HIPPOCAMPUS 8:313–322 (1998)

RAPID COMMUNICATION

Hippocampal PET Activations of Memory Encoding and Retrieval: The HIPER Model

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ABSTRACT: A meta-analysis of experimentally induced changes in blood flow (''activations'') in positron emission tomography (PET) studies of memory has revealed an orderly functional anatomic pattern: Activations in the hippocampal region associated with episodic memory encoding are located primarily in the rostral portions of the region, whereas activations associated with episodic memory retrieval are located primarily in the caudal portions. These findings are based on an analysis of a sample of 54 ''hippocampal encoding and retrieval'' activations that were culled from an overall database consisting of 52 published PET studies of memory. We refer to this general pattern of rostrocaudal gradient of encoding and retrieval PET activations as the HIPER (Hippocampal Encoding/Retrieval) model. The model suggests a division of memory-related labor between the rostral and caudal portions of the hippocampal formation. Because functional anatomic pattern of encoding and retrieval activation that defines the HIPER model was unprecedented and unexpected, it is difficult to relate the model to what is already known or thought about functional neuroanatomy of episodic memory in the hippocampal regions. The model is interesting primarily because its exploration may yield fresh insights into the neural basis of human memory. *Hippocampus 1998;8:313–322.* **© 1998 Wiley-Liss, Inc.**

KEY WORDS: medial temporal lobe; episodic memory; encoding; retrieval; functional neuroanatomy

INTRODUCTION

The involvement of the medial temporal lobes (MTL) in memory processes has been known for a long time, but the precise role of these brain regions in memory has remained elusive. The pursuit of the understanding of the memory functions of the hippocampus and its adjacent cortical regions has been especially frustrating in studies of human memory, because there have been few useful methods available for in vivo analyses of the relation between memory as mental activity and memory as brain activity. Now, however, research with the recently adopted and still evolving techniques of functional brain imaging has begun to identify specific neuroanatomical regions that seem to be differentially involved in memory-related processes such as encoding and retrieval (Buckner and Tulving, 1995; Cabeza and Nyberg, 1997; Fletcher et al., 1997). A number of positron emission tomography (PET) and functional magnetic resonance imaging (FMRI) studies have reported memory-related changes in blood flow or BOLD signal ('activations') in the hippocampal, or medial temporal lobe, regions that have been associated with particular memory-related cognitive tasks (Grady et al., 1995; Kapur N. et al., 1995; Roland and Gulyas, 1995; Schacter et al., 1995, 1996a,b, 1997; Haxby et al., 1996; Nyberg et al., 1996b; Owen et al., 1996b; Stern et al., 1996; Tulving et al., 1996; Henke et al., 1997; Gabrieli et al., 1997; Martin et al., 1997).

The overall picture that has emerged so far from these early studies until now has been rather fuzzy. On the basis of the results of individual studies, a number of different ideas have been proposed concerning the nature of the 'memory function' of the hippocampus and other medial temporal lobe structures. The most salient characteristic of these accounts of PET studies of hippocampal memory, however, has been their heterogeneity, leading to the general assessment that "as yet no meaningful pattern of MTL activations and their connections to activations of other brain regions in relation to memory processes has emerged" (Tulving and Markowitsch, 1997, p. 212). This assessment was rendered against the backdrop provided by the HERA model, which describes an orderly, hemispherically asymmetric pattern of encoding and retrieval activations in the frontal lobes (Tulving et al., 1994a,b; Buckner, 1996; Nyberg et al., 1996a), as well as rather striking differences in the functional anatomy of episodic-memory encoding and retrieval produced in a meta-analysis in which data were pooled from four separate PET studies (Tulving and Markowitsch, 1997, Fig. 2).

Given the anatomical and physiological complexity of the medial temporal lobes, the equal complexity of the processes of human memory, and the rather limited evidence on which interpretations of the MTL function have been offered, the heterogeneity of theoretical

Grant sponsor: NSERC; Grant number: A8632; Grant sponsor: Anne and Max Tanenbaum Foundation.
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Accepted for publication 6 May 1998

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proposals that have been offered is unsurprising. Under the circumstances, it becomes important to search for empirical generalities of brain/cognition relations yielded by broader-based meta-analyses of multiple studies (Fox et al., 1998).

In this article we describe one such pattern of memory-related activations in the hippocampal region. The pattern emerged from the analysis of a number of published reports of PET studies of memory.

METHODS AND PROCEDURE

The overall method we used was the simplest kind of meta-analysis imaginable. Briefly, we searched the literature for memory-related PET studies, and used the results of the search to establish an overall database of "memory-related PET activations." We then used this database to extract a subset of activations that (1) cognitively were associated with either episodic-memory encoding or episodic-memory retrieval processes, and that (2) neuroanatomically were located in or near the medial-temporal lobe regions. Finally, we plotted the subset of "hippocampal encoding and retrieval activations" thus identified in the space of Talairach's stereotaxic atlas of the human brain (Talairach and Tournoux, 1988) to produce an orderly topographical map on which encoding and retrieval activations were spatially separated.

