

Activation of the hippocampus in normal humans: A functional anatomical study of memory

(amygdala/declarative memory/priming/frontal cortex)

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ABSTRACT We studied regional cerebral blood flow using the $H_2^{15}O$ method while normal subjects performed four similar tasks involving three-letter word beginnings (stems). Prior to each task, subjects studied a list of words. Local blood flow was then monitored during a 40-sec period while subjects (i) silently viewed word stems, (ii) completed stems to form the first words to come to mind, but the stems were not the beginnings of any study words (baseline), (iii) completed stems and half of them could form study words (priming), or (iv) tried to recall study words, and half of the stems could form these words (memory). There were three major findings. (i) The memory task engaged the right hippocampal region when the memory task was compared to either the baseline or the priming condition. The right hemispheric locus suggests that performance is driven by the visual characteristics of the words rather than by semantic or phonetic analysis. (ii) In the priming-minus-baseline comparison, there was reduction in blood flow in the right posterior cortex. (iii) Right prefrontal cortex was activated in the memory-minus-baseline condition. The results provide evidence for selective activation of the human hippocampal region in association with memory function. The results also lead to a suggestion about the neural basis of repetition priming: following presentation of a stimulus, less neural activity is required to process the same stimulus.

Considerable information about the anatomical structures and connections involved in memory functions has come from histopathological studies of memory-impaired patients (1–3) and from a model of human amnesia in the monkey (4–7). This work is based on analysis of the effects of brain lesions and has converged on the view that the hippocampus, together with adjacent anatomically related cortex, is necessary for the formation of long-term memory. This brain system is involved particularly in the acquisition, temporary storage, and retrieval of explicit memory for facts and events (declarative memory) (1, 8, 9). Priming—that is, improved facility for detecting or identifying recently presented stimuli (10, 11)—does not depend on the hippocampal formation nor does skill-learning, conditioning, or other forms of nondeclarative (implicit) memory (1, 12). The development of neuroimaging technology based on positron emission tomography (PET) raises the possibility of studying the anatomy of declarative and nondeclarative memory directly in normal human subjects. Using this technique, we have demonstrated activation of the right hippocampal region in normal subjects during a task of cued-recall (declarative memory), and we have demonstrated changes in right occipital cortex during priming.

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METHODS

Subjects. The subjects were 18 normal volunteers [7 males and 11 females; mean age, 21.9 years (range, 18–24 years); all right-handed]. These studies were approved by appropriate institutional review boards of Washington University, and all subjects gave informed consent.

Scanning Methods. Brain activity was monitored as changes in local blood flow using the $H_2^{15}O$ method. Subject preparation was as described (13), except that no arterial catheters were used. Because the change in local tissue radioactivity (referred to as PET counts) is linearly related to blood flow under the conditions of this study (14, 15), relative changes in tissue activity are taken to indicate relative changes in blood flow. All subjects underwent six scans ≈ 10 min apart. Subtraction images between scans, used to isolate changes related to task differences, were calculated using pixel-by-pixel subtraction after linear normalization for changes in the global activity of the brain (arbitrarily set to 1000 PET counts). Anatomical normalization was performed by linear scaling to the Hd6 brain of the 1967 atlas of Talairach *et al.* (16). Stereotaxic image-averaging across subjects, to increase signal-to-noise in the subtraction images, was performed as described (17, 18). All difference scans for each subject were screened for movement artifact prior to anatomical normalization and stereotaxic image-averaging.

Task Design. The fact that many brain regions can be activated by learning and memory tasks in human subjects (19) emphasizes the importance of carefully selecting tasks in order to isolate functional changes related to specific memory processes. To achieve this, we attempted to manipulate a small number of hypothesized task components among the different scans.

Prior to each scan, subjects studied a list of 15 common English words four to eight letters in length (20). Different lists were presented before each scan. The list of 15 words (10 target and 5 filler words printed in capital letters, each letter subtending $\approx 0.8^\circ$ of visual angle) was presented twice in succession on a computer screen (3.5 sec per word). The filler words were placed at the beginning and end of the list to minimize primacy and recency effects. To ensure that the words were attended, we asked subjects to rate each word on a 1–5 scale according to how much they liked the word.

