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Functional–Anatomic Study of Episodic Retrieval Using fMRI

I. Retrieval Effort versus Retrieval Success

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A number of recent functional imaging studies have identified brain areas activated during tasks involving episodic memory retrieval. The identification of such areas provides a foundation for targeted hypotheses regarding the more specific contributions that these areas make to episodic retrieval. As a beginning effort toward such an endeavor, whole-brain functional magnetic resonance imaging (fMRI) was used to examine 14 subjects during episodic word recognition in a block-designed fMRI experiment. Study conditions were manipulated by presenting either shallow or deep encoding tasks. This manipulation yielded two recognition conditions that differed with regard to retrieval effort and retrieval success: shallow encoding yielded low levels of recognition success with high levels of retrieval effort, and deep encoding yielded high levels of recognition success with low levels of effort. Many brain areas were activated in common by these two recognition conditions compared to a low-level fixation condition, including left and right prefrontal regions often detected during PET episodic retrieval paradigms (e.g., R. L. Buckner *et al.*, 1996, *J. Neurosci.* 16, 6219–6235) thereby generalizing these findings to fMRI. Characterization of the activated regions in relation to the separate recognition conditions showed (1) bilateral anterior insular regions and a left dorsal prefrontal region were more active after shallow encoding, when retrieval demanded greatest effort, and (2) right anterior prefrontal cortex, which has been implicated in episodic retrieval, was most active during successful retrieval after deep encoding. We discuss these findings in relation to component processes involved in episodic retrieval and in the context of a companion study using event-related fMRI.

Episodic memory retrieval involves accessing previously learned information that is associated with a particular time and place (Tulving, 1983). Episodic retrieval in everyday life might involve, for example, remembering what one ate for breakfast or where one parked one's car on a particular day. In experimental settings, episodic retrieval most often takes the form of recalling or recognizing information presented during a specific study episode. A key task for cognitive neuroscientists interested in human memory has been to identify functional–anatomic correlates of episodic retrieval and to use these correlates to better understand episodic retrieval itself. The advent of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques provides a powerful means for approaching this task in normal, awake humans. PET methods have already been successfully applied during a wide range of episodic retrieval tasks and have converged on a number of findings.

The majority of data suggest that two regions are often activated during episodic retrieval: anterior prefrontal cortex (usually right > left) (Squire *et al.*, 1992; Tulving *et al.*, 1994b; Andreasen *et al.*, 1995; Buckner *et al.*, 1995a, 1996; Fletcher *et al.*, 1995; Grady *et al.*, 1995; Haxby *et al.*, 1996; Rugg *et al.*, 1996; Schacter *et al.*, 1996a; see Buckner, 1996; Fletcher *et al.*, 1997, for reviews) and posterior medial parietal cortex, near precuneus (Andreasen *et al.*, 1995; Buckner *et al.*, 1995a, 1996; Fletcher *et al.*, 1995; Petrides *et al.*, 1995; Schacter *et al.*, 1996a). The consistent observation of right prefrontal activation during episodic retrieval led Tulving and colleagues (Tulving *et al.*, 1994a; Nyberg *et al.*, 1996) to propose the hemispheric encoding/retrieval asymmetry (HERA) model, which highlights the preferential involvement of right prefrontal cortex in episodic retrieval. More recent analyses of many episodic retrieval tasks, as well as tasks outside the domain of episodic retrieval, have further suggested that the common anterior prefrontal activation is confined to a relatively small region of anterior Brodmann area 10 (Buckner, 1996) and that the domain of anterior prefrontal involvement may sometimes extend to certain semantic and working memory tasks (MacLeod *et al.*, 1998). Medial temporal lobe and diencephalic structures have also been activated by episodic retrieval

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tasks (Squire *et al.*, 1992; Schacter *et al.*, 1995, 1996a; Owen *et al.*, 1996; Fletcher *et al.*, 1997; Gabrieli *et al.*, 1997), but less consistently than the anterior prefrontal and parietal regions.

In addition to these regions, a larger set of brain regions (perhaps to be considered a brain pathway) is often activated across a wide range of high-level verbal processing tasks that include but extend beyond episodic retrieval, such as word generation and verbal working memory tasks. This pathway includes areas within left prefrontal cortex, anterior cingulate, and right lateral cerebellum (see Buckner, 1996, for discussion). Depending on the task comparisons being examined in an individual episodic retrieval study, these more general areas may either be detected or missed (Petrides *et al.*, 1995; Buckner, 1996). There has also been a recent suggestion that bilateral anterior insular cortex near frontal-operculam is activated by verbal retrieval tasks including those involving episodic retrieval (Buckner *et al.*, 1996). This combination of areas, some differentially activated during episodic retrieval and some generalizing beyond episodic retrieval, represents a starting point for further exploration into their processing functions.

To begin an exploration of processing function, we need ideas about the component processes that are involved in performance of retrieval tasks relying on episodic memory. Two readily apparent component processes are *retrieval effort* and *retrieval success*. As described by Rugg *et al.* (1996), "Retrieval effort refers to processes engaged by an attempt to retrieve information from memory in response to a retrieval cue, such as a test word in a recognition task. Retrieval success refers to processes that are selectively engaged when a retrieval attempt is successful." In any given retrieval situation both processes (assuming there are some instances of successful retrieval) play a role. This distinction parallels the concepts of *retrieval attempt* and *ecphory* as originally described by Tulving (1983) and later applied to neuroimaging studies (Kapur *et al.*, 1995). Such a processing distinction, although far from complete, captures two important components of retrieval. Moreover, it is possible to operationally define retrieval effort and retrieval success in terms of observable dependent measures. For example, retrieval effort can be measured by the time it takes to make the retrieval decision and retrieval success can be measured by how many items are correctly recognized or recalled. These processes can be varied together or independently of one another, depending on how a retrieval condition is manipulated.

Several neuroimaging studies have already begun to make distinctions along these lines, but have yielded mixed outcomes. With regard to the specific areas described above, most studies have failed to find consistent evidence of differential activation associated with retrieval effort versus retrieval success, especially for the right anterior prefrontal region that has been consistently activated by tasks involving episodic retrieval. For example, Kapur *et al.* (1995) observed right anterior prefrontal cortex activation, but did not find a difference in relation to retrieval success (retrieval effort was nominally held constant in that study). Schacter *et al.* (1996a) examined high and low recall conditions but did not detect a difference in right anterior prefrontal cortex when the two conditions were directly compared (a left prefrontal region showed activation correlated with retrieval effort). Nyberg *et al.* (1995) detected prefrontal activations extending into anterior prefrontal cortex, but did not report differential involvement of these activations in retrieval effort versus success. Taken collectively, these studies fail to consistently detect a differential role for anterior prefrontal cortex in either retrieval effort or retrieval success.

