48	−52	4 (3.3)
							−50	−50	8 (3.9)
							−52	−50	12 (3.5)
Right medial temporal gyrus									
	52	−46	12 (2.2)	54	−46	8 (3.5)	NIL		
	54	−46	−4 (3.0)						

These data were collected in three separate studies: the present study with pictures, the episodic/semantic recognition study of single words (Kapur et al., 1995), and the auditory sentence recognition study (Tulving et al., 1994b). The regions shown in the table yielded higher volumes of blood flow during the viewing of novel items (pictures, sentences, or single words), which the subjects had not encountered in the experimental context before, in comparison with familiar items, which the subjects had already seen in the experimental context, 24 hr previously (pictures and sentences) or 30 min previously (words). *Z* scores of pixels are given in parentheses.

the OLD/NEW paradigm (Tulving et al., 1994a), retrieval mode was nominally the same in the two comparison conditions, yet bilateral prefrontal familiarity activation was observed. The issue clearly needs further thought.

The posterior familiarity activations included the left retrosplenial region whose peak was near one previously reported in the Tulving et al. (1994a) auditory sentence recognition study (xyz = −14, −60, and 28). Retrosplenial activation has also been noted in other PET studies of memory. Grasby et al. (1993) found an rCBF increase in the retrosplenial region in a supraspan auditory verbal memory task, when a comparable subspan task was used as the reference ("baseline"). Shallice et al. (1994; see also Fletcher et al., 1995) reported retrosplenial activation during episodic encoding of paired associates, in comparison with the reference task of passive listening to a single repeated pair of words. These findings are in good agreement with neuropsychological reports of "retrosplenial amnesia" (Valenstein et al., 1987; Bowers et al., 1988; Takayama et al., 1991; Katai et al., 1992; Iwasaki et al., 1993), as well as with physiological findings of uptake of glucose by monkey retrosplenial cortex in memory tasks (Matsunami et al., 1989).

The peak of the familiarity activation (recognition of pictures) observed in the right angular gyrus (area 39) is close to activations shown by subjects recognizing words (Kapur et al., 1995) or faces (Haxby et al., in press). It probably signifies a component process of episodic recognition, although it is too early to say what that component is. The remaining posterior familiarity activations appear to have no close parallels in other OLD/NEW PET memory studies, and their reliability and significance therefore remain uncertain.

In the remainder of the discussion, we focus on novelty activations, which have been presented and briefly reviewed in an earlier report (Tulving et al., 1994c).

Novelty and Hippocampus

The role of the hippocampal formation and related structures in memory is well known (Squire and Zola-Morgan, 1991; Markowitsch, 1995; Squire and Knowlton, 1995), but until recently hippocampus had remained somewhat elusive in cognitive activation PET studies (Frackowiak, 1994; Buckner and Tulving, 1995). Now, however, a number of reports of PET activations of the hippocampal regions have appeared. In a study by Squire et al. (1992), the relevant subtraction (cued episodic recall to old word stem cues minus semantic memory-based completion of new word stems) yielded an activation in the right parahippocampal gyrus. Although similar subsequent studies in the same laboratory (Buckner et al., 1995) did not replicate the finding, Schacter et al. (in press) have reported right hippocampal activation during stem-cued recall, and Schacter et al. (1995) observed blood flow increases, associated with processing of novel line drawings, in the vicinity of the left hippocampal formation. In a study on free recall of auditorily presented words (Grasby et al., 1993), in which both encoding and retrieval processes affected changes in rCBF, hippocampal activation was inversely correlated with the length of the list and, hence, the proportion of words recalled by the subjects.

In our present picture recognition study, the right expanded limbic system, including the hippocampus, was more active while subjects viewed novel pictures rather than previously encountered pictures. There was also some hippocampal novelty activation in the left hemisphere. By definition, then, the hippocampal formation is a part of the novelty en-

coding (or novelty assessment) circuit. As such, the hippocampus can be said to be more involved in encoding than in retrieval. However, the decision of whether an input is novel or familiar obviously requires that the incoming information be compared with relevant stored information (Rolls et al., 1982), and thus depends on retrieval. One possible hypothesis is that the hippocampus subserves retrieval in the service of novelty assessment even if it may have less to contribute to retrieval of highly familiar information.

