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Effects of size and orientation change on hippocampal activation during episodic recognition: A PET study

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To determine whether physical match between studied and tested items influences blood flow increases in the hippocampal formation associated with recognition memory, positron emission tomography (PET) was used to measure changes in regional cerebral blood flow while healthy volunteers made old/new judgements about line drawings of objects. Some objects were tested in the same size and orientation as they had appeared earlier during the study phase of the experiment; other objects were tested in a different size or orientation than when they were studied. Blood flow increases in the vicinity of the hippocampal formation were observed in the same object condition compared with the size change and the orientation change conditions, even though recognition accuracy was affected significantly only by orientation change. Results add to previous findings suggesting that physical similarity between studied items and test cues may contribute to hippocampal activation during episodic retrieval.

Key words: Episodic recognition; Hippocampal activation; PET

Introduction

Understanding the role played by the hippocampal formation in the explicit retrieval of recent experiences (episodic memory) constitutes a major problem in memory research. Studies of brain-damaged patients and experimental animals have implicated the hippocampal formation in episodic memory.[1–3] More recently, neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have begun to explore the role of hippocampal activity in episodic memory. Neuroimaging studies have revealed hippocampal activation during the encoding of novel information[4–6] and learning of new associates.[7] By contrast, neuroimaging studies of hippocampal activity during retrieval of episodic memories have yielded mixed results: some experiments have shown hippocampal activity during explicit retrieval[8–11] whereas numerous others have failed to document such effects[12,13] (for a recent review see Ref. 14). However, several recent studies converge on the conclusion that hippocampal activation during explicit retrieval is closely related to successful conscious recollection, rather than to retrieval efforts or attempts.[15–19]

Hippocampal activity during explicit retrieval may also depend on whether or not test cues physically match previous studied items. In an early study by Squire *et al.*[11] using the stem cued recall task, where subjects try to remember recently studied words in response to three-letter word beginnings, hippocampal blood flow increases were observed when stem cues were presented in the same typecase as studied words, compared to a baseline condition in which subjects generate the first words that come to mind (see also Ref. 17). In a follow-up study, Buckner *et al.*[20] found no significant hippocampal blood flow increases over baseline when stem cues

were presented in different typecases at study and test, even though changing typecase did not significantly affect the overall level of recall. Although the results of the these previous studies are consistent with the idea that physical match between study and test items influences hippocampal blood flow increases, this possibility must be treated cautiously because it depends on a cross-experiment comparison.

To investigate further whether physical match between studied items and test cues reliably affects hippocampal activation during explicit retrieval, we used a recognition memory task that was associated with hippocampal blood flow increases in a previous PET study.[16] In that experiment, subjects studied novel objects, some structurally possible and some structurally impossible, and later made old/new recognition decisions about studied and non-studied objects. Hippocampal blood flow increases were observed for previously studied possible objects compared with non-studied possible objects, but not for studied *vs* non-studied impossible objects. Recognition accuracy was higher for possible than for impossible objects. thus suggesting a link between successful recognition and hippocampal blood flow increases.

In the present experiment, we compared hippocampal blood flow increases when the identical object was studied and tested and when the orientation or the size of studied objects was changed between study and test (Fig. 1). Pilot data indicated that recognition performance in our paradigm declines significantly with orientation change, but not with size change. This pattern of recognition performance allows us to determine whether hippocampal activity is influenced by physical similarity between study and test objects, both when recognition performance varies significantly as a function of study/test similarity and when it does not.