We next describe these steps of our method in somewhat greater detail.

Overall Data Base

We searched through papers published in widely available journals for studies that reported memory-related changes in the regional cerebral blood flow measured by the subtraction method (Fox, 1991; Friston et al., 1995) of positron emission tomography (PET). Briefly, the subtraction method consists in making a pairwise comparison between scans for a target (or experimental) condition and a reference condition (Buckner and Tulving, 1995) and then evaluating the difference in blood flow between conditions on a pixel-by-pixel basis with the *t* statistic (Friston et al., 1995). Because changes in blood flow, measured by PET, are directly related to the level of neuronal (presumably synaptic) activity (Raichle, 1994), these changes can be regarded as an index of the differential physiological involvement of a given region in the two tasks being compared. The "difference image" yielded by a subtraction shows regions of the brain in which blood flow was significantly higher in the target task than in the reference task, regions in which it was lower, and regions in which there was no statistically significant difference. Each region can be specified in terms of its spatial extent (number of pixels meeting the threshold criterion) and the peak intensity (center of mass) of the activated region. This peak intensity of activation represents the highest activation signal for a given region. Characterizing brain activations solely in terms of a peak activity is to ignore the spatial extent of such activation. Since spatial extent depends heavily on statistical thresholds and the size of the filter used for smoothing the data (Friston et al., 1994), it is more appropriate for meta-analysis to use only peak intensity.

The Talairach and Tournoux (1988) stereotaxic brain atlas allows one to represent any given point (pixel) in the brain as a set of three coordinates, one for each of three orthogonal planes. Virtually all PET researchers now report their findings in terms of the three-dimensional coordinates of the Talairach system. It is also a standard procedure to effect a mathematical transformation of the observed data (Friston et al., 1996) so that each brain scan conforms to that three-dimensional space. This practice makes it possible not only to pool the brain scans for a group of subjects, thus enhancing the reliability of the data, it also allows to compare the findings from different studies and different laboratories.

We harvested a total of 52 PET studies of memory-related activations for our overall database. In order to keep the subject sample as homogeneous as possible, we included only studies with young healthy subjects, and excluded studies with aged subjects or clinical populations. All the studies in the overall database are included in the list of references (Andreasen et al., 1995; Bäckman et al., 1997; Blaxton et al., 1996; Buckner et al., 1995, 1996; Cabeza et al., 1997a,b; Decety et al., 1997; Démonet et al., 1992; Dolan and Fletcher, 1997; Fink et al., 1996; Fletcher et al., 1995, 1996; Frith et al., 1991; Fujii et al., 1997; Ghaem et al., 1997; Grady et al., 1998; Grasby et al., 1993; Haxby et al., 1996; Henke et al., 1997; Jennings et al., 1997; Kapur N. et al., 1995; Kapur S. et al., 1994, 1995, 1996; Klingberg et al., 1994; Köhler et al., 1998; Maguire et al., 1996, 1997, 1998; Martin et al., 1997; Menard et al., 1996; Moscovitch et al., 1995; Nyberg et al., 1995, 1996c; Owen et al., 1996a,b; Petersson et al., 1997; Petrides et al., 1995; Raichle et al., 1994; Roland and Gulyas, 1995; Rugg et al., 1996, 1997; Schacter et al., 1995, 1996a,b, 1997; Shallice et al., 1994; Squire et al., 1992; Tulving et al., 1994b, 1996; Vandenberghe et al., 1996). The data from these studies comprised 1,145 sets of 3-D stereotaxic coordinates in the Talairach space. We refer to each set of coordinates as the "site" of an activation. Each of them represented the peak intensity of a region in the cerebrum that had shown a statistically significant difference in a comparison of two scanned tasks. The spatial extent and the shape of the activated "blobs" are ignored in the database. Each of the 1,145 activations in the overall database is identified by (1) its site (i.e., its Talairach coordinates), (2) the study or the paper in which it was reported, and (3) the two comparison conditions ("target" and "reference,") whose difference yielded the activation. Although the statistical significance levels that had been adopted by the authors of the reports varied somewhat across the studies, we accepted just about all the activations reported in the studies without questioning their reliability or validity.

We did not include in our database any data from memory studies using functional magnetic resonance imaging (FMRI), although we did keep them in a separate file. The total number of published FMRI studies of memory is still small, and the number of studies that would have been useful for our purposes is even smaller, because (1) some studies report data only from selected slices of the brain, rather than the whole brain as do typical PET studies, and (2) sometimes the reports of the FMRI studies do not include any quantitative measures of localization of the observed

"signal." Furthermore, although there are good reasons for believing that localization of "memory function" by PET and by FMRI should yield similar results, there are as yet no decisive studies on this score, and the pooling of the data from the two techniques may be premature (Xiong et al., 1998).