Findings reported by Grady et al. (1995) and Haxby et al. (1993) are similar to ours in that they observed activation of the right hippocampus, but not the left, in the encoding phase of studies of face memory. The fact that we found no comparable activations in our previous OLD/NEW study with auditory sentences (Tulving et al., 1994a) suggests that the hippocampus is differentially less sensitive to linguistic than to nonlinguistic information (cf. Markowitsch, 1988). The hippocampal findings with pictures and faces are compatible with the results of studies with nonhuman animals that point to a special role of the hippocampal formation in spatial learning and memory (Nadel, 1991; Bingham, 1992; Jarrard, 1993) and in discriminating and responding to novel and familiar objects, pictures, and other nonlinguistic inputs (Rolls et al., 1993, 1994; Gaffan, 1994).

Thus, hippocampal activation has now been reported in a number of memory-related PET studies, although it is not yet quite clear how the various findings fit together.

Novelty and Temporal Lobes

The interexperiment consistency of novelty activations, summarized in Table 3, is remarkable in light of the differences in the materials and sensory modalities in the three studies. The convergence of novelty activations from the different studies on the temporal/parietal regions specified in Table 3, and the virtual absence of familiarity activations in the same regions, in any of the relevant studies, strongly suggests that these regions have something to do with novelty, even if it is not yet clear exactly what that something is. The fact that most of these temporal/parietal regions showed novelty activations with both generically novel pictures and generically familiar words suggests that these regions are involved in processing of episodic (situational) novelty, rather than semantic (generic) novelty. The fact that some of these regions were "silent" in the auditory sentence study may point to their sensory-modality specificity. By and large, however, the whole pattern of the data suggests that, in addition to neurons that are known to react to novelty of specific stimuli (Li et al., 1993), there exist "novelty" regions whose computations seem to extend beyond single sensory modalities and particular materials. We think of these regions as components of "transmodal" novelty detection networks of the brain (Tulving et al., 1994c).

The idea that novelty detection may play an important role in memory has been widely discussed in the context of single-cell recording (Fahy et al., 1993; Li et al., 1993), a technique that has been used by a number of investigators to identify "novelty detecting" and "familiarity detecting" neurons in the brains of experimental animals such as monkeys, cats, and rabbits. These studies have established two main facts: (1) neurons exist that respond differentially to stimulus objects, including pictures of complex scenes, depending upon their novelty/familiarity (or recency of earlier exposure), and (2) these neurons are distributed selectively in the brain, they have been identified in some regions but not others. "Novelty detecting" neurons have been found in the lateral and medial temporal cortex, including the amygdala, the anterior and medial thalamus, and in inferior and lateral prefrontal regions of monkeys, cats, and rabbits (Markowitsch and Pritzel, 1978, 1987; Gabriel et al., 1988; Wilson and Rolls, 1990, 1993; Riches et al., 1991; Rolls et al., 1993). They therefore exist mainly in regions of Nauta's (1979) "expanded limbic system," in good agreement with the PET findings reported here.

The close agreement of the novelty data from relevant PET studies also nicely illustrates the viability of the basic premise of the Human Brain Mapping Database project (Fox et al., 1994), namely that it is possible to use data from different studies and different laboratories for the purposes of wide-ranging meta-analyses of the neuronal substrates of cognitive functions (cf. Markowitsch and Tulving, 1994, 1995; Buckner, in press).

Novelty and Priming

Like familiarity, novelty is a broad concept that embraces a number of potentially separable processes. In two earlier studies (Squire et al., 1992; Tulving et al., 1994a) findings resembling what we here refer to as novelty activations were interpreted as signifying perceptual priming. Perceptual priming refers to the enhanced facility of identifying objects from impoverished perceptual inputs by virtue of the individual's previous encounters with the same or similar objects. A great deal of evidence is available showing that perceptual priming differs radically from other forms of memory (Tulving and Schacter, 1990; Roediger and McDermott, 1993; Schacter, 1990, 1994). Therefore, it can be assumed that it is subserved by different neuronal substrates as well, and the suggestions that rCBF decreases observed in OLD-NEW subtractions signify priming are appropriate in this sense.

It is possible that some of the novelty activations do, indeed, reflect priming. But it is clear that not all of them do, and that the whole matter requires further study and thought. The right limbic novelty activations observed in the present study probably have little to do with processes required for priming, because it is known that medial temporal lobe damage does not produce impairment in perceptual priming (Schacter 1987; Squire 1987). The transmodal nature of the novelty activations also argues against the priming interpretation. Finally, in a PET study recently completed in our laboratory (Nyberg et al., in press) we observed prominent novelty activation in the left parietal/temporal operculum, one of the sites reported in Table 3, although the encoding modality (auditory) was different from the retrieval modality (visual), an experimental treatment that is known to greatly reduce perceptual priming (Roediger and McDermott, 1993). These kinds of observations suggest that attribution of deactivations in retrieval tasks to perceptual priming (Squire et al., 1992; Tulving et al., 1994a) is an overstatement; some deactivations may reflect priming, but others clearly do not.

