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Functional-Anatomic Correlates of Object Priming in Humans Revealed by Rapid Presentation Event-Related fMRI

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Summary

Human functional-anatomic correlates of object repetition were explored in a cohort of 20 subjects using fMRI. Subjects performed an object classification task where the target objects were either novel or repeated. Objects appeared rapidly, one every 2 s, in a randomly intermixed task design similar to traditional behavioral, event-related potential (ERP), and single-unit physiological studies. Recently developed event-related fMRI methods were used to analyze the data. Clear effects of repetition were observed. Brain areas in midlevels of the processing hierarchy, including extrastriate visual cortex extending into inferotemporal cortex and left dorsal prefrontal cortex, showed reductions in the amount of activation after repetition. By contrast, early visual areas and output motor areas were activated equally by both novel and repeated objects and did not show effects of repetition, suggesting that the observed correlates of repetition were anatomically selective. We discuss these findings in relation to previous positron emission tomography (PET) and fMRI studies of item repetition and single-unit physiological studies; we also address the broad impact that rapid event-related fMRI is likely to have on functional neuroimaging.

Introduction

Repeated exposure to a stimulus item during a task facilitates behavioral performance. This well-established phenomenon, often referred to as priming, has been observed reliably in a range of task situations involving words, pictures, and auditory sounds (reviewed by Schacter et al., 1993; Schacter and Buckner, 1998a [this issue of *Neuron*]). Facilitation can take the form of decreases in the amount of time necessary to complete a task or biased response selection, with prior exposure to a stimulus often increasing the likelihood that it will subsequently be given as a response. In spite of the robustness of the behavioral phenomenon and its importance in understanding human learning, we are only beginning to unravel the functional-anatomic correlates that underlie repetition priming.

Several functional neuroimaging techniques in normal human subjects have recently provided evidence that, in many instances, net reductions in activity may correlate with priming. In a series of interrelated studies, priming during several verbal processing tasks has been observed to correlate with reduced activation in both posterior visual brain areas (Squire et al., 1992; Buckner et al., 1995, 1997; Blaxton et al., 1996; Schacter et al., 1996; Backman et al., 1997; Halgren et al., 1997) and higher-level prefrontal brain areas (Raichle et al., 1994; Demb et al., 1995; Buckner et al., 1997; Halgren et al., 1997; Koutstaal et al., 1997; Wagner et al., 1997; for a discussion see Buckner and Koutstaal, 1998; Schacter and Buckner, 1998a).

Of theoretical interest, these findings have further suggested anatomic specificity, with only certain higher-level visual and prefrontal brain areas benefitting from repeated exposure, depending on the particular task and context (Buckner and Koutstaal, 1998; Schacter and Buckner, 1998b). However, repetition of picture-object stimuli during silent object naming has shown generalized reductions in all areas that were activated during initial processing of target objects (Martin et al., 1995, Soc. Neurosci., abstract). Wagner et al. (1998) examined object repetition as well, but their study imaged only a limited region of frontal cortex, where repetition-related reductions were noted in specific prefrontal regions. Still other evidence from positron emission tomography (PET) suggests that blood flow may sometimes be increased, rather than decreased, during object priming (Schacter et al., 1996). Thus, these initial findings do not provide support for the notion that, of the areas activated by object processing tasks, certain areas are preferentially affected by priming. However, one methodological limitation is shared by all of these initial studies that complicates interpretation.

All previous functional neuroimaging studies of repetition priming have been limited by a technical constraint: novel and repeated stimuli have been presented either in entirely separate "blocks" of items or with different probabilities across the stimulus blocks. Such blocked presentation is problematic in that it may allow subjects to anticipate or change strategies based on the likelihood that items will be repeated. Because attentional modulation has been observed to enhance or attenuate activations within posterior visual regions as well as prefrontal regions (Corbetta et al., 1991; Kawashima et al., 1995; Beauchamp et al., 1997; O'Craven et al., 1997; Shulman et al., 1997), it is possible that modulation interpreted as being priming related may be attributable,

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completely or in part, to differential attentional resources being allocated to blocks of novel or repeated items. Thus, although evidence from studies using blocked trials raises the possibility that priming is associated with reduced activity in specific cortical regions, the question of whether neuroimaging provides evidence of anatomically specific activation reductions in relation to repetition priming is currently unresolved. This uncertainty is especially pronounced with object stimuli, for which there has been little evidence of priming-related, anatomically specific activation reductions.

Recently developed methods for event-related fMRI offer a possible means of exploring this issue in paradigms with randomly intermixed trial types. Event-related fMRI takes advantage of the finding that brief stimulus events and individual cognitive task trials produce hemodynamic responses that are detectable by currently available MRI scanners (Boynton et al., 1996; Buckner et al., 1996; Konishi et al., 1996; Josephs et al., 1997; Zarahn et al., 1997a; reviewed by Rosen et al., 1998), although the hemodynamic response is delayed and temporally extended well beyond the stimulus events themselves (on the order of 10 to 12 s). The clear implication of these studies is that fMRI can map brain function in relation to separate task events provided that those events are well separated in time. Several studies have effectively demonstrated applications for these procedures (Cohen et al., 1997; Courtney et al., 1997; Schacter et al., 1997; Buckner et al., 1998a).

A key further finding is that long temporal separation may not be necessary for event-related fMRI even though individual hemodynamic events are extended in time. Such a possibility is predicted if a linear model of the summation of the blood oxygenation level–dependent (BOLD) contrast hemodynamic response is correct. Recent data collected in several different laboratories suggest a linear model is a good first approximation of BOLD contrast summation (Boynton et al., 1996; Cohen, 1997; Dale and Buckner, 1997). In particular, Dale and Buckner (1997) demonstrated that separate stimulus events spaced as closely as 2 s apart can add linearly on top of one another and hence could also be separated if the timing of the task events is known. As a feasibility demonstration, they randomly intermixed trials of left versus right visual-hemifield stimulation, with one trial presented every 2 s. Robust hemisphere-specific activation maps resulted.

In the context of our present goals, such a finding opens up the possibility of examining repetition priming in continuous runs of randomly intermixed novel and repeated stimuli. With intermixed presentation, complications resulting from participants' anticipation of trial types and subject-initiated block-specific strategies could be eliminated. Moreover, rapid presentation would allow examination of repetition priming effects in a task paradigm very similar to those typically used in behavioral, event-related potential (ERP), and single-unit physiological studies. Clark and colleagues (1997; see also Rosen et al. 1998) have recently presented an abstract that shows rapid presentation task paradigms are feasible for cognitive functional imaging studies.

In the present paper, we apply rapid presentation event-related fMRI to explore object repetition priming. We first describe, using simulated data, how a linear model and appropriate task counterbalancing allow separation of rapidly presented task events. We then examine a large subject group in our main experimental manipulation ($N = 20$) to measure object repetition priming effects and a second control subject group ($N = 12$) to determine false-positive rates for our statistical analysis methods. Three interrelated questions are asked. (1) Can rapid presentation event-related fMRI be used to determine brain areas activated during an object classification task? (2) Do these activated areas show reduced activation for repeated as compared to novel items? (3) Are activation reductions, if observed, anatomically selective for certain brain areas? In exploring these questions, we also demonstrate the feasibility of conducting rapid event-related fMRI experiments in the context of cognitive tasks, thus extending our earlier results with sensory stimulation (Dale and Buckner, 1997) and complementing the efforts of Clark and colleagues (Clark et al., 1997).