Data Extraction

Once having assembled a database as just described, we extracted from it all the activations that qualified as "hippocampal encoding and retrieval activations" by the criteria we established for the purpose. To qualify, an activation had to (1) be associated with ("produced by") either an episodic memory encoding or an episodic memory retrieval condition, and (2) lie at or near the medial temporal lobes as reported by the authors of the original papers. We checked all MTL activations against the brain atlases by Talairach and Tournoux (1988) and Mai et al. (1997), both of which conform to the same (Talairach) space, and confirmed the published medial-temporal lobe ("hippocampal") sites in all cases.

We defined an encoding condition as yielded by any task comparison in which the target task would require elaborative processing of the materials to a larger extent than that required in the reference task. Thus, for example, the target task might consist of explicitly instructing subjects to study words or visual patterns (e.g., Roland and Gulyas, 1995; Kapur S. et al., 1996) for a later memory task, while the corresponding reference task might involve reading words or merely looking at "low level" visual noise fields (e.g., Martin et al., 1997). Or the target task might be memorizing faces (Haxby et al., 1996) or word pairs (Dolan and Fletcher, 1997), and the reference task in a perceptual matching task (Haxby et al., 1996) or a less demanding (shallower) encoding tasks (e.g., Kapur S. et al., 1996; Dolan et al., 1997). In all the encoding conditions thus defined, we either knew or, on the basis of evidence from the cognitive literature, had good reasons to expect that the encoding of information into episodic memory would be more efficacious in the target task than in the reference task.

Many target tasks in comparisons defined as episodic encoding conditions required that subjects make use of their knowledge of language and knowledge of the world in successfully performing the encoding tasks, whereas the corresponding comparison tasks did not. For this reason, it is possible to think of episodic encoding tasks as also representing semantic retrieval (Tulving et al., 1994b; Nyberg et al., 1996a). We will not pursue the implications of this ambiguity here, but simply note it for possible future discussion.

A retrieval condition was defined as one yielded by any task comparison in which the target task would involve greater use and recovery of previously experimentally encoded material than would the corresponding reference task. For example, the target task might consist in recognition, cued recall, or free recall; whereas the reference task might be any one of (1) simply "resting with eyes closed" (Roland and Gulyas, 1995), (2) a response generation task (e.g., Blaxton et al., 1996), or (3) a retrieval task characterized by a significantly reduced level of behavioral performance (e.g., Schacter et al., 1996a).

It is important to note explicitly what kinds of task comparisons we excluded; that is, comparisons that did not qualify as "encoding" or "retrieval" conditions by our criteria. First and foremost, we excluded all task comparisons involving the encoding of different *kinds* of information, as well as those involving the retrieval of different *kinds* of information. Examples of studies involving encoding of different kinds of materials included those in which word encoding was compared with picture encoding (e.g., Grady et al., 1998), and those in which word encoding was compared with the temporal tag of the encoded words (e.g., Nyberg et al., 1996c). Examples of studies involving retrieval of different kinds of materials included those in which retrieval of information about the identity of studied items was compared with retrieval of information about the order of presentation of the studied items (Cabeza et al., 1997b; Nyberg et al., 1996c), and those in which retrieval of information about object location was compared with retrieval of information about spatial location only (Owen et al., 1996b). We excluded these comparisons, because in every case there exists a confounding between processes and materials, which leaves open the possibility that the resultant PET activations reflect material-specific differences in brain activity, or interactions between processes and materials, rather than the process (encoding or retrieval) as such.

Second, we excluded studies involving task comparisons in which the target task required retrieval of novel (i.e., previously unencoded) stimulus items (Tulving et al., 1996; Fujii et al., 1997, experiment 1). These comparisons are insufficiently analytic to allow sufficiently confident judgments regarding encoding and retrieval aspects of the task: The novelty of stimuli may induce encoding operations (Tulving et al., 1996) while the task instructions induce retrieval operations, and the resultant activation is likely to reflect an unknown mixture of both.

The screening procedure as just described netted 54 "hippocampal encoding and retrieval activations." Of these, 22 represented encoding conditions, and 32 retrieval conditions. The 22 encoding activations originated from eight studies representing 13 task comparisons. The 32 retrieval activations came from 13 different studies, representing 19 task comparisons. These 54 activation data points are listed in Table 1.

