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Late Onset of Anterior Prefrontal Activity during True and False Recognition: An Event-Related fMRI Study

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Previous studies using PET and fMRI to examine memory retrieval have been limited by the requirement to test different types of items in separate blocks and to average data across items and response types within blocks. We used recently developed procedures for analyzing event-related mixed trial data from fMRI experiments to compare brain activity during true recognition of previously studied words and false recognition of semantic associates. A previous PET study using blocked testing procedures reported similarities and differences in rCBF patterns associated with true and false recognition (Schacter *et al.*, 1996a). We examined brain activity during blocked testing of studied words and nonstudied semantic associates (similar to PET), and also during event-related mixed trials, where studied words and nonstudied semantic associates are intermixed. Six subjects initially heard lists of semantically related words and were later tested for old/new recognition with studied words and nonstudied semantic associates, either in separate blocks or intermixed randomly for the event-related analysis. Compared to a fixation control condition, a variety of regions previously reported in the PET study showed significant activation for both true and false recognition, including anterior prefrontal, frontal opercular, medial parietal, and visual cortex extending into hippocampal/parahippocampal regions. Differences across trial types were not clearly present. Event-related analyses of time course data show a relatively late onset and sustained duration for anterior prefrontal signal changes compared to signal changes in other activated regions. Further study is needed to resolve whether this late onset originates from variance in hemodynamic response properties or is attributable to delayed neural activity. The delayed onset is consistent with the idea that anterior prefrontal regions participate in postretrieval monitoring processes. © 1997 Academic Press

INTRODUCTION

A growing number of studies have examined brain regions involved in memory using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI; for reviews, see Buckner and Tulving, 1995; Cabeza and Nyberg, 1997; Ungerleider, 1995). However, previous neuroimaging studies of memory have all been characterized by an important limitation: In order to increase signal characteristics, items belonging to a particular experimental condition are presented together in a consecutive series or "block" of items, and measures of brain activity reflect averaged activity across the entire block. Thus, for example, in studies of recognition memory, the items presented during a particular scan are either all or mostly "old" (i.e., previously presented in the experiment) or all or mostly "new" (not previously presented in the experiment). Analyses of brain activity for the scan are based on all of the items, regardless of the subject's responses to the items (that is, correct or incorrect, and "old" and "new" responses) (cf., Nyberg *et al.*, 1995; Rugg *et al.*, 1996; Schacter *et al.*, 1995, 1996b; Tulving *et al.*, 1994b; Buckner and Koutstaal, in press). The blocking procedure does not permit separate analyses of brain activity for recognized and nonrecognized items, nor does it allow examination of the time course of memory retrieval. Moreover, blocking target items (in contrast to the standard practice in most cognitive studies of randomly intermixing different item types) could affect participants' test strategies.

Recent advances in fMRI, which is sensitive to oxygenation-level-dependent changes in the magnetic properties of blood, make it possible to examine brain activity during individual trials. Although most fMRI studies have used blocked designs in which data are averaged across intervals of 16 to 40 s, fast echoplanar fMRI allows acquisition of individual images in less than a second (Cohen and Weiskoff, 1991). Buckner *et al.* (1996a) recently reported procedures for acquiring reli-

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able fMRI data from averaged individual trials of a word stem completion task, which requires retrieval of lexical items from semantic memory. Procedures for analyzing single, or event-related, fMRI data have been developed by several laboratories (e.g., Dale and Buckner, 1997; Josephs *et al.*, 1997; Konishi *et al.*, 1996; Zarahn *et al.*, 1997). In the present article, we report initial results from an experiment employing the event-related procedure in episodic memory retrieval.

Perhaps the most consistent finding from recent PET studies of episodic retrieval is that regions of anterior prefrontal cortex, particularly in the right hemisphere, show increased activity compared to various control conditions (for reviews, see Buckner and Petersen, 1996; Tulving *et al.*, 1994a). Schacter *et al.* (1996b) recently reported robust anterior frontal activation during retrieval of both veridical and false or illusory memories. They adapted procedures developed previously by Deese (1959) and Roediger and McDermott (1995) for producing high levels of false recognition. Participants were exposed to lists of semantic associates (e.g., *candy, sour, sugar, bitter, good, taste, tooth,* and so forth) and were then tested for recognition of previously studied "true targets" (e.g., *taste*) and non-studied "false targets" (e.g., *sweet*) that are strong associates of previously studied items. As in earlier cognitive studies (e.g., Roediger and McDermott, 1995; Schacter *et al.*, 1996c; for reviews, see Roediger, 1996; Schacter *et al.*, in press), behavioral data documented a significant false recognition effect. Analyses of PET data indicated that compared to a common fixation control condition, a variety of brain regions showed significant blood flow increases for both true and false recognition, including several areas previously activated by episodic retrieval tasks: anterior prefrontal, medial parietal, cerebellum, and left parahippocampal gyrus. Although direct comparison between true and false recognition yielded little evidence of significant blood flow differences, there were trends for increased right anterior prefrontal activity during false recognition and for increased left superior temporal activity during veridical recognition.

In view of the pervasive finding of anterior prefrontal increases during episodic retrieval with PET, and the recent finding of prefrontal activity during both true and false recognition (Schacter *et al.*, 1996b), the main purpose of the present experiment is to determine whether anterior prefrontal activations can be observed under blocked and event-related fMRI procedures for both veridical and illusory recognition. The blocked vs event-related comparison is especially relevant to the true/false recognition paradigm. A recent study using event-related potentials (ERPs) recorded from the scalp (Johnson *et al.*, 1997) revealed that ERP differences between true and false recognition under blocked testing conditions (mainly at frontal electrode sites) were not observed when different item types were randomly intermixed—as in the mixed event-related fMRI conditions reported here. Johnson *et al.* reasoned that in blocked test conditions, in which all items are either studied or not studied, subjects may be more likely to focus on specific information that differentiates otherwise highly similar items from one another than in randomly intermixed conditions (where there is more variability among the test items). Thus, subjects in blocked conditions might engage in more careful scrutiny of specific attributes of the test item which, in turn, could produce differences in brain activity during true and false recognition that are not observed in randomly intermixed conditions.