Approximately 3 min after word list presentation, a scan was begun. The first and last scans of the series were always fixation-point conditions, in which subjects simply fixated a cross hair on the computer screen. The other four scans were task conditions. In each case, subjects saw 20 word stems (three-letter word beginnings) presented one at a time in the same size, location, and typecase as the words (3 sec per stem with a 0.5-sec interval between stems). Each word stem could

Abbreviation: PET, positron emission tomography.

form at least 10 common English words. Presentation of the word stems was begun about 15 sec before the beginning of the scan itself. Brain activity was then monitored continuously for 40 sec while subjects performed one of four tasks: (i) *no response*: subjects viewed the word stems but made no verbal response, and none of the stems could form words that had been presented; (ii) *baseline*: subjects completed the word stems aloud to form the first word to come to mind, but again none of the stems could form words that had been presented; (iii) *priming*: subjects completed the stems aloud to form the first word to come to mind, and half of the stems could form words that had been presented; and (iv) *memory*: subjects were instructed to use the stems to recall words aloud from the list that had just been presented, and half of the stems could be completed to form these words. Subjects were instructed to guess, if necessary, and word completions were obtained in nearly every case.

The order of the four task conditions was mixed for 8 of the subjects and in the order just listed for an additional 10 subjects. No order effects were seen. The behavioral performance of the subjects was similar to the performance of normal subjects in similar studies of word completion priming (20): baseline, 7.5% of the target words were produced (baseline priming was calculated as the percent of words produced that matched the list from which the stems had been taken, even though the list had not been presented); priming, 71.5%; memory, 76.4%. The score for priming and memory is the percent of words produced from the study list for those word stems that could potentially form study words. The assignment of word lists to the different task conditions (i.e., as study words prior to each scan or as a source of word stems) was counterbalanced across subjects.

Regional Analysis. Regions of interest were selected for analysis in the following manner. The subjects were randomly assigned to two equal groups. Images for these two groups were separately averaged. Three candidate regions (right hippocampus, right prefrontal cortex, and right occipital cortex) were selected from the mean-difference image from the first group using computer search routines (18). The hippocampal and prefrontal regions contained the two largest changes in the memory-minus-baseline subtraction, and the occipital region contained the largest change in the priming-minus-baseline subtraction. Beginning with the maximum pixel for each region (Table 1), boundaries were expanded in

three dimensions in a stepwise fashion over a set of contiguous pixels that followed isocontour values in the mean-difference image. Then, for this *first* group of subjects, regional *t* values were computed for each newly defined region using the individual component images from two task conditions [*t*(defining), Table 2]. The region with boundaries that produced the maximum regional *t* value was then used to test the statistical replicability of the response in the *second* group of subjects [*t*(replication), Table 2]. A Bonferroni correction was applied to adjust for multiple comparisons.

RESULTS

Fig. 1 shows a coronal section of the difference image for the 14 subjects who successfully completed the memory and the baseline conditions without movement artifact. The largest local blood flow change resulting from this subtraction was located in the right posterior medial temporal lobe in the area occupied by the hippocampus and the parahippocampal gyrus (Fig. 1, Fig. 2A, Table 1). Activation was greater in the right than in the left hippocampal region [paired *t* test, $t(13) = 4.29$, $P < 0.001$, Fig. 2A]. To compare activation in the left and right hippocampal regions, a region of interest in each subject's left hippocampus was defined that was precisely symmetrical to that subject's region of interest on the right side. There was no detectable change in the amygdala (Fig. 2D). In regions centered on the right and left amygdala (Fig. 2D, boxes; coordinates: $x = \pm 25$ mm, $y = -5$ mm, $z = -10$ mm), changes were minimal in the memory-minus-baseline subtraction, being less than one standard error different from zero [right = 4.5 ± 8.3 counts (SE); left = 9.4 ± 11.2 counts (SE); $n = 14$].