RESULTS

Given the 54 hippocampal encoding and retrieval activations, the search for a cognitively and anatomically orderly pattern was essentially a hit-and-miss procedure. We "looked at the data this way and that way," considering different distinguishing features of the activations, such as process (encoding/retrieval), type of stimulus items involved (verbal/figural), hemispheric laterality of activation (left/right), and, what turned out to be the "winner," namely the distribution of the activation sites along the rostrocaudal axis of the hippocampus.

The 54 "hippocampal encoding and retrieval activations" are listed in Table 1 in an order that approximates the rostral-caudal

TABLE 1.

Summary Table for the 54 Hippocampal Region Activations*

Talairach coordinates						
x	y	z	Study	Tasks comparison	Process	Material
24	0	−24	Decety et al. (1997)	Enc actions: mngful–mngless	ENC	F
−42	−10	−24	Dolan and Fletcher (1997)	Enc word pairs: novel–familiar	ENC	V
28	−10	−20	Haxby et al. (1996)	Enc faces–match faces	ENC	F
−34	−12	−20	Martin et al. (1997)	Enc nonsense words–view NF	ENC	V
−16	−14	−12	Dolan and Fletcher (1997)	Enc word pairs: novel–familiar	ENC	V
−33	−15	−20	Martin et al. (1997)	Enc words–view NF	ENC	V
−34	−16	−20	Martin et al. (1997)	Enc words / pictures–view NF	ENC	V/F
32	−16	−20	Henke et al. (1997)	Enc pictures: deep–shallow	ENC	F
−18	−16	−12	Vandenberghe et al. (1996)	Enc words: deep–shallow	ENC	V
−18	−16	−12	Vandenberghe et al. (1996)	Enc pictures: deep–shallow	ENC	F
26	−18	−20	Martin et al. (1997)	Enc nonsense objects–view NF	ENC	F
22	−18	−20	Martin et al. (1997)	Enc words / pictures–view NF	ENC	V/F
30	−18	−16	Ghaem et al. (1997)	Recall landmarks–rest	RET	F
28	−18	−12	Ghaem et al. (1997)	Recall route–rest	RET	F
−34	−20	−16	Martin et al. (1997)	Enc objects–view NF	ENC	F
−32	−20	−12	Ghaem et al. (1997)	Recall landmarks–rest	RET	F
−30	−22	−16	Martin et al. (1997)	Enc nonsense objects–view NF	ENC	F
−40	−22	−12	Decety et al. (1997)	Enc actions: mngful–mngless	ENC	F
24	−24	−20	Martin et al. (1997)	Enc objects–view NF	ENC	F
34	−24	−12	Haxby et al. (1996)	Enc faces–match faces	ENC	F
−19	−25	−9	Roland and Gulyas (1995)	Enc visual patterns–rest	ENC	F
−28	−26	−20	Dolan and Fletcher (1997)	Enc word pairs: novel–familiar	ENC	V
30	−26	−12	Henke et al. (1997)	Enc pictures: deep–shallow	ENC	F
22	−26	−8	Schacter et al. (1997)	Recog old items–view items	RET	F
24	−26	−8	Schacter et al. (1997)	Recog old items–recog new items	RET	F
36	−28	−15	Fujii et al. (1997)	Recog old items–recog new items	RET	V
15	−28	−13	Roland and Gulyas (1995)	Enc visual patterns–rest	ENC	F
22	−28	−12	Schacter et al. (1997)	Recog old items–view items	RET	F
−20	−28	−8	Schacter (1996b)	Recog true targets–control task	RET	V
21	−29	−4	Squire et al. (1992)	Word stem: cued recall–compl	RET	V
28	−30	−12	Nyberg et al. (1995)	Recog old items–recog new items	RET	V
26	−32	−16	Ghaem et al. (1997)	Recall route–rest	RET	F
−16	−32	−8	Schacter et al. (1996b)	Recog false targets–control task	RET	V
−30	−34	−8	Schacter et al. (1997)	Recog old items–recog new items	RET	F
−38	−34	−4	Kapur et al. (1996)	Enc words: deep–reading	ENC	V
−30	−34	−4	Schacter et al. (1997)	Recog old items–view items	RET	F
25	−34	0	Schacter et al. (1996a)	Recall words: high–low perform	RET	V
−34	−36	−8	Schacter et al. (1997)	Recog old items–recog new items	RET	F
22	−36	−8	Grasby et al. (1993)	Word recall (supraspan)–rest	RET	V
18	−36	−4	N. Kapur (1995)	Recog faces–rest	RET	F
28	−36	0	Schacter et al. (1995)	Recog old items–view items	RET	F
15	−37	0	Schacter et al. (1996a)	Recall–word generation	RET	V
18	−38	−4	Blaxton et al. (1996)	Paired assoc CR–word generation	RET	V
−28	−38	0	Schacter et al. (1997)	Recog old items–recog new items	RET	F
8	−38	1	Roland and Gulyas (1995)	Recog visual patterns–rest	RET	F
−28	−38	4	Blaxton et al. (1996)	Word frag CR–word generation	RET	V
−32	−38	4	Rugg et al. (1997)	Recall words: deep enc–shallow enc	RET	V
−28	−38	4	Schacter et al. (1995)	Recog old items–view items	RET	F
−11	−38	10	Roland and Gulyas (1995)	Recog visual pattern–rest	RET	F
−19	−39	−4	Schacter et al. (1996a)	Recall–word generation	RET	V
16	−42	−8	Grasby et al. (1993)	Word recall (subspan)–rest	RET	V
−6	−42	4	Ghaem et al. (1997)	Recall landmarks–rest	RET	F
−10	−44	4	Ghaem et al. (1997)	Recall route–rest	RET	F
16	−48	−10	Fujii et al. (1997)	Recog old items–recog new items	RET	V

