Object and spatial alternation tasks with minimal delays activate the right anterior hippocampus proper in humans

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Substantial evidence indicates that the hippocampus plays a critical role in long-term declarative memory. In contrast, the role of the human hippocampus in working memory, particularly when information needs to be maintained only for a few seconds, remains controversial. Using PET, we show robust activation of the right anterior hippocampus proper during the performance of both object and spatial alternation tasks. Hippocampal activation emerged even though subjects only had to remember a single, simple stimulus over a minimum delay of 1 s. No hippocampal activation occurred when the delay was increased to 5 s. This suggests that the role of the hippocampus in working memory is not to maintain information across a delay interval. Instead, its activity reflects a more transient function during encoding and/or retrieval. These data are among the first observations to demonstrate human hippocampal involvement in working memory. *NeuroReport* 11:2203–2207 © 2000 Lippincott Williams & Wilkins.

Key words: Memory; Object alternation; PET; Positron emission tomography; Prefrontal cortex; Spatial alternation; Working memory

INTRODUCTION

Research into the cognitive neuroscience of memory has revealed that multiple memory systems exist that are subserved by separate neural substrates [1–3]. The division between long and short-term storage of information is thought to be one of the clearest. Lesions of the hippocampus produce deficits in long-term memory with relative preservation of short-term memory. Studies of patients [4–6] and monkeys [1,7] with medial temporal lobe lesions indicate that if information must be maintained for longer than several seconds, an intact hippocampus is necessary to perform normally on tests of declarative or episodic memory. In contrast, patients and animals with medial temporal lobe damage perform normally on most memory tasks in which information only needs to be maintained for a few seconds [4,5,7]. A recent neuroimaging study [8] suggests that the hippocampus is recruited only when material must be maintained for longer than several seconds. This has led to the belief that the hippocampus is a necessary neural substrate for long-term memory, while short-term and working memory can operate independent of a hippocampal contribution.

However, animal data suggest that the hippocampus contributes to working memory even at short delay intervals. First, neuronal activity [9–11] and local cerebral glucose metabolism [12,13] in the monkey hippocampus increase during working memory tasks even at delays insufficient to cause impairment in hippocampal lesioned animals. Second, lesions to the rodent hippocampus severely disrupt performance of alternation tasks at relatively brief delays [14]. Alternation tasks require the continual updating of information from trial to trial based on previous responses, and thus make significant demands on working memory [15]. Taken together, these animal studies suggest that the hippocampus plays an as yet undefined role in working memory processes. To date, however, no data have directly supported a role for the human hippocampus in mnemonic processes at brief delays.

Here, we used PET to study the mediating neuroanatomy of alternation tasks. Correct performance on both object and spatial alternation tasks requires that subjects use a mnemonic representation of the stimulus (object or location) chosen on the just-preceding trial to determine the correct object or location on the current trial. Subjects simply alternate responses to either of two objects (OA) or of two spatial locations (SA) from trial to trial. A very brief delay (1 s) was used, substantially less than that required to produce memory impairments in hippocampal lesioned animals.

Alternation tasks differ from most memory tasks in that they do not require the subject to encode or recognize new objects. Subjects must merely remember which one of two objects or locations was selected on the preceding trial. To examine regional cerebral blood flow (rCBF) attributable to

performance of the alternation tasks, a control condition scan, matched for perceptual and motoric demands, was subtracted from the OA and SA scans.

MATERIALS AND METHODS

Subjects: Informed consent was obtained in writing from all participants after the nature and possible risks of the experiment were explained. Eleven right-handed [16] healthy volunteers (six females, five males; mean age 22 years, range 19–26 years; mean years of education 15.7, range 13–18 years) were included for study. Due to time limitations, only nine of the 11 subjects participated in the OA experiment.