Further analysis (Fig. 3) suggested that the priming task may also have engaged the right hippocampal region but to a lesser degree than the memory task (priming minus baseline, $P < 0.05$). Many of the subjects became aware of the link between the word stems and the target words, and some explicit visual recognition probably occurred during the priming condition for word stems that were familiar. In other words, some explicit memory likely occurred during the priming task, even though the performance measure in the priming task does not depend materially on explicit memory. Indeed, patients with damage to the hippocampal formation exhibit intact word-stem completion priming on this same task (20). Importantly, the memory task engaged the hippo-

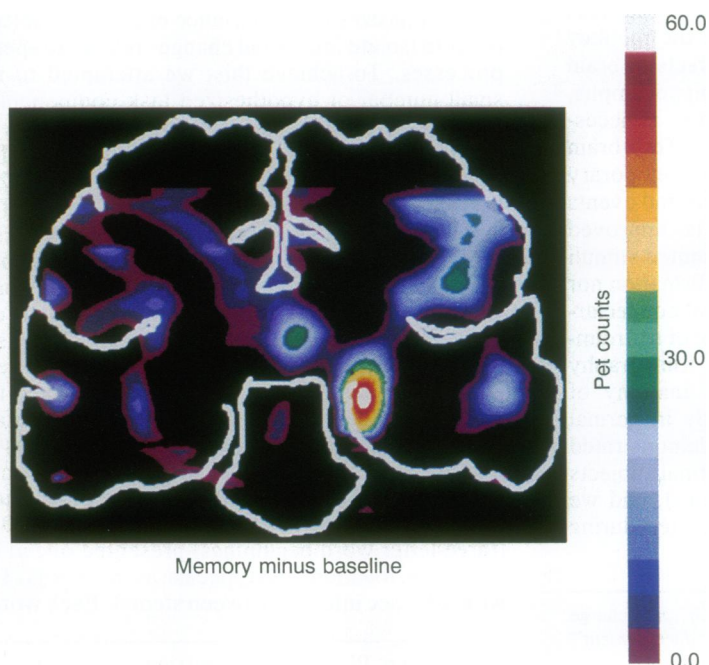


FIG. 1. Coronal, 2-mm-thick section 14 mm posterior to the midpoint of the line joining the anterior and posterior commissures. The section shows the major finding induced by the memory task in comparison to the baseline condition. The color scale is linear in units of PET counts and represents increases in blood flow (60 counts = 6% increase). The area of activation is in the right medial temporal lobe in the region occupied by the hippocampus and the parahippocampal gyrus (also see Fig. 2A).