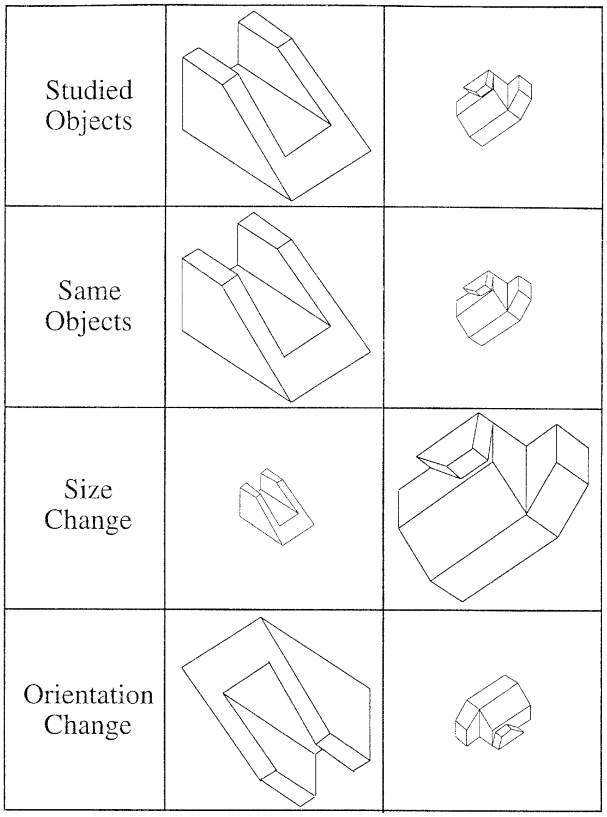

FIG. 1. Examples of studied objects and their formats in each of the studied test conditions. The actual objects were larger, but the figure maintains the 6.25:1 ratio of areas for large to small objects.

Materials and Methods

Subjects: For the off-line behavioral study that was performed prior to the experiment in order to evaluate the behavioral manipulation, subjects were four male and seven female Harvard University undergraduates. For the PET study, subjects were 12 healthy female, right-handed volunteers (age (mean ± s.d.) 23 ± 4.8 years). All subjects in the PET study had a normal neurological examination and no evidence of psychiatric disorders using a structured psychiatric interview.

PET: Five 31-slice PET images of regional cerebral blood flow were obtained using the ECAT 951/31 scanner (Siemens, Knoxville, TN), 45 mCi intravenous bolus injections of [^{15}O]water and 60 s scans separated by 10–15 min. PET images were reconstructed with an in-plane resolution of about 10 mm full-width at half-maximum (FWHM) and a slice thickness of about 5 mm FWHM. For data analysis, a Gaussian filter yielded an in-plane resolution of about 20 mm FWHM and a slice thickness of about 10 mm FWHM.

Automated algorithms were used to align the five PET images from each subject, spatially transform them into the coordinates of a standard brain atlas, control for variations in whole brain measurements, compute z-score maps of significant increases in regional blood flow for each comparison (z-score > 2.58, $p < 0.005$, uncorrected for multiple comparisons; for detailed discussion of statistical basis for this threshold (see Ref. 21) and superimpose the maps onto an average of 12 spatially standardized brain MRIs.[22–25]

Materials, design and procedure: The materials, design and procedure were the same for the off-line behavioral study and the PET study, except that subjects in the PET study were scanned during the test phase of the experiment. Stimuli were 60

line-drawings of novel 3-D objects ('possible objects' from Ref. 26). Four different formats of each object were created by combining changes in the size and orientation of the objects. Large objects were 300 × 300 pixels and small objects were 120 × 120 pixels. The two different orientations were 180° rotations from each other. The objects were divided into five 12-object sets that were rotated through each of five main experimental conditions (see below). The experiment was counterbalanced across subjects so that each object appeared in each condition for either two or three subjects. Each of the five object sets included eight large objects and four small objects.

Subjects were first given a study list of 38 objects, presented sequentially in the center of a computer monitor. Each object remained on the screen for 4.5 s and the screen was blank for 0.5 s between objects. The first and last objects on the study list were non-tested fillers. We used an encoding task previously described by Schacter and Cooper,[27] in which subjects decided whether each studied object could be best used as a tool (e.g., scooping, cutting, or pounding) or for support (e.g., stepping, sitting, or leaning on it), and indicated their choice by pressing one of two keys. Study list order was random with the constraint that no more than three consecutive objects were in the same test condition.