*For each activation, the reference, a short description of the task comparison, the memory process isolated by the task comparison, and the type of material are presented. x, y, and z represent the three orthogonal planes of the Talairach system. Negative X values are located in the left hemisphere and positive X values in the right hemisphere. Assoc, associate; compl, completion; CR, cued-recall; Enc, encoding; F, figural; frag, fragment; mngful, meaningful; mngless, meaningless; NF, noise field; perform, performance; recog, recognition; RET, retrieval; V, verbal.

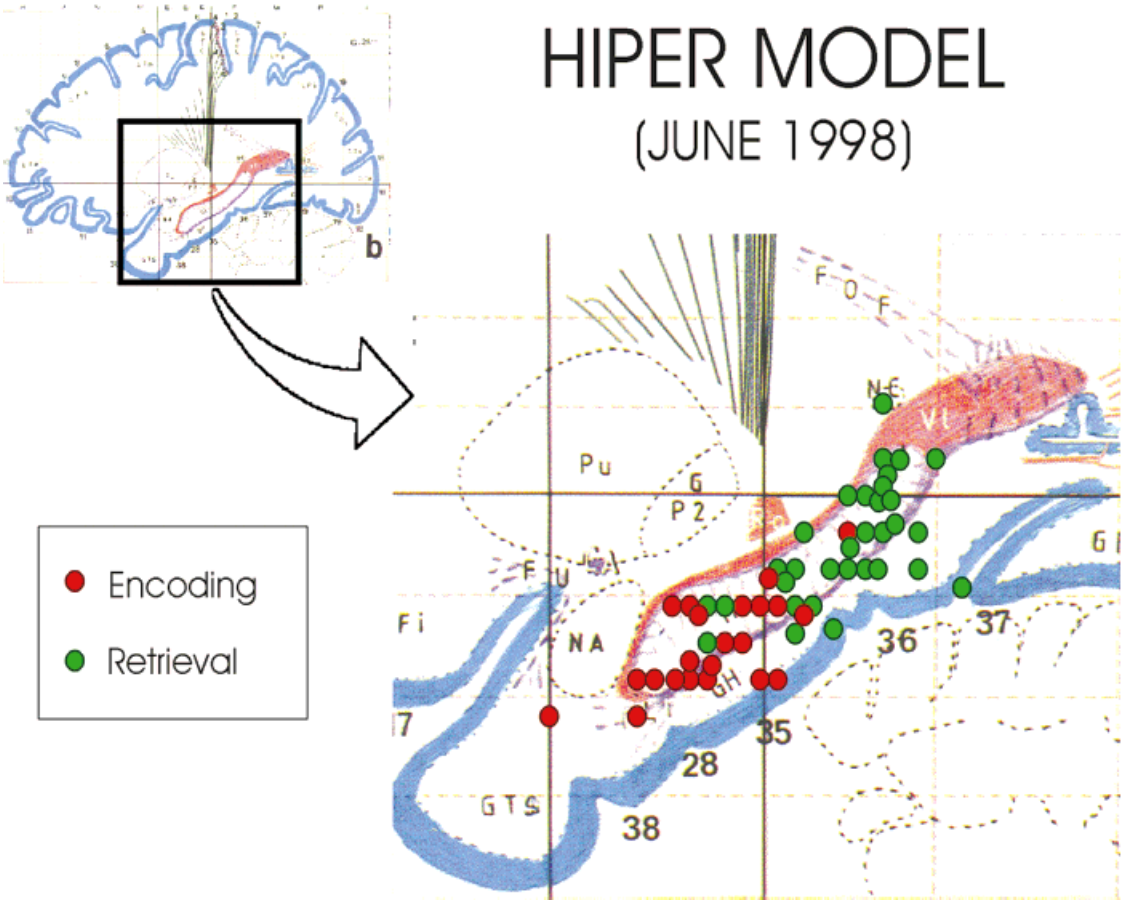

FIGURE 1. Schematic representation of 22 encoding and 32 retrieval activations in the hippocampal regions. Data from the left and the right hemisphere were pooled and projected onto a single sagittal slice (25 mm laterally from the midline) of the Talairach and Tournoux (1988) stereotaxic atlas. Overlapping activations were slightly moved.