MATERIALS AND METHODS

Subjects

Six right-handed adults (two male and four female) between the ages of 18 and 26 years participated in the experiment. Informed consent was obtained prior to scanning in a manner approved by the Human Studies committee at Massachusetts General Hospital.

General fMRI Procedure

Imaging was performed on a 1.5 T General Electric scanner with an echo planar imaging upgrade (Advanced NMR Systems, Wilmington, MA). The standard General Electric (GE) quadrature head coil was used. Visual stimuli were presented using a PowerMacintosh (Apple Computer) connected to a Sharp 2000 color LCD projector. Images were projected through a collimating lens (Buhl Optical) onto a screen attached to the head coil which could be viewed through mirrors. Performance and reaction times were measured with a custom-designed magnet compatible keypress.

Participants lay on the flat scanner bed with their heads snugly fit into the head coil, using pillows and cushions as a means of reducing motion. Conventional structural images as well as echo planar functional images were acquired over a 2-h session. For each participant, high resolution anatomic images were acquired (conventional T1-weighted 3-D Spoiled GRASS (SPGR), 60 slice sagittal, 2.8-mm thickness). An automated echo planar shim procedure was used to improve B_0 magnetic field homogeneity (Reese *et al.*, 1995). Conventional flow-weighted 2-D TOF images coplanar with the functional echo planar images (16 slice, 7-mm skip, 1-mm between slices) were then acquired as an intermediate to align the echo planar images to the SPGR images. These flow sensitive images also provide a means to visualize large vascular structures. Finally, T2* weighted functional images were acquired using an asymmetric spin echo sequence sensitive to BOLD contrast (TE = 50 ms, offset = −25 ms). Such a se-

quence was chosen because it has diminished sensitivity to large vessel contributions (Baker *et al.*, 1993).

Functional images were acquired within runs of 128 timepoints, with each time point acquiring data over the entire brain including the cerebellum (16 slice, in plane resolution 3.125 mm, 7-mm skip, 1-mm thickness, aligned to the plane intersecting the anterior and posterior commissures, TR = 2 s). Four discarded timepoints were acquired prior to each run to allow T1 stabilization. Data from functional runs were normalized across subjects to a set whole-brain signal level of 1000 and the time series was corrected for linear slope on a voxel-by-voxel basis to remove drift (Bandettini *et al.*, 1993).

fMRI Data Analysis

Data from individual participants were transformed into the stereotaxic space of the Talairach and Tournoux (1988) atlas. This transformation was first accomplished by manually identifying the anterior and posterior commissures, the highest point in the midsagittal plane, and the bounding edges of the brain as viewed in the conventional SPGR images. These points were used to linearly orient and scale the sagittal images into the stereotaxic space of the Talairach and Tournoux (1988) atlas (using trilinear interpolation). Resulting brains in atlas space included 39 transverse slices of isotropic 3.125-mm voxels.

The transformation matrix of the acquired SPGR images to the atlas space was stored and then separately applied to each of the images in the functional runs. Additional transformations were required for this step because the functional images were not inherently aligned to the SPGR images. These additional transformations were derived from the GE header information except for a misalignment in the y-axis. Y-axis alignment was derived from a contour tracing algorithm used to match the functional images to a transverse conventional image acquired as an intermediate.

Once in atlas space, data were averaged across individuals in two separate manners. For the blocked runs, the functional runs were averaged to yield a single mean run of 256 timepoints for each of the 39 transverse slices (the two 128 timepoint runs from each subject were concatenated sequentially). To compare the combined true and false recognition conditions to the fixation reference condition, and to compare the true and false recognition conditions to each other, timepoints within these runs were assigned to one of the blocked conditions. Activation maps were constructed using the nonparametric Kolmogorov–Smirnoff test (K-S; Press, 1992). Time points were shifted 4 s for this analysis to account for hemodynamic delay. A spatial smooth with a one-voxel wide Hanning filter was applied prior to activation map generation.

For the event-related data, selective averaging procedures were performed in a manner highly analogous to how ERP data are analyzed except that trials were spaced relatively far apart (16 s; fMRI procedures developed by Dale and Buckner, 1997). A long trial duration was cautiously selected to minimize overlap of the hemodynamic response across trials (Savoy *et al.*, 1995; Boynton *et al.*, 1996; Buckner *et al.*, 1996a; Konishi *et al.*, 1996). Each trial was isolated in relation to the onset of the word stimuli and assigned to one of four memory conditions: Hits ("old" response to a studied word, indicating true recognition), False Alarms ("old" response to a nonstudied semantic associate, indicating false recognition), Misses ("new" response to a studied word), Correct Rejections ("new" response to a nonstudied semantic associate). Trials on which responses were not recorded were classified as errors and are not considered further.

Once separated, the average response for each of the four trial conditions was computed for the 16-s time window (eight time points). The mean and variance were computed for each time point and the results compiled into a set of averaged time-series for each trial condition. Statistical comparisons were made using these averaged time series.

