NeuroImage **13,** 129–142 (2001)
doi:10.1006/nimg.2000.0664, available online at http://www.idealibrary.com on IDEAL®

Dissociating State and Item Components of Recognition Memory Using fMRI

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Received May 8, 2000; published online November 27, 2000

Cognitive functions such as memory retrieval involve a combination of state- and item-related processes. State-related processes are sustained throughout a task (e.g., "retrieval mode" associated with ongoing goals), whereas item-related processes are transient and allied to individual stimuli (e.g., "retrieval success" associated with the recovery of information from memory). The present study employed a mixed "blocked and event-related" experimental design to identify neural mechanisms that support state- and item-related processes during a recognition memory task. Subjects alternated between blocks of fixation and recognition memory (discriminating between old and new words). Critically, event-related procedures were embedded within the recognition blocks, including the jittering of sequential trials. This design ensures that the temporal profiles of state- and item-related activity differ and consequently renders them separable; without this procedure item-related activity would summate to produce a state-like response. Results suggest three classes of brain region support recognition memory, exhibiting: (1) predominantly transient activity (including regions in medial parietal, lateral parietal, and anterior left frontal cortex) reflecting item-related processing associated with "retrieval success," (2) predominantly sustained activity (including decreased activity in bilateral parahippocampal cortex) reflecting state-related processing associated with "retrieval mode," (3) concurrent sustained and transient activity (including regions in left middle frontal gyrus, bilateral frontal operculum, and medial frontal gyrus), reflecting a combination of state- and item-related processing. The present findings support the idea that recognition memory tasks are dependent upon a combination of state- and item-related processes that have dissociable neural correlates identifiable using fMRI. Moreover, the mixed "blocked and event-related" design employed here provides a general procedure for separating state- and item-related processes.

INTRODUCTION

Studies of episodic memory retrieval examine how events from the past can be remembered in the present. Recognition memory is one of the simplest tasks that taps episodic retrieval, whereby subjects discriminate between old and new stimuli. Task analyses and theoretical models suggest recognition memory likely engages multiple component processes (cf. Tulving, 1983; Rugg and Wilding, 2000; Johnson, 1992; Koriat and Goldsmith, 1996; Moscovitch, 2000; Kelley and Jacoby, 2000; Schacter *et al.*, 2000). In particular, a distinction can be drawn between two general types of process. Namely, state-related processes associated with ongoing task demands (e.g., retrieval mode) and item-related processes associated with individual trial events (e.g., retrieval success). These processes likely differ in their neural bases. Namely, the timecourse of changes in neural activity associated with state- and item-related processes should be sustained and transient, respectively (cf. Duzel *et al.*, 1999; Chawla *et al.*, 1998; Cabeza, 2000; LePage *et al.*, 2000; Rugg and Wilding, 2000; Donaldson and Buckner, in press).

To date, state- and item-related processes have been difficult to dissociate using neuroimaging techniques. Blocked procedures potentially confound these processes because neural activity is averaged over a series of trials (providing a time integrated measure of all on-going activity), whereas event-related procedures examine item-related activity in isolation. Nonetheless, the findings from neuroimaging studies of recognition memory have been interpreted in terms of one or other of these processes (for reviews see Fletcher *et al.*, 1997; Buckner and Koutstaal, 1998; Nolde *et al.*, 1998; Nyberg, 1998; Rugg and Wilding, 2000). For example, activity in prefrontal cortex has variously been taken to reflect "retrieval mode" processes associated with ongoing goals (cf. Kapur *et al.*, 1995; Nyberg *et al.*, 1995; LePage *et al.*, 2000) and "retrieval success" pro-

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1053-8119/01 $35.00

cesses associated with the recovery of information from memory (cf. Rugg *et al.*, 1996; Buckner *et al.*, 1998a; Henson *et al.*, 1999; but see Schacter *et al.*, 1997; Buckner *et al.*, 1998b; Wagner *et al.*, 1998).

To examine state- and item-related processes, and to distinguish their relative roles in supporting task performance, the measured neural response must be analyzed in a manner that can separate the independent contribution of sustained and transient signal changes. Previous studies have investigated different components of the neural response to individual trial events (cf. Courtney *et al.*, 1997; Cohen *et al.*, 1997; Shulman *et al.*, 1999, in relation to working memory). The present study examines the different components of the neural response across multiple trials, analysing activity across on-going task blocks rather than focusing in upon the sub-components associated with individual trials (cf. Fernandez *et al.*, 1999, in relation to encoding processes, Chawla *et al.*, 1999, in relation to attention, and Duzel *et al.*, 1999, for related work using event-related potentials).

In this investigation of the role of state- and item-related processes during recognition memory we combine features of event-related and blocked procedures in a mixed paradigm design (cf. Donaldson and Buckner, in press). Within recognition blocks an event-related randomized trial design was employed using variable gaps between trials (jitter), and these recognition blocks were embedded within extended fixation blocks (cf. Fig. 1). The logic behind this design is that state-related activity should remain constant throughout the recognition blocks, even during the gaps between trials, whereas item-related activity should decline during these gaps. This pattern of signal change provides leverage that allows transient and sustained components of the measured hemodynamic response to be separated. Using this novel approach we demonstrate specific functional-anatomic correlates of state- and item-related processes during recognition memory.

METHOD

Subjects and Materials

Nine subjects (6 male; mean age 21, range 18–28 years; right-handed, native English speakers, with normal vision) from the Washington University community participated for a $75 payment. Subjects were screened using a questionnaire to ensure that they had no history of neurological problems or drug abuse. Informed consent was obtained in accordance with the guidelines and approval of the Washington University Human Studies Committee. Behavioral stimuli consisted of 112 nouns and verbs (range 4–8 letters long; mean frequency 19.1 per million, range 10–30 per million) randomly selected from Francis and Kucera (1993). Mapping of stimuli to item type (old and new) was counterbalanced across subjects. Stimuli were presented in central vision, in white capital letters, on a black background and subtended approximately 0.5 degrees of visual angle per letter.

Data Acquisition

MRI data were acquired using a Siemens 1.5 Tesla Vision System (Erlangen, Germany) with a standard circularity-polarized head coil. Pillows and thermoplastic facemasks minimized head movement. Headphones dampened scanner noise and enabled communication. A power Macintosh computer (Apple, Cupertino, CA) and Psyscope software (Cohen *et al.*, 1993) controlled stimulus display and recorded responses from a fiber-optic key-press device. An LCD projector (AmPro model LCD-150) projected stimuli onto a screen at the head of the bore, viewable via a mirror attached to the coil.

Structural images were acquired first, using a sagittal MP-RAGE three-dimensional T1-weighted sequence (repetition time [TR] = 9.7 ms, echo time [ET] = 4 ms, flip angle $a = 12°$, inversion time [TI] = 300 ms, voxel size = $1 \times 1 \times 1.25$ mm voxels). Functional images were acquired using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygen-ation level-dependent (BOLD) contrast ($T2*$) (TR = 2.5 s, $T2*$ evolution time = 50 ms, flip angle = 90°, voxel size = 3.75×3.75 mm in-plane resolution). Subjects performed two functional runs (following performance of an additional experiment, reported separately) during which 128 sets of 16 contiguous 8-mm-thick axial images were acquired parallel to the anterior posterior commissure plane.

Behavioral Paradigm

Subjects performed a recognition memory task during the functional runs, requiring discrimination between old (studied) and new (unstudied) words. Each old stimulus was previously studied as a member of a word-pair; subjects were instructed to generate a sentence containing each pair. The word-pairs were also shown a second time, in a recognition task to be reported separately, over a 30- to 45-min period prior to the present experiment. The recognition test was then performed, whereby subjects were required to respond as quickly and accurately as possible, using the first (old) and second (new) fingers of the *left hand*.