However, a recent report does suggest a role for right anterior prefrontal cortex in retrieval success. Rugg *et al.* (1996) manipulated the number of old target items that were presented across multiple PET recognition task conditions, thereby providing a gradient of retrieval success (while holding study conditions constant). Using this gradient as a factor, they found right anterior prefrontal cortex (as well as other prefrontal areas) to be activated during all retrieval conditions, but more so for the higher levels of retrieval success. A key feature of their data analysis involved a two-stage process wherein they first determined voxels that were activated by the recognition tasks, regardless of target probability and then, as a secondary analysis, interrogated those activated voxels to determine which (if any) varied along the gradient of retrieval success. Such a procedure is powerful because the potentially subtle effects of different degrees of retrieval success are examined in a hypothesis-driven manner, considering only those voxels activated by the recognition tasks. Taken in the context of the earlier null findings, it seems likely that if some areas are differentially involved with greater retrieval success (Rugg *et al.*, 1996; Schacter *et al.*, 1996a), these effects are also likely to be comparatively modest and are best examined in hypothesis-driven experiments.

In the present study we explored the relation between retrieval effort and retrieval success in the context of a focused fMRI investigation of those prefrontal areas, commonly activated by episodic retrieval paradigms—including areas specific to episodic retrieval as well as those that generalize to other verbal retrieval tasks. This focus allowed us to explore a small number of hypotheses in a priori defined regions (compared to an exploratory analysis at a voxel-by-voxel level). We used shallow and deep encoding tasks to produce recognition conditions that differed in relation to both retrieval effort and retrieval success.

MATERIALS AND METHODS

Subjects

Twenty-six right-handed subjects between the ages of 18 and 35 years volunteered and received $50 as payment for participation. Fourteen subjects participated in the main experiment involving memory recognition (8 male). Three subjects from this group were either unable to complete the study or produced data with sufficient artifacts to preclude further analysis. Thus, fMRI data from 11 subjects are reported for the main experiment. The additional 12 subjects (4 male) contributed control data (see below). Informed consent was obtained prior to scanning in a manner approved by the Human Studies Committee of the Massachusetts General Hospital.

Magnetic Resonance (MR) Procedures

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 quadrature head coil was used. Visual stimuli were presented to the subject using a PowerMacintosh (Apple Computer) connected to a Sharp 2000 color LCD projector. Images were projected onto a screen attached to the head coil through a collimating lens (Buhl Optical). Subjects viewed the screen through mirrors. Performance and reaction times were measured through a custom designed magnet compatible keypress.

Subjects 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. For each subject, conventional structural images as well as echo planar functional images were acquired over a 2-h session. Multiple experiments were performed within the session. Discussed below are only those imaging sequences relevant to this report.

High-resolution anatomic images were acquired [conventional rf-spoiled GRASS sequence (SPGR), 60 slice sagittal, 2.8 mm thickness]. B_0 magnetic field homogeneity was improved using an automated echo planar shim procedure (Reese *et al.*, 1995). Conventional flow-weighted anatomic images in plane with the functional echo planar images (16 slice, in plane resolution 0.78 mm, 7 mm thickness, skip 1 mm between slices) were then acquired as an intermediate to align the echo planar images to the SPGR images. Finally, T2*-weighted functional images were acquired using an asymmetric spin echo sequence sensitive to blood oxygenation-level-dependent (BOLD) contrast (TE, 50 ms; offset, 25 ms). Such a sequence was chosen because it is minimally sensitive to large vessel contributions (Baker *et al.*, 1993).

Functional images were acquired within runs of 118 time points, with each time point acquiring data over the entire brain including the cerebellum (16 slice, in plane resolution 3.125 mm, 7 mm thickness, skip 1 mm between slices, acquisition aligned to the plane intersecting the anterior and posterior commissures; TR, 2 s). Four discarded dummy time points were acquired prior to each run to allow T1 stabilization.

Data for each individual subject were transformed into the stereotaxic space of the Talairach and Tournoux (1988) atlas. The anterior and posterior commissures, the highest point in the midsagittal plane, and the bounding edges of the brain were manually identified in the sagittal SPGR images. These landmark points were used to linearly orient and scale the sagittal images (using trilinear interpolation; resulting matrix included 39 transverse slices of isotropic 3.125 mm voxels).

The transformation matrix of the acquired SPGR images to the atlas space was then applied to each of the images in the functional runs, similar to Schacter *et al.* (1997). Once in atlas space, data were averaged across subjects. First, the interpolated SPGR images were averaged to yield a mean anatomy image. Second, the functional runs were averaged to yield averaged runs of 118 images for each of the 39 transverse slices.

Behavioral Procedures

The goal of the behavioral procedures was to create two retrieval conditions that differed in relation to *retrieval effort* and *retrieval success.* Subjects first studied words under shallow or deep encoding conditions. Then, during test trials, they were exposed to blocks of words either exclusively from the shallow encoding condition or exclusively from the deep encoding condition. The idea behind this manipulation is that words in the shallow encoding condition would be associated with less frequent successful recognition (Low Recognition) while words in the deep encoding condition would be associated with highly successful recognition (High Recognition) (similar to Nyberg *et al.*, 1995; Schacter *et al.*, 1996a). Moreover, because items were associated with less elaborate processing in the shallow encoding condition than in the deep encoding condition, it should be more difficult to reject or accept the items in the Low Recognition condition compared to the High Recognition condition. This latter effect was measured by examining reaction times (RTs); longer RTs were predicted for the Low Recognition condition than for the High Recognition condition. In this way, retrieval effort varied inversely with retrieval success. The test trial blocks for both conditions contained only studied or “old” items; however, because subjects were not 100% accurate in their recognition decisions, from their perspective the lists appeared as different mixes of old and new items. In addition, the experimental instructions stressed the importance of responding to each word individually, so as to minimize the consequences of the blocked design for subjects' decision-making strategies or their approach to the task.