Two sets of analyses were performed on the event-related data. For the first set of analyses, regions were first defined on peak activations in the blocked data sets and then examined in the event-related conditions (similar to Buckner *et al.*, 1996a). This analysis asked the question: How do regions that were activated in the blocked paradigm behave in response to averaged individual trials? Regions were examined for the composite of all trial conditions as well as for individual trial conditions. For the second set of analyses, individual trial conditions (or averaged combinations of trial conditions) were used to create statistical activation maps. No contrast between conditions was considered for this analysis; the absolute signal change in the averaged trials was used. However, because subjects fixated between trials, the absolute signal change can be considered a change from fixation. This analysis asked the question: Which voxels showed signal change in a manner predicted by the trial onsets? To create statistical maps, the observed hemodynamic response at each voxel was regressed against a predicted hemodynamic response based on a gamma function (See Boynton *et al.*, 1996; Dale and Buckner, 1997). The result is a *t* statistic map. By considering a basis set of gamma functions with multiple delay onsets, these statistical activation maps were used to identify activations across brain areas that demonstrate different hemodynamic lags. Contrasts across trial conditions were made in a similar manner but the difference in timecourses between trial types was regressed against

the predicted hemodynamic timecourse rather than the absolute signal change.

Data were displayed using a pseudo-color scale reflecting statistical significance overlaid on top of an averaged anatomic image (average of all SPGR images across subjects). Statistical activation maps from the blocked trial runs (based on the *K-S* statistic) and data from the event-related runs (based on the *t* statistic) were both displayed using the same pseudo-color scale.

Coordinates for peak activations are included in relation to the coordinate system of the Talairach and Tournoux (1988) atlas (x, y, z; positive x values indicate right). Coordinates were obtained by searching the entire image volume and identifying local maxima significant to $P < 10^{-5}$. Peaks were only considered if they were within a cluster of 5 significant voxels and at least 8 mm away from a larger peak. This procedure, when applied to a control data set where 8 subjects (16 runs of data) stared continuously at a fixation cross-hair, yielded no false positives in the entire image volume.

Experimental Materials, Design, and Behavioral Test Procedures

The experimental materials were 36 sets of semantically associated words, many of which were used in previous studies (Roediger and McDermott, 1995; Schacter *et al.*, 1996b, 1996c), together with additional sets that were constructed in a similar manner. Each set consisted of 15 semantic associates (e.g., *candy, sour, sugar,* and so forth) of a "theme word" or critical lure (e.g., *sweet*). In previous behavioral studies, all of the semantic associates were presented during the study phase of the experiment; the nonstudied theme word was presented at test. We followed the same general procedure, except that the third strongest associate from the set of 15 was not presented during the study phase of the experiment; this word, along with the theme word, was presented as a related lure during the recognition test. In addition, the first and second associates from the study list were presented on the recognition test. (This procedure allowed twice as many related lures to be tested, and also approximately equated the average associative value of the targets and lures.) Thus, prior to scanning participants studied 36 sets of items, each consisting of 14 semantically related words. Each list was recorded using SoundEdit resource files by a male speaker, and was presented auditorily at a rate of 1700 ms per word. Words were presented in order of decreasing strength of association to the theme word. Subjects were instructed to listen carefully to each list and to try to remember the words in preparation for a later memory test. Presentation of each of the 36 lists was separated by a 20-s interval, during which participants completed simple arithmetic problems. The subsequent recognition test included two true targets and two false targets from each of the 36 lists.

After presentation of all lists, there was a delay of approximately 45 min during which participants were taken from the behavioral testing room into the scanner. For each participant, recognition memory was tested during two runs of blocked trials and six runs of single mixed trials; blocked trials were always carried out prior to single mixed trials. For all runs, words were presented visually in 36 pt. Geneva font, white on black background (see Fig. 1; study items were presented auditorily but tested visually in order to maximize procedural comparability with previous behavioral (Roediger and McDermott, 1995) and neuroimaging (Schacter *et al.*, 1996b, 1996c) studies of true and false recognition). Each run was followed by an unfilled rest period of approximately 3 min, corresponding to the time required for image reconstruction in the scanner. Participants were instructed to make old/new recognition judgments about each word, pressing the left key of a magnet-compatible key-press to indicate "old" and the right key to indicate "new" judgments. Participants responded using their left (i.e., nondominant) hand. Words appeared for 1500 ms, immediately followed by a cross-hair. Participants were instructed that they could make a response either while the word was displayed or after stimulus offset.

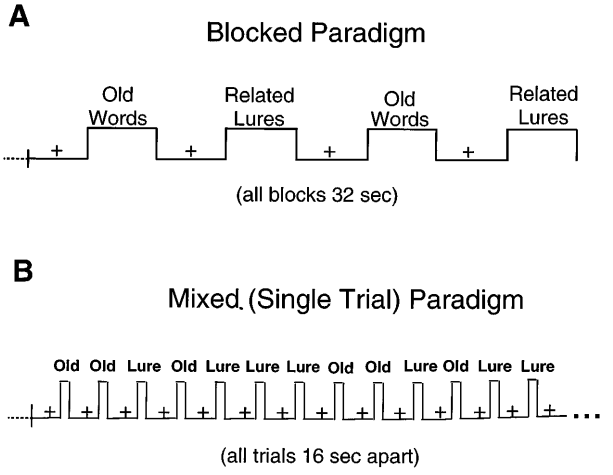

FIG. 1. (A) In the blocked testing condition, two runs were collected for each subject. During each run, two 32-s blocks of six previously studied words (OLD WORDS) and two 32-s blocks of six nonstudied semantic associates (RELATED LURES) alternated with four blocks of crosshair fixation (+). Words were presented visually immediately followed by a crosshair. Subjects made old/new recognition decisions about each word, either while the word was presented or immediately after stimulus offset (5.3-s interval, stimulus duration, 1500 ms; words presented in 36 pt Geneva font, white on black background). (B) In the event-related mixed trial condition, six runs were collected for each subject. During each run, 8 previously studied words (OLD WORDS), and 8 nonstudied semantic associates (RELATED LURES) were presented one word every 16 s.

For the blocked testing condition, there were two runs. During each run, four separate 32-s blocks consisting of six true targets in each of two blocks or six false targets in each of two blocks alternated with four 32-s blocks of crosshair fixation (e.g., fixation/six false targets/fixation/six true targets/fixation/six false targets/fixation/six true targets). These critical runs were preceded by a brief practice run in which the words "Old" and "New" were repeatedly presented and participants were required to press the appropriate keys.