Each functional run lasted approximately 5.3 min (128 acquisitions, 1 acquisition every 2.5 s), separated by a 3-min break. As Fig. 1 shows, during each run subjects alternated between blocked periods of memory and blocked periods of fixation. Each block period began with a visual prompt (2.5-s duration), reminding subjects to either “fixate” or “remember.” Each fixation block lasted 30 s, during which a fixation cross-hair was continuously displayed. Each memory block lasted

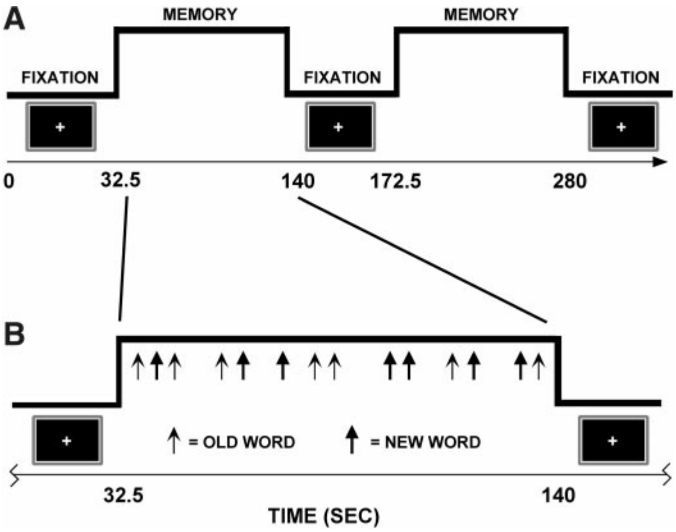

FIG. 1. The mixed "blocked and event-related" experimental design used during a single fMRI run. Top: Each functional run was blocked, such that subjects alternated between fixating on a cross-hair, and performing the recognition memory task. Bottom: Within each memory block subjects' were presented with temporally jittered test items.

for 105 s during which stimuli were presented (14 old word trials, 14 new word trials, 14 fixation trials). Test items presented during the recognition task were jittered by interspersing gaps (i.e., fixation trials) throughout the memory blocks. The presentation of test items was time-locked to the onset of successive whole brain image acquisitions. Trial order within each memory block was pseudorandomized so that each type of event (presentation of old, new and fixation trials) was equally likely to follow each other, using procedures described in Buckner *et al.* (1998c) and Miezin *et al.* (2000).

Data Analysis

Data from each subject was preprocessed to remove noise and artifacts, including: (a) correction for movement within and across runs using a rigid-body rotation and translation algorithm (cf. Friston *et al.*, 1994; Snyder, 1996), (b) whole brain normalization to a common mode of 1000 to allow for comparisons across subjects (cf. Ojemann *et al.*, 1997), and (c) temporal realignment (using sinc interpolation) of all slices to the midpoint of the first slice, accounting for differences in the acquisition time of each individual slice. Data were then resampled into 3-mm isotropic voxels, warped into standardized atlas space (cf. Talairach and Tournoux, 1998), and smoothed with a gaussian filter (6 mm FWHM).

Preprocessed data was analyzed using the General Linear Model (GLM; Friston *et al.*, 1994; Worsley and Friston, 1995; Josephs *et al.*, 1997; Zarahn *et al.*, 1997; Miezin *et al.*, 2000) on a voxel-by-voxel basis. Estimates of the magnitude of effects were derived from the model. Transient effects (i.e., responses to hits, misses, correct rejections and false alarms) were accounted for by coding the seven timepoints (i.e., image acquisitions) immediately following each stimulus onset. The sustained effect was also coded into the GLM. This can be done either by coding the sustained effect during the same intervals as the transient effects or by coding the sustained effect during the extended fixation block periods. The second approach was used here, with the sustained effect modeled as a boxcar function lasting the duration of the fixation blocks, delayed by 5 s to account for the hemodynamic rise time (cf. Blamire *et al.*, 1992; Kwong *et al.*, 1992). Factors were also coded to account for the visual prompts at the beginning of each block and the within-run linear trend (linear drift and a constant term).

Z statistical maps were derived from the GLM, averaged across subjects, and multiplied by the square root of the number of subjects. For the transient effects, model estimates were cross-correlated with a series of 5 lagged hemodynamic response functions (each separated by 1 s; cf. Boynton *et al.*, 1996; Dale and Buckner, 1997), accounting for possible variation in the onset of the hemodynamic response (cf. Schacter *et al.*, 1997; Buckner *et al.*, 1998b). All effects are described in terms of percent signal change, defined as signal magnitude divided by the mean signal intensity across all functional runs after the components of linear drift and effects of interest are removed. This mean is given by the average over all runs of the constant term of the linear trend. A statistical threshold of $P < 0.0001$ (within clusters of at least 10 voxels) was set to protect against the possibility of false positives.

Three specific contrasts were formed for focused analysis. First, a "transient effect," revealing regions transiently active in response to all test items (i.e., hits, misses, correct rejections and false alarms, relative to baseline). Second, a "retrieval success effect," directly comparing the transient responses for hits to those for correct rejections, revealing regions that are differentially activated according to whether information was successfully retrieved from memory. Third, a "sustained effect," contrasting the memory task periods and the extended fixation block periods. This effect highlights regions that are differentially active in a continuous (sustained) manner while performing the memory task relative to the low-level baseline of fixating.

Regions of interest were defined separately for each contrast. A peak-search algorithm identified the location (in atlas coordinates) of peak activation points. Peaks had to be: (a) more significant than $P < 0.0001$, (b) within a cluster of at least 10 significant voxels, and (c) separated from other peaks by at least 12 mm. Peak locations were used with a second algorithm to define