Novelty/Encoding Hypothesis

We believe that novelty detection plays a critical role in memory, and that it does so by influencing encoding, and thus engram formation and storage. One function served by the neuronal novelty assessment networks is determining the necessity of the encoding of the information for long-term storage. We conjecture that encoding of incoming information for long-term storage depends on the novelty of the on-line information. A stronger form of this conjecture is that novelty is a necessary, although not a sufficient, condition for the long-term storage of information.

We will refer to this conjecture as the "novelty/encoding hypothesis." The hypothesis is rooted in an earlier suggestion that left-frontal cortical regions are involved in encoding of novel information for episodic memory storage (Tulving et al., 1994b). Here, we add the suggestion that novelty of information is determined by the neuronal networks in the limbic/

insular/temporal regions whose output provides the necessary information for the frontal encoding networks.

The novelty/encoding hypothesis holds that novelty assessment represents an early stage of encoding. The neuronal novelty assessment network identifies adaptively significant novel happenings, transmitting the relevant information for further processing. Similar ideas have been proposed by Fabiani and Donchin (1995), Kohonen et al. (1989), Metcalfe (1993), Siddle et al. (1991), and Sokolov (1963), among others.

The PET data we have considered allow us to speculate about the cortical and subcortical substrates of the encoding processes as traditionally conceptualized (Craik and Lockhart, 1972; Tulving, 1983). According to the novelty/encoding hypothesis, encoding consists of two sets of concatenated subprocesses: (1) novelty assessment, subserved by subcortical and cortical neuronal networks in the limbic system, the insular and temporal/parietal regions, and (2) higher level, meaning-based encoding operations, subserved by cortical regions that include left frontal lobes. The end product of these concatenated processes is the engram, or memory trace.

When novelty of the input is held constant, efficiency of encoding depends on the "depth" of encoding operations (Craik and Lockhart, 1972; Craik and Tulving, 1975). A large number of cognitive experiments support this generalization. Neuroimaging studies have shown that left frontal regions are differentially involved in encoding operations that determine the efficiency of subsequent retrieval (Kapur et al., 1994a; Shallice et al., 1994; Tulving et al., 1994b).

On the other hand, when the frontal encoding operations are held constant, along with all other variables, efficiency of encoding varies directly with the novelty of the stimulus items: novel items are recognized more readily than familiar items (Kinsbourne and George, 1974; Tulving and Kroll, 1995). The only relevant PET study on this issue has been reported by Raichle et al. (1994), who found that the left-frontal activation observed in the verb-generation task was diminished, eventually becoming undetectable, when subjects engaged in practicing the task. A related functional magnetic resonance imaging study (Demb et al., 1995) has also demonstrated a decrease in left-frontal activation encoding activation from the first to the second presentation of the material. We have interpreted this type of finding as suggesting that the left-frontal activation signifies episodic encoding of the novel aspects of semantic information processing in the verb-generation task, and that the decrease of this activation reflects decreasing novelty of the incoming information (Tulving et al., 1994b). Left frontal regions contribute to encoding of information by virtue of their special ability of "working with meaning" (Kapur et al., 1994b).

Some of the novelty activations may reflect processes that are only incidentally related to memory—arousal, anxiety, surprise, shift of attention, and the like. Others may reflect nonspecific factors concerned with "modulatory" mechanisms of memory (McGaugh, 1989). It is also conceivable that what we identify as "novelty detection," especially that in the hippocampal formation, represents mnemonic "binding" or "gluing" that has been postulated by some theorists, that is, integrating separate aspects of perceptual inputs into coherent representations of events, scenes, and facts of the world (Metcalfe et al., 1992; Cohen and Eichenbaum, 1993; Johnson and Chalfonte, 1994; Eichenbaum and Bunsey, 1995; Kroll et al., in press). This hypothesis is in accord with the notion that the role of the hippocampus in memory processing is an "early" rather than a "late" one. It is also compatible with the well-established findings that hippocampal damage impairs new learning and remembering of recent experiences. If novelty detection fails, encoding and all subsequent memory processes also fail, and no retrieval is possible even when all the structures required for retrieval are intact.

Memory Circuits in the Brain

The overall broad picture of encoding circuits of the brain that emerges from the data is as follows: material and modality-specific limbic novelty detection (or binding) circuits feed the temporal/parietal transmodal circuits whose computational outputs interact with the meaning-based encoding mechanisms in the frontal regions. Thus, the left-frontal localization of encoding processes, as specified by the HERA model, does not signify novelty detection, but rather further processing of novelty-related preprocessed information. It is reasonable to assume that the encoding circuit includes feedback loops from the frontal cortical regions to the limbic/insular/temporal novelty detectors. According to the HERA model, the results of semantic retrieval processes, whose neuroanatomical bases include left frontal cortical regions, are encoded into episodic memory, depending upon their novelty. The frontal to limbic/temporal feedback loop would make possible the evaluation of the novelty status of these results.