After the study list, subjects completed five separate test blocks, during which PET images were obtained. Each block included 12 objects presented sequentially with a duration of 4.5 s and an interstimulus interval of 0.5 s. Subjects made old/new recognition judgements in four of the blocks and passively viewed new, non-studied objects in the remaining block. Three of the recognition blocks included studied objects. The experimental condition for a particular block was defined by the relationship of the format in which the objects were tested to the format in which they had been studied. In the same object condition, tested objects were identical to 12 of the studied objects. In the orientation change condition, tested objects were rotated 180° compared with the orientation in which they were studied. In the size change condition, tested objects were presented in a different size than at study. The fourth recognition condition (the new object condition) included new objects that were not previously studied in any format. In all recognition blocks, subjects pressed one key for objects they recognized from the study list and another key for non-studied objects.

Subjects were informed that some studied objects would be tested in different sizes and/or orientations, but they were told that these changes were not relevant to their recognition judgements, and that they should indicate 'old' when they recognized an object from the study list regardless of whether it was tested in the same size or orientation. The order of the five conditions was counterbalanced such that each condition appeared in each of the five possible sequential positions for two or three subjects.

Results

Behavioral results: Behavioral data obtained off-line during the pilot study and on-line during the PET study were quite consistent: the proportion of 'old' responses to studied objects in the same condition (68% off-line, 74% on-line) was significantly greater than the proportion of 'old' responses to studied objects in the orientation change condition (56% off-line, 62% on-line; both $ts > 2.74$, $p < 0.02$)), but was not significantly greater than the proportion of 'old' responses to studied objects in the size change condition (71% off-line, 67% on-line; both $ts > 1$). Each proportion of 'old' responses to studied objects was, however, significantly greater than the corresponding proportions of 'old' responses to new objects (32% off-line, 42% on-line; all $ts > 2.92$, $p < 0.02$).

PET results: Table 1 presents significant blood flow increases for the main recognition test comparisons of interest, and Fig. 2 shows the major hippocampal increases. In the same object minus new object comparison, we found bilateral blood flow increases in the vicinity of the hippocampus and parahippocampal gyrus. This comparison yielded only one other significant finding, a relatively modest increase in the left middle temporal gyrus (BA 37). Most important, the same object versus size change and same object *vs* orientation change comparisons each revealed significant increases in the left hippocampus and parahippocampal gyrus. Whereas there was no evidence of hippocampal blood flow increases in the size change *vs* new object comparison, there were right hippocampal increases in the orientation change *vs* new object comparison. Neither the orientation change minus size change comparison nor the size change minus orientation change comparison yielded evidence of significant hippocampal increases.

Table 2 shows the significant blood flow increases observed when each recognition memory test condition (same object, orientation change, size change, and new object) was compared to the passive viewing control condition. Although there were significant blood flow increases in several regions, the only significant hippocampal effects were observed in the same object minus passive viewing comparison, where there was a significant bilateral blood flow increase. There were no significant hippocampal blood flow increases for the orientation change, size change, or new object conditions compared with passive viewing.

Table 1. Brain regions, coordinates and z-scores of peak blood flow increases in the main experimental conditions

Comparison	Region	Coordinates	z
Same object–new object	Hippocampal formation	–28,–38,–0	3.61
		24,–26,–8	2.77
	Parahippocampal gyrus	–34,–36,–8	3.37
		22,–28,–12	3.00
	Middle temporal gyrus (BA 37)	–36,–58,4	2.63
Same object–orientation change	Hippocampal formation	–28,–36,–0	3.17
	Parahippocampal gyrus	–34,–36,–8	3.55
Same object–size change	Hippocampal formation	–28,–36,–4	2.81
	Parahippocampal gyrus	–32,–38,–8	2.80
	Posterior cingulate	–8,–42,16	3.03
	Fusiform gyrus (BA 37)	–34,–40,–12	2.66
Orientation change–new object	Hippocampal formation	24,–20,–12	2.81
	Lenticular nucleus	26,4,4	3.37
Size change–new object	Midbrain	–2,–26,–8	3.25
Orientation change–size change	Middle temporal gyrus (BA 21)	52,6,–20	2.60
Size change–orientation change	Midbrain	–2,–26,–8	2.95
	Posterior cingulate	–6,–44,16	3.07
Orientation change–same object	Middle frontal gyrus (BA 46)	–52,40,16	2.60
	Middle frontal gyrus (BA 9)	–34,20,36	2.81
	Anterior cingulate (BA 32)	0,38,16	2.67
	Middle temporal gyrus (BA 21)	54,4,–20	2.89
	Superior temporal gyrus (BA 22)	58,8,–4	2.72