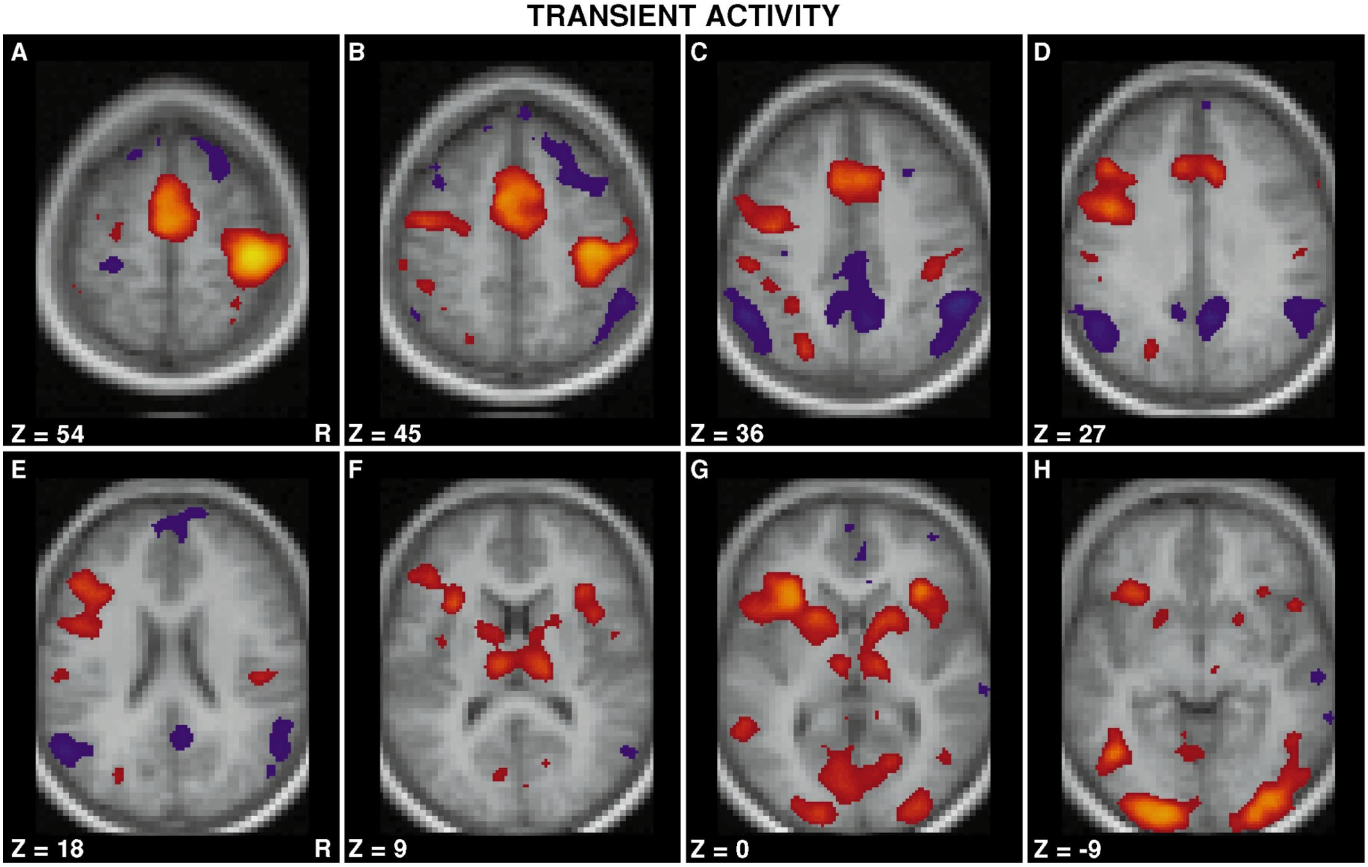

FIG. 2. Transient effects. Statistical activation maps showing significant transient activity, superimposed onto the average structural brain images. Regions showing increased activity relative to baseline are shown in red, regions showing decreased activity in blue. Significant activation peaks are listed in Tables 1 and 2.

regions of active voxels. To be included in a region, voxels had to be more significant than $P < 0.0001$ and within 12 mm of the seed location. For regions exhibiting significant retrieval success effects the hemodynamic response profile was examined by extracting the mean magnitude (percent signal change, defined above) at each of seven poststimulus timepoints. Finally, the timecourse of the hemodynamic response for the sustained effect was extracted over the course of the entire functional run. Estimates of the magnitude of the response were extracted at each timepoint, averaged over the two runs, averaged across subjects and temporally smoothed with a five-point Hanning filter.

RESULTS

Behavioral

All nine subjects showed highly accurate performance, responding on 98% of recognition trials, with a mean hit rate of 85% and false alarm rate of 13%. Reaction time data revealed that responses to hits were significantly faster than those to correct rejections (1008 and 1183 ms, respectively; $t\,[8] = 6.51$, $P < 0.001$).

fMRI: Transient Activation

Figure 2 shows the transient activation maps (all recognition trials relative to baseline). A network of areas commonly activated by visually cued recognition memory was observed, including visual, frontal, and parietal regions. The location of activated regions, identified by peaks, are listed in Tables 1 and 2 (positive and negative differences are listed). As is clear from the tables, many regions revealed significant increased activity in response to the test items relative to baseline, although some regions exhibited decreased activity.

A number of regions in the prefrontal cortex showed increased activity, including bilateral regions in inferior frontal gyrus, frontal operculum, medial frontal gyrus (at or near pre-SMA), and left middle frontal gyrus. Increases in activation were also found in the parietal and temporal lobes, along with regions in left and right cerebellum (both medially and laterally) and

TABLE 1

Frontal, Temporal, Parietal, and Occipital Regions Showing Significant Transient Activity

Significant transient activity											
Increases relative to baseline						Decreases relative to baseline					
X	*Y*	*Z*	*Z* value	BA	Region	*X*	*Y*	*Z*	*Z* value	BA	Region
−43	3	27	9.05	6/44	L inferior frontal gyrus	−40	15	48	4.65	6	L middle frontal gyrus
−49	12	3	6.47	45/47	L inferior frontal gyrus	−19	30	54	4.40	8	L superior frontal gyrus
37	9	9	6.45	44/45	R inferior frontal gyrus	25	18	48	5.94	8	R superior frontal gyrus
−43	24	27	8.74	9	L middle frontal gyrus	19	33	51	5.52	8	R superior frontal gyrus
−31	21	3	10.76	44/45/47	L frontal operculum	1	57	21	5.03	9/10	Medial frontal gyrus
31	21	3	9.07	44/45/47	R frontal operculum						
−7	6	51	11.49	6	Medial frontal gyrus						
7	9	48	8.46	6	Medial frontal gyrus						
−55	−48	3	6.23	21	L middle temporal gyrus	−52	−63	24	6.89	33	L middle temporal gyrus
46	−66	0	4.97	19/37	R inferior temporal gyrus	55	−63	18	6.02	39	R middle temporal gyrus
46	15	−6	5.53	38	R superior temporal gyrus	58	−24	−3	5.54	21	R middle temporal gyrus
						46	−75	21	4.65	19	R middle temporal gyrus
−25	−72	39	6.72	19	L inferior parietal lobe	52	−45	42	7.54	40	R inferior parietal lobe
−43	−36	45	5.61	40	L inferior parietal lobe	40	−69	42	6.22	19/40	R inferior parietal lobe
−31	−48	39	5.31	40	L inferior parietal lobe	55	−51	24	5.53	39/40	R inferior parietal lobe
16	−69	6	6.33	31	R cuneus	−10	−54	36	5.10	7/31	L precuneus
						7	−54	33	7.09	7	Precuneus
						13	63	24	4.84	31	R precuneus
−40	−63	−9	9.90	19/37	L middle occipital gyrus						
−28	−75	21	4.98	19	L middle occipital gyrus						
34	−87	−6	9.92	18	R inferior occipital gyrus						

Note. Talairach coordinates (*X*, *Y*, *Z*), significance (*Z* value), and approximate Brodmann Area (BA) based on peak locations in the Talairach and Tournoux (1988) atlas. L, Left; R, Right.

several subcortical regions including thalamus (bilaterally). These regions are similar to those that have been observed in previous studies employing episodic retrieval (cf. Squire *et al.*, 1992; Andreasen *et al.*, 1996; Buckner *et al.*, 1996, 1998a,b; Wagner *et al.*, 1998; Fletcher *et al.*, 1998; Nyberg, 1998).

fMRI: Retrieval Success Effects

Figure 3 shows activation maps for the retrieval success contrast. Analysis revealed that medial parietal, lateral parietal, and anterior left frontal cortex were more active for hits than correct rejections. The locations of peak activations are identified in Fig. 3. As is clear from a comparison of Figs. 2 and 3, many fewer regions revealed significant retrieval success effects than show significant transient activity per se, suggesting anatomic specificity, although differential power may also a contributing factor.

Areas showing greater activity for hits than correct rejections include left and right regions of lateral parietal cortex and medial parietal cortex (precuneus). Two areas in the left middle frontal gyrus (dorsal prefrontal cortex and anterior prefrontal cortex) also show greater activity for hit than correct rejection responses. Only one region revealed significantly greater activity for correct rejections than hits, right precentral gyrus (at or near motor cortex). This difference possibly reflects the response time differences noted in the Behavioral Results.