Results and Discussion

Simulation Results

Simulation of the fMRI response based on a linear model demonstrated, as expected, differential responses across the three trial types for our paradigm (see Figure 1). When subtractions across trial types were considered, hemodynamic response functions resulted that were quite similar to the input functions: the basic shapes were preserved as well as the relative magnitudes of the responses (Figure 1). The observation that appropriately shaped hemodynamic response functions resulted from the subtractions demonstrates that, within the present counterbalancing scheme, overlap across the closely spaced trials subtracts. However, the responses did not match the input functions precisely. At the beginning and end of the trial, the baselines of the two responses were slightly divergent. This slight divergence resulted because first-order counterbalancing was insufficient to completely remove cross-talk over adjacent trials. Given our 2 s stimulus presentation rate, first-order counterbalancing considers only pairs of trials which span 4 s, whereas the "memory" of the hemodynamic response is on the order of 10 s. To the extent that the counterbalancing did not equate higher-order sequences, some divergence from a perfect subtraction occurs. In this regard, this simulation, which was developed in parallel to the actual experiment, immediately demonstrates how rapid presentation event-related designs might be improved in future experiments: counterbalancing should be considered for higher-order multiples of the trial types.

The simulation showed that the magnitude difference between hemodynamic events after selective averaging was a reasonable estimate of the initial magnitude difference of the input functions. Moreover, the relative quantitative estimates of the hemodynamic response reductions were well preserved over a range of shapes, even when the hemodynamic response functions were allowed to saturate. Thus, the simulation suggests that if a linear model is correct (or even close to being correct),

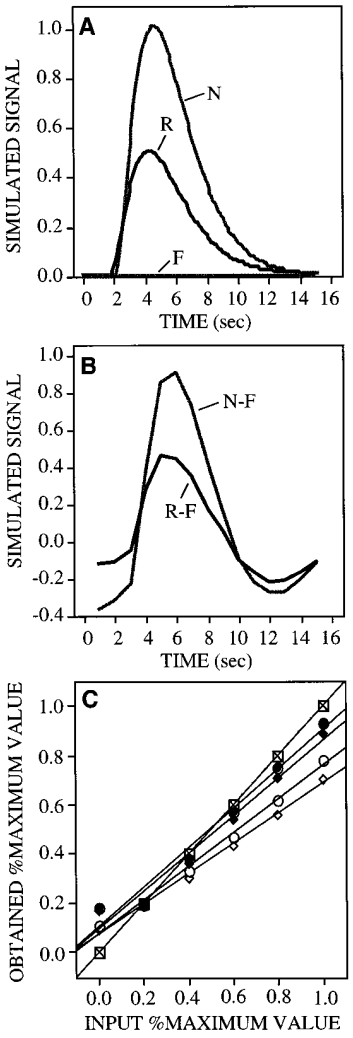

Figure 1. Input Hemodynamic Response Functions and Results from the "Bay Zero" Simulation for the Rapid Presentation Object Repetition Paradigm

(A) The assumed hemodynamic response for one simulation of the three trial types is shown: N, Novel objects that elicit a maximum response equal to 1; R, Repeated objects that elicit a response at 50% of the maximum; and F, Fixation, which does not elicit a hemodynamic response.

(B) The simulated results for the responses in (A) are shown. N − F, Novel minus Fixation response; R − F, Repeated minus Fixation response. Note the similarity of the output responses in (B) to the input functions in (A).

(C) Simulated results are depicted for a range of response reductions and input conditions. The ideal response output is shown across the diagonal (crossed open squares). The closed symbols represent responses assuming a linear model and the open symbols represent responses assuming saturation. Circles represent a hemodynamic response using $\tau = 1.5$; for diamonds, $\tau = 2.0$. Note that the relative reduction in magnitude observed is reasonably stable across reduction values but slightly underestimates the actual reduction. These simulation results suggest that if a linear model is correct, or close to being correct, relative reductions in response magnitude should be detectable within our current paradigm.

the current paradigm and predicted hemodynamic response functions provide sufficient information to extract (1) the main effects of the two conditions (Novel and Repeated) against Fixation, and (2) the magnitude of the difference between the Novel and Repeated conditions—the predicted repetition priming effect.

Behavioral Results

Performance on the object classification task was highly accurate, with subjects, on average, classifying 91.4% of the items correctly (range, 79%–97%). As predicted, classification response times decreased across repetitions during the study blocks (ANOVA, $F[5,19] = 65.08$, $p < 0.0001$), and there was a highly significant effect of repetition (priming effect) during the test blocks for which fMRI data were collected (ANOVA, $F[1,19] = 65.85$, $p < 0.0001$). These behavioral data are shown graphically in Figure 2.

fMRI Results: Novel and Repeated Items

Figure 3 shows the main results. Many brain areas were activated by the Novel and Repeated object classification tasks, as contrasted with Fixation. Several of these activations were in expected locations, including right motor/somatosensory cortex and medial cerebellar cortex (attributable to the left-hand key press) and extensive bilateral activation of visual cortex extending into inferotemporal (IT) cortex. In addition, robust activations were observed in left dorsal prefrontal cortex and anterior cingulate, qualitatively more so for the novel than the repeated objects. Talairach and Tournoux (1988) stereotaxic atlas coordinates are listed in Tables 1 and 2.

Direct comparison of the Novel and Repeated trial events demonstrated that only a subset of the areas activated by the object classification task showed modulation in relation to item repetition, thereby suggesting that the priming-related task facilitation was anatomically selective. Activation in response to novel objects was significantly greater than to repeated objects in bilateral extrastriate cortex extending into IT cortex, left dorsal prefrontal cortex, and anterior cingulate. The regions showing repetition reductions included fusiform gyrus and the middle occipital gyrus, extending clearly into the parahippocampal cortex. Visual areas early in the processing stream nearer to the occipital pole as well as motor regions including right motor cortex and medial cerebellum, associated with response output, showed no significant facilitation effects. Talairach and Tournoux (1988) stereotaxic atlas coordinates are listed for the direct contrast of Novel and Repeated trial events. Examination of the actual time courses showed, as expected, that hemodynamic responses for areas with no significant signal reductions largely overlapped with each other, whereas areas with large reductions showed Repeated hemodynamic responses that peaked at lower values (Figure 3).

The finding of overlapping time courses for Repeated and Novel trial events in the early visual areas and motor areas further suggests that the anatomically selective effects observed in the statistical maps were not a consequence of differential power to detect such effects across areas—a consistent concern when using fixed threshold maps. Overlap in the time courses provides evidence that both Novel and Repeated trial events are indeed showing similar levels of response. Moreover,

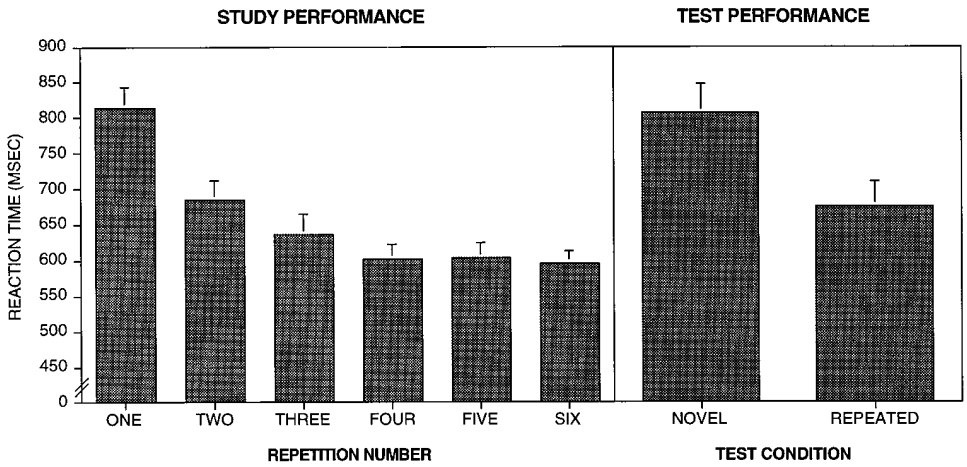

Figure 2. Mean Reaction times for the Object Classification Decision Task after Varied Numbers of Repetitions during Study and then for the Novel and Repeated Objects at Test