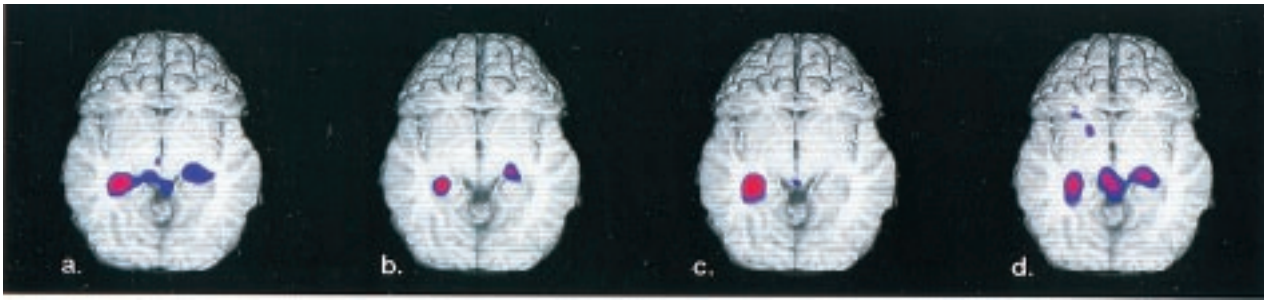

FIG. 2. Statistical maps showing blood flow increases in the vicinity of the hippocampal formation during recognition memory judgements in the same object condition (i.e., visual objects that had been studied previously in the same size and orientation in which they appeared on the recognition test), compared with recognition memory judgements about (**a**) new objects, (**b**) studied objects with size change, and (**c**) studied objects with orientation change; blood flow increases in the same object condition compared to a passive viewing control condition are shown in (**d**). For each comparison, automated algorithms were used to characterize significant increases in regional cerebral blood flow (those with maximum z-scores > 2.58, $p < 0.005$, uncorrected for multiple comparisons.[21,23] For (a–d) z-score maps were superimposed onto a magnetic resonance image that was transformed into the coordinates of a brain atlas,[25] volume rendered, and resected to a coronal plane to reveal hippocampal blood flow increases in a horizontal section 8 mm inferior to this plane. Increases in hippocampal blood flow (and additional increases in the vicinity of the parahippocampal gyrus and midbrain) are shown in red and blue, which correspond to z-scores > 2.58 and 1.65, and uncorrected probabilities of 0.005 and 0.05, respectively. Atlas co-ordinates corresponding to the maximal blood flow increases in images (a–c) are presented in Table 1 and for image (d) in Table 2.

Unlike our previous experiment,[16] there was little evidence of frontal lobe blood flow increases in any of the main comparisons. It is worth noting in this regard that recognition accuracy in the present experiment was considerably lower than recognition accuracy in our previous study, perhaps reflecting less effortful processing on the part of subjects in the present experiment. However, we did observe significant blood flow increases in the left dorsolateral frontal region (and several other areas) in the orientation change minus same object comparison (Table 1). These increases could reflect cognitive processes associated with attempts to mentally rotate objects that were tested in a different orientation to that in which they were studied (see Ref. 28). No significant blood flow increases were observed in the size change minus same object comparison, suggesting that the observed left frontal increases are specific to orientation change.