The time courses for each region are shown in Fig. 3 (identified in the activation map), revealing clear variation in the temporal profile of activity. For example, in left parietal cortex, the retrieval success difference apparently reflects a robust positive response to hits, in association with relatively little response to correct rejections (3 and 4 in Fig. 3). By contrast, in right parietal cortex the difference appears to reflect a robust decrease in activity to correct rejections, in the absence of a strong response to hits (5 and 6 in Fig. 3).

fMRI: Sustained Activation

Figure 4 shows activation maps generated for the sustained effect (shown for the same slices as the transient effects in Fig. 2) revealing a network of regions that exhibit a significant sustained signal change during the memory task period relative to the extended fixation periods. It is important to note that this sustained signal is independent from (and additional to) the transient modulation described above. Locations of peak activations are listed in Table 3. As can be seen in Fig. 4, regions were found to exhibit significant sustained modulations that reflect either increased or decreased activity.

TABLE 2

Additional Regions Showing Significant Transient Activity

Additional regions showing significant transient activity											
Increases relative to baseline						Decreases relative to baseline					
X	*Y*	*Z*	*Z* value	BA	Region	*X*	*Y*	*Z*	*Z* value	BA	Region
−40	−6	42	8.16	6	L precentral gyrus	−31	−27	57	5.88	4	L precentral gyrus
37	−24	57	16.56	3/4	R pre/postcentral gyrus						
−52	−27	39	5.80	2/40	L postcentral gyrus						
−55	−21	27	5.06	2	L postcentral gyrus						
43	−24	24	6.53	40	R postcentral gyrus						
1	18	42	8.83	32	Anterior cingulate gyrus	1	−33	39	5.29	31	Posterior cingulate gyrus
−28	−51	−24	9.78		L cerebellum						
31	−54	−21	8.19		R cerebellum						
−40	−66	−21	8.67		L lateral cerebellum						
−34	−81	−18	7.35		L lateral cerebellum						
37	−72	−18	7.52		R lateral cerebellum						
−4	−69	−18	6.21		Medial cerebellum						
−4	−57	−15	6.17		Medial cerebellum						
10	−75	−24	6.22		R medial cerebellum						
−7	−78	3	6.10	18	L lingual gyrus						
−16	−96	−9	12.07	17	L lingual gyrus						
−19	9	3	7.62		L putamen						
13	6	3	7.03		R caudate/putamen						
−10	−18	9	8.03		L thalamus						
10	−18	9	8.22		R thalamus						

Note. Talairach coordinates (*X*, *Y*, *Z*), significance (*Z* value), and approximate Brodmann Area (BA) based on peak locations in the Talairach and Tournoux (1988) atlas. L, Left; R, Right.

One feature of the results is intriguing; all of the regions showing significant increases in sustained activity during the memory task period are located in frontal cortex. This includes left inferior and middle frontal gyrus, left medial frontal gyrus, and bilateral frontal operculum. A number of regions showed the opposite pattern (i.e., decreased activity during the memory task). However, these regions were not limited to frontal cortex, including temporal and occipital cortex, cingulate gyrus, and parahippocampus. Left middle frontal gyrus and right superior frontal gyrus also exhibited a *decrease* in activity during the memory task.

"Transient and Sustained" versus "Transient or Sustained" Activity

To characterize the complex behavior revealed here, activity is shown for three regions, illustrating: (1) concurrent transient and sustained activity, (2) relatively isolated transient activity, and (3) relatively isolated sustained activity. In each case a figure is provided, including activation maps that show: (a) the region of interest, (b) the transient effect, (c) the sustained effect, and (d) the retrieval success effect. For each region two timecourses are provided; the transient hemodynamic response to hits and correct rejections, and the sustained response over the entire run (including the mean activity level during each block). All timecourse information is expressed as percent change from baseline.

Figure 5 illustrates activity in bilateral frontal operculum regions, revealing a sustained increase in activity during the task period, along with additional transient activation in response to individual test items. This pattern of behavior provides strong evidence that, at least under the conditions tested here, regions in the anterior frontal operculum are activated by the requirement to perform the recognition task and further modulated in response to individual test items.

Figure 6 reveals a quite different pattern of activity within the left inferior parietal lobe; namely, significant transient activity in response to the individual test items in the absence of a significant sustained signal change. These regions in inferior parietal cortex are not significantly activated by the general requirement to perform the memory task, however, they are strongly activated by the individual items presented during the recognition test.

Figure 7 illustrates the most unexpected finding; namely that bilateral regions within parahippocampal cortex exhibit an exclusively sustained decrease in activity during the memory task relative to the fixation periods—a pure state effect. In contrast to regions in frontal cortex that exhibit both sustained activation