In the study phase, blocks of words were presented between 20 and 40 min prior to recognition testing, as part of a separate fMRI experiment. Words were presented centrally on the screen (one word every 2 s, stimulus duration of 1 s; words presented in 36-point Geneva font, white on black; fixation cross-hair displayed between words). One-half of the words denoted concrete entities (e.g., finger) and one-half were abstract (e.g., thought). In addition, one-half of the items (half abstract, half concrete) were presented in uppercase letters (e.g., STRING) and half were in lowercase (e.g., paper). In the shallow encoding condition, subjects decided whether words were in uppercase or lowercase. In the deep encoding condition, subjects decided whether the words were abstract or concrete. Responses were indicated by a left-hand key press. Word stimuli were provided by John Gabrieli and colleagues and were previously used by Demb *et al.* (1995). Words were counterbalanced such that words in the deep encoding condition for one subject were in the shallow encoding condition for another subject. Shallow and deep encoding conditions were presented in four blocks of 20 items, alternating back and forth between the two encoding conditions to balance order. Encoding blocks were separated by 24-s periods of fixation.

Recognition testing occurred in two separate fMRI runs. Each run contained three conditions: (i) Low Recognition, (ii) High Recognition, (iii) and Fixation, a low-level reference control task consisting of visual fixation. The Low and High Recognition conditions alternated in a fixed order, as shown in Fig. 1, to allow the runs to be averaged in a manner that allows observation of the time course of activity. Possible order effects could be assessed in the present design because it contained a complete A-B-A-B design.

For the recognition test, subjects were instructed to press one of two keys with the left (i.e., nondominant) hand to indicate whether each individual word was "old" (previously presented) or "new" (not previously presented). A left-handed keypress was used because left prefrontal activation, extending into regions near premotor cortex, is often associated with tasks in which subjects respond to or process words. By employing a left-handed keypress, activation associated with the motor response would be predominantly in right premotor and motor cortex and thus separable from left prefrontal activations attributable to the higher-order processing demands of the task. Predicted right anterior prefrontal activations are distant from right motor and premotor cortex. Words appeared in the same format as during study, one word per 2 s. Subjects were instructed to be attentive and to make a decision based on each individual word. Subjects were further instructed to fixate on the cross-hair between words.

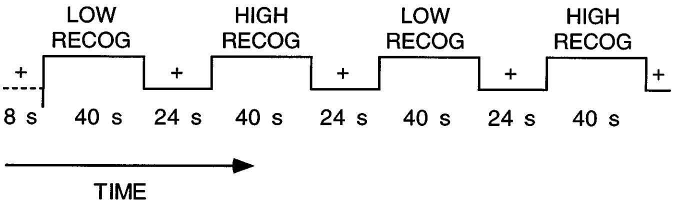

FIG. 1. A schematic illustration of the temporal organization of the task paradigm. Critical task blocks (Low Recognition and High Recognition conditions) were 40 s long separated by 24-s blocks of fixation (+). 8 s of fixation preceded the first task block where dummy timepoints were acquired (dashed line) to allow T1 stabilization.

Eight seconds prior to the first task block, while dummy images were being acquired to allow T1 stabilization (see MR Procedures), a fixation cross-hair appeared to establish a constant task baseline before data acquisition.

fMRI Data Analysis

Data exploration phase. Activation maps were constructed using the nonparametric Kolmogorov-Statistic (K-S) (Press *et al.*, 1992) to compare the combined Recognition conditions to the Fixation reference condition. Time points were shifted 4 s for this analysis to account for hemodynamic delay. This Recognition-minus-Fixation image contained all of the areas activated during the Recognition tasks, both those specific to episodic retrieval and those that were more general. A spatial smooth with a one-voxel wide Hanning filter was applied prior to activation map generation. Peak activations were identified using the Talairach and Tournoux (1988) coordinate system by selecting local statistical activation maxima that were $P < 10^{-5}$ and within clusters of five contiguous significant voxels. Using this procedure in a control data set (in which 12 subjects were instructed to simply fixate on a cross-hair across two runs) yielded no false positives. Such a test empirically establishes that, under the null hypothesis, false positives are highly unlikely and that the test is conservative in our particular implementation with averaged subject data (similar to the approach of Zarahn *et al.*, 1997). Moreover, for all regions of theoretical interest, the signal time courses were examined for task-related signal change and are presented to assure confidence in the data reported (see below).

Hypothesis testing phase. In order to examine the effect of recognition condition, three-dimensional regions were automatically defined around a subset of peak activations of theoretical interest. Peak activations were selected based on our previous report (Buckner *et al.*, 1996) to include all prefrontal areas targeted in that article and replicated in the present study (see Tables 1 and 4 and Fig. 8 in Buckner *et al.*, 1996). For this analysis, regions were defined using an automated algorithm that identified all contiguous voxels within 12 mm of the peak that reached a significance level of $P < 0.0001$. Important to this analysis, these regions were defined based on the *combined* Recognition conditions, without reference to any differences between the conditions. In this manner, these regions could provide a small number of a priori regional hypotheses to test for differences between the Low Recognition and High Recognition conditions. Considerable power was afforded by this analysis, compared to voxel-based statistical maps, because each region contained multiple voxels and only a small number of regions were tested, negating the need for a large correction for multiple comparisons. Such a method shares a number of features in common with procedures previously used for PET data analysis (e.g., Buckner *et al.*, 1995a, 1996; Fiez *et al.*, 1996; Rugg *et al.*, 1996). Finally, regions within visual cortex and posterior supplementary motor area (SMA) were also defined based on the most robust peak activations within those areas. These last two regions served as controls as these regions were not predicted to vary in relation to retrieval demands.

Direct comparison between the two Recognition conditions was accomplished by contrasting *regional* signal intensities for each time point during Low Recognition to those acquired during the High Recognition condition. Complete unsmoothed time course data for those regions that were found to vary significantly were generated by obtaining the regional signal value at each time point. A linear drift correction was applied to this time course by subtracting away the slope found when considering only those images from the Fixation reference condition (modification from Bandettini *et al.*, 1993). Statistical tests were performed using a nonparametric Mann-Whitney U test (significance $P < 0.05$ Bonferroni corrected for multiple regional comparisons).

For completeness, a K-S statistical activation map was generated that contrasted the two Recognition conditions directly. This analysis was used to support the hypothesis-directed regional analyses, rather than as a means of establishing significance. Foci of peak activation were generated to determine whether the direct comparison yielded foci consistent with those showing modulation in the hypothesis-driven regional analyses.