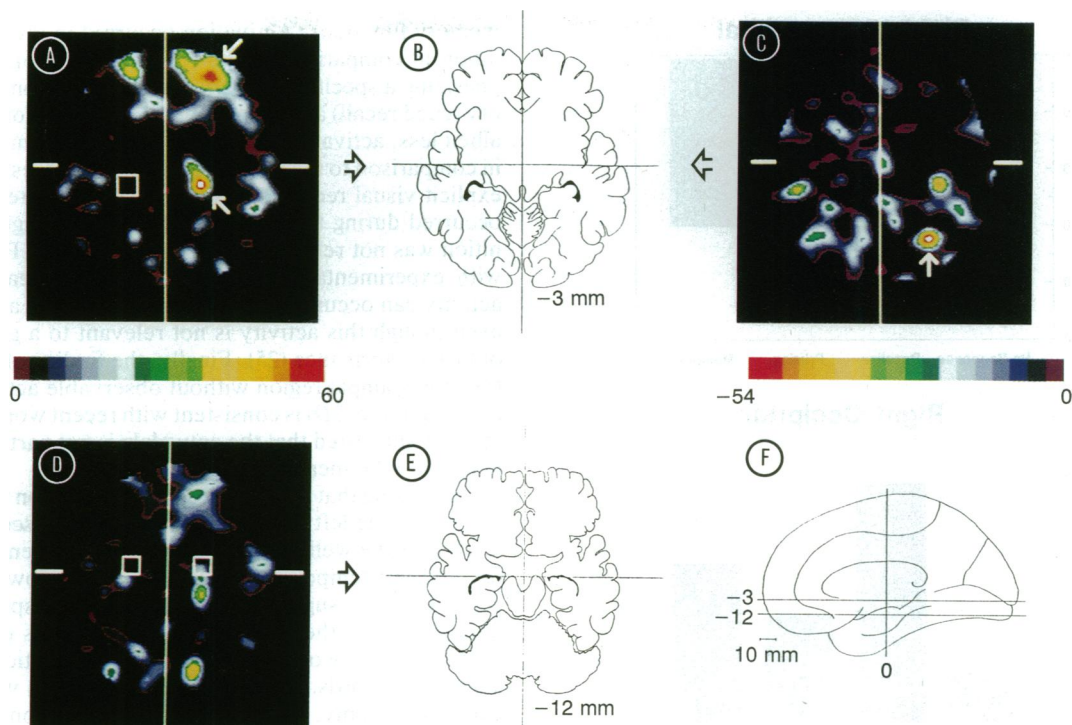


FIG. 2. Stereotaxically oriented, horizontal PET sections of blood flow change induced by a memory task (A and D) and by a priming task (C) (see text). In all cases, the sections show differences in blood flow between the task condition and the baseline condition (see text). The orientation of these sections is anterior (top), posterior (bottom), left (to the left), and right (to the right). The vertical line marks the midline of each image [$X = 0$ in stereotaxic coordinates (16)], and the lateral lines mark the midpoint of the bicommissural line [$y = 0$ in stereotaxic coordinates (16)]. The left color scale is linear in units of PET counts and represents blood flow increases in the memory-minus-baseline comparison (A and D). The right color scale represents blood flow decreases in the priming-minus-baseline comparison (C). The line drawings of horizontal brain sections (B and E) were made to scale from the Hd6 brain in the 1967 stereotaxic atlas of Talairach *et al.* (16) to indicate the level of the PET sections. The accompanying midsagittal drawing (F) shows the level of the sections and the scale for this figure. In the memory-minus-baseline comparison note the increase in blood flow in the right hippocampal region (A, lower arrow; mean \pm SE = 39 ± 7.2 counts) and the right prefrontal cortex (A, upper arrow; mean \pm SE = 28.5 ± 4.8 counts) and the absence of an increase in the left hippocampal region (A, box; mean \pm SE = -12.4 ± 9.8 counts). When the right hippocampus is compared to the left hippocampus in the memory-minus-baseline comparison, activation is significantly greater on the right (paired *t* test, $t = 4.29$, $P < 0.001$). Also note the absence of change in the amygdala (D, boxes). In the priming-minus-baseline comparison there was a focus of decreased blood flow in right occipital cortex (C, arrow; mean \pm SE = -31.3 ± 6.4 counts). The stereotaxic centers of these responses are given in Table 1.

campal region to an even greater extent than the priming task (memory minus priming, $P < 0.05$).

The second major finding (Fig. 2C) occurred in the priming-minus-baseline comparison for the 15 subjects without movement artifact for this subtraction. Specifically, in the priming condition as compared to the baseline condition, there was a significant reduction in blood flow in right posterior cortex (Table 2) in the region of the lingual gyrus (Table 1). Further analysis (Fig. 3) showed that there was a tendency ($P < 0.07$) for activity in this region also to be reduced in the memory condition, as compared to the baseline condition, presumably because the priming and memory conditions were similar with respect to the features that should be relevant for priming. That is, the memory task (like the priming task) involved the presentation of word stems, and some priming could have occurred during the memory task, even though the task condition required the subjects to engage in cued recall—i.e., to engage explicit memory strategies.

Table 1. Stereotaxic coordinates of regions of interest

Region	x	y	z
Right hippocampal	-23	-15	-4
Right occipital	-33	-47	-4
Right prefrontal	-33	+59	+6

x, Right (negative)/left (positive) axis; y, anterior (positive)/posterior (negative) axis; and z, vertical axis (positive, superior). These coordinates are referable to the Hd6 brain in the 1967 atlas of Talairach *et al.* (16). Distances are in millimeters. The coordinates represent the center of the regions illustrated in Fig. 2.

Activation in the same region of the right posterior cortex has been observed previously during the visual presentation of words (13, 21) and was related to processing of the visual features of words rather than their orthographic regularity (23).

Finally, the right prefrontal cortex was activated in the memory condition in comparison to the baseline condition (Fig. 2A; Table 1). There was also a tendency for the activity of this region to be inversely correlated with the number of correct matches made between the word list and the word stems in the memory condition ($r = -0.44$, $P = 0.10$). No such correlation was observed in the right hippocampal region ($r = +0.21$, $P = 0.45$). This variation across subjects probably accounts for the higher variance and, hence, lower replication *P* values observed for the prefrontal region (see Table 2). Activation of a similar region of right prefrontal cortex has been reported in tasks requiring response selection during a complex visual discrimination (36).