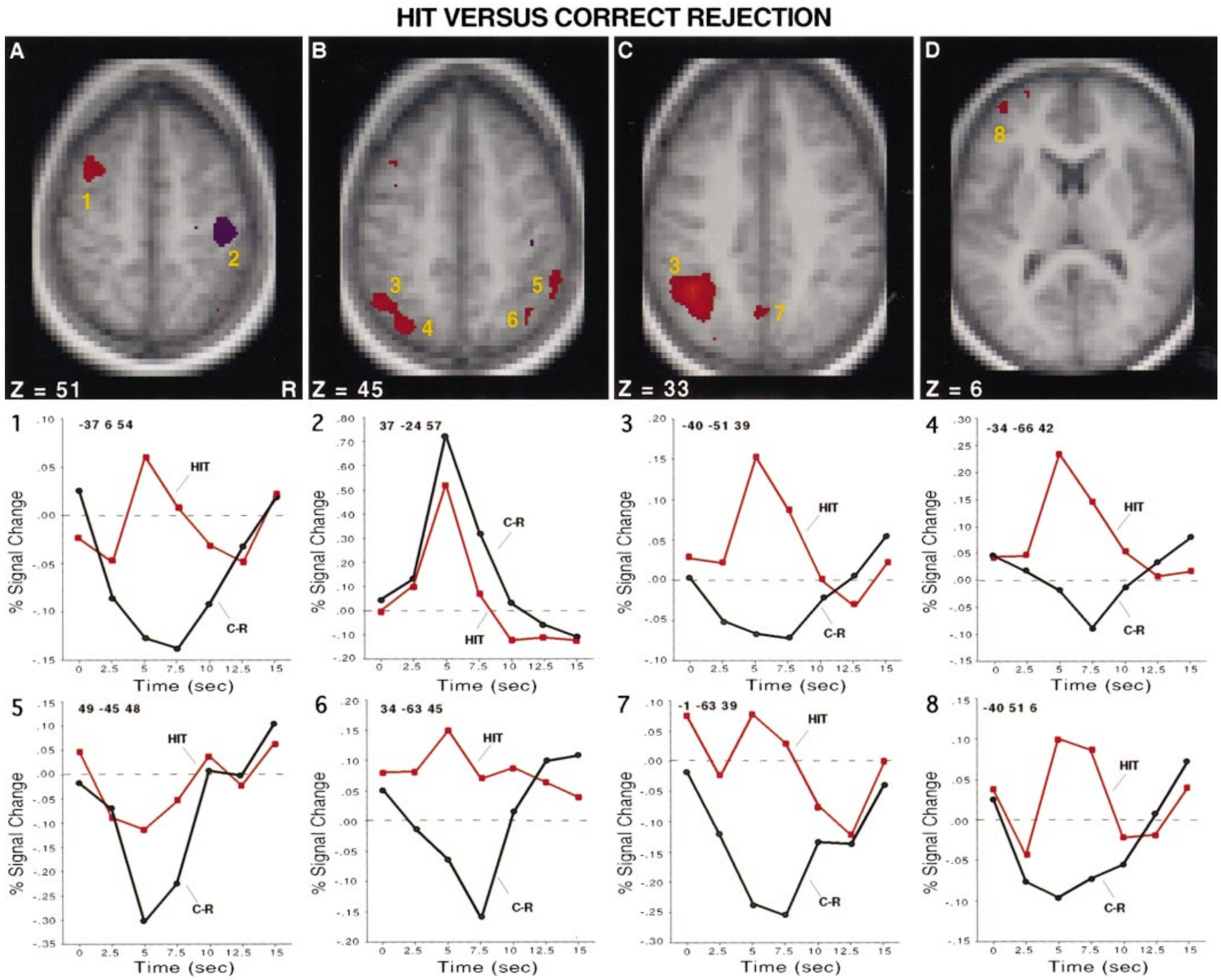

FIG. 3. Retrieval success effects. Top: Statistical activation maps showing significant differences in transient activity between correctly recognized old items (hits) and correctly rejected new items (correct rejections, C-R), superimposed onto the average structural brain images. Regions showing increased activity for hits relative to correct rejections are shown in red. Regions showing increased activity for correct rejections relative to hits are shown in blue. Regions corresponding to significant activation peaks are numbered in yellow; left inferior frontal gyrus (1), right precentral gyrus (2), left lateral inferior parietal (3, 4), right lateral inferior parietal (5, 6), medial parietal (7), and left anterior prefrontal cortex (8). Bottom: Timecourse of the transient hemodynamic response to hits and correct rejections for regions identified in the activation maps. Activity is expressed as percentage signal change.

changes and transient modulations, there was no evidence of a significant transient response to the individual test items in parahippocampal cortex.

DISCUSSION

Neural correlates of state- and item-related processes were identified and separated using fMRI. Several results are noteworthy: (1) The present findings reveal that some regions exhibit predominantly transient activity change (e.g., inferior parietal cortex, cf. Fig. 6), whereas others exhibit predominantly sustained activity change (e.g., parahippocampal cortex, cf. Fig. 7). (2) It was unknown whether state- and item-related processes always exist in separate regions; clearly they need not. Activity associated with quite different time courses can co-occur within a given brain region (e.g., left middle frontal gyrus, bilateral frontal operculum, and medial frontal gyrus, cf. Fig. 5). (3) The results further revealed that regions associated with transient “retrieval success” effects do not always exhibit significant sustained “retrieval mode” effects.

Together these findings provide strong support for the theoretical claim that recognition memory demands a combination of state- and item-related pro-

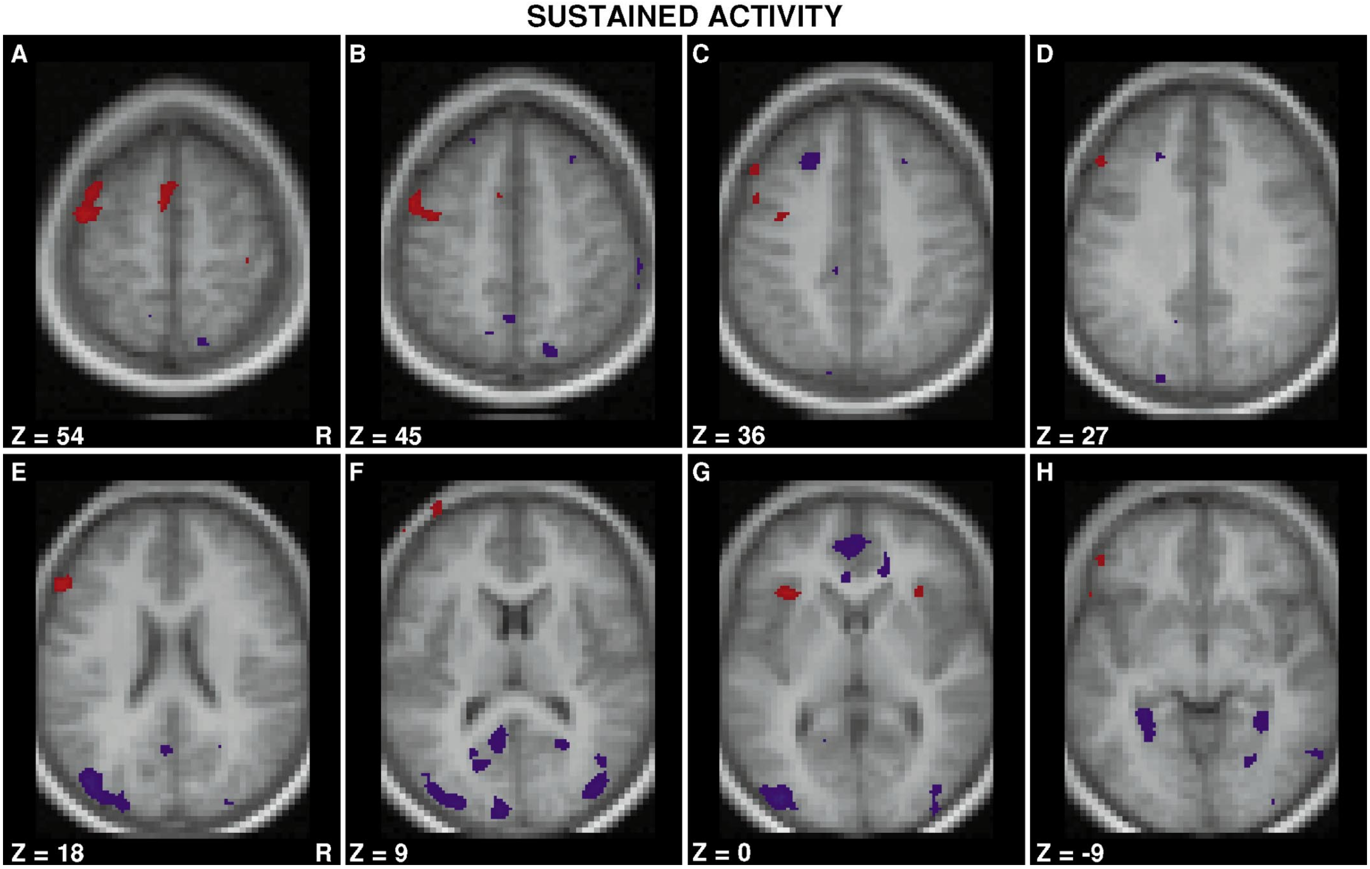

FIG. 4. Sustained effects. Statistical activation maps showing significant sustained activity. Regions showing increased activity during the memory task period are shown in red. Regions showing decreased activity in blue. Significant activation peaks are listed in Table 3.

cesses (cf. Tulving, 1983; Rugg and Wilding, 2000) and provides evidence for the candidate brain regions supporting these processes. Regions identified as showing solely significant item- or state-related activity inherently rest upon a negative finding. This clearly necessitates some caution—the absence of an effect in neuroimaging data should not be over-interpreted. Nonetheless, confidence in the sensitivity of the procedures employed here comes from the fact that regions were also identified that show *both* item- and state-related activity. This finding is stronger; it does not rest upon a negative result and suggests that such co-occurring effects can be identified when they are present. By contrast, methods that average activity over the course of a block confound these different sources of activity, whereas methods that compare averaged event-related responses typically exclude the sustained component. Neither approach reveals the full spectrum of behavior seen here.

Dissociating State- and Item-Related Components

It is notable that all regions showing significant increases in sustained activity during recognition memory were located in the frontal cortex, including left inferior and middle frontal gyrus and left medial frontal gyrus along with bilateral frontal operculum. The pattern of behavior revealed here suggests that these regions support state-related processing, such as "retrieval mode," that occurs throughout task performance.