Alternation tasks: During each scan, subjects responded using a stylus and touch-pad to computerized presentations of two objects (Fig. 1) whose positions changed according to a Gellermann randomization schedule. Selections were accomplished by moving the cursor (i.e. arrow) from the fixation point to the desired object. After making a selection, visual feedback (green correct/red incorrect) was presented for 1 s just below the objects. Then, a 1 s delay was imposed where the monitor was darkened and the subject focused on a central fixation point. For each trial during the object alternation (OA) condition, subjects selected the object that was not chosen on the preceding trial, regardless of the spatial location of the object. During the spatial alternation (SA) condition, subjects selected the spatial location that was not chosen on the preceding trial, regardless of which object occupied the location. For each trial during a sensorimotor control condition, subjects chose whichever object had a 10-point font asterisk embedded on top of the figure, providing baseline images that controlled for visual stimulation and motoric response. To address the effect of delay, a SA task with a 5 s instead of 1 s delay was also performed by 10 of the 11 subjects. Prior to scanning, all subjects were informed of the rule that governs correct performance and practiced the tasks to criterion. Only one error occurred during scanning across all pooled trials. Scan order was approximately counterbalanced across subjects.

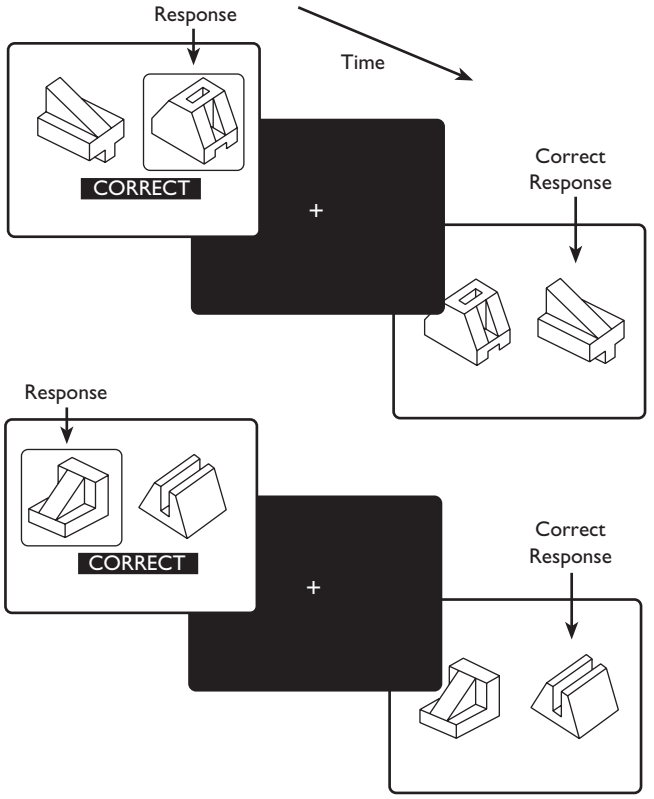

Fig. 1. Schematic illustration of the object (top) and spatial (bottom) alternation tasks. For each trial during the object alternation (OA) condition, subjects selected the object that was not chosen on the preceding trial, regardless of the spatial location of the object. During the spatial alternation (SA) condition, subjects selected the spatial location that was not chosen on the preceding trial, regardless of which object occupied the location.

Functional imaging: PET images of regional cerebral blood flow (rCBF) were obtained using an ECAT 953B scanner (Siemens, Knoxville, TN) with septa retracted, a slow-bolus injection of $H_2{}^{15}O$ (0.25 mCi/kg; e.g. 17.5 mCi (648 MBq) injection for a 70 kg person) infused at a constant rate over 30 s, and a 90 s scan acquisition. Subjects were placed in the scanner to optimize visualization of ventral frontal and ventral temporal regions: we excluded extreme superior frontal regions for which not all subjects contributed data. Automated software algorithms provided by Minoshima *et al.* [17] adjusted whole brain activity, coregistered intra-subject images, and non-linearly warped images to a reference stereotactic atlas [18]. Statistical analyses were based on global variance of all pixels in the brain. A significance threshold of $p = 0.0005$ was utilized based on a bootstrap analysis from our laboratory on the rate of false positive foci emerging due to chance. In the group analysis, each subject's data comprised single scan pairs and final image resolution was 9.8 mm full-width at half-maximum (FWHM). In the single subject high-resolution study, the subject received seven OA and seven sensorimotor control conditions. Each of the scan pairs (one OA and its corresponding sensorimotor control condition) utilized a different pair of objects. The PET data were analyzed as described above for the group data. However, minimal spatial smoothing was used resulting in a final image resolution of approximately 7 mm FWHM. The subject's PET images were coregistered to his T1 MRI using SPM95 (Wellcome Department of Cognitive Neurology; London, UK).