Behavioral Results

As predicted, subjects recognized significantly more words following deep encoding (High Recognition condition, 85.4%) than following shallow encoding (Low Recognition condition, 47.1%) ($t[13] = 9.85$, $P < 0.0001$). Also as predicted, subjects took longer to make their decisions in the low encoding (Low Recognition) condition (1005 ms) as compared to the deep encoding (High Recognition) condition (875 ms) ($t[13] = 4.94$, $P < 0.001$), indicating increased effort in the Low Recognition condition. These results are shown graphically in Fig. 2. Moreover, the reaction time difference between High and Low Recognition was not attributable to the unequal numbers of old and new responses in the two conditions, because the difference was still significant when only correctly recognized words (hits) were considered (Low Recognition, 984 ms; High Recognition, = 854 ms; $t[13] = 5.1$, $P < 0.001$).

fMRI Results

Data exploration phase. Many brain areas showed BOLD signal increases (activation) when the combined Recognition conditions were contrasted with Fixation (Fig. 3, Tables 1–3). Several of these activations were located within visual striate and extrastriate regions, as expected given the use of visual word targets. Extrastriate activation extended more anteriorally on the left consistent with previous work utilizing visual word stimuli (Petersen *et al.*, 1989; Howard *et al.*, 1992). Right lateralized motor and premotor regions were also robustly activated, presumably due to the programming and execution of the keypress response (Fig. 3, activation labeled B). Multiple regions within the supplementary motor area were activated and may reflect activation of preSMA (Table 2; −6, 9, 50, and 9, 9, 53) and separate activation within SMA proper (Table 2; 0, −3, 59) (Buckner *et al.*, 1996; Picard and Strick, 1996). If so, the anterior pre-SMA activation may reflect higher-level task demands rather than simple guidance of the motor response, as has been observed in other verbal memory retrieval studies (Buckner *et al.*, 1996). Similarly, the premotor/motor activations on the left are also possibly attributable to higher-level cognitive demands of the task or covert

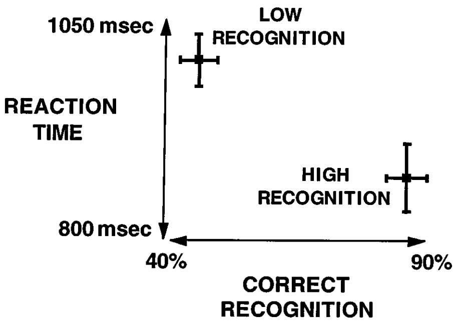

FIG. 2. Behavioral data are plotted for the Low and High Recognition conditions with Reaction Time (a measure of retrieval effort) plotted against Correct Recognition percentage (a measure of retrieval success). The two conditions vary inversely on the two dimensions. Standard error bars are included for both axes.

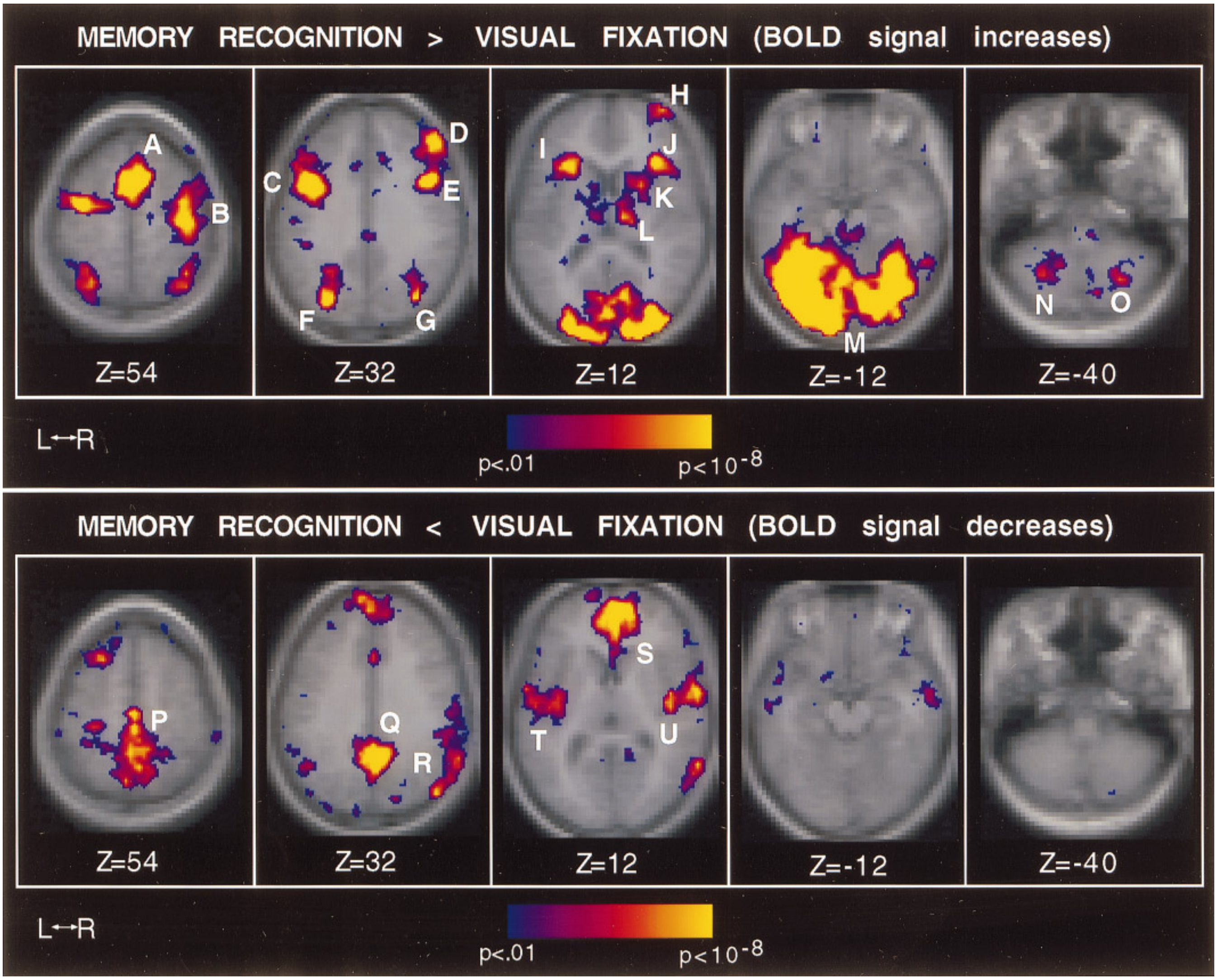

FIG. 3. BOLD signal increases (top) and BOLD signal decreases (bottom) are shown for the combined Recognition conditions versus Visual Fixation. Statistical maps (colored scale) overlay the averaged SPGR anatomic image. Many areas are activated including (A) supplementary motor area (SMA), (B) right motor/somatosensory cortex, (C) left dorsal prefrontal/motor cortex, (D and E) right dorsal prefrontal/motor cortex, (F and G) lateral parietal cortex, (H) right anterior prefrontal cortex, (I and J) bilateral anterior insular cortex near the frontal-operculam, (K) basal ganglia, (L) medial thalamus, (M) striate and extrastriate visual cortex, and (N and O) lateral cerebellum. Signal decreases include (P and Q) anterior medial parietal cortex, (R) lateral parietal cortex, (S) medial frontal cortex, and (T and U) bilateral posterior insular cortex.