Bars represent standard error of the mean (SEM). Clear effects of repetition are observed with faster reaction times exhibited following object repetition. These effects carried to the test trials, where novel and repeated objects were randomly intermixed.

the finding that the region in motor cortex evidences a more modest repetition effect than earlier areas is informative because it is likely the last cortical processing step in the hierarchy of brain areas. If the priming-related modulations were simply a reflection of general facilitation effects, then one might expect this region to benefit the most, as it is farther along in the processing hierarchy than earlier areas showing clear effects of repetition.

Thus, by all measures, clear anatomic specificity was present with relation to brain areas showing reduced fMRI signal changes via priming. Brain areas earliest in the processing hierarchy showed little or no effect. Areas at mid-levels of the processing hierarchy, including extrastriate visual areas extending into IT cortex and left dorsal prefrontal cortex, showed clear and robust effects of priming. Areas late in the information processing hierarchy involved in response selection and/or initiation showed little effect.

An interesting—but currently unexplained—result was that the shape of the hemodynamic response varied across regions as well. Most notably, the primary visual and motor areas showed an undershoot following the hemodynamic response. While the undershoot has been observed across many block-designed paradigms (Kwong et al., 1992; Binder and Rao, 1994) and some event-related experiments (Dale and Buckner, 1997), we had not anticipated a differential undershoot across regions in averaged subject data. Cross-talk over adjacent trials cannot explain the differential shapes, as the exact same counterbalancing, and hence cross-talk, was impacting each region. We cannot currently explain the differential shapes. Other researchers have anecdotally suggested that primary cortical areas may exhibit a more pronounced undershoot, as contrasted with secondary cortical areas (e.g., K. Kwong, personal communication; Tootell et al., 1995, Figure 5). Our data appear to support this possibility.

We explored all of the findings noted above within individual subjects. While a few of the subjects showed effects consistent with the averaged group analysis, most showed nonsignificant effects in relation to object repetition; among this latter subset of subjects, many showed some but not all of the main effects (e.g., activation of visual cortex and motor cortex in relation to the contrast with Fixation). These findings suggest that the present study does not have sufficient power to detect reliable activations at the level of individual subjects. This does not, however, limit our interpretation of the averaged subject analysis, which was based on 20 times more data than was the analysis of individual subjects. Such findings do limit our ability to make precise statements about the locations of activation changes (see Discussion).

fMRI Results: Control Data Set

The control data set yielded no false positives at the chosen significance levels, indicating that our statistical methods and analysis procedures, if anything, were conservative rather than liberal.

General Discussion

Repetition of objects during an object classification task showed clear effects on behavioral task performance, which in turn correlated with clear—and selective—differences in neural activation as measured by BOLD contrast fMRI. Moreover, these effects were observed within the context of rapid presentation event-related fMRI. A pathway of brain areas including striate and extrastriate cortex, left dorsal prefrontal cortex, anterior cingulate, supplementary motor area (SMA), and right motor cortex were activated by the Novel object classification task when it was compared with Fixation. A subset of these areas, including extrastriate cortex extending into IT and left dorsal prefrontal cortex, showed activation reductions when items were repeated. We believe these reductions represent a human neural correlate of priming and are consistent with previous single-unit physiological studies that have shown activity reductions in IT following item repetition (reviewed by

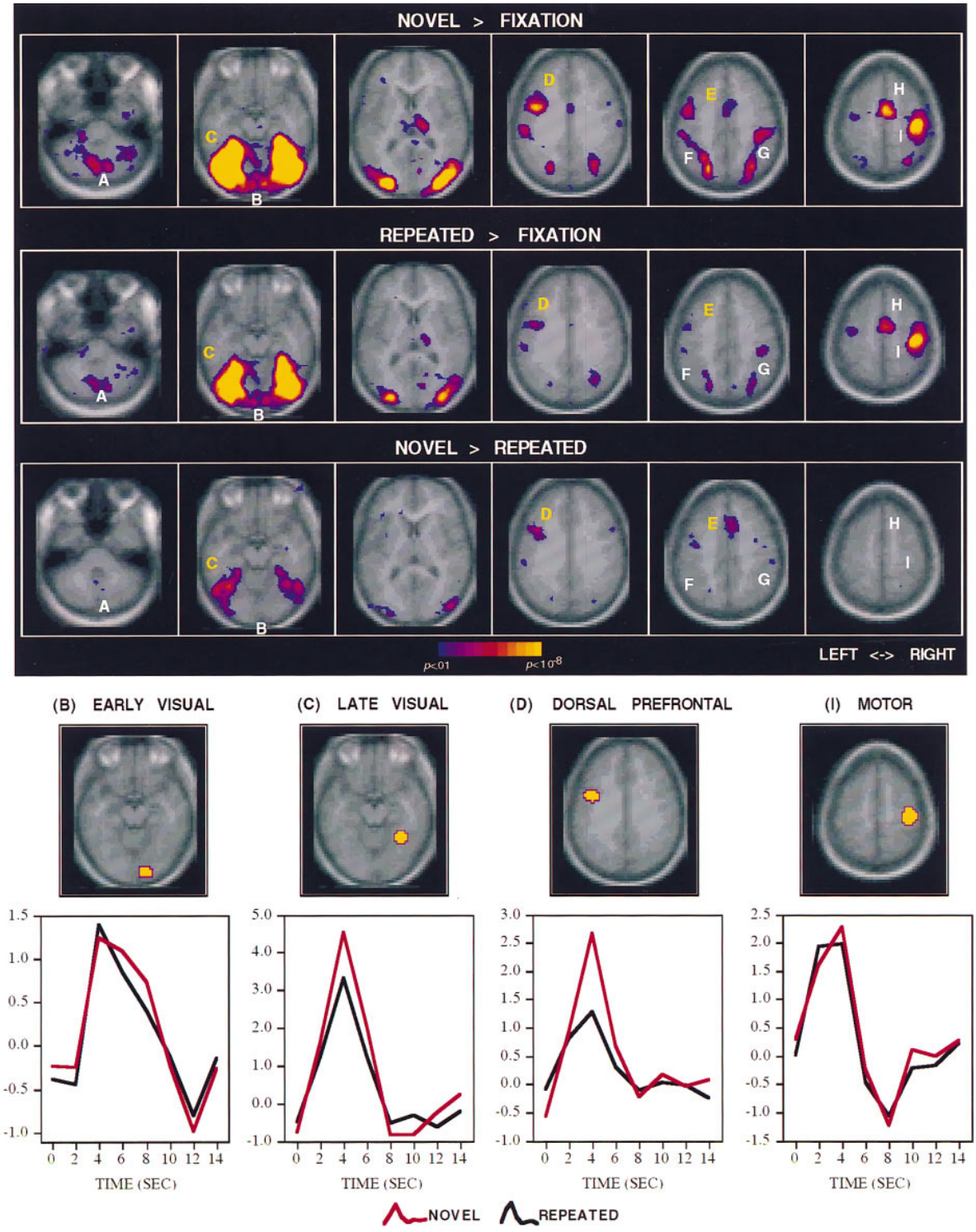

Figure 3. BOLD-Contrast fMRI Data

(Top) Whole-brain statistical activation maps are shown for the three trial comparisons: Novel objects > Fixation; Repeated objects > Fixation, and Novel objects > Repeated objects. Images are axial sections in Talairach and Tounoux (1988) atlas space for an average data set from 20 subjects. In the Novel object classification condition, clear activation is present in medial cerebellum (A), posterior visual cortex (B) extending into extrastriate visual cortex (C), left dorsal prefrontal cortex (D), anterior cingulate (E), lateral parietal cortex ([F] and [G]), SMA (H), and motor cortex (I). A subset of these areas, labeled with yellow letters, show less or minimal activation in the Repeated object classification task. Direct comparison between the Novel and Repeated object tasks reveals significant differences in these areas.