extent of the hippocampus: from the most rostral to the most caudal regions. Each entry is identified by the authors' names; by the symbol "E" or "R," designating encoding and retrieval conditions, respectively and the kind of stimulus material used; "V" for verbal, and "F" for figural (nonverbal). The tabulation of the data in this fashion reveals at a glance the fact that rostral entries tend to represent encoding conditions and caudal entries retrieval conditions. If we, purely arbitrarily, split the 54 listed activation sites into two parts, those rostral to the site designated as xyz = 30, −26, −12 (Henke et al., 1997), and those caudal to the site designated as xyz = 22 −26 −8 (Schacter et al., 1997), we can summarize the data quantitatively by saying that 83% of the rostral sites were occupied by encoding conditions, and 94% of the caudal sites were occupied by retrieval conditions.

The data tabulated in Table 1 are displayed graphically in Figure 1. The 22 encoding activations and the 32 retrieval activations are projected onto the sagittal slice of the Talairach and Tournoux (1988) that lies 25 mm laterally from the midline. The hemispheric origin of the activations (left/right) is ignored in Figure 1, because it did not vary systematically with other variables. Figure 1 also "hides" the differences in the lateral displacement of the activations from the midline (along the x-axis of the Talairach atlas). The lateral dimension did not show any obvious systematic variability and therefore, at present, is not considered as a part of the overall pattern of interest.

Figure 1 shows a clear pattern of the clustering of activation sites by encoding and retrieval conditions. Encoding activations are concentrated in the rostral portions and retrieval activations in the caudal portions of the hippocampal region. As a rough guide, the plane of the posterior commissure can be used as an arbitrary divider between the two clusters. Most of the retrieval activations were located caudally to the posterior commissure, whereas most of the encoding activations were located rostrally to the posterior commissure.

The pattern is not completely clean: Figure 1 shows that there are exceptions to the general rule. Nevertheless, all 13 studies that yielded hippocampal retrieval activations reported at least one such activation in the caudal region of the hippocampus, and seven out of eight studies that yielded encoding activations reported such activations in the rostral portion of the hippocampus.

We have defined two hippocampal regions based on the observation of two clusters of activations in relation to the posterior commissure. The description by Amaral and Insausti

TABLE 2.

Summary Table for the Hippocampal Region Activations as a Function of the Process Involved, Type of Material, and Side of Activation*

	Left hippocampal region	Right hippocampal region
ENCODING		
Verbal	7	0
Figural	5	8
RETRIEVAL		
Verbal	5	9
Figural	9	9

*Two encoding activations are not included in the table as they involved encoding of both verbal and figural information.

(1990) of the rostrocaudal extent of various hippocampal fields provides some precision as to the underlying anatomical regions. The rostral region comprises most of the entorhinal cortex as well as the rostral portion of the hippocampus (subiculum and dentate gyrus), which extend caudally to the posterior commissure. The caudal region comprises the remaining portion of the hippocampus as well as the caudal portion of the parahippocampal gyrus. Perirhinal cortex occupies the border area between these two regions. It is worth noting that, if we ignore the many hazards entailed in a precise localization of PET activations, the peaks of the majority of the 54 "hippocampal encoding and retrieval" areas could be identified as falling within the hippocampus proper (15/22 encoding and 21/33 retrieval conditions) according to the brain atlas of Talairach and Tournoux (1988). The remaining 18 were located in the surrounding cortex.

Table 2 provides summary data on the distribution of the 54 activations listed in Table 1 in terms of processes (encoding/retrieval), type of stimulus items (verbal/figural), and hemisphere of the activation (left/right). This summary reveals that whereas for retrieval conditions there is no apparent asymmetry between the left and right hippocampal regions, for encoding conditions there is a hint of material-specific asymmetry. Encoding activations of figural information appeared in both hemispheres, but all encoding activations of verbal information in our sample were confined to the left hemisphere.

DISCUSSION

Data from a meta-analysis of PET studies of episodic memory have yielded a picture of an orderly spatial distribution of changes in blood flow associated with encoding-related and retrieval-related processes in the medial-temporal lobe (hippocampal) regions of the brain. PET-based encoding activations are found predominantly in the rostral hippocampal regions whereas retrieval activations occur predominantly in caudal regions. We refer to this general pattern of rostral encoding and caudal retrieval activations as the HIPER (Hippocampal Encoding/Retrieval) model. We think of the patterned spatial distribution as a 'model' because it is formulated in terms of the relation between neuroanatomic sites of changes in blood flow, on the one hand, and abstract concepts borrowed from cognitive psychology—encoding versus retrieval processes, and episodic versus semantic memory, on the other hand.