For the event-related testing condition, there were six runs. Each run consisted of eight studied words and eight related lures. Presentation of each word for 1.5 s was followed by a fixation period of 14.5 s for a total intertrial length of 16 s.

The individual blocked and mixed runs were constructed with the constraint that none of the 36 study lists was tested more than once (with either a studied word or a related lure) in a given run, and that an equal number of related targets from the highest (theme word) and third associate positions, and an equal number of targets from the first and second associate positions were tested in each run. In addition, event-related mixed runs were subject to the constraint that no more than two studied words or related lures appeared consecutively. We constructed six different blocked lists and 18 different mixed lists. These lists were in turn subdivided into three sets, such that each set comprised two blocked lists and six mixed lists. In each set, each target and each lure was tested once. Across the three sets of lists, each of the 72 targets and 72 lures was tested once in a blocked run. Subject 1 received (in order) blocked lists 1 and 2 and mixed lists 1 through 6; Subject 2 received blocked lists 3 and 4 and mixed lists 7 through 12, Subject 3 received blocked lists 5 and 6 and mixed lists 13 through 18; the remaining three subjects received the same lists as Subjects 1, 2, and 3, respectively, except that within the blocked and mixed runs, the order of list presentation was reversed. Finally, mixed lists were constructed such that the pattern of lures and targets was counterbalanced across runs.

To obtain sufficiently stable fMRI data in both blocked and event-related mixed trial conditions, it was necessary to test only studied words and related lures; we could not include unrelated, nonstudied words as controls for the studied words and related lures (cf., Schacter *et al.*, 1996b). However, it is important to obtain some estimate of the false alarm rate to unrelated nonstudied items in order to determine whether presentation of semantic associates produced a significant false recognition effect. To address this issue, we conducted an off-line behavioral study in which six female participants, aged 17–23 years, heard the identical study lists as did participants in the fMRI study. However, during recognition testing, for one-half of the related lures we substituted unrelated, nonstudied words that allowed us to estimate the "baseline" false alarm effect. Specifically, in each of the blocked runs we replaced one set of related lures with a set of unrelated nonstudied words. In each of the mixed runs, we replaced four of the related lures with unrelated nonstudied words. The unrelated lures were selected to be of approximately the same letter length and word frequency as the related lures they replaced. For each of the six subjects, a different subset of related lures was replaced. For three of these subjects, the first set of related lures in the first blocked run was replaced with unrelated items, and the second set of related lures in the second blocked run was replaced; for the remaining three subjects, the order of substitutions was reversed. Replacements of related lures in the mixed runs were made such that, wherever possible, only one of the two possible lures from a given study list was replaced.

RESULTS

Behavioral Data

Results of the off-line behavioral pilot study indicated that during the blocked trial conditions, participants made 69% "old" responses to studied words, 44% "old" responses to related lures, and 14% "old" responses to unrelated lures; the corresponding numbers for the mixed trial condition were 71, 58, and 17%. Participants made significantly more "old" responses to related lures than to unrelated lures in both the blocked ($t(5) = 2.98$, $P = 0.03$) and mixed ($t(5) = 4.54$, $P = 0.006$) trial conditions, thus confirming a robust false recognition effect. In the blocked condition, participants also made significantly more old responses to studied words than to related lures ($t(5) = 2.78$, $P = 0.04$). For the blocked trial conditions, mean RTs for hits and misses were 1465 and 1717 ms, respectively; mean RTs for correct rejections of unrelated lures and of related lures were 1656 and 1839 ms, respectively; for false alarms to unrelated and related lures the mean RTs were 1914 and 1564 ms, respectively. For the mixed trial conditions, mean RTs for hits and misses were 1749 and 2110 ms, respectively; for correct rejections of unrelated lures and of related lures they were 1740 and 1909 ms, respectively; for false alarms to unrelated and related lures they were 1895 and 1787 ms, respectively. Analyses of the RT data revealed that correct rejection responses during the blocked runs (mean RT = 1839 ms) were significantly slower than were hits or correct acceptances (mean RT = 1465 ms), $t(5) = 5.86$, $P = 0.002$.

Behavioral data obtained during scanning were similar to the pilot study. During blocked trials, participants made 73% "old" responses to studied words and 54% "old" responses to related lures; during mixed trials, participants made 77% "old" responses to studied