(Bottom) The time course of activation for selected areas is shown separately for the novel and repeated objects. For each activation, separate time courses were derived for each condition within a 3-dimensional region surrounding the peak voxel. Regions were defined using an automated algorithm that identified all contiguous voxels within 12 mm of the peak that reached the significance level. Early visual and motor regions show nearly identical responses, whereas late visual and dorsal prefrontal regions show a hemodynamic response of attenuated magnitude to the repeated objects, consistent with the data visualized in the statistical activation maps.

Table 1. Identification of BOLD Signal Increases during Repeated (Primed) and Novel (Unprimed) Classification versus Fixation

Coordinates			Significance		
X	Y	Z	-log(p)	Location	BA
−34	−68	−15	113	L. Extrastriate	19
−28	−52	−15	108	L. Extrastriate	37
−31	−49	−18	107	R. Extrastriate	37
34	−62	−15	96	R. Extrastriate	19
34	−74	−12	93	R. Extrastriate	18
37	−83	−3	83	R. Extrastriate	18
−34	−83	−9	81	L. Extrastriate	18
−28	−90	9	42	L. Extrastriate	18
37	−21	53	38	R. Motor	4
−43	0	34	22	L. Dorsal Prefrontal	44/9
0	−3	53	21	SMA	6
−21	−68	40	20	L. Lat. Parietal	7/19
−3	−74	−18	18	Med. Cerebellum	—
31	−65	43	17	R. Lat. Parietal	7
9	−90	−12	16	R. Extrastriate	18
−28	−55	40	15	L. Lat. Parietal	40
12	−18	9	15	R. Med. Thalamus	—
−25	−71	31	14	L. Extrastriate	19
9	−71	−34	14	R. Med. Cerebellum	—
28	−68	31	14	R. Extrastriate	19
34	−24	−21	14	R. Hippocampal Formation	—
−6	−65	−37	14	L. Med. Cerebellum	—
−53	−24	31	13	L. Lat. Parietal	40
53	−24	43	12	R. Somatosensory	1/2
0	−43	−15	11	Medial Cerebellum	—
−3	−62	−18	11	Medial Cerebellum	—
3	−3	25	11	R. Corpus Callosum	—
−37	−12	−34	11	L. Inferior Temporal	20
−6	−55	−12	11	Med. Cerebellum	—
−18	−49	−43	11	Med. Cerebellum	—
−9	−55	−40	11	Med. Cerebellum	—
−53	−27	40	11	L. Lat. Parietal	40
9	−71	9	10	R. Striate	17
−31	−46	34	10	L. Lateral Parietal	40
15	−83	43	9	R. Extrastriate	19
−43	−37	34	9	L. Lateral Parietal	40
18	−37	21	9	R. Ventricle	—
59	−46	−15	8	R. Inferior Temporal	37

Coordinates are from the Talairach and Tournoux (1988) atlas; R, right; L, left; Lat, Lateral; Med, Medial; BA, approximate Brodmann area based on atlas coordinates.

Desimone et al., 1995), as well as previous human functional neuroimaging studies that have noted such effects in relation to verbal stimuli (reviewed by Buckner and Koutstaal, 1998; Schacter and Buckner, 1998a).

The finding that priming-related reductions were constrained to distinct brain areas is important to our understanding of priming and to the theoretical clarification of which task processes might be facilitated through item repetition. Our ability to identify these anatomically selective priming-related reductions with rapid presentation event-related fMRI has important methodological implications for functional neuroimaging in general. We discuss these two issues separately.

Anatomically Selective Priming-Related Activation Reductions

Clear effects of priming were observed in late visual areas extending into IT cortex (fusiform and middle occipital gyri) and even parahippocampal cortex. These reductions were bilateral and extended over a region likely to contain multiple visual areas within the ventral processing stream. At a cognitive level, these findings are consistent with the notion that priming can have effects in perceptual processing stages and are consistent with predictions based on some cognitive models concerning the involvement of higher-order visual areas such as IT cortex in object priming (Schacter, 1992). Overlap between the location of our repetition effects and areas activated during prior face, object, and picture processing studies supports this possibility (reviewed by Ungerleider, 1995; Van Essen and Drury, 1997). At a neural level, these findings are anticipated by several single-unit physiologic studies in nonhuman primates, which demonstrate that certain populations of neurons show less activity following repeated exposure to objects and faces than during the initial or novel presentation of these stimuli (Rolls et al., 1989; Riches et al., 1991; Miller and Desimone, 1994; Li et al., 1994). This phenomenon, which has been termed adaptive filtering by Desimone and colleagues (Desimone, 1992; Desimone et al., 1995), is believed to represent a learning-dependent change by which information processing

Table 2. Identification of BOLD Signal Increases for Novel (Unprimed) Minus Repeated (Primed) Items

Coordinates			Significance		
X	Y	Z	-log(p)	Location	BA
−43	−65	−6	19	L. Inferior Temporal	37
−34	−55	−12	15	L. Inferior Temporal	37
40	−83	25	14	R. Extrastriate	19
−25	−40	−15	13	L. Extrastriate	20
46	−55	−12	13	R. Inferior Temporal	37
34	−52	−15	12	R. Extrastriate	37
43	−83	9	11	R. Extrastriate	19
−40	9	31	11	L. Dorsal Prefrontal	44
28	−40	−15	11	R. Extrastriate	20
−37	−87	−15	9	L. Extrastriate	18
3	22	40	9	Ant. Cingulate	32
−43	−87	18	9	L. Extrastriate	19
3	9	43	8	Ant. Cingulate/SMA	24/6
−34	−43	−21	8	L. Lat. Cerebellum	—

Coordinates are from the Talairach and Tournoux (1988) atlas; R, right; L, left; Lat, Lateral; Med, Medial; BA, approximate Brodmann area based on atlas coordinates.

comes to represent familiar as compared to novel items. Reductions in the fMRI BOLD contrast signal, as observed here, are quite possibly revealing a human correlate of the same underlying neural phenomenon.