articulation as the keypress response would be expected to correlate with well-lateralized activation on the right, although ipsilateral motor cortex activation cannot be explicitly ruled out.

A number of brain areas in prefrontal, parietal, and associated medial thalamic structures were activated, including bilateral anterior insular cortex near the frontal-operculam, left dorsal and dorsolateral prefrontal cortex (with homologous activation in right dorsal prefrontal cortex), and right anterior prefrontal cortex near the superior frontal sulcus. These activations were similar to activations that have been previously detected during episodic retrieval tasks. For example, Buckner *et al.* (1996) reported PET activation of bilateral frontal opercular cortex, left dorsolateral prefrontal cortex, and right anterior prefrontal cortex during a paired-associate episodic recall task. The locations of the Buckner *et al.* (1996) activations are highly similar to the peak activations identified in the present study, thus establishing generality across methodologies (PET versus fMRI). The one notable exception to these consistencies was the lack of activation in posterior medial parietal cortex, which has often been observed during episodic retrieval tasks as studied with PET (Fletcher *et al.*, 1995). As this area has been activated by a previous episodic retrieval task studied with fMRI in our laboratory (Schacter *et al.*, 1997) and during the event-related procedure reported in the companion paper, the absence is unlikely due to technical considerations. Activation was present in posterior medial parietal cortex if the significance level was dropped to $P < 0.05$ uncorrected, which is at an alpha level where false positives can be detected in our control data set and must therefore be considered equivocal. Cerebellar activation was seen in a number of locations including medial and lateral cerebellum; a complete listing of these activations is given in Table 3.

BOLD signal decreases, representing comparatively greater activation during Fixation than during Recognition, were found in several areas (Table 4). The most prominent signal decreases were along ventral medial prefrontal cortex extending dorsally along portions of the anterior cingulate and into posterior medial parietal cortex near precuneus. These medial parietal decreases were anterior (e.g., $y = -49$ to -52) to regions typically observed as increases in episodic retrieval studies. This anterior/posterior dissociation in medial parietal cortex has been observed using PET (Buckner *et al.*, 1996). Parietal regions, located considerably more laterally than the signal increases, were also observed as signal reductions, as were regions within bilateral posterior insular cortex.

TABLE 1

Identification of BOLD Signal Increases in Recognition Minus Fixation (Visual and Motor Cortex Activations)

Coordinates			Significance		
x	*y*	*z*	$-\log(P)$	Location	BA
31	−87	0	48.96	R. extrastriate cortex	18
18	−93	−3	47.73	R. extrastriate cortex	19
−12	−90	−9	46.51	L. striate cortex	17
31	−77	−3	46.51	R. extrastriate cortex	18
−28	−90	−3	45.31	L. striate/extrastriate cortex	17/18
−34	−52	−15	45.31	L. inferotemporal cortex	37
−34	−80	−3	45.31	L. extrastriate cortex	18/19
18	−80	0	45.04	R. striate/extrastriate cortex	17/18
−31	−40	−15	44.12	L. inferotemporal cortex	20
12	−93	9	43.86	R. striate cortex	17/18
15	−74	−12	43.86	R. extrastriate/cerebellum	18
−18	−83	−12	42.69	L. extrastriate/cerebellum	18
21	−96	9	39.28	R. extrastriate cortex	18
37	−65	−9	39.28	R. extrastriate cortex	18/19
37	−15	59	37.93	R. motor/sensory cortex	4/6
31	−46	−15	35.77	R. inferotemporal/cerebellum	37
−28	−96	9	34.95	L. extrastriate cortex	18
−34	−6	59	31.64	L. motor cortex	6
−28	−74	31	26.42	L. extrastriate cortex	19
0	−83	12	24.22	Striate cortex	17
34	−6	53	21.93	R. motor cortex	6
46	9	43	21.75	R. motor cortex	6/8
34	−3	62	21.65	R. motor cortex	6
9	−71	12	21.01	R. striate cortex	17/18
31	−71	28	20.11	R. extrastriate cortex	19

Note. Coordinates are listed in the Talairach and Tournoux (1988) atlas space with negative *x* on the left. Because visual and motor cortex boundaries are approximate in average subject atlas coordinates, this division should be considered tentative and only used as a heuristic. R, right; L, left. BA is the Brodmann area nearest to the coordinate in atlas space (such anatomic labeling should also be considered a rough rather than a precise estimate).

TABLE 2

Identification of BOLD Signal Increases in Recognition minus Fixation (Higher Order Activations)

Coordinates			Significance		
x	*y*	*z*	$-\log(P)$	Location	BA
−37	6	34	41.03	L. dorsal prefrontal cortex	44/9
−6	9	50	37.93	preSMA	6
0	−3	59	35.30	SMA proper	6
9	9	53	31.42	preSMA	6
40	9	31	30.98	R. dorsal prefrontal cortex	44
31	25	9	25.51	R. ant. operculam	44/45/13
12	16	46	24.81	Ant. cingulate/SMA	32/6
−31	−65	43	24.61	L. lat. parietal cortex	7
34	−65	46	24.22	R. lat. parietal cortex	7
46	34	31	24.03	R. ant. prefrontal cortex	9
−25	−55	43	22.49	L. lat. parietal cortex	7
−28	19	6	22.30	L. ant. operculam	44/45/13
25	−55	43	21.10	R. lat. parietal cortex	7
−25	−52	34	20.65	L. parietal cortex, subgyral	—
37	−55	46	20.02	R. lat. parietal cortex	7
9	−15	12	18.36	R/med. thalamus	—
37	59	12	16.53	R. ant. prefrontal cortex	10
9	−15	0	14.25	R/med. thalamus	—
−50	22	34	13.95	L. prefrontal cortex	9

Note. See legend for Table 1. Coordinates for higher order brain areas are listed. Certain areas, such as SMA, are arbitrarily assigned to one of the two tables.