Of course, "retrieval mode" is an umbrella term, broadly defined as state-related processing that supports memory retrieval. A major challenge for future studies is to explicate the specific functional role of the multiple regions involved in state-related processing. In the present study state-related activity reflects differences between recognition memory and a low-level fixation baseline task, providing a very broad operational definition of retrieval mode regions. It will be of particular interest to see to what extent these findings are specific to recognition memory, or generalize to other tasks (e.g., semantic or working memory). Different forms of recognition such as those based on controlled as opposed to automatic processes may reveal different correlates of mode. Regardless, the present results reveal that regions can either support state-related activity alone, or can support state- and item-

TABLE 3

Regions Showing Significant Sustained Activity

Significant sustained activity											
Increases during memory task						Decreases during memory task					
X	*Y*	*Z*	*Z* value	BA	Region	*X*	*Y*	*Z*	*Z* value	BA	Region
−55	24	21	5.40	44/45/46	L inferior frontal gyrus	−22	27	39	5.4	8	L middle frontal gyrus
−43	0	51	5.73	4/6	L middle frontal gyrus	25	27	45	5.0	8/9	R superior frontal gyrus
−40	63	9	4.78	10	L middle frontal gyrus						
−52	21	36	4.59	9	L middle frontal gyrus						
−34	21	3	5.14	44/45/47	L frontal operculum						
28	21	6	4.50	44/45/47	R frontal operculum						
−7	9	54	5.85	6	Medial frontal gyrus						
						55	−63	−3	4.9	19/37	R inferior temporal gyrus
						−40	−78	21	6.4	19	L middle temporal gyrus
						40	−66	15	4.7	39	R middle temporal gyrus
						−7	−93	12	5.7	18	Cuneus
						−19	−75	15	4.7	18/19	L cuneus
						22	−60	15	5.4	31	L precuneus
						−22	−87	27	4.7	19	L occipital gyrus
						−37	−87	6	6.9	19	L middle occipital gyrus
						37	−84	15	5.6	19	R middle occipital gyrus
						−1	45	3	5.2	32	Anterior cingulate gyrus
						−7	−54	9	5.2	23/30	Posterior cingulate gyrus
						−28	−54	−9	4.7	19/37	L fusiform gyrus
						−28	−42	−9	7.1	36/37	L parahippocampus
						31	−42	−9	6.0	36/37	R parahippocampus

Note. Talairach coordinates (*X*, *Y*, *Z*), significance (*Z* value), and approximate Brodmann Area (BA) based on peak locations in the Talairach and Tournoux (1988) atlas. L, Left; R, Right.

related activity concurrently, suggesting one way in which "retrieval mode" regions may be differentiated. Evidence of concurrent transient and sustained activity also allows results from event-related and blocked studies to be reconciled. For example, frontal operculum has been shown to exhibit transient event-related activity (cf. Buckner *et al.*, 1998b) and has also been characterized as reflecting state-related processing that differs across retrieval blocks (cf. LePage *et al.*, 2000). The present results reveal a combination of state- and item-related activity in the frontal operculum, suggesting that an account integrating both kinds of effect is most appropriate.

Previous neuroimaging evidence for state-related processing has been indirect. For example, LePage *et al.* (2000) explored state-related activity by looking for specific patterns of activity across multiple PET studies. The present results overlap with the regions identified using the meta-analysis approach of LePage *et al.* For example, both approaches reveal state-related activity in regions of left frontal operculum and left middle frontal gyrus. Several differences between the two studies should be noted. First, a number of state-related regions identified here were not reported by LePage *et al.* (2000). In particular, regions that show decreased activity, extending beyond the frontal cortex, including regions in temporal and occipital cortex, cingulate gyrus, and parahippocampal cortex. The parahippocampal finding is particularly intriguing because few fMRI studies of recognition memory have revealed activity in parahippocampal regions at retrieval, whereas a wealth of studies have shown activity at encoding (cf. Schacter and Wagner, 1999, for review). The present findings present a potential explanation for this asymmetry; entering into a retrieval mode may result in the parahippocampal cortex being deactivated. However, whether this finding is specific to recognition memory, or even episodic memory in general, awaits further study.

Second, LePage *et al.* report a region in anterior cingulate cortex associated with state-related processing, similar to a region found in the present study (peaks at: 1, 22, 40, and 1, 18, 42, respectively). LePage *et al.* define retrieval mode using the criteria that a region "(i) becomes differentially active during attempted retrieval of past events and (ii) does so independently of the level of ecphory" (p. 506). This pattern is present here; the anterior cingulate is transiently activated by all item types, but does not modulate based upon retrieval success. In the present results however, this region does not exhibit a significant sustained response, and therefore makes an unlikely candidate for a region that supports a cognitive state "established by task instructions" and "maintained