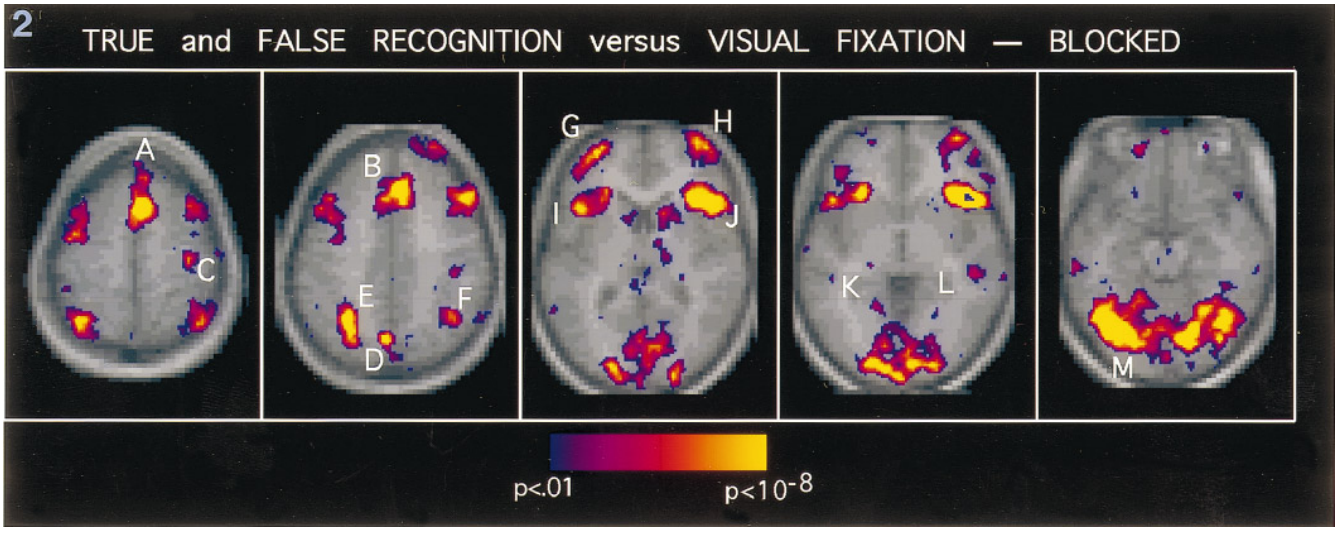

FIG. 2. K-S statistical activation maps contrasting the combined true and false recognition conditions compared to fixation are shown overlaid on top of an averaged anatomic image. Images are in Talairach (1988) atlas space and are averaged across the 12 runs in six subjects. These images represent only data from the blocked paradigm. Many brain regions were activated, including (selected Talairach 1988 atlas peak coordinates listed x, y, z; $P < 10^{-5}$ and within clusters of at least 5 significant voxels): (A) SMA [6, 16, 50], (B) SMA extending into anterior cingulate [0, 25, 43 and 6, 28, 34], (C) motor/premotor cortex [34, −21, 50], (D, E, F) medial [−3, −71, 37] and lateral parietal cortex [−28, −58, 40; 40, −58, 50 and −37, −58, 53], (G, H) bilateral anterior prefrontal cortex [34, 56, 18; −28, 56, 18 and 34, 59, 0], (I, J) bilateral frontal-opercular cortex [40, 19, 0; −28, 25, 3 and −43, 16, 6], (K, L) hippocampal/parahippocampal region (−18, −52, 0; $P < 10^{-3}$; see also Fig. 3), (M) extrastriate and striate visual cortex [many peak coordinates]. Complete Talairach coordinate listings available on request from authors.

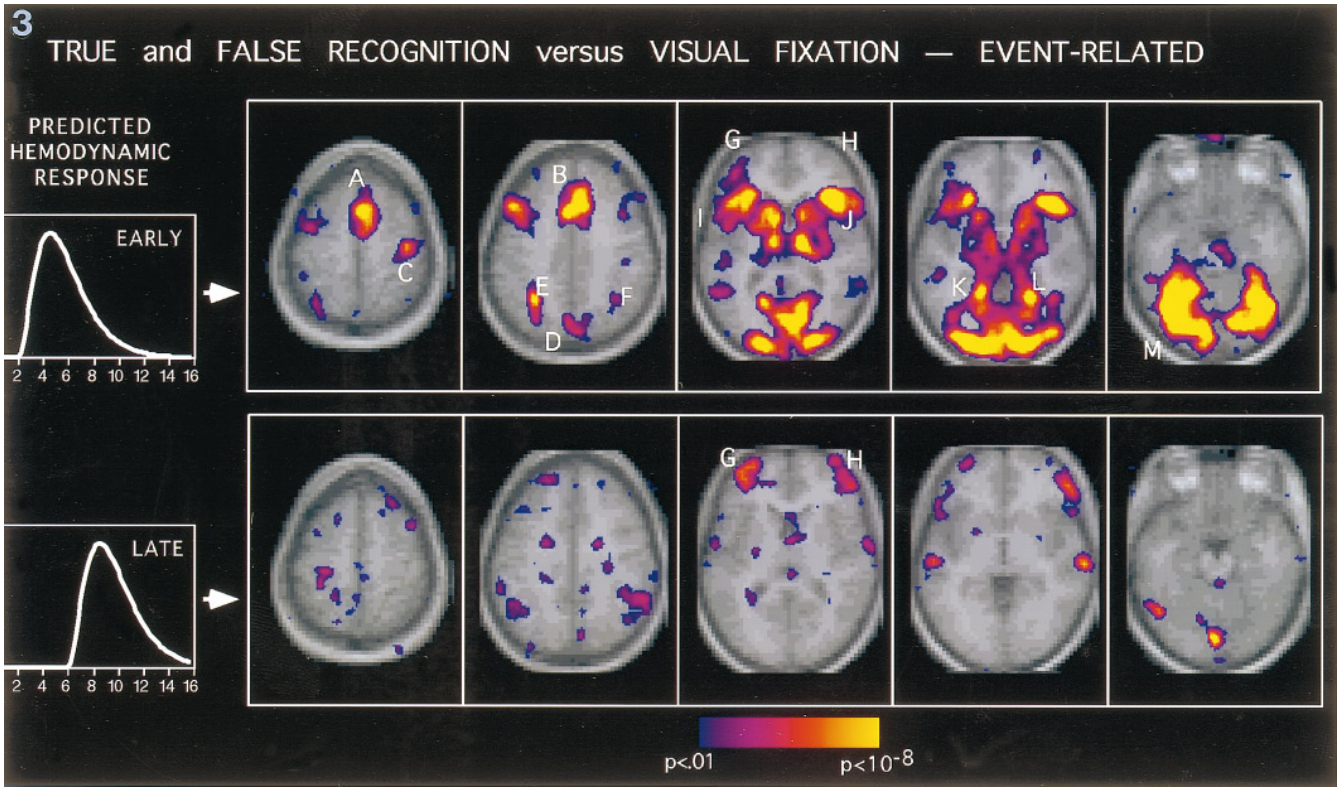

FIG. 3. T-statistic activation maps based on regression of the predicted hemodynamic response function against the obtained signal from the individual recognition trials. These data are based on a combination of all trial types (hits, misses, false alarms, and correct rejections) including a total of 576 trials. Two separate activation maps are shown which are each based on hemodynamic response functions with different delays. The TOP panel shows areas activated with a relatively early hemodynamic delay while the BOTTOM panel shows areas