Hypothesis testing phase. Three critical activations were identified for further hypothesis-directed analysis: right anterior prefrontal cortex (37, 59, 12), left

TABLE 3

Identification of BOLD Signal Increases in Recognition minus Fixation (Cerebellar Activations)

Coordinates			Significance	
x	*y*	*z*	$-\log(P)$	Location
−31	−71	−18	48.96	L. lat. cerebellum
25	−71	−12	46.51	R. lat. cerebellum
−12	−77	−15	46.51	L. cerebellum
−21	−77	−18	46.24	L. cerebellum
−6	−65	−18	33.22	Med. cerebellum
6	−71	−28	32.88	Med. cerebellum
6	−65	−12	23.16	Med. cerebellum
0	−58	−9	22.12	Med. cerebellum
0	−49	−18	19.93	Med. cerebellum

Note. See legend for Table 1. No Brodmann areas are listed. Some of the activations lie on the border between visual cortex and cerebellum and cannot be unequivocally assigned to either structure.

dorsolateral prefrontal cortex (−37, 6, 34), and bilateral anterior insular cortex (31,25, 9 and −28, 19, 6). These three activations are near areas previously identified as being activated by episodic retrieval (Buckner *et al.*, 1996), although the left dorsal activation fell slightly medial to the dorsolateral response identified in that earlier study. The other responses were within 1 cm of the peaks previously identified.

Regions defined around all three peak activations showed significant differences as a function of recognition condition, but not in the same direction (Table 5, Fig. 4). Bilateral anterior insular cortex and left dorsal prefrontal cortex showed increased activation in the Low Recognition condition where maximum effort (as measured by reaction time) was required. Right anterior prefrontal cortex, by contrast, showed the opposite pattern with greatest activation in the High Recognition condition where less effort was demanded. This latter finding is particularly relevant because the BOLD signal is not correlated with time on task (duty cycle). Subjects took less time to make the response in the High Recognition condition, yet significantly more activation was detected. Order effects were unlikely to account for the results, because the data showed clear condition-dependent changes across the A-B-A-B design (see Fig. 4, Table 5). Neither control region showed a significant effect of Recognition condition.

TABLE 4

Identification of BOLD Signal Decreases in Recognition minus Fixation

Coordinates			Significance	Location	BA
x	*y*	*z*	−log (*P*)		
6	53	12	37.69	Med. prefrontal	10
6	−49	28	34.02	Precuneus/pos. cingulate	31
3	34	15	33.67	Med. prefrontal/ant. cingulate	32/9
12	47	6	32.65	Med. prefrontal/ant. cingulate	32/10
−3	−52	46	32.20	Med. parietal/precuneus	7
0	−49	34	32.20	Med. parietal/precuneus	31/7
56	−55	18	31.86	R. Superior temporal sulcus	22
−3	−21	46	30.98	Cingulate	24
59	−9	18	29.99	R. lat. parietal	40
0	−30	46	29.67	Cingulate	31
3	44	12	29.67	Med. prefrontal/ant. cingulate	32/10
43	−71	25	28.49	R. lat. parietal	19/39
−40	−74	18	26.72	L. lat. parietal	19/39
56	−40	40	26.42	R. lat. parietal	40
−6	47	6	25.81	Med. prefrontal/ant. cingulate	32/10
−56	−27	15	24.03	L. temporal	22/42
−21	19	50	23.93	L. dorsal prefrontal	8
40	−15	3	23.83	R. pos. insular	—
−53	−12	12	22.78	L. lat. parietal	40
−37	−15	3	21.93	L. pos. insular	—
−3	−49	59	21.28	Pos. med. parietal	7
−9	59	34	20.83	Med. prefrontal	9
21	−74	43	20.29	R. parietal	7
−34	0	−3	20.20	L. pos. insular	—
−3	50	31	19.66	Med. prefrontal	9
62	−21	40	17.94	R. motor/sensory	3/4
−18	−43	62	17.02	L. lat. parietal	7
−43	−24	18	16.77	L. pos. insular	—
−53	−3	15	16.69	L. motor	4/6
59	−15	34	15.33	R. motor	4/6

Note. See legend for Table 1. All BOLD signal decreases are listed.

TABLE 5

Mean Percentage of Signal Change for Each of the Four Recognition Blocks

		Percentage of signal change				
Location	BA	Low (1)	High (1)	Low (2)	High (2)	Significance
Bilateral ant. insular	44/45	0.33	0.27	0.35	0.25	$P < 0.005$
L. dorsal prefrontal	44/9	0.41	0.28	0.41	0.36	$P < 0.001$
R. ant. prefrontal	10	0.52	0.68	0.43	0.68	$P < 0.005$
R. extrastriate	18	0.96	0.77	0.79	0.90	ns ($P > 0.5$)
SMA (SMA proper)	6	0.39	0.31	0.42	0.50	ns ($P > 0.5$)

Note. Percentage of BOLD signal change noted for each block with order of block within the run noted in parentheses (Low, Low Recognition condition; and High, High Recognition condition). Typeface in bold indicates that there was a significant difference between the two Recognition conditions (all $P < 0.05$ Bonferroni corrected for the five comparisons; uncorrected significance listed under significance). Neither control region (labeled in italics) showed a significant effect of condition.