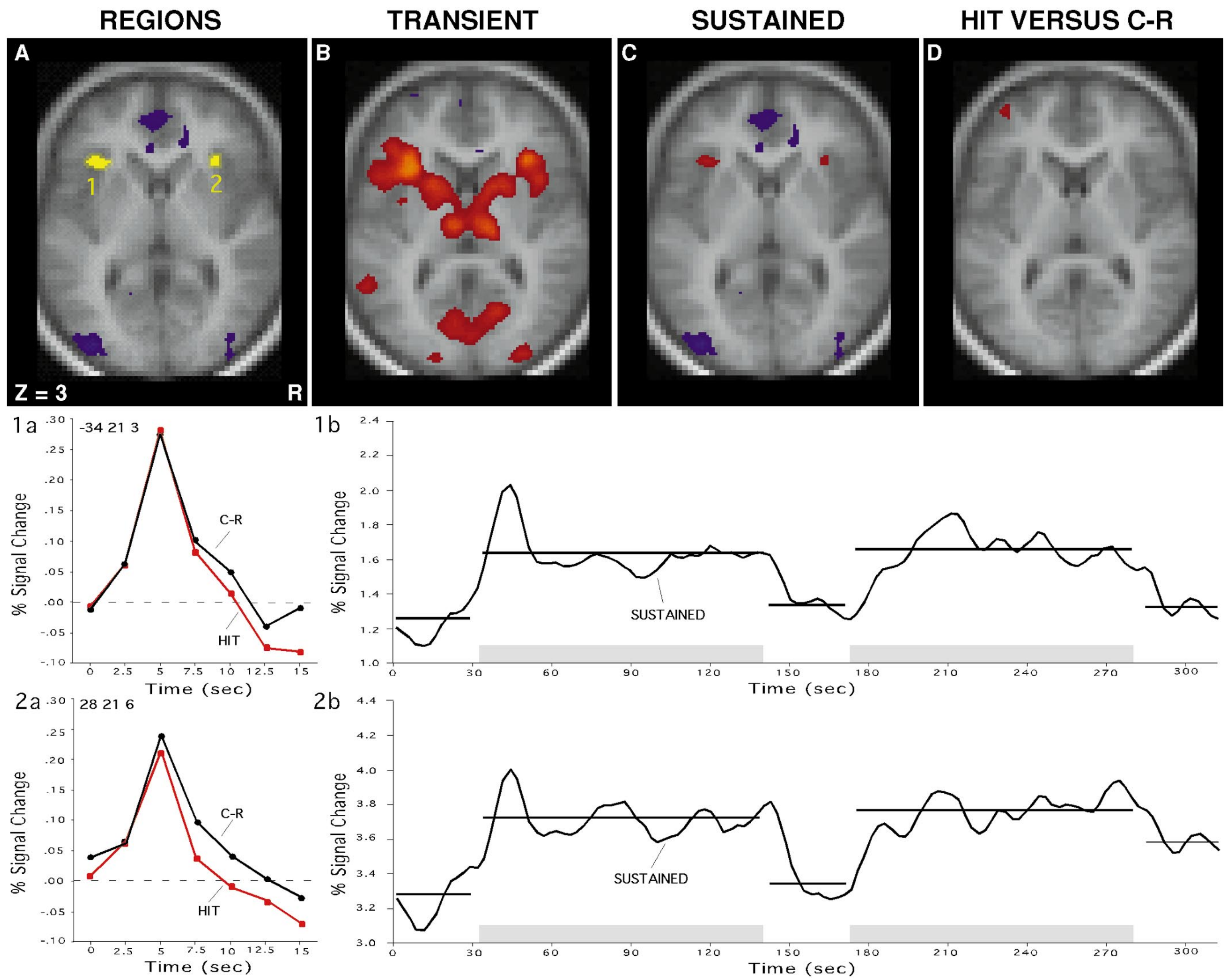

FIG. 5. Significant transient and sustained activity. Top: Statistical activation maps (increases in red, decreases in blue) highlighting regions of interest in bilateral frontal operculum. The regions are identified in yellow (A), shown alongside activation maps from the transient (B), sustained (C), and retrieval success (D) effects for the same transverse section ($z = 3$). Bottom: For each region, the timecourse of the transient hemodynamic response to hits and correct rejections identified in the activation maps are shown on the left (1a and 2a), revealing robust response for both hits and correct rejections. The timecourse of the hemodynamic response for the sustained effect is shown on the right (1b and 2b; memory task blocks are shown by grey bars and mean signal during each block period is shown by straight lines), revealing a robust modulation across the fixation and memory blocks.

throughout performance of a task." This finding highlights the fact that directly characterizing differences in the underlying temporal profile of neural activity will aid discrimination between state- and item-related processes.

Retrieval Success Effects

A number of regions were more active for hits than correct rejections, including medial parietal, lateral parietal and anterior left frontal cortex, suggesting a network of brain areas that are specifically modulated by successful retrieval on an item-by-item basis. This finding is in general agreement with the findings from two other event-related fMRI studies of recognition memory (cf. Henson *et al.*, 1999; Konishi *et al.*, 2000). The present results extend the findings from these studies by demonstrating that the regions sensitive to "retrieval success" do not exhibit significant sustained state-related activity associated with "retrieval mode."

The retrieval success findings also receive support from a recent meta-analysis of PET data (cf. Habib and Lepage, 1999). Across five studies of recognition memory regions in left middle frontal gyrus, inferior and medial parietal lobe showed increased blood flow in response to old items. However, these regions only appear sensitive to "oldness" when stimuli are re-

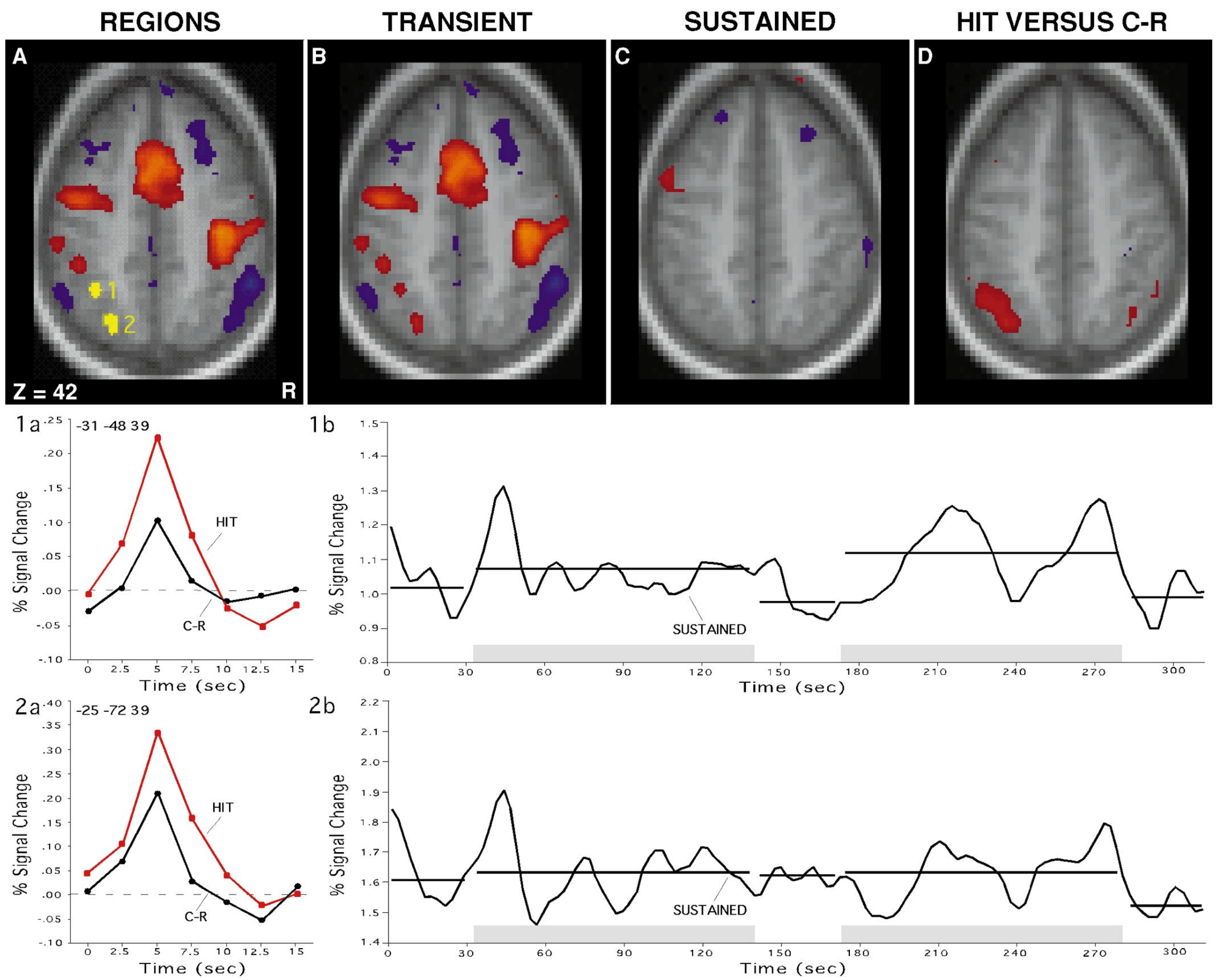

FIG. 6. Significant transient activity but no significant sustained activity. Top: Statistical activation maps (increases in red, decreases in blue) highlighting regions of interest in left inferior parietal lobes. The regions are identified in yellow (A), shown alongside activation maps from the transient (B), sustained (C), and retrieval success (D) effects for the same transverse section ($z = 42$). Bottom: For each region, the timecourse of the transient hemodynamic response to hits and correct rejections identified in the activation maps are shown on the left (1a and 2a), revealing a robust response for both hits and correct rejections. The timecourse of the hemodynamic response for the sustained effect is shown on the right (1b and 2b; memory task blocks are shown by grey bars and mean signal during each block period is shown by straight lines) revealing relatively little modulation across fixation and memory blocks.

peated in the same modality; little activity was present in these regions when modality of presentation was changed between study and test. Whether this simply reflects poorer memory, or provides an important clue as to the functional significance of these regions, awaits further investigation.

A second potential clue to the functional role of “retrieval success regions” stems from variability in the timecourse of the hemodynamic response seen here. For example, left anterior prefrontal cortex appeared to reveal a positive response to hits and showed relatively little response to correct rejections, suggesting specific sensitivity to “oldness.” By contrast, right inferior parietal cortex showed little or no response to hits and exhibited a decrease in response to correct rejections, making this region a poor candidate for supporting retrieval success per se. We are, however, unsure how strongly to interpret these differences because some regions of cortex are known to exhibit primarily increases in activation in response to task demands, whereas others exhibit decreases (cf. Shulman *et al.*, 1997). Nonetheless, the temporal profile of activity may prove important in determining the functional role of each region.