Moreover, as noted above, we observed minimal effects of repetition in early visual areas more likely to lie at or near retinotopically defined visual regions (e.g., V1, V2, V3, and V3a). Time course data for these early areas revealed largely overlapping responses for novel and repeated stimuli—with both types of trial event showing significant activation. These results are consistent with previous PET and fMRI studies of word repetition effects that have noted extrastriate activation reductions in putatively higher-level visual areas but not within structures lying near gross anatomic landmarks for early visual areas (Squire et al., 1992; Buckner et al., 1995; Blaxton et al., 1996; Schacter et al., 1996). Taken collectively, we believe the data support the hypothesis that, even within visual cortex, priming-related reductions are anatomically selective for object repetition. We also anticipate that the degree of specificity will likely be modulated by task factors such as the stimulus type, familiarity of the overall stimulus set, intertrial intervals, and task context, as has been noted for single-unit physiologic studies (Desimone et al., 1995). It seems quite possible that repetitions of visual stimuli that are differentiated at the level of earlier visual areas will show priming effects in these regions. Further experiments are needed to distinguish between the possibility that later visual areas are inherently more sensitive to stimulus repetition and the possibility that repetition effects are manifested most prominantly in those visual areas that are selective for the stimulus class being examined.

A limitation of the present study is that we are only able to make relatively coarse statements about the location of the observed visual repetition effects. The reductions are clearly anterior to early visual areas and likely at or beyond V4, perhaps falling near the lateral occipital complex (LO) as defined by functional-anatomic responses in previous studies (Malach et al., 1995). However, we did not collect enough data to localize the effects within individual subjects or to specifically define the boundaries of mapped human visual areas. In this regard, one natural direction for this kind of research is to better localize these repetition effects in relation to mapped visual areas within individual subjects (Sereno et al., 1995; DeYoe et al., 1996; Tootell et al., 1996; Engel et al., 1997) or perhaps in relation to retinotopic maps averaged over subjects. Halgren et al. (1997) have recently reported analyses of word repetition in relation to retinotopic maps and, consistent with the results presented here, suggest that repetition effects are most robust in areas anterior to those defined by retinotopy.

Clear reductions were also observed in left dorsal prefrontal cortex and SMA extending into anterior cingulate. Like the results obtained in visual cortex, the frontal effects appear to be selective, in that areas farther along in the processing hierarchy (e.g., motor cortex) benefit to a lesser degree (in terms of BOLD contrast) from this facilitation. These reductions are likely a neural correlate of conceptual priming (Demb et al., 1995; Wagner et al., 1997; reviewed by Buckner and Koutstaal, 1998; Schacter and Buckner, 1998a).

The location of these prefrontal areas overlaps with regions that have been activated during verbal word generation tasks and verbal working memory tasks (Petrides et al., 1993; Smith and Jonides, 1997; Cohen et al., 1994, 1997). In a particularly careful series of studies, dorsal prefrontal cortex and other regions within prefrontal cortex were demonstrated to track working memory load (Braver et al., 1997). The basic task used in our repetition study involved categorizing known (and nameable) visual objects, a decision that likely demands manipulation of the concept of the object in working memory. It would appear that after repetition the demand on these resources decreases, as indexed by the decreasing response latency and the reduction of activation of left dorsal prefrontal cortex and SMA/anterior cingulate. This idea is similar to a notion put forth by Raichle and colleagues (1994), who suggested that item repetition can lead to decreases in nonautomatic task processing in word generation tasks, and to those of Gabrieli et al. (1996), who suggested that item repetition

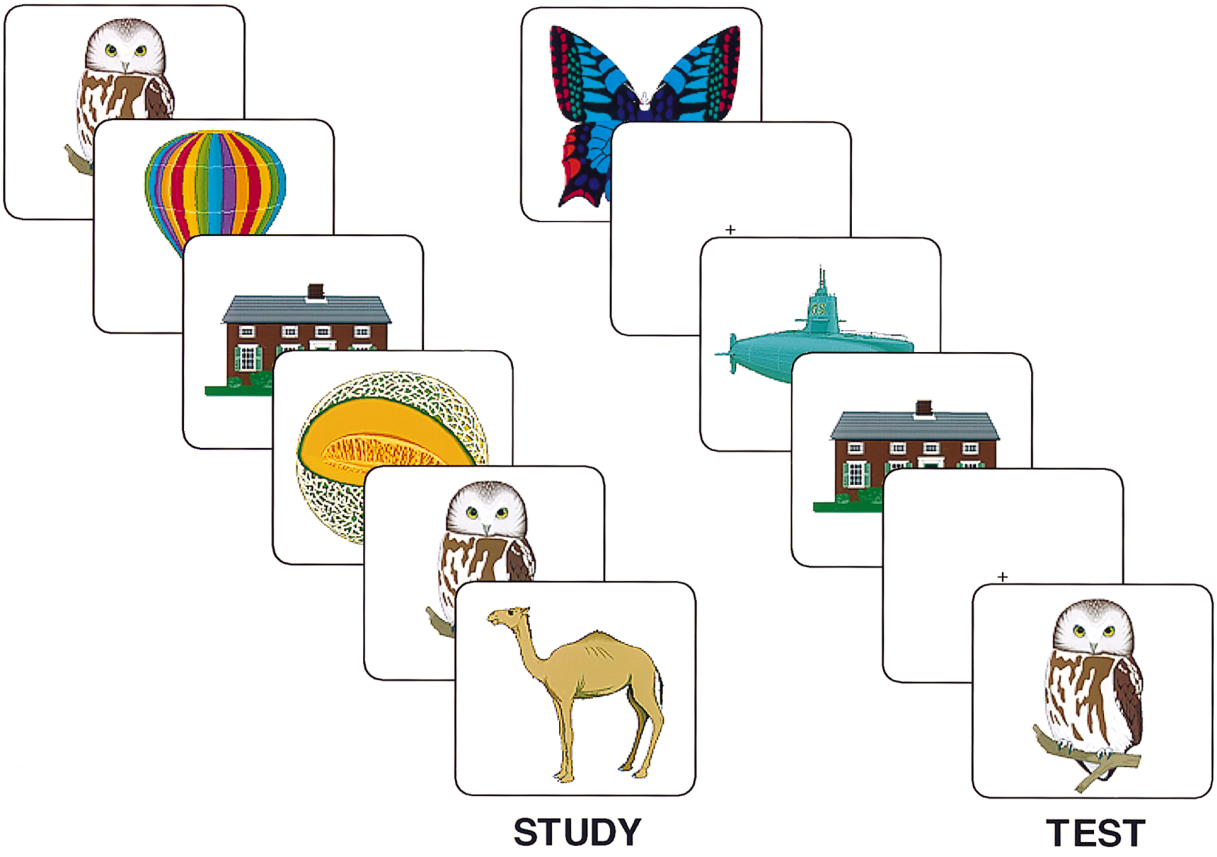

Figure 4. Examples of the Colored Object Stimuli Used in the Present Experiment

At both study and test, stimuli were randomly intermixed, and one stimulus was presented every 2 s. At test, three stimuli types were examined: novel objects (e.g., the butterfly), repeated objects (e.g., the owl), or a simple cross-hair fixation point.

effects in left prefrontal cortex may be related to decreased demands for semantic working memory processes. Our results may be revealing a similar phenomenon in terms of effortful elaboration within working memory for an object classification task. These ideas are also similar to several well-formulated cognitive models of item repetition, which propose that conceptual task demands can be primed via transfer of appropriate processes across repetitions (Blaxton, 1989; Roediger et al., 1989).

Subsequent work might explore whether such reductions can be selectively modulated in a task-specific manner as is postulated by the transfer appropriate processing framework and has been previously observed for verbal stimuli (Demb et al., 1995; Blaxton et al., 1996; Wagner et al., 1997). Our present data do not clearly inform us as to whether the visual and prefrontal cortex reductions are process-specific in the object classification task examined. Based on the prior data discussed above, it seems likely that the visual and prefrontal reductions correlate with perceptual and conceptual processes, respectively. Further experiments that modulate specific task variables (e.g., changes in the stimulus format across repetition or changes in the task demands holding stimulus format constant) will be required to explore these possibilities.