Discussion

In this experiment we have extended our earlier findings of hippocampal blood flow increases during episodic recognition of structurally possible objects,[16] and shown that left hippocampal increases are reliably greater when the same object is presented at study and test than when either the orientation or

Table 2. Brain regions, coordinates and z-scores of peak blood flow increases in the main experimental conditions

Comparison	Region	Coordinates	z
Same object–passive viewing	Occipital cortex (BA 17)	–18,–66,8	2.63
	Posterior cingulate (BA 24/31)	–14,–26,36	2.59
	Parietal cortex (BA 40)	–32,–34,36	3.29
	Midbrain	– 4,–30,–8	3.20
		20,–22,–4	2.73
	Parahippocampal gyrus	–30,–34,–8	3.15
	Hippocampus	–30,–34,–4	3.15
		22,–26,–8	2.67
Size change–passive viewing	Temporal gyrus (BA 22)	–42,–34,16	2.89
	Parietal cortex (BA 40)	–36,–32,40	3.09
	Precentral gyrus	–32,–26,40	2.68
	Midbrain	– 2,–26,–8	4.11
Orientation change–passive viewing	Temporal gyrus (BA 22)	–46,–34,16	3.08
	Parietal cortex (BA 40)	–40,–30,40	3.20
	Precentral gyrus	–50,–26,36	2.74
	Insula	–30,8,4	3.27
New object–passive viewing	Parietal cortex (BA 40)	–38,–36,40	3.55
	Occipital cortex (BA 19)	–18,–60,–4	2.70
	Cerebellum	–14,–62,–8	2.99

the size of objects is changed between study and test. Because recognition accuracy did not differ reliably between the same object and size change conditions, our data suggest that physical match between studied and tested objects contributes to hippocampal blood blood flow increases during episodic recognition. Previous data reported by Squire *et al.*[11] and by Buckner *et al.*[20] concerning the stem cued recall test provided suggestive evidence from between-experiment comparisons that physical match influences hippocampal blood flow increases; our data provide evidence from within-subject comparisons that confirm this possibility. Whereas the present results suggest that the left hippocampus is especially sensitive to physical matches when drawings of objects are used, the results of Buckner *et al.* suggest greater right-hippocampal sensitivity to physical matches when words are used. However, when we performed tests that compared left and right hippocampal blood flow increases none approached significance. Thus, additional studies will be needed to examine further the relationship between behavioral memory performance and laterality of blood flow changes. In the experiment of Buckner *et al.*, no hippocampal blood flow increases were observed when the typecase of studied and tested words differed. In our experiment, there were no hippocampal increases in the size change condition compared to the new object condition, but there were significant right hippocampal blood flow increases in the orientation change condition compared to the new object condition. However, the magnitude of these changes was relatively modest, and we did not observe hippocampal increases in the orientation change condition compared to the passive viewing condition (whereas we did observe hippocampal increases in the same object condition compared to passive viewing). Thus, we believe that the hippocampal increases in the orientation change condition must be viewed cautiously pending further research.

Some caution is also warranted concerning the conclusion, based on behavioral testing, that size change produced no effect on the level of recognition accuracy. We observed a numerical trend for a size change effect during the PET session, although it did not approach statistical significance. In a previous behavioral study, Cooper *et al.*[29] reported that study-to-test size changes produced significant decrements in recognition accuracy for possible objects. However, this study differed in numerous ways from ours (e.g. impossible objects were included at study and test, objects were not blocked according to condition during recognition testing, as they were here).

Conclusion

Though our data are consistent with the idea that hippocampal blood flow increases during explicit retrieval and are influenced by physical match between studied and tested items (e.g. Ref. 20), they do not contradict other evidence showing hippocampal sensitivity to the overall level of recollection under conditions in which physically matching stimuli are used.[15,17–19] Further studies will be required to determine whether these two factors operate independently, or whether they reflect the operation of a single, as yet unspecified factor. For example, Schacter *et al.*[18] suggested that hippocampal activations during retrieval might reflect subjective aspects of recollection, such as the confidence with which an item is recalled or recognized. Higher levels of recognition would be expected to be associated with higher levels of confidence. However, it is

conceivable that physical match between studied and tested items might increase or in some way influence subjects' confidence, or related aspects of subjective experience, even though it does not increase overall accuracy. Although the exact role of the hippocampal region in retrieval of episodic memories remains to be specified, these and other possibilities merit exploration in future neuroimaging studies.