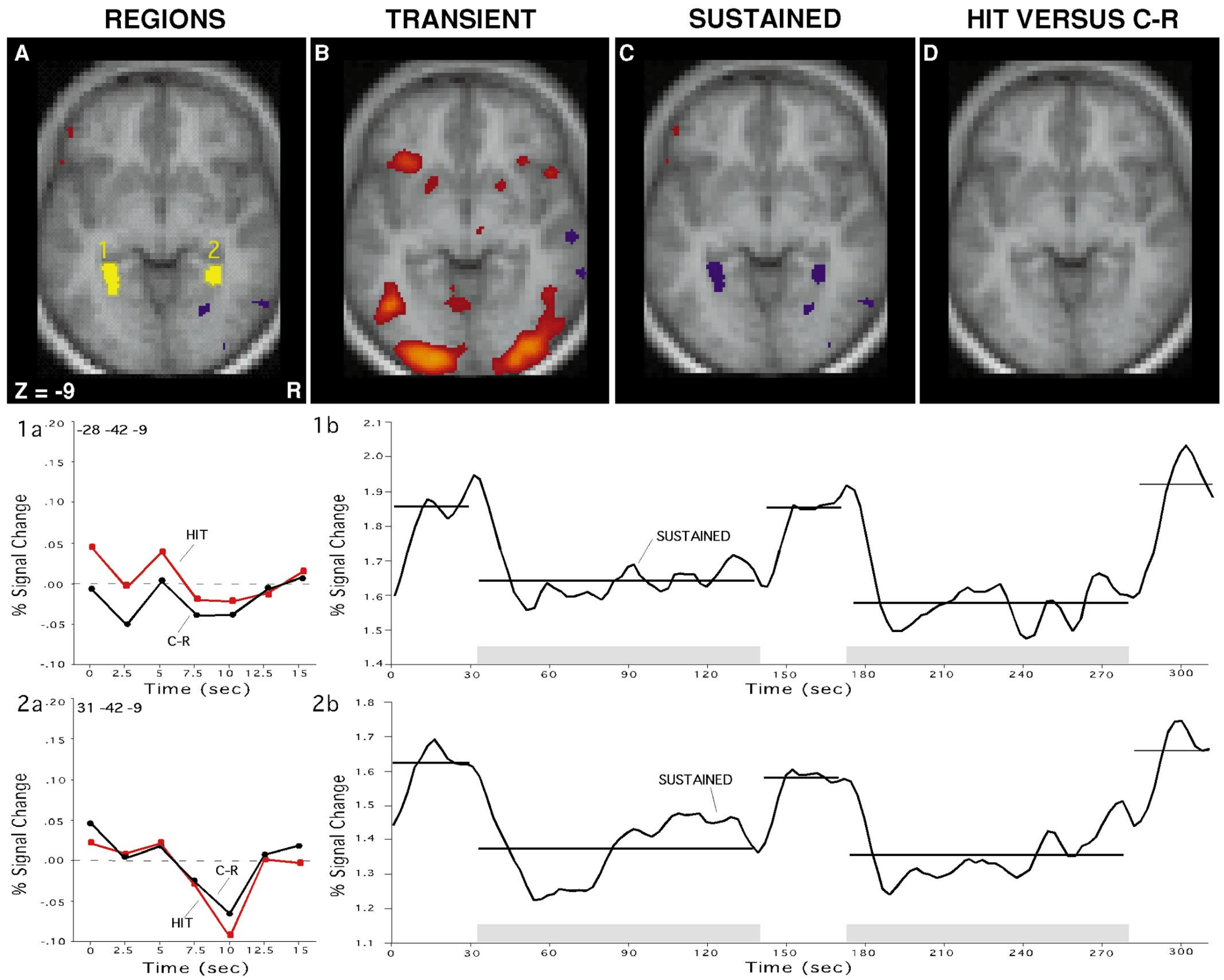

FIG. 7. Significant sustained activity but no significant transient activity. Top: Statistical activation maps (increases in red, decreases in blue) highlighting regions of interest in bilateral parahippocampus. The regions are identified in yellow (A), shown alongside activation maps from the transient (B), sustained (C), and retrieval success (D) effects for the same transverse section ($z = -9$). Bottom: For each region, the timecourse of the transient hemodynamic response to hits and correct rejections identified in the activation maps are shown on the left (1a and 2a), revealing relatively little response for hits and correct rejections. The timecourse of the hemodynamic response for the sustained effect is shown on the right (1b and 2b; memory task blocks are shown by gray bars and mean signal during each block period is shown by straight lines) revealing a robust modulation across the fixation and memory blocks.

The Possibility of Investigating Interaction between State- and Item-Related Processes

All neural activity present during task performance may be a result of an interaction between the items presented and the current cognitive state. Interactions between state- and item-related processes were not examined here however, because this would require a fully factorial design, employing at least two different task blocks. Nonetheless, the possibility of interaction effects is worth discussing here because it highlights the importance of separating the neural correlates of item- and state-related processes. By "interaction" we refer to the modulation of item-related processing by changes in state-related processing, or conversely, the modulation of state-related processing by changes in item-related processing. Consider a situation in which task demands are held constant but items differ across blocks, e.g., studies of recognition memory employing a single task, with variable proportions of old and new stimuli across blocks (cf. Rugg *et al.*, 1996). Despite the fact that subjects are performing nominally the same task throughout, variation in the pattern of items presented may result in subjects employing different strategies to perform the test, and consequently, a different pattern of state-related activity may result.

A second example involves the opposite effect; holding the items constant but altering the demands of the task. For example, in studies of attention subjects are often presented with multifeatured stimuli (e.g., objects that vary in color and motion) and asked to attend to one or other feature (cf. Corbetta *et al.*, 1991). Changing task instructions across blocks may lead to differences in the subject's cognitive set, as indexed by sustained activity. However, there may also be differences in the transient response to individual items (e.g., a region sensitive to color may be more or less active depending on whether this was a currently salient feature). The processes involved in controlling or directing such attentional modulations are important, but may be difficult to investigate using blocked or event-related techniques if interactions between sustained and transient activity are involved. By contrast, the procedure employed here for separating transient and sustained signal changes should allow such interactions to be investigated in future studies (see also Chawla *et al.*, 1999).

Summary

Identifying the neural mechanisms that support cognition requires identifying the brain areas involved *and* characterizing the behavior within those regions. The mixed "event-related and blocked" procedure employed here provides a novel method for identifying two types of behavior, state- and item-related processes, associated with continuous task demands and individual trial events, respectively. We provide support for this cognitive distinction at a neural level, revealing dissociable neural correlates of each process. Of course, state-related modulations need not be implemented as sustained activity changes; state changes may reflect the attenuation or enhancement of item-related activity via neurochemical modulations that do not directly affect ongoing neural activity. Nonetheless, the approach used here opens up avenues of research that have proved difficult to investigate, such as claims of task specificity versus stimulus specificity, and interactions between state and item-related processes. In addition to the specific results obtained in the present study of memory, the approach employed here should prove useful for a broad range of cognitive neuroscience topics and questions.

ACKNOWLEDGMENTS

We thank Mark Wheeler for help with data collection, Kevin Allan, Deanna Barch, William Kelley, Seiki Konishi, and Edward Wilding for valuable comments and discussion. This work was supported by the McDonnell Center for Higher Brain Function (R.L.B.), a James S. McDonnell Foundation Program in Cognitive Neuroscience Grant (R.L.B.), NIH Grants MH57506 (R.L.B.) and NS32979 (S.E.P.), and a Wellcome Trust International Travelling Research Fellowship (D.I.D.).

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