Although the findings just described in relation to memory and priming occurred in the right hemisphere, other changes presumably related to the processing of words and word-like stimuli did occur in the left hemisphere. Thus, in the no-response condition (i.e., the passive viewing of word stems minus fixation point), changes occurred in occipital cortex bilaterally as well as in the left prefrontal cortex, left temporal cortex, and right cerebellum. Activation of these regions or closely adjacent regions has been observed previously during a task in which subjects generated appropriate verbs in response to visually presented nouns (21, 24). These findings probably reflect the fact that the subjects in the present study tended to

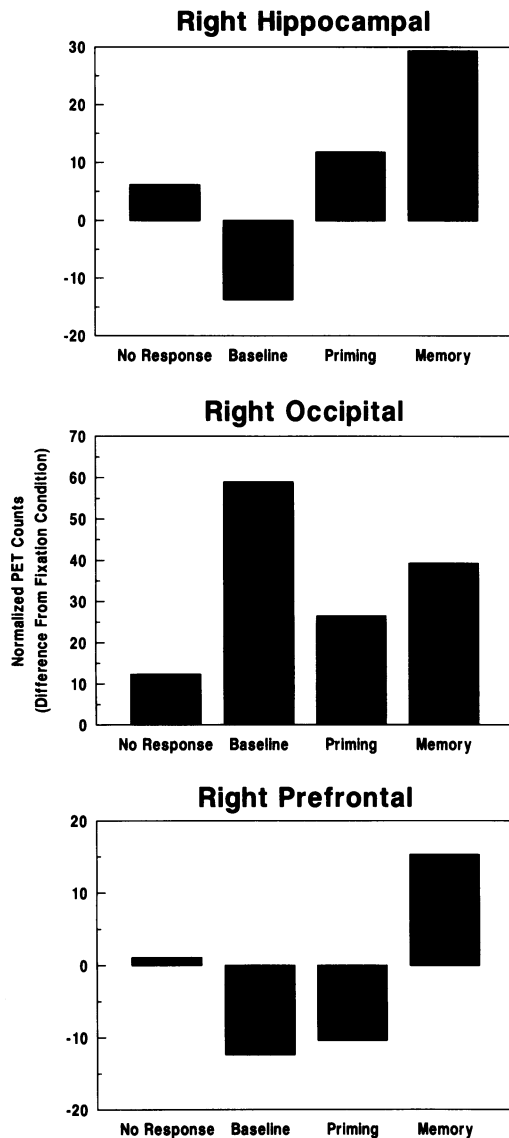


FIG. 3. Behavior of the right hippocampal (*Top*), right occipital (*Middle*), and right prefrontal (*Bottom*) regions (see Figs. 1 and 2 and Table 1) in the four activation conditions as compared to the fixation-point control condition for the 11 subjects who completed all four conditions without movement artifact. This analysis shows that the right hippocampal response observed in the memory-minus-baseline subtraction (Fig. 2A, Table 1) did not arise simply as the result of reduced hippocampal activity in the baseline condition. Indeed, a right hippocampal response was observed in the priming-minus-baseline subtraction as well as in the memory-minus-priming subtraction. The analysis also provides further insight into the behavior of the other two regions across conditions.

form words silently from the word stems during the no-response condition (as confirmed by questioning subjects after the scans). Additionally, during the baseline condition (i.e., in the baseline-minus-no response comparison), an area was activated in left medial extrastriate cortex. This region has been identified as responsive to orthographically regular letter strings (23). Thus, changes related to the processing of words and word-like stimuli occurred in the left hemisphere of our subjects, but under the conditions of the present study the task components related specifically to priming and explicit recall engaged primarily the right cerebral hemisphere.

DISCUSSION

The results provide clear evidence in humans of selective activation of the hippocampal region in association with

memory functions. Activation occurred in the memory condition in comparison to the priming condition (Fig. 3), emphasizing a specific link between retrieval from recent memory (cued recall) and the hippocampal formation. Significant, albeit less, activation also occurred in the priming condition, in comparison to the baseline condition, suggesting that some explicit visual recognition of familiar word stems may have occurred during the priming task, even though such recognition was not relevant to task performance. Previous work with experimental animals shows that increased neuronal activity can occur in the hippocampus during a learning task even though this activity is not relevant to a given measure of task performance (25). Finally, the finding of activation in the hippocampal region without observable activation in the amygdala (Fig. 2D) is consistent with recent work in monkeys that has suggested that the amygdala is not part of the medial temporal lobe memory system (7, 26–29).