RESULTS

Significant blood flow increases localized to the right anterior hippocampus proper during both the OA (Z-score = 4.1, $p = 0.00003$) and SA (Z-score = 3.3, $p = 0.0005$) conditions (Fig. 2). In both conditions, the peak area of activation within the hippocampus mapped to identical standardized coordinates (x, y, z = 26, −10, −16). Other areas with significant rCBF increases are beyond the scope of this report but are listed in Table 1.

Increasing evidence indicates that the hippocampus proper and neighboring parahippocampal and rhinal cortices play distinct roles in mnemonic processing [19,20]. To confirm that the hippocampal focus maps to the anterior

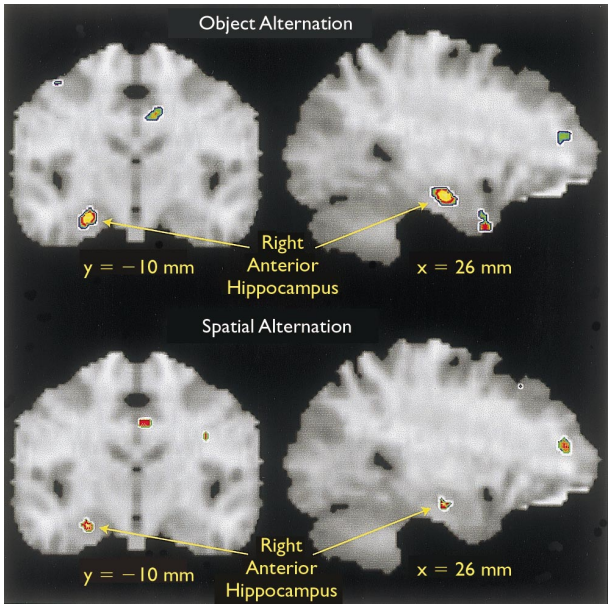

Fig. 2. Coronal and sagittal sections showing rCBF during practiced performance of the two alternation tasks. Activations are projected on a coronal MRI slice though $y = -10$ mm and a sagittal slice through $x = 26$ mm. The rCBF data were thresholded to only show rCBF increases with $p < 0.005$.

hippocampus proper, we performed a high-resolution single-subject mapping study with multiple OA and control scan pairs. We used high-resolution PET, which possesses a mapping resolution of < 2 mm [21], and avoids the distortion in spatial localization due to the effects of draining veins in fMRI [22]. Figure 3 shows the results with the rCBF increases overlayed on a MRI of the subject's brain. The activation falls clearly within the right anterior hippocampus proper.

To test whether the observed hippocampal activity was delay-dependent, we had subjects perform SA with a delay of 5 s. The increased delay did not accentuate the level of anterior hippocampal activation. In fact, no significant activation occurred in the right hippocampus at this longer delay, and activation in this region was significantly greater in the 1 s than in the 5 s condition ($Z(9) = 3.27$, $p < 0.001$; difference between the activation induced by SA at 1 s delay and the activation induced by the SA at 5 s delay, relative to 1 and 5 s sensorimotor controls). Thus, the activity observed in the right anterior hippocampus during the performance of alternation tasks does not appear to reflect the active maintenance of information over the delay, but instead reflects a more transient function. If so, the observed rCBF increases in the hippocampus may depend on the total number of alternation trials imaged, with more trials per scan resulting in an improved signal-to-noise ratio. During the 90 s acquisition period, subjects