The HIPER model, by specifying a topographical pattern of hippocampal encoding-related and retrieval-related activations produced by PET studies of memory, is purely descriptive. It is not a neurocognitive theory of the role of the hippocampus in memory, nor does it offer any explanations. It is essentially an empirical regularity that itself requires explanation. Nevertheless, the orderly pattern of HIPER does suggest a gross division of memory-related labor between two regions of the hippocampal formation: rostral regions more involved in a process or processes related to encoding, and caudal regions more involved in a process or processes related to retrieval. Why such a division should exist is not immediately clear. Because of the novelty of the HIPER pattern, there is little in the otherwise voluminous literature on hippocampal "memory function" that could be used to guide the search for its physiological meaning. Future research no doubt will clarify the issue. The thought has occurred to us that, in some ways, the best "solution" of the problem that the HIPER pattern poses might be the "discovery" that the pattern is not real, or that it crumbles under more detailed scrutiny. We suspect, however, that no such simple "solution" is forthcoming, and that the HIPER findings will end up complicating the scientific lives of all who would study memory in the hippocampus.

The HIPER model as described seems to hold for both verbal and figural (nonverbal) materials, and largely too for both hemispheres. With a single exception, our data showed little hemispheric asymmetry for verbal and figural materials. The exception was provided by the absence of activations in the right hippocampal region during the encoding of verbal information. Because of the relatively small database on which this observation rests, and in light of the fact that absences of activations in neuroimaging studies of cognition and memory are difficult if not impossible to interpret (Buckner and Tulving, 1995), we wish to make no strong claims about the possible hemispheric asymmetry in encoding of verbal materials at this time. Future research no doubt will clarify the situation. With respect to retrieval, however, the situation is clearer: Because the activations produced by both verbal and figural stimuli are distributed more or less evenly in both hemispheres, there is little evidence of any systematic hemispheric asymmetry.

The neuroscience literature is replete with theories of hippocampal functions. Models of hippocampal function in memory that are based on observations made at the molecular or cellular level are not directly relevant to, nor directly affected by, the data reported here. Although some of these models are concerned with the distinction between encoding and retrieval, they frequently assume that encoding and retrieval processes are subserved largely by the same neurons (Deadwyler et al., 1996; Hasselmo and Wyble, 1997), retrieval representing 'reactivation' of the neuronal

circuits involved in the original encoding (Gluck and Myers, 1997). These models have little to say about gross neuroanatomical differences between encoding-related regions and retrieval-related regions, such as those suggested by both the HIPER model described here, and the HERA model described previously (Tulving et al., 1994a; Buckner, 1996; Nyberg et al., 1996a). Conversely, the gross functional anatomic models, such as HIPER and HERA, have nothing to say about processes occurring at the level of individual neurons. Most models of hippocampal memory that are based on work with animals such as rats (Eichenbaum et al., 1994, 1996) or monkeys (Gaffan, 1994; Murray, 1996; Mishkin, 1982; Squire, 1992; Zola-Morgan et al., 1994) also are not directly relevant to, nor directly affected by, the data reported here, because encoding and retrieval processes are typically not separated in the behavioral tasks on which these models are built (e.g., Morris Water-Maze task, Olton's Radial-Maze task, delayed nonmatching to sample task).

Speculations concerning the role of the hippocampus in memory that have been based on neuroimaging studies (PET, FMRI, and EEG), on the other hand, usually do distinguish between encoding and retrieval processes in episodic memory at the level of gross functional anatomy. Some have suggested a role for the hippocampus in the initial encoding of the information (Haxby et al., 1996; Stern et al., 1996; Henke et al., 1997; Martin et al., 1997). Others have focused on the role of the hippocampus in novelty detection or novelty assessment (Knight, 1996; Tulving et al., 1996; Grunwald, et al., 1998). A third category of theories has been concerned with the role that the hippocampus plays in the successful recovery and use of information from episodic memory (Owen et al., 1996b; Schacter et al., 1995, 1996a,b, 1997). A few papers have even dealt with both hippocampal encoding and hippocampal retrieval (Gabrieli et al., 1997; Owen et al., 1996b), an issue that has also been a subject for neural network modeling (Hasselmo et al., 1996; Hasselmo and Wyble, 1997). Finally, suggestions have been made for material-specific hippocampal activations (Martin et al., 1997; Milner et al., 1997). None of the ideas offered, however, have had much to say about the division of the hippocampal encoding and retrieval functions along the rostrocaudal axis. In this sense, the HIPER model is unheralded and unexpected.