Rapid Event-Related fMRI

The field of functional neuroimaging has seen a number of important innovations in the past few years (Rosen et al., 1998). The observation that fMRI is sensitive to rapid changes in hemodynamics (Blamire et al., 1992; Savoy et al., 1995; Boynton et al., 1996; Konishi et al., 1996) quickly led to the demonstration that hemodynamic signals from single cognitive task events can be detected (Buckner et al., 1996). This finding, coupled with the observation that the BOLD contrast fMRI signal adds in a roughly linear fashion (Boynton et al., 1996; Dale and Buckner, 1997), served as the methodological basis for the present study. As discussed at length above, rapid event-related fMRI procedures were applied to the question of object repetition priming, and several functionally significant results were noted. Our results thus complement a recent report by Clark and colleagues (1997), which also examined the fMRI response across randomly intermixed rapidly presented trials. These two studies clearly demonstrate that rapid event-related fMRI is a technique currently available for psychological and neuroscientific questions. These developments are likely to have a broad impact on the field of functional neuroimaging, as they allow the examination of task paradigms that are identical to those used in typical behavioral, ERP, and single-unit physiological studies.

Experimental Procedures

Subjects

Thirty-six right-handed native English-speaking subjects between the ages of 18 and 35 volunteered and received $50 as payment for participation. Twenty-four subjects participated in the main experiment involving object priming (thirteen male). Four subjects from this group were either unable to complete the study or produced data with sufficient artifacts to preclude further analysis. The additional twelve subjects (four male) contributed control data (see below). These control data have been used in previous studies (Buckner et al., 1998b). For all subjects, informed consent was obtained prior to MR imaging 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). Visual images were projected to subjects (Sharp 2000 color LCD projector) through a collimating lens (Buhl Optical). A screen attached to the standard General Electric quadrature head coil received the projected images. Subjects viewed the screen through a mirror. A custom-designed magnet-compatible key press was used to record subject performance and reaction times on an Apple PowerMacintosh computer (Apple Computer, Cupertino, CA). Subjects' heads were immobilized with pillows and cushions to reduce motion artifact.

For each subject, a series of conventional structural images was first collected to provide detailed anatomic information. Then, a series of echo planar functional images was collected to provide both anatomy and functional images sensitive to BOLD contrast. The entire session, including both structural and functional sequences, lasted between 1.5 and 2 hr.

Conventional imaging consisted of (1) a high resolution rf-spoiled GRASS sequence (SPGR; 60 slice sagittal, 2.8 mm thickness) and (2) a set of T_1 flow-weighted anatomic images in plane with the functional echo planar images (16 slice, 1.6 mm in-plane resolution, 7 mm thickness, skip 1 mm between slices). The flow-weighted images served as an intermediate to align the echo planar images to the SPGR images. Echo planar imaging consisted of (1) an automated shim procedure to improve B_0 magnetic field homogeneity (Reese et al., 1995) and (2) T_2*-weighted functional image runs using an asymmetric spin echo sequence (TR = 2 s; TE = 50 ms, 180° offset = −25 ms). Such a sequence was chosen because it has decreased sensitivity to large vessels (Baker et al., 1993). Functional image runs consisted of 98 sequential whole-brain acquisitions (16 slice, 3.125 mm in-plane resolution, 7 mm thickness, skip 1 mm between slices, acquisition aligned to the plane intersecting the anterior and posterior commissures and covering the whole brain). Prior to each run, four images were acquired and discarded to allow longitudinal magnetization to reach equilibrium.

Behavioral Procedures

The goal of the behavioral procedures was to contrast performance of trials with novel and repeated objects during an object classification task. By repeating both the exact same stimuli and the same task demands, our paradigm was designed to allow both perceptual (data-driven) and conceptual priming effects to be observed (Blaxton, 1989; Roediger et al., 1989). Subjects were presented pictures of colored objects, one at a time, centered on the projection screen (one stimulus per 2 s, 0.5 s stimulus duration; a fixation cross-hair was presented between stimulus objects). The objects were selected from a large set of CD-ROM clip-art collections (MasterClips, IMSI, San Rafael, CA; Corel GALLARY, Corel Corporation, Salinas, CA). Objects were selected only if they represented simple, unique, and easily identified objects. Examples of object stimuli are shown in Figure 4.

The task was to decide whether the objects tended to move on their own or not. Participants were instructed to "look at each picture and decide if it is something that tends to move on its own or not. A goat, for example, does tend to move on its own, as does a fan. A potato does not. Most objects can be moved. The decision here is about whether they tend to move on their own." Subjects were further instructed to respond accurately and quickly and to maintain fixation. Key-press responses were made with their left (i.e., non-dominant) hand. A demonstration block of 10 items was given and repeated until each subject performed the task accurately.

During the study phase, subjects were presented with a new subset of pictured objects prior to each fMRI functional run. For the study phase, subjects were presented with 10 unique items, six times each (for a total of 60 items), for 2 min. A total of six repetitions through the list was chosen in order to maximize the likelihood of generating sufficiently robust reduction effects, consistent with previous functional neuroimaging studies with verbal stimuli (Raichle et al., 1994; Buckner et al., 1997; Halgren et al., 1997; Koutstaal et al., 1997).

During the fMRI functional runs, three trial types were presented equally often in a continuous series of 90 intermixed trials over ~3 min. The trial types were (N) Novel items, (R) Repeated items from the study list, or (F) a Fixation cross-hair. Trial types were pseudo-randomly intermixed with first-order counterbalancing (each trial type followed every other trial type equally often). Importantly, because three runs were performed for each subject, the item types could be rotated to ensure counterbalancing across runs. To accomplish this, all item positions for a specific trial type in run one became an item position for a different trial type in run two and then the third trial type in run three (e.g., order R-N-F-N... became F-R-N-R... became N-F-R-F...). Counterbalancing was critical in the present experiment because of the predicted overlap of the hemodynamic response across adjacent trials (trials were spaced every 2 s apart, whereas the hemodynamic response lasts 10–12 s). By ensuring that each trial type followed every other trial type equally often, and by systematically rotating the positions of trials across runs, the average "trial history" preceding and following a given trial type was the same as any other trial type. In this way, when differences between trial types are considered within a linear model, overlap (cross-talk) of the hemodynamic response across trials simply cancels out (Dale and Buckner, 1997).

To create a stable task baseline, each functional run began and ended with 8 s of visual fixation. Across subjects, items were counterbalanced such that novel items for one subject were repeated items for another subject.

Event-Related fMRI Analysis Methods

The procedures for selective averaging and statistical map generation have been described previously (Dale and Buckner, 1997; Schacter et al., 1997). Briefly, data from individual fMRI runs were first normalized to correct for signal intensity changes and temporal drift. Normalized data were then selectively averaged in relation to the beginning of each trial type both within subjects and across subjects (much like ERP data are averaged). Finally, statistical activation maps were constructed based on the averaged event-related responses for each trial type. Specifics of the procedure as applied here are given below.