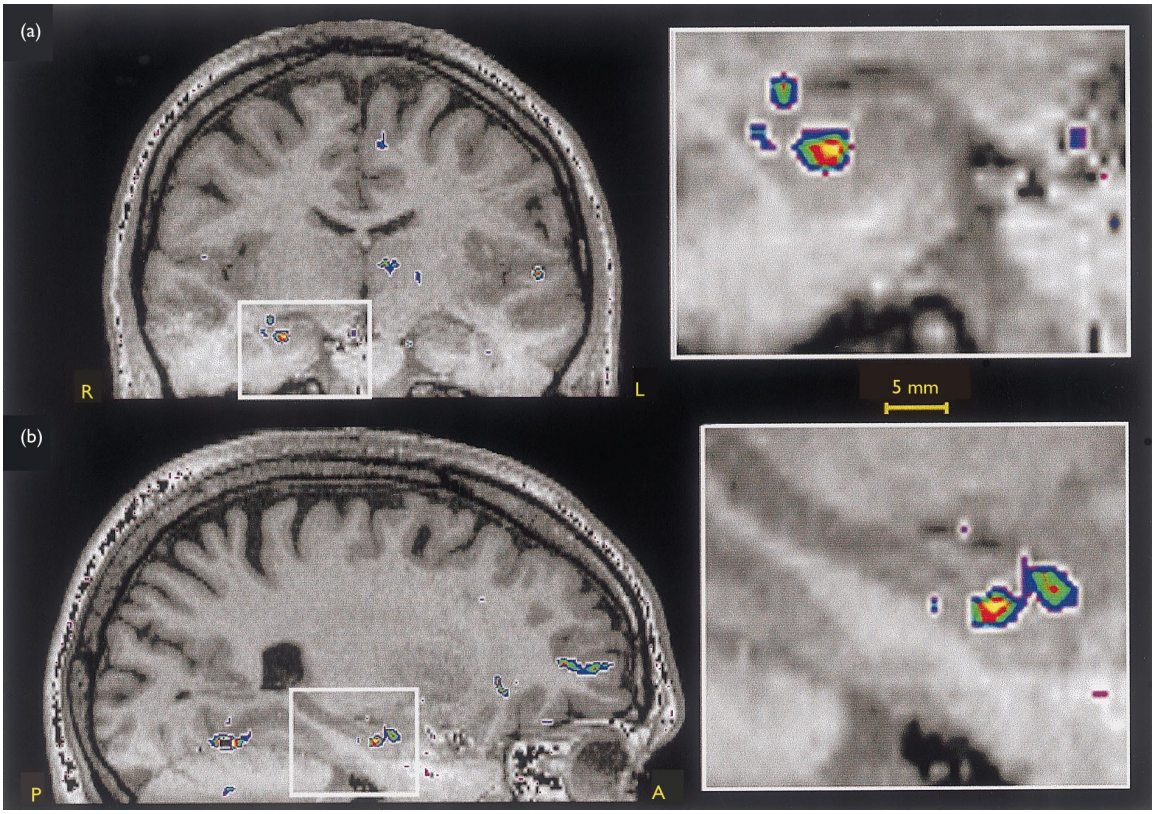

Fig. 3. Single-subject high-resolution mapping of hippocampal activation during object alternation. The rCBF data were thresholded to only show areas demonstrating a greater than 6% increase in rCBF and overlayed on the subject's co-registered T1 MRI. The highest magnitude rCBF increases appear in yellow. (**a**) Coronal slice through the anterior hippocampus. (**b**) Sagittal slice through the right hippocampus. The area inside the white rectangle is displayed at higher magnification on the right side of the image. The maxima in the anterior hippocampus is highly significant (Z-score = 4.8). R = right, L = left, A = anterior, P = posterior.

Table 1. Peak areas of activation during object and spatial alternation.