This outline of the encoding circuits extends earlier ideas, based on neuropsychological and lesion data, that episodic encoding takes place via structures of the limbic system, that is, by one or more of the three interconnected complexes: medial diencephalon, medial temporal lobe, and basal forebrain (Markowitsch, 1995). It also complements existing ideas about components of circuits of other memory-related processes, such as those concerning the association between left prefrontal cortex and higher level, contextually determined, and meaning-based encoding (Kapur et al., 1994a,b; Shallice et al., 1994; Tulving et al., 1994b; Buckner and Tulving, 1995; Fletcher et al., 1995). The putative components of retrieval circuits, suggested on the basis of PET findings, include right prefrontal, anterior cingulate, posterior cingulate (retrosplenial), and parietal cortex, together with cerebellar portions (Squire et al., 1992; Shallice et al., 1994; Tulving et al., 1994b; Andreasen et al., 1995a; Fletcher et al., 1995; Kapur et al., 1995). Hippocampal (Squire et al., 1992; Grasby et al., 1993; Schacter et al., in press; Nyberg et al., in press b) and thalamic areas (Andreasen et al., 1995) may also contribute to retrieval.

Future research undoubtedly will lead to the revision, modification, and refinement of these early suggestions regarding the neuroanatomical identity of the memory circuits of the brain, but there is little doubt that, out of the collaborative efforts of many researchers in a number of laboratories, a promising beginning has been made.

Conclusion

The data that we have presented and discussed here come from a very simple paradigm that we have referred to as OLD/NEW. By subtracting the rCBF image associated with the viewing and processing of novel objects from that of familiar objects, and vice versa, we have differentiated "novelty" activations from "familiarity" activations. The information about memory processes that such a simple procedure can provide is clearly limited. Nevertheless, some hazy outlines of the neuroanatomy of episodic-memory encoding and retrieval seem to be emerging.

Our data and discussion reinforce the widely held view that memory operations in the brain are based on extensively distributed cortical and subcortical components that are specialized for the execution of various subprocesses of memory (Mesulam, 1990; Wise et al., 1991; Fazio et al., 1992; Perani et al., 1993; Zappoli, 1993; Andreasen et al., 1995a,b; Shallice et al., 1994; Fuster, 1995). The data we have reviewed point to temporal/limbic novelty detection and frontal meaning-based, or "working-with-meaning," encoding operations as subpro-

cesses of encoding. The overall picture is similar to the situation that holds for retrieval—widely distributed networks that integrate the outputs of the many subprocesses of retrieval, including familiarity detection, retrieval mode and ecphory, into coherent patterns of recollective experience.

The major finding from the present study is that novelty and familiarity reactions are correlated with rCBF changes in different regions of the brain. This finding suggests that novelty and familiarity activations, as operationally defined here, reflect different memory processes. We have interpreted novelty activations as indexing novelty detection, or novelty assessment, and suggested that it represents an early stage of encoding of new information into long-term memory, although dependent on retrieval of previously stored information. Familiarity activations, on the other hand, are related to retrieval, marking neuroanatomical circuits subserving its various subprocesses.

In summary, the present study has shown that the PET technique can provide valuable information not only about the brain regions associated with aspects of memory encoding and retrieval, but also about the behavioral and experiential correlates of memory processes. The HERA model implies that encoding and retrieval must be regarded as substantially different processes. The PET evidence discussed in the present article suggests that it may be useful to conceptualize encoding processes as consisting of at least two stages, an early (novelty-assessment) and a later (meaning-based elaborative) stage. Widely distributed cortical and subcortical networks subserve processes at each of these stages. Together with the results of other studies, our results suggest that novelty assessment involves the limbic system and temporal/opercular regions, that elaborative encoding is associated with neuronal activity in the left prefrontal cortex, and that explicit retrieval is based on the activity of the right frontal, anterior cingulate, parietal, and cerebellar regions. By hinting at the existence of these circuits, PET and other neuroimaging techniques are playing a critical role in the integration of behavioral and biological theories of memory, and in helping to elucidate the great scientific puzzle that we call memory.

Notes

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Address correspondence to Endel Tulving, Rotman Research Institute, Baycrest Centre for Geriatric Care, 3560 Bathurst Street, North York, Ontario, Canada, M6A 2E1.

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