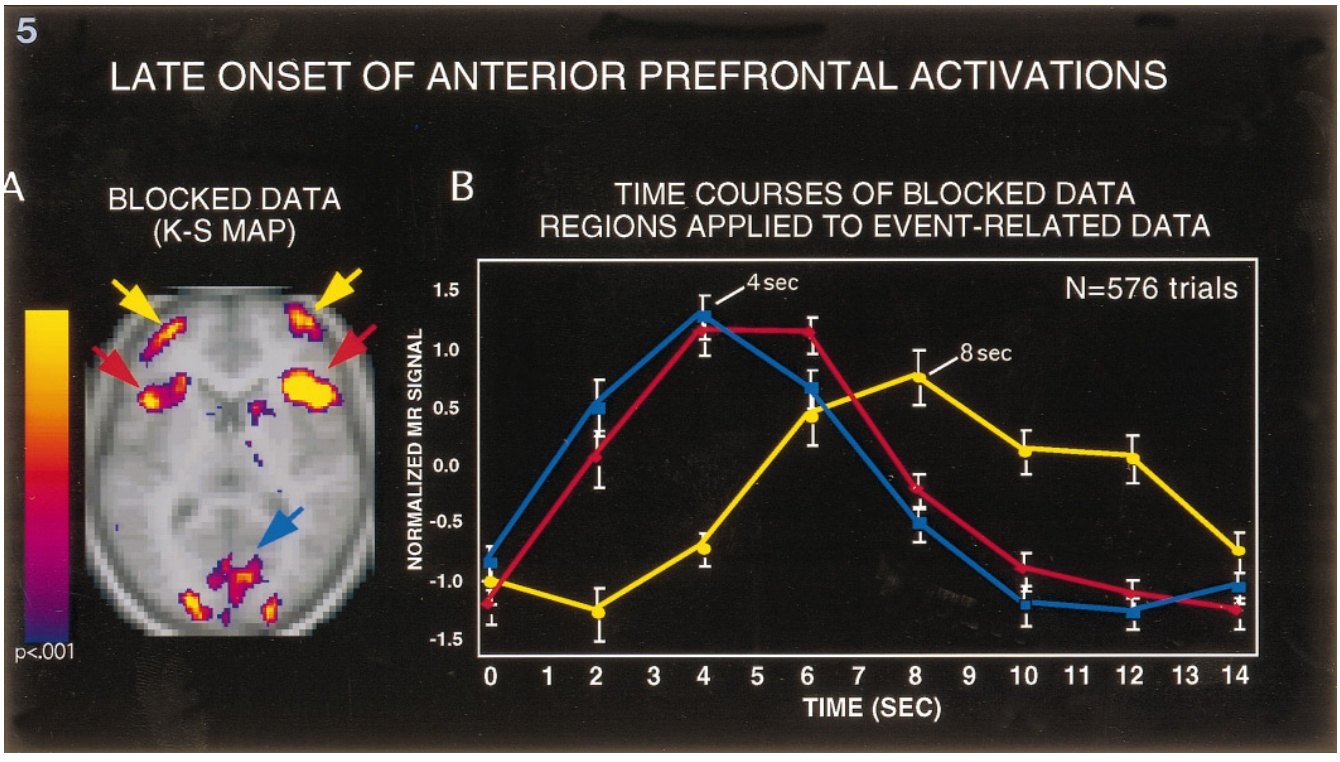

FIG. 5. A K-S statistical activation map from the blocked trial data is shown on the left. This map is from a section containing the anterior prefrontal activations (yellow arrows), frontal opercular activations (red arrows), and visual cortex activations (blue arrow). To determine the time-course of these activations in the event-related runs, regions were defined around the activations in the blocked trial runs and then examined in the event-related data (similar to the procedure of Buckner *et al.*, 1996a). All regions were contained on a single slice so as to remove contributions from differential MRI slice acquisition times. The graph in the right panel shows the results, with anterior prefrontal activations peaking later and lasting considerably longer than the frontal opercular and visual cortex activations.

words and 67% "old" responses to related lures. Participants made significantly more "old" responses to studied words than to related lures in the blocked trials, $t(5) = 5.07$, $P = 0.004$. For the blocked trials, mean RTs for hits and misses were 1891 and 2131 ms, respectively; the mean RT for correct rejections was 2011 ms, and for false alarms it was 1876 ms. For the mixed trials, mean RTs for hits and misses were 1984 and 2268 ms, respectively; the mean RT for correct rejections was 2386 ms and for false alarms was 2043 ms. Analyses of response times indicated that, in the mixed trials, participants were significantly slower to correctly reject (mean RT = 2386 ms) than to correctly accept (mean RT = 1984 ms) items, $t(5) = 3.04$, $P = 0.03$; incorrect rejections (mean RT = 2268 ms) were also slower than correct acceptances in the mixed trials, $t(5) = 2.69$, $P = 0.04$.

fMRI Analyses

A large number of brain areas showed significant (K-S test, $P < 0.0001$) increases in signal intensity in the blocked recognition conditions compared to fixation. These areas overlapped considerably with those activated for the combined recognition conditions from the event-related runs. Areas showing significant activation for both true and false recognition in the blocked condition included SMA extending into anterior cingulate, motor/premotor cortex, medial and lateral parietal cortex, bilateral anterior prefrontal cortex, bilateral

activated with a relatively late delay (see Fig. 5). The graphs to the left show the predicted hemodynamic responses used as a basis for these activation maps. Importantly, when the two delays are considered, all of the areas activated by the blocked task paradigm are activated within the event-related task paradigm. These areas include: (A) SMA [9, 3, 59], (B) SMA extending into anterior cingulate [4, 11, 43 and −3, 13, 40], (C) motor/premotor cortex [37, −18, 50], (D, E, F) medial [−3, −71, 43 and −3, −74, 34] and lateral parietal cortex [−31, −55, 43 and 34, −52, 40], (G, H) bilateral anterior prefrontal cortex [− 28, 56, 12; −37, 50, 9 and 50, 41, 3], (I, J) bilateral frontal-opercular cortex [37, 22, 3; −28, 25, 3 and −40, 19, 6], (K, L) hippocampal/parahippocampal region [−15, −49, 0], (M) extrastriate and striate visual cortex [many peak coordinates]. Complete Talairach coordinate listings available on request from authors.