Area	x	y	z	Z-score	Cluster size
Object alternation					
Superior/inferior temporal gyri (BA 38)	28	10	−32	4.3	20
Right inferior parietal lobule (BA 40)	48	−58	38	4.1	47
Right anterior hippocampus	26	−10	−16	4.1	22
Right medial orbital gyrus (BA 11)	19	39	−18	3.7	10
Left gyrus rectus (BA 14)	−6	26	−20	3.4	2
Left precentral gyrus (BA 6)	−37	−8	47	3.4	6
Left superior temporal gyrus (BA 38)	−48	5	−11	3.3	7
Spatial alternation					
Superior frontal gyrus/anterior cingulate (BA 6/32)	−17	5	43	5.1	63
Right inferior parietal lobule (BA 40)	53	−35	43	4.7	44
Right frontal pole (BA 10)	35	62	7	4.1	28
Left rolandic cortex (BA 3/4)	−37	−19	29	3.7	24
Left medial orbital gyrus (BA 13)	−17	26	−11	3.7	12
Right paracentral lobule (BA 5)	15	−26	43	3.6	8
Left middle frontal gyrus (BA 10)	−33	62	2	3.6	15
Left frontal pole (BA 10)	−19	59	11	3.5	8
Left inferior frontal gyrus (BA 44)	−48	14	4	3.4	9
Left putamen	−24	−4	14	3.3	5
Right anterior hippocampus	26	−10	−16	3.3	3

Stereotactic coordinates in mm: x = medial-lateral relative to the midline (+ = right); y = anterior-posterior relative to the anterior commissure (+ = anterior); z = inferior-superior (+ = superior) relative to intercommissural plane. Cluster size represents the number of 2.25 mm^3 pixels exceeding the $p = 0.0005$ threshold.

on average completed 31 trials for the 1 s delay compared with only eight trials for the 5 s delay.

DISCUSSION

We observed activation of the right anterior hippocampus proper while subjects performed object and spatial alternations. Hippocampal activation emerged even though subjects only had to remember a single, simple stimulus over a minimum delay of 1 s. These data lead us to an intriguing question. Why is it that the hippocampus activated during performance of this working memory task and not during other more classical tests of medial temporal lobe function, with substantially greater mnemonic demands? Although this initial report cannot furnish an answer, it does provide several avenues for future research. A few task features stand out when comparing the cognitive demands of the alternation tasks used here to other memory tasks that have not resulted in hippocampal activation. Alternation tasks induce a substantial degree of proactive interference (i.e. no longer relevant information on past trials becomes a source of interference on each current trial). Use of similar, or in this case the same, stimuli across trials and brief inter-trial intervals are both known to increase proactive interference. High levels of proactive interference tax processes that bind features in temporal context because such processes must be highly specific and focused enough to separate these episodes upon recall. Computational models of working memory suggest that the hippocampus uses a process of pattern separation to prevent interference from past episodes that posses a high degree of overlapping features [23]. The hippocampal activation reported here may also reflect the important role of the hippocampus in relational or contextual binding [24,25]. Since the subjects saw the objects repeatedly before scanning and the objects (or locations) were readily distinguishable, it is unlikely that much object (or spatial) feature binding was demanded. Instead, the task requires a union between the object or location, the memory of the last response, and the memory of when the response took place (context). The need for this contextual binding was particularly heightened in the current experiments due to the high proactive interference of the alternation tasks.

CONCLUSION

We find that the exact same area of right anterior human hippocampus activates during both spatial and object alternation. These results converge with findings from other non-lesion imaging techniques [9–13] and show that the hippocampus participates in some working memory tasks even at very brief delays. These findings are particularly striking for two reasons. First, demonstrating activation of the hippocampus proper has been difficult even during tasks requiring substantially greater mnemonic demands. Second, hippocampal lesions do not typically produce deficits in working memory. Perhaps other more specific circuits (particularly prefrontal circuits) can compensate for hippocampal processes in lesioned animals at least over short intervals in the absence of interference. While most studies of hippocampal function have focused on the long-term and delay-dependent features of memory, our data indicate a more transient function in working memory that should be addressed by future models and studies of hippocampal function.

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