Normalization of each fMRI run involved (1) scaling of whole-brain signal intensity to a fixed value of 1000, (2) linear slope removal on a voxel-by-voxel basis to counteract effects of drift (Bandettini et al., 1993), (3) spatial filtering with a one-voxel radius Hanning filter, and (4) removal of the mean signal intensity on a voxel-by-voxel basis. Normalized fMRI runs were then selectively averaged within each subject, such that eight mean images (16 s at TR = 2 s) were retained for each trial type as well as the variance for each of the eight images per trial type (see Dale and Buckner, 1997, for details of method). Three trial types were included: Novel items, Repeated items, and Fixation. Once all trials were selectively averaged for each subject, the mean and variance images were transformed into stereotaxic atlas space (Talairach and Tournoux, 1988). For this transformation, the bounding edges of the brain, the highest point in the midsagittal plane, and the anterior and posterior commissures were manually identified using the sagittal SPGR images, which contained detailed anatomic information. These landmark points were used to linearly orient and scale the sagittal images (using trilinear interpolation; the resulting matrix included 39 transverse slices of isotropic 3.125 mm voxels).

The atlas transformation matrix was applied to each of the selectively averaged event and variance images. Once in atlas space,

data were then averaged across subjects, weighting the means and variance by the number of trials contributed by each subject (in this particular instance, this procedure is the same as weighting each subject equally, because all subjects contributed the same number of trial events per condition). As a second step, the interpolated SPGR images were averaged to yield a mean anatomy image, which was then used as a reference anatomic backdrop for the functional data.

Activation maps were constructed using a t statistic as described by Dale and Buckner (1997; see also Schacter et al., 1997). For this analysis, a set of predicted hemodynamic curves was generated with the onset delay of the hemodynamic response varied over time. Varying onset delay is critical for being sensitive to activation change across the entire brain cortex, as regional variance in the timing onset of the hemodynamic response has been observed previously (Schacter et al., 1997; Buckner et al., 1998a). Specifically, gamma functions were used as the base shape with fixed parameters $\delta = 2.5$ s and $\tau = 1.25$ s (see Boynton et al., 1996; Dale and Buckner, 1997) and a latency delay parameter.

Statistical maps were generated based on the differences between trial types. The time courses for the Fixation trial events were subtracted from the Novel and Repeated object classification trial events, and the Novel and Repeated trial events were subtracted from each other directly. Difference time courses were examined because, given our short intertrial interval (2 s) and the relatively long length of the hemodynamic response, the raw unsubtracted time courses are dominated by cross-talk from adjacent trials. Having counterbalanced the trial orders, direct subtraction cancels out the cross-talk and leaves the basic response function for the difference between each trial type. Dale and Buckner (1997) have empirically shown that subtraction of cross-talk across trials is possible. A simulation of the present paradigm is provided below.

Having constructed statistical activation maps, peak activation coordinates in Talairach and Tournoux (1988) atlas space were generated using the constraint that only peaks significant at the $p < 10^{-3}$ level and in clusters of five or more significant voxels were considered. When significant peaks occurred within 8 mm of one another, the most significant peak was kept.

In order to empirically provide confidence that our methods were not yielding inappropriate false-positive rates, the exact same set of normalization and statistical test procedures was performed on the control data set, where subjects simply visually fixated on a cross-hair for the entire run (similar to Zarahn et al., 1997b). For this analysis, three sham event types were used in a paradigm identical to that used in the true experimental manipulation. We have used this control data set previously but not for the specific analyses performed here (Buckner et al., 1998b).

Simulation of fMRI Time Series Data

The basis of our proposed analysis of selectively averaged trials is that the BOLD contrast hemodynamic response adds roughly linearly across successive trial events. This assumption has held up well for sensory-related responses in visual striate cortex at stimulus rates of 1 per 2 s (Boynton et al., 1996; Dale and Buckner, 1997) and for peri-auditory cortex at similar rates but not for faster rates (Friston et al., 1997; see Rosen et al., 1998, for a discussion). For these reasons, we believe the assumption of linearity is likely to hold up in our present repetition priming study and can provide the basis for comparing rapidly presented Novel and Repeated item events to each other as well as both of these trial events to a third Fixation condition. However, the expected behavior of a linear system within such a paradigm cannot be easily intuited. For these reasons, we formalized a linear response hemodynamic model in a simulation called "Bay Zero" (Burock et al., 1998; similar to Cohen, 1997). Assumed hemodynamic response functions and the exact stimulus paradigms used in our present experiment were then input into the simulation. Predicted fMRI time series were returned for data across runs and for selectively averaged data in relation to separate event types and subtractions of event types. We also provided a range of possible hemodynamic response functions and possible reductions in BOLD signal intensity due to priming. As a final step, we simulated the possibility of the linear model being inaccurate, resulting in response saturation, and compared those results with the input functions to determine the robustness of our estimates across violations of a linear model. The simulation was implemented using MATLAB (MathWorks, Natick, MA).

Taken directly from Dale and Buckner (1997; see also Boynton et al., 1996; Cohen, 1997), the assumed fMRI impulse-response function to each stimulus event was given by:

$$h(t) = \left(\frac{(t-\delta)}{\tau}\right)^2 e^{-\frac{(t-\delta)}{\tau}},$$

where an arbitrary scaling factor of 1 was used. Parameters were set to $\delta = 2.5$ s and $\tau = 1.25$ s. We modeled the time course as a summation of the responses to individual trial types where the fMRI signal s(t) at time t was given by:

$$s(t) = \sum_{i}^{N} x_i(t) * h_i(t) + n(t),$$

where * denotes the convolution operator, $x_i(t)$ is the experimental paradigm associated with trial type i, $h_i(t)$ is the hemodynamic impulse-response function of trial type i, N is the number of trial types, and n(t) represents noise. The $h_i(t)$'s were defined according to a priori assumptions about the shapes of the hemodynamic impulse responses in specific regions of the brain. We varied the relative amplitudes of the response to simulate priming (range, 0% magnitude to 100% magnitude). The constants δ and τ were systematically varied to simulate different shaped responses. Temporally autocorrelated noise n(t) was based on Purdon and Weisskoff (personal communication) and was modeled as a white component plus a first-order autoregressive component. The noise spectrum of this form is similar to that proposed by Zarahn et al. (1997b); however, the autoregressive model is easily implemented as the output of a linear system. For the purposes of this study, n(t) was in general set to zero, and the resulting s(t) can be viewed as the "ideal" time course on a voxel-by-voxel basis.

We considered the effect of a simple saturating nonlinearity. Response saturation was modeled as an amplitude reduction that was proportional to the difference between the current signal level and the saturation level, given by the following equation:

$$A_{red} = \left[\frac{A_{max} - s(t)}{A_{max}}\right] A_i,$$

where A_{red} is the reduced amplitude of the hemodynamic response, A_i is the relative amplitude of trial type i, s(t) is the signal given above, and A_{max} is the saturation level. A_{max} was chosen to give a $\sim$25% maximum reduction in amplitude as compared to the ideal linear response. The form of this nonlinearity is reasonable, given that the hemodynamics of the brain, like any real system, must saturate at high enough levels.

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References

Backman, L., Almkvist, O., Andersson, J., Nordberg, A., Winblad, B., Reineck, R., and Langstrom, B. (1997). Brain activation in young and older adults during implicit and explicit retrieval. J. Cog. Neurosci. *9*, 378–391.

Baker, J.R., Hoppel, B.E., Stern, C.E., Kwong, K.K., Weisskoff, R.M., and Rosen, B.R. (1993). Dynamic functional imaging of the complete human cortex using gradient-echo and asymmetric spin-echo echo-planar magnetic resonance imaging. Proc. Soc. Magn. Reson. Sci. Meet. Exhib. *1*, 1400.

Bandettini, P.A., Jesmanowicz, A., Wong, E.C., and Hyde, J.S.

(1993). Processing strategies for time-course data sets in functional MRI of the human brain. Magn. Reson. Med. *30*, 161–173.