References

1. Cohen NJ and Eichenbaum H. *Memory, Amnesia, and the Hippocampal System*. Cambridge, MA: MIT Press, 1993.
2. Vargha-Khadem F, Gadian DG, Watkins KE *et al. Science* **277**, 376–380 (1997).
3. Squire LR. *Psychol Rev* **99**, 195–231 (1992).
4. Martin A, Wiggs CL and Weisberg J. *Hippocampus* (in press).
5. Stern CE, Corkin S, Gonzalez RG *et al. Proc Natl Acad Sci* **93**, 8660–8665 (1996).
6. Tulving E, Markowitsch HJ, Kapur S *et al. NeuroReport* **5**, 2525–2528 (1994).
7. Henke K, Buck A, Weber B *et al. Hippocampus* **7**, 249–256 (1997).
8. Gabrieli JDE, Brewer JB, Desmond JE *et al. Science* **276**, 264–266 (1997).
9. Grasby PM, Frith CD, Friston KJ *et al. Brain* **116**, 1–20 (1993).
10. Owen AM, Milner B, Petrides M *et al. J Cogn Neurosci* **8**, 588–602 (1996).
11. Squire LR, Ojemann JG, Miezin FM *et al. Proc Natl Acad Sci USA* **89**, 1837–1841 (1992).
12. Tulving E, Kapur S, Markowitsch HJ *et al. Proc Natl Acad Sci USA* **91**, 2012–2015 (1994).
13. Shallice T, Fletcher P, Frith CD *et al. Nature* **368**, 633–635 (1994).
14. Cabeza R and Nyberg L. *J Cogn Neurosci* **9**, 1–26 (1997).
15. Nyberg L, McIntosh AR, Houle S *et al. Nature* **380**, 715–717 (1996).
16. Schacter DL, Reiman E, Uecke A *et al. Nature* **376**, 587–590 (1995).
17. Schacter DL, Alpert NM, Savage CR *et al. Proc Natl Acad Sci USA* **93**, 321–325 (1996).
18. Schacter DL, Savage CR, Alpert NM *et al. NeuroReport* **7**, 1165–1169 (1996).
19. Rugg MD, Fletcher PC, Frith CD *et al. NeuroReport* **8**, 1283–1287 (1997).
20. Buckner RL, Petersen SE, Ojemann JG *et al. J Neurosci* **15**, 12–29 (1995).
21. Reiman EM, Lane RD, Ahern GL *et al. Am J Psychiatry* **154**, 918–925 (1997).
22. Collins DL, Neelin P, Peters TM *et al. J Comput Assist Tomogr* **18**, 192–205 (1994).
23. Friston KJ, Frith CD, Liddle PR *et al. J Cerebr Blood Flow Metab* **10**, 458–466 (1991).
24. Woods RP, Cherry S and Mazziotta J. *J Comput Assist Tomogr* **16**, 620–633 (1992).
25. Talairach J and Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain*. New York: Thieme, 1988.
26. Schacter DL, Cooper LA, Delaney SM *et al. J Exp Psychol: Learn Mem Cogn* **17**, 3–19 (1991).
27. Schacter DL and Cooper LA. *J Exp Psychol: Learn Mem Cogn* **19**, 995–1009 (1993).
28. Tagaris GA, Kim S, Strupp JP *et al. J Cogn Neurosci* **9**, 419–432 (1997).
29. Cooper LA, Schacter DL, Ballesteros S *et al. J Exp Psychol: Learn Mem Cogn* **18**, 43–57 (1992).

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