The conclusions arrived at in three previous FMRI studies seem to go directly against the HIPER model in that all pointed to encoding activations in the caudal portion of the hippocampal region (Stern et al., 1996; Gabrieli et al., 1997; Fernandez et al., 1998). The reasons for the apparent lack of agreement are no clearer at the present time than are the reasons for the exceptions to the general pattern shown by the data summarized in Table 1 and Figure 1.

Fernandez et al. (1998) conclusion was based on an observed correlation between FMRI BOLD signal during encoding and subsequent behavioral retrieval performance. The apparent discrepancy between their conclusion and the HIPER model, therefore, may be attributable to different ways of defining and measuring encoding. Gabrieli et al. (1997) also reported an encoding-related FMRI BOLD signal in the caudal parahippocampal region. In that study, encoding was measured in terms of the constrast between previously not seen ("new") pictures and repeated presentation of two pictures. Similarly, Stern et al. (1996) observed caudal hippocampal activation during complex picture encoding when compared to the repetitive presentation of a single image.

Stern et al. (1996) and Gabrieli et al. (1997) studies are similar in that the critical comparisons involved situationally 'novel' stimuli versus repetitive, and therefore situationally less novel stimuli. But whether the two studies produced results at variance with the HIPER model because of differences in the novelty of the compared material, or for some other reasons, cannot be ascertained, because of multiple procedural differences among the studies.

It is possible that the HIPER pattern does not hold for stimuli such as landscapes or complex scenes, and that the processing of such 'spatial' information (Maguire et al., 1996, 1997, 1998; Gabrieli et al., 1997; Köhler et al., 1998) involves activation of the caudal hippocampal formation. The future will tell. At any rate, the studies apparently at variance with the HIPER model were not part of our meta-analysis because they did not fit our inclusion criteria. They do, however, complicate matters by suggesting that stimuli involving spatial representation may be treated differently from nonspatial stimuli, a suggestion in line with findings from lesion studies in rats showing that spatial processing is impaired by caudal but not rostral hippocampal lesions (Moser et al., 1993, 1995).

The retrieval conditions in the various studies included in our survey typically involved recall or recognition of the to-be-remembered material soon (minutes rather than days) after encoding. It is not known, therefore, whether retrieval after longer retention intervals also differentially involves caudal hippocampal regions. At this time, it is quite possible that the retrieval part of the HIPER model holds only for short-term retrieval, as suggested by some (Alvarez and Squire, 1994), and that it might not hold for really long-term retrieval that has been postulated as one of the hippocampal memory functions by others (Nadel and Moscovitch, 1997). This matter too will be clarified by future research. In this context it has not escaped our attention that H.M., whose dense amnesia was described by Corkin et al. (1997) as caused by the surgical resection of rostral hippocampal regions, while caudal regions were spared, is capable of retrieving information that he had acquired premorbidly.

Finally, we wish to emphasize that our paper, and the HIPER model, is about PET activations. It is not about the role of the hippocampus or MTL in memory. The two topics are related, of course. If they were not, PET studies of memory would be meaningless. But the relation between the two issues, the role of MTL in memory and the pattern of memory-related PET activations in the MTL, is clearly much more complex than what might appear to be the case at first glance. The very concepts of episodic memory encoding and retrieval are fuzzy, incapable of translation into cleanly separable empirical operations. Encoding tasks used in PET studies no doubt include retrieval-related component processes, as retrieval tasks used in PET studies no doubt include encoding-related processes. Although we have couched the HIPER model in terms of the distinction between

encoding and retrieval, a more appropriate distinction is that between encoding-related and retrieval-related processes. There is no way of telling now which aspects of these processes give rise to the rostrocaudal gradient that the HIPER model represents, or how they do it. These and other similar complications have to be remembered when the challenges posed by the HIPER model are faced.

For the time being, the value of the HIPER model, apart from its sheer novelty, resides in its ability to suggest new ideas for research. We provide just one illustrative example. Ryoo and Joyce (1994) have suggested that dopamine D2 receptors are expressed in the form of a double gradient: one for the dentate gyrus and CA3 and CA4 subfields; the other for the subiculum, organized along the rostrocaudal axis of the hippocampus. Is it possible that dopamine D2 plays a role in memory, generally, or that there is a relation between the HIPER model and Ryoo and Joyce's double D2 gradient, specifically? No one knows, but there is no reason why the possibility could not be explored. Although there are some exceptions (Arnsten et al., 1995; Podgornaya et al., 1997; Sigala et al., 1997), memory researchers have not paid much attention to dopamine, and neuroscientists interested in dopamine have largely ignored memory. The HIPER model may encourage researchers to take a closer look at the situation.

Acknowledgments

Research supported by NSERC (Grant A8632) and a foundation by Anne and Max Tanenbaum in support of research in cognitive neuroscience. M.L. supported by a Tanenbaum postdoctoral fellowship.

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