The finding that the right hippocampal region was activated more than the left in the present study may seem surprising in view of the well-known association between verbal memory and left temporal lobe function (30). However, several considerations suggest that the right hemisphere is more important than the left when performance is driven by the visual form of words rather than by phonetic or semantic analysis of words. For example, for patients with forebrain commissurotomy, the right hemisphere is dominant for the visual recognition of words when recognition is based on the visual form of the words, but the left hemisphere is dominant when recognition is based on semantic or phonetic analysis (31). In addition, recent divided visual field studies with normal subjects indicate that, when words and word stems are presented in the same modality and in the same lettercase, word-stem completion priming depends more on the right hemisphere than the left (32). Specifically, more priming occurred when word stems were presented to the left visual field than to the right visual field. In the present task both priming and cued recall were apparently supported by the visual form of the word stems.

We considered the possibility that the left hippocampal region might have been active in all of the scan conditions and that its involvement in memory could therefore not be detected in any subtractions between conditions. However, this scenario requires that the left hippocampal region was as active in the fixation-point condition as in each of the other task conditions, including the memory condition. This seems unlikely. The right hippocampal region was especially active in just those task conditions potentially relevant to memory—namely, the two conditions in which the word stems presented during the test were related to the words that had been presented during study (priming and memory conditions). Moreover, in an earlier study of glucose metabolism in the monkey, the hippocampus was engaged during the performance of tasks known to require the integrity of the hippocampal formation but *not* during the performance of tasks that do not require this structure (29).

The decrease in activation in right posterior cortex associated with word priming provides a clue about its neural basis. Priming has been studied extensively in normal subjects and amnesic patients, and it has been suggested that repetition priming reflects transient changes in cortical sensory processing areas (1, 10, 33), with the result that processing of information is more rapid and/or efficient when a stimulus is presented for the second time. The present findings are consistent with this idea and lead to a specific proposal about the neural basis of priming: for a period of time following presentation of a word or other perceptual object, less neural activity is required to process the same stimulus. In monkeys performing a recognition memory task, many neurons in cortical visual areas show reduced unit

Table 2. Reproducibility of right hippocampal, occipital, and frontal responses

Region	Activation	Control	<i>t</i> (defining)	<i>t</i> (replication)	<i>P</i>
Right hippocampal	Memory	Baseline	2.58 (7)	7.62 (7)	<0.001
Right occipital	Priming	Baseline	-3.69 (7)	-3.47 (8)	<0.03
Right prefrontal	Memory	Baseline	10.66 (7)	2.61 (7)	0.06

t(defining) refers to the optimized *t* value for the indicated region, based on one-half of the subjects that contributed to the given comparison. *t*(replication) refers to the paired *t* statistic that resulted when the region of interest defined in the first group of subjects (hypothesis-generating group) was tested in the second group of subjects (hypothesis-testing group). The number of subjects in each group for each condition is shown in parentheses. The *P* value reflects the one-tailed probability that the result could have occurred by chance. The *P* values were multiplied by 3 to correct for the multiple comparisons. The regions identified here were the most active regions in the task conditions listed. There were a limited number of other regions that would be considered significantly active, based on change distribution analysis and statistical criteria described previously (21, 22). These include regions of right prefrontal cortex adjacent to the focus illustrated in Fig. 2 as well as a weaker focus in left prefrontal cortex ($x = 25, y = 61, z = 8$; memory-minus-baseline condition, see Fig. 2A). Two additional regions of reduced activity could also be identified in the priming-minus-baseline subtraction, one in right temporal cortex ($x = -39, y = -15, z = 0$, see Fig. 2D) and another in the left anterior insula ($x = 35, y = 19, z = 14$, not illustrated in the figures).

activity in response to the second of two presentations of a visual stimulus (34, 35).

A somewhat different, but related, view of the decreased activation in right posterior cortex during the priming condition is that the level of activity is determined by task requirements, which influence how fully the word stems are processed. For example, word stems presented during the priming and memory conditions might be less attended to than word stems presented during the baseline condition, perhaps because explicit memory for recent events is engaged during the latter two conditions but not during the baseline condition.

The present findings for priming and explicit memory illuminate the brain organization of two fundamental ways in which experience can modify the nervous system and affect subsequent performance. Enhanced performance due to perceptual priming of visually presented words or other objects depends on changes at visual processing centers, located prior to the interaction that occurs between representations of visual objects and the hippocampal region. Participation of the hippocampal region with such representations is required for explicit, declarative memory.

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