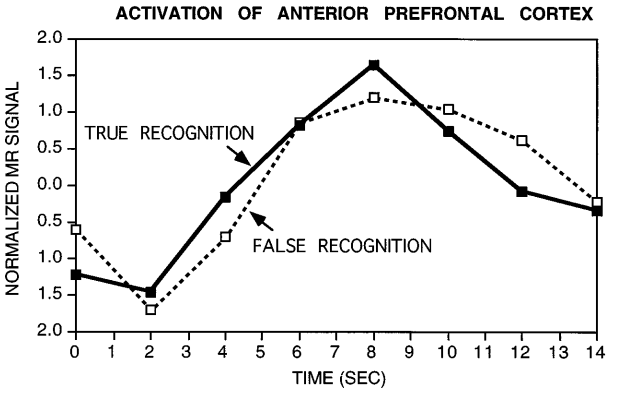

FIG. 4. Timecourse data are shown for anterior prefrontal cortex regions separately for true and false recognition conditions. These averages come from regions defined on the peak activations in the combined (true and false recognition) images. Timecourse data are normalized and shifted to account for baseline drift. True and false recognition produced nearly identical hemodynamic curves.

frontal-opercular cortex, hippocampal/parahippocampal region, and extrastriate and striate visual cortex (Fig. 2). The same areas also showed significant signal intensity increases in the event-related mixed trial condition compared to fixation (Fig. 3). In addition to the areas shown in Figs. 2 and 3, we also found significant activations in the cerebellum during both true and false recognition compared to the fixation control in both block and event-related studies. The apparent increase in statistical significance in the event-related data as compared with the blocked data is probably attributable to the greater amount of data contributing to the event-related analysis.

Further analyses of the event-related trials were conducted in which the data were separated into the different response categories noted earlier: hit, miss, false alarm, and correct rejection. In general, the same pattern of results observed in the overall analyses were found in each of the four separate analyses; however, little power existed to detect activations in the correct rejection and miss conditions owing to the high hit and false alarm rates. Examination of hits (true recognition) and false alarms (false recognition) revealed approximately equal activation in anterior prefrontal cortex in both conditions, consistent with the lack of significant differences when the two conditions were compared directly.

Separate analyses of the time course of anterior prefrontal activations for true and false recognition in the event-related trials are shown in Fig. 4. True and false recognition were characterized by nearly identical hemodynamic curves, suggesting that these regions respond similarly to both old words and related lures in the event-related procedure.

We also constructed K-S statistical activation maps that contrasted the true and false recognition conditions directly (Fig. 5). For the blocked trials, this analysis indicated that a right anterior prefrontal area appeared more activated during the false than during the true recognition. However, this change was present near the edge of the brain, where motion artifacts can occur, especially when small amounts of data are considered. Therefore, we consider this finding tentative. Nonetheless, the location of the prefrontal region that showed greater activation for false than true recognition partially overlaps with the anterior prefrontal area activated by the recognition conditions when considered separately (Figs. 2 and 3). No significant differences between true and false recognition were observed in this or other regions during the event-related trials.

Figure 3 shows the activations in the event-related trials separately for early and late hemodynamic delays. These data indicate that anterior prefrontal regions showed their most significant activations when regressed against gamma functions with a relatively late hemodynamic delay, whereas the other areas mentioned earlier showed their most significant activations for gamma functions with a relatively early hemodynamic delay. The two optimal gamma functions that showed the highest t values for these separate regions are displayed in Fig. 3. These gamma functions were 4 s offset at their peaks.

Figure 5 shows the behavior of the anterior prefrontal regions in more detail, comparing the time course of activation for anterior prefrontal, frontal opercular, and visual (i.e., occipital) regions. The regions were constrained to the same slice to avoid spurious identification of delays associated with the timing of slice acquisition. Using this procedure, the visual and opercular regions showed a peak signal increase between 4 and 6 s, whereas the anterior prefrontal regions showed an increase between 8 and 10 s. This relative delay of about 4 s occurred even though the trials were completed in about 2 s. Moreover, the length of the anterior prefrontal response was prolonged considerably relative to the posterior responses. Analysis of individual subjects showed the delay in a few instances but, by and large, the activation could not be easily identified within single subjects, probably owing to the fact that the signal is quite small.

While certain regions showing delayed onsets (such as those in mesial occipital cortex) may represent large draining vessels (e.g., see rightmost section in Fig. 3), these anterior prefrontal regions show no overlap with visualized vascular structures on our flow-sensitive images.

DISCUSSION

This study has provided evidence of anterior prefrontal activation using event-related fMRI analyses. Evi-

dence from both blocked and event-related mixed trial conditions revealed robust anterior prefrontal activity during veridical and illusory recognition, with indications in the blocked runs for greater right anterior frontal activity during illusory recognition than during veridical recognition. Our results therefore replicate and extend the results of Schacter *et al.* (1996b) with PET and Johnson *et al.* (1997) with ERPs. Behavioral data indicated that in the blocked condition, subjects made more "old" responses to true targets than to false targets, whereas there were no corresponding differences in the randomly intermixed conditions. Although this finding should be treated with caution because the intermixed condition always followed the blocked condition, it is consistent with Johnson *et al.*'s (1997) suggestion that subjects are more likely to consider specific information that differentiates true from false targets in the blocked condition than in the randomly intermixed condition. Event-related analyses of data from the mixed runs showed further that significant anterior prefrontal signal increases could be obtained both when participants responded "old" to true targets and when they responded "old" to false targets—a result only detectable within the context of mixed trial procedures. Thus, anterior prefrontal responses occurred regardless of whether participants showed veridical or illusory recognition for target items.