Peak activation foci in the direct comparison between High and Low Recognition supported these findings. A more lenient criterion was adopted ($P < 0.001$ with at least five contiguous significant voxels) in order to allow all activations to be detected. This significance level yielded several false positives in the control data set and would, therefore, in the absence of the previous hypothesis-driven analysis, not be considered acceptable to rule out false positives. When considering the Low Recognition greater than High Recognition comparison, peak coordinates were identified at −34, 3, 31 in left dorsolateral prefrontal cortex; 40, 28, 15 and −40, 22, 0 in bilateral frontal opercular cortex; and 0, −9, 9 in medial thalamus. The medial thalamic activation should be considered tentative having not been targeted in the previous hypothesis-directed analysis. No other activations were significant. When considering the High Recognition greater than Low Recognition comparison, right anterior prefrontal activation was detected at 34, 59, 3 with a response on the left also present at −34, 53, 6. A number of other activations were identified (3, −87, −6; 6, 9, 6; 6, 44, −6; −15,56, 6; 6, 56, 3; 21, −77, 28; −3, 44, 0; 9, 19, 3; −9, 50, 6; 37, −52,−37; and 53, −46, −21). These latter 11 activations

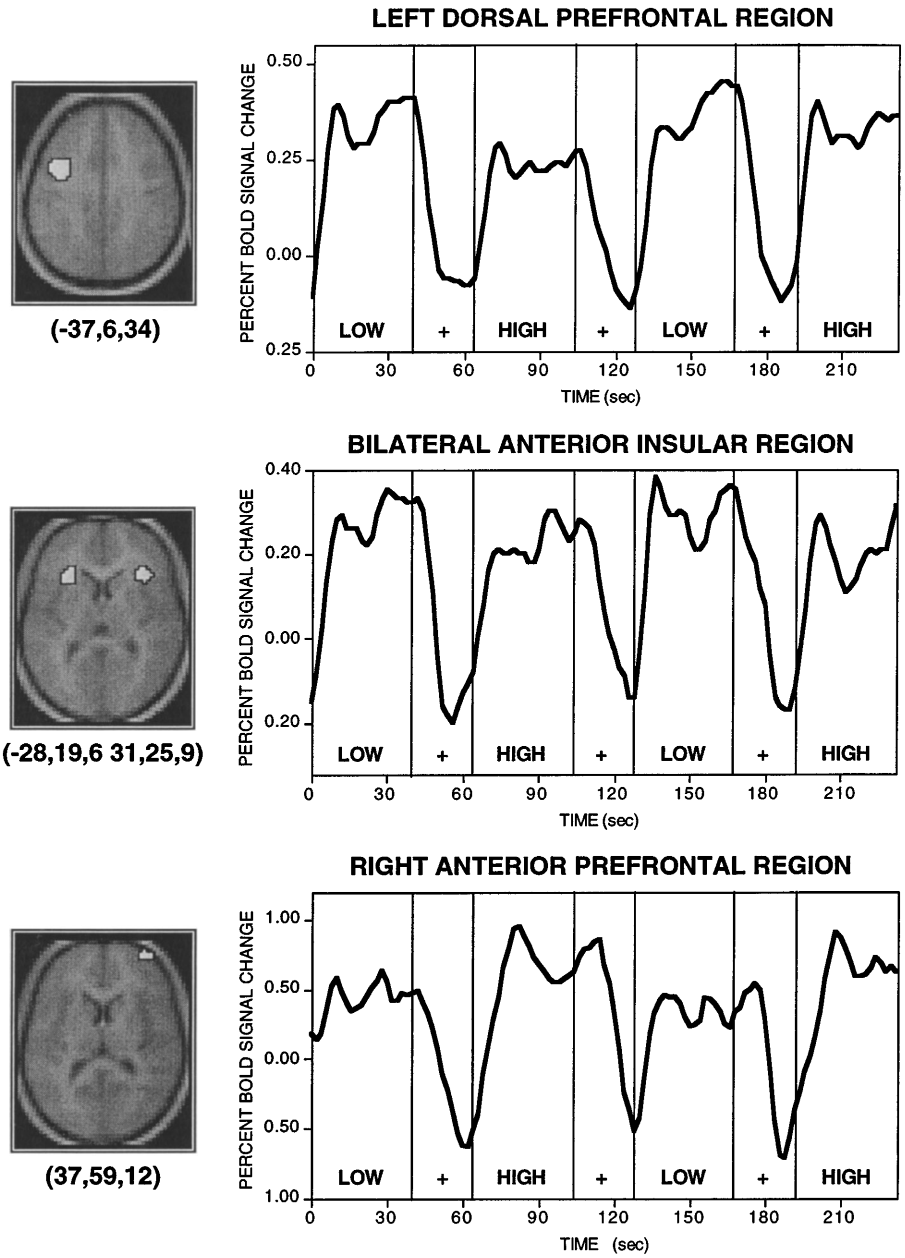

FIG. 4. The BOLD signal time course is displayed for each of the three regions found to be significantly modulated by retrieval effort or retrieval success. For each region, one slice from the region is shown superimposed on the averaged anatomic image (leftmost panels) with the peak coordinates of the region listed below [*x*, *y*, *z*, Talairach and Tournoux (1988) atlas]. BOLD signal, in all instances, is significantly increased in the Low and High Recognition condition when contrasted with fixation (+). Additionally, the left dorsal prefrontal and bilateral anterior insular regions show their greatest signal change in the Low Recognition (high effort) condition, while the right anterior prefrontal region shows the opposite pattern with greatest BOLD signal change in the High Recognition (low effort) condition.

should be considered highly tentative but are reported in order to provide a complete description of the data.

DISCUSSION

fMRI was used to investigate the functional anatomy underlying episodic memory retrieval during an old/new recognition task, where both the likelihood of successful retrieval (retrieval success) and the relative ease of retrieval (retrieval effort) were manipulated through encoding instructions. Whole brain imaging was employed and data were averaged across subjects in Talairach and Tournoux (1988) atlas space. Results indicated that a pathway of brain areas including visual, motor, bilateral frontal-opercular, left dorsolateral prefrontal, and anterior prefrontal (right > left) were activated relative to a low-level control task involving visual fixation. The data therefore demonstrate that fMRI based on BOLD contrast is capable of exploring functional anatomy related to episodic memory retrieval and, for averaged subject-group data, yields results largely consistent with PET studies (e.g., Buckner *et al.*, 1996). These consistencies extended to brain regions showing decreases in signal, where BOLD signal in the reference task condition was greater than in the recognition task condition (e.g., ventral medial prefrontal cortex and posterior medial parietal cortex), further suggesting that the entire spectrum of functional changes detected with PET techniques based on blood flow are also visible with fMRI techniques utilizing BOLD contrast.

Of more theoretical interest was the finding that certain brain regions showed differential activation across conditions that varied processing demands related to retrieval effort and retrieval success. Three prefrontal regions demonstrated such changes. On the one hand, two regions—a bilateral frontal-opercular region and a left dorsal prefrontal region—were differentially affected by retrieval effort. These regions showed significantly more activation when (as a consequence of relatively shallow encoding) retrieval demanded the most effort and was rarely successful.