However, the data do not definitively support differential involvement across the retrieval conditions. In the blocked trial data, a trend was noted for greater involvement in the false recognition condition as compared to the true recognition condition but no effects were detectable in the event-related trials. It is currently difficult to draw conclusions as to whether this distinction supports the previously discussed idea that different strategies are adopted across blocked and mixed trial procedures (Johnson *et al.*, 1997) or whether a Type II error has occurred for the event-related mixed trials (note, however, that power was greater in the mixed than in the blocked trials). Thus, while our data are clear with regard to the detection of significant anterior prefrontal activation across all trial conditions, we believe the question of whether anterior prefrontal cortex is differentially involved in true and false recognition under conditions that encourage examining specific differentiating information (i.e., blocked testing) requires further study.

Perhaps the most striking result of our experiment concerns the late onset and prolonged response of the anterior prefrontal responses relative to other regions. Although it is possible that some or all of this effect may be attributable to hemodynamic factors (see Lee *et al.*, 1995, and Buckner *et al.*, 1996a for a discussion of these factors), this region does not contain large draining vessels known to lead to BOLD signal delays as visualized on our flow-sensitive images.

Several previous studies have lent support to the idea that anterior prefrontal activations, particularly in the right hemisphere, reflect activities involved in trying to retrieve or verify target items, variously characterized as establishing a retrieval "set" or "mode" (Nyberg *et al.*, 1995), engaging in retrieval effort (Schacter *et al.*, 1996a), or performing postretrieval verification or monitoring (Rugg *et al.*, 1996; Schacter *et al.*, 1996b). To the extent that our observations show that anterior prefrontal activity is maximal only after an item has been judged as old or new, they suggest that the role of anterior prefrontal regions in recognition has less to do with initiating a retrieval attempt, and more to do with either maintaining the retrieval set or carrying out postretrieval verification or monitoring processes. This possibility is consistent with work by Wilding and Rugg (1996), who have made similar suggestions based on electrophysiological recordings that showed a sustained and late developing right frontal scalp distribution during a source monitoring retrieval task. The exact task used by Wilding and Rugg (1996) differed from ours, and their effect was sustained across a briefer time interval (i.e., on the order of 2 s) than was the delayed activity reported here. Nonetheless, it is noteworthy that using a technique with considerably higher temporal resolution than fMRI, they also observed a late developing response associated with recognition and reflecting activity in prefrontal cortex.

This observation of late and sustained activation of anterior prefrontal cortex is also consistent with recent fMRI data reported by Courtney *et al.* (1997) in a study of visual working memory. They found that anterior prefrontal regions similar to those activated in our study showed sustained activity during a delay period that required active maintenance of stimulus information. When Courtney *et al.* compared the activity of the anterior prefrontal region with a more posterior frontal/opercular region, they found that the anterior frontal region showed most activity during the memory delay period and least activity during perceptual encoding of the target visual stimulus, whereas the opposite pattern was observed for the frontal/opercular region. These observations fit well with the different time courses for anterior and posterior frontal regions reported here. Although a role for hemodynamic factors unrelated to delayed neural activity cannot be ruled out, Courtney *et al.*'s (1997) findings are consistent with the possibility that the delayed anterior prefrontal activity we observed reflects memory-based monitoring of the subjects' previous recognition response.

Other possible explanations should also be considered. It is conceivable that delayed anterior prefrontal activity reflects cognitive activities that are unrelated to the preceding recognition response, or cognitive activities that are related to preparing for the upcom-

ing recognition trial. Future studies will be required to differentiate between these and other possibilities.

In addition to the anterior prefrontal activations, we also replicated and extended Schacter *et al.*'s (1996a) findings concerning areas that were active during both true and false recognition relative to a fixation control, including medial parietal, cerebellum, and visual cortex extending into parahippocampal gyrus. Bilateral frontal opercular cortex activation was observed, as in several studies of veridical retrieval (see Buckner *et al.* 1996b for discussion). Because we did not include a baseline condition involving unrelated nonstudied words, it is not possible to determine whether these regions are specifically involved in true and false recognition or whether they indicate some aspect of the visual or lexical response to tested words.

The one notable difference between our results and those of Schacter *et al.* (1996b) is that we did not observe activation of the left superior temporal lobe during veridical recognition, whereas Schacter *et al.* reported consistent increases in this region during veridical recognition relative to control conditions and to false recognition. This outcome could reflect a Type II error in the present study or a Type I error in the PET study. Alternatively, it is possible that the contrasting results reflect differences in experimental procedure (Schacter *et al.* used unrelated nonstudied control words, whereas we did not), low power in the present study to detect what may be a subtle effect, or some combination of the two. In view of Johnson *et al.*'s (1997) ERP finding that differences in brain activity during veridical and illusory recognition depend on the exact format of the test, and our own finding of trends for greater prefrontal activity in false than true recognition during blocked testing but not during event-related mixed trial testing, it appears that the relation between brain activity during true and false recognition may vary across testing formats.

Although test format effects may be observed under some conditions, it is worth emphasizing that, in general, we found the same regions to be active during blocked and event-related testing; moreover, some of the differences that were observed may be attributable to increased statistical power in the event-related condition. Our results, and recent results from other laboratories (e.g., Aguirre *et al.*, 1997), thus demonstrate that event-related fMRI procedures can be usefully applied to the analysis of episodic memory, thereby providing a basis for more flexible and informative fMRI studies of memory in the future.

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