On the other hand, a right anterior prefrontal region showed the opposite pattern, and was activated to a greater degree in a condition where (as a consequence of relatively deep or elaborative encoding) a large number of items were successfully retrieved. This latter effect was observed even though these recognition trials were completed comparatively more quickly than trials in the low recognition condition (i.e., less "time on task"). By demonstrating that this task manipulation modulated separate prefrontal regions in opposite directions, the fMRI data point to a clear dissociation of their functional roles, with an anterior prefrontal region differentiating itself from more posterior prefrontal regions consistent with previous ideas about specificity within human prefrontal cortex (Petrides *et al.*, 1993, 1995; Buckner *et al.*, 1995b).

A caveat in interpreting these findings from a functional perspective is that retrieval effort and success were not manipulated independently. It is possible that either the lower effort or the failure to successfully recognize items were factors in modulating the bilateral frontal-opercular and left dorsal regions. Similarly, either the high rate of recognition success or the relative ease of retrieval may have been factors contributing to the modulation of the right anterior prefrontal region. Furthermore, the encoding manipulation used to yield the varied retrieval conditions may have influenced the content and/or strength of the information being retrieved. These factors are further addressed in our companion paper (Buckner *et al.*, submitted for publication).

The finding that activation levels in bilateral frontal-opercular and left dorsal prefrontal cortex increase with retrieval effort (and/or low success) is consistent with observations from recent studies of repetition priming. Several studies have demonstrated that left prefrontal regions that were activated by a semantic retrieval task were less active when the items were repeated than during naive task performance; repeated retrieval was also associated with facilitated performance in the form of faster response times (Raichle *et al.*, 1994; Demb *et al.*, 1995; Buckner *et al.*, 1997; Wagner *et al.*, 1997). The simplest interpretation of these finding is that these regions are sensitive to the amount of effort or time on task with regard to elaborative processing and semantic retrieval of verbal information. In addition, studies of verbal working memory have shown that similar left prefrontal regions track memory load (Braver *et al.*, 1997; Cohen *et al.*, 1997). Our task, while not formally a semantic retrieval or working memory task, activated left prefrontal regions that overlapped with those seen in studies of semantic retrieval and working memory [consistent with many other episodic retrieval tasks (Buckner, 1996)]. These regions, observed here in the context of episodic retrieval, appear to be generally sensitive to overall task effort. Thus, we propose that the past priming results and the present results on episodic retrieval effort may be directly linked: Priming-related activation reductions may result because of the reduced time on task associated with the facilitatory nature of item repetition, while the effort-related modulation observed here may reflect the reduced time on task achieved due to the presence of deep encoding at the time of study.

Our observations are similar to a previous finding reported by Schacter *et al.* (1996a) using a stem-cued recall task. They reported that regions of left dorsolateral prefrontal cortex (areas 10/46) showed significant blood flow increases in a low recall condition that followed shallow encoding compared to a high recall condition that followed deep encoding, for both young adults (Schacter *et al.*, 1996a) and elderly adults (Schacter *et al.*, 1996c), although their activation was anterior to the present location and quite possibly not in a region homologous to the present finding.

Right anterior prefrontal cortex, by contrast, demonstrated the opposite pattern of increased activation in the high retrieval success condition where effort was minimal. The peak coordinate of this anterior prefrontal region was located at $x = 37$, $y = 59$, $z = 12$ in Talairach atlas space (centered at or near Brodmann area 10 in superior frontal sulcus). This region is quite close to a location commonly activated by episodic retrieval tasks (Buckner and Petersen, 1996). This region is also near the location of one area showing success-related modulation in the study by Rugg and colleagues (1996) and an area identified by Tulving *et al.* (1994b). Tulving *et al.* showed activation of this area when they contrasted episodic recognition of sentences in blocks containing many old sentences (high success) versus blocks with few old sentences (low success). The simplest explanation for this collective set of findings is that the region is sensitive to factors correlated with retrieval success.

However, it is not possible to draw this conclusion definitively. An alternative possibility is that task blocks that have many successful events tend to engender subject-initiated task strategies that activate anterior prefrontal cortex—regardless of experimental instructions that attempt to minimize these effects (Wagner *et al.*, 1996). The present study and the previous studies of Rugg and Tulving and their colleagues manipulated retrieval success in blocks of trials where many trials of one kind are presented in succession (or in clusters). Thus, two potential sources of anterior prefrontal modulation are confounded. Prefrontal activation might be attributable to the greater proportion of successful events, as implied by the retrieval success hypothesis, or alternatively (or in addition) it may be attributable to subject-initiated strategies that might differ during blocks of many successful trials. In other words, the probability of a certain event type occurring in a block may alter the task context (between-trial contingencies) and hence how the subjects perform the task. Such processes could involve postretrieval monitoring or evaluation that might sometimes occur after episodic retrieval but not obligatorily or always to the same level (cf., Rugg *et al.*, 1996; Schacter *et al.*, 1996b, 1997).

Two sources of data suggest that such a possibility has merit. First, while modulation related to retrieval success has been observed, a substantial proportion of anterior prefrontal activation can be accounted for by processes related to episodic retrieval mode, regardless of successful target probability (Kapur *et al.*, 1995; Rugg *et al.*, 1996). This pattern is evidenced in our current data in that both Recognition conditions activate anterior prefrontal cortex when it is contrasted with fixation. To account for the activation, an explanation that allows for modulation by retrieval success as well as activation during unsuccessful retrieval events is required. Second, several studies where retrieval success has been modulated have not observed anterior prefrontal changes consistent with those reported here. Most notable among these is the study by Schacter *et al.* (1996a) where subjects recalled words after extensive study, yielding high recall (four times through deep encoding study), versus after minimal study, yielding low recall (one time through shallow encoding study). It might be the case that, under certain conditions involving retrieval success, modulation of anterior prefrontal cortex is minimal because subjects' perception of the high likelihood of target items (perceived target probability) begins to discourage retrieval monitoring and/or evaluation. A context account can accommodate these findings while an account based purely on item-specific processes related to retrieval success cannot.

These considerations suggest that, to further test the retrieval success hypothesis, it will be necessary to create retrieval situations where context effects are minimal and unsuccessful versus successful trials can nonetheless be interrogated separately. Under such circumstances, the retrieval success hypothesis can be tested directly. The companion paper of Buckner *et al.* (1998) conducts such a test using recently developed event-related fMRI procedures where intermixed trial types can be presented and interrogated *post hoc* based on successful or unsuccessful retrieval of individual items.

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