Beauchamp, M.S., Cox, R.W., and DeYoe, E.A. (1997). Graded effects of spatial and featural attention on human area MT and associated motion processing areas. J. Neurophysiol. *78*, 516–520.

Binder, J.R., and Rao, S.M. (1994). Human brain mapping with functional magnetic resonance imaging. In Localization and Neuroimaging in Neuropsychology, A. Kertesz, ed. (San Diego: Academic Press), pp. 185–212.

Blamire, A.M., Ogawa, S., Ugurbil, K., Rothman, D., McCarthy, G., Ellerman, J.M., Hyder, F., Rattner, Z., and Shulman, R.G. (1992). Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging. Proc. Natl. Acad. Sci. USA *89*, 11069–11073.

Blaxton, T.A. (1989). Investigating dissociations among memory measures: support for a transfer-appropriate processing framework. J. Exp. Psychol. [Learn. Mem. Cognit.] *15*, 657–668.

Blaxton, T.A., Bookheimer, S., Zeffiro, T.A., Figlozzi, C.M., Gaillard, W.D., and Theodore, W.H. (1996). Functional mapping of human memory using PET: comparisons of conceptual and perceptual tasks. Can. J. Exp. Psychol. *50*, 42–56.

Boynton, G.M., Engel, S.A., Glover, G.H., and Heeger, D.J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. J. Neurosci. *16*, 4207–4221.

Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., and Noll, D.C. (1997). A parametric study of prefrontal cortex involvement in human working memory. Neuroimage *5*, 49–62.

Buckner, R.L., and Koutstaal, W. (1998). Functional neuroimaging studies of encoding, priming, and explicit memory retrieval. Proc. Natl. Acad. Sci. USA, in press.

Buckner, R.L., Petersen, S.E., Ojemann, J.G., Miezin, F.M., Squire, L.R., and Raichle, M.E. (1995). Functional anatomical studies of explicit and implicit memory retrieval tasks. J. Neurosci. *15*, 12–29.

Buckner, R.L., Bandettini, P.A., O'Craven, K.M., Savoy, R.L., Petersen, S.E., Raichle, M.E., and Rosen, B.R. (1996). Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. Proc. Natl. Acad. Sci. USA *93*, 14878–14883.

Buckner, R.L., Koutstaal, W., Schacter, D.L., Petersen, S.E., Raichle, M.E., and Rosen, B.R. (1997). FMRI studies of item repetition during word generation. Cog. Neurosci. Soc. Annu. Meet. *4*, 67.

Buckner, R.L., Koutstaal, W., Schacter, D.L., Dale, A.M., Rotte, M.R., and Rosen, B.R. (1998a). Functional-anatomic study of episodic retrieval: II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. Neuroimage, in press.

Buckner, R.L., Koutstaal, W., Schacter, D.L., Wagner, A.D., and Rosen, B.R. (1998b). Functional-anatomic study of episodic retrieval using fMRI: I. Retrieval effort versus retrieval success. Neuroimage, in press.

Burock, M., Buckner, R.L., Dale, A.M. (1998). Understanding differential responses in event related fMRI through linear simulation. Proc. Soc. Magn. Reson. Sci. Meet. Exhib., in press.

Clark, V.P., Maisog, J.M., and Haxby, J.V. (1997). fMRI studies of face memory using random stimulus sequences. Neuroimage *5*, S50.

Cohen, J.D., Forman, S.D., Braver, T.S., Casey, B.J., Servan-Schreiber, D., and Noll, D.C. (1994). Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. Hum. Brain Map. *1*, 293–304.

Cohen, J.D., Perlstein, W.M., Braver, T.S., Nystrom, L.E., Noll, D.C., Jonides, J., and Smith, E.E. (1997). Temporal dynamics of brain activation during a working memory task. Nature *386*, 604–607.

Cohen, M.S. (1997). Parametric analysis of fMRI data using linear systems methods. Neuroimage *6*, 93–103.

Corbetta, M., Miezin, F.M., Dobmeyer, S., Shulman, G.L., and Petersen, S.E. (1991). Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. J. Neurosci. *11*, 2383–2402.

Courtney, S.M., Ungerleider, L.G., Keil, K., and Haxby, J.V. (1997). Transient and sustained activity in a distributed neural system for human working memory. Nature *386*, 608–611.

Dale, A.M., and Buckner, R.L. (1997). Selective averaging of rapidly presented individual trials using fMRI. Hum. Brain Map. *5*, 329–340.

Demb, J.B., Desmond, J.E., Wagner, A.D., Vaidya, C.J., Glover, G.H., and Gabrieli, J.D.E. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. J. Neurosci. *15*, 5870–5878.

Desimone, R. (1992). The physiology of memory: recordings of things past. Science *258*, 235–246.

Desimone, R., Miller, E.K., Chelazzi, L., and Lueschow, A. (1995). Multiple memory systems in the visual cortex. In The Cognitive Neurosciences, M.S. Gazzaniga, ed. (Cambridge, MA: MIT Press), pp. 475–486.

DeYoe, E.A., Carman, G.J., Bandettini, P., Glickman, S., Wieser, J., Cox, R., Miller, D., and Neitz, J. (1996). Mapping striate and extrastriate visual areas in human cerebral cortex. Proc. Natl. Acad. Sci. USA *93*, 2382–2386.

Engel, S.A., Glover, G.H., and Wandell, B.A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. Cerebral Cortex *7*, 181–192.

Friston, K.J., Josephs, O., Rees, G., and Turner, R. (1997). Nonlinear event-related responses in fMRI. Magn. Res. Med. *39*, 49–52.

Gabrieli, J.D.E., Desmond, J.E., Demb, J.B., Wagner, A.D., Stone, M.V., Vaidya, C.J, and Glover, G.H. (1996). Functional magnetic resonance imaging of semantic memory processes in the frontal lobes. Psychol. Sci. *7*, 278–283.

Halgren, E., Buckner, R.L., Marinkovic, K., Rosen, B.R., and Dale, A.M. (1997). Cortical localization of word-repitition effects. Cog. Neurosci. Soc. Annu. Meet. *4*, 34.

Josephs, O., Turner, R., and Friston, K. (1997). Event-related fMRI. Hum. Brain Map. *5*, 243–248.

Kawashima, R., O'Sullivan, B.T., and Roland, P.E. (1995). Positron-emission tomography studies of cross-modality inhibition in selective attention tasks: closing the "mind's eye." Proc. Natl. Acad. Sci. USA *92*, 5969–5972.

Konishi, S., Yoneyama, R., Itagaki, H., Uchida, I., Nakajima, K., Kato, H., Okajima, K., Koizumi, H., and Miyashita, Y. (1996). Transient brain activity used in magnetic resonance imaging to detect functional areas. Neuroreport *8*, 19–23.

Koutstaal, W., Buckner, R.L., Schacter, D., and Rosen, B.R. (1997). An fMRI study of item repetition during auditorily cued word generation. Cog. Neurosci. Soc. Annu. Meet. *4*, 68.

Kwong, K.K., Belliveau, J.W., Chesler, D.A., Goldberg, I.E., Weisskoff, R.M., Poncelet, B.P., Kennedy, D.N., Hoppel, B.E., Cohen, M.S., and Turner, R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc. Natl. Acad. Sci. USA *89*, 5675–5679.

Li, L., Miller, E.K., and Desimone, R. (1994). The representation of stimulus familiarity in anterior inferior temporal cortex. J. Neurophysiol. *69*, 1918–1929.

Malach, R., Reppas, J.B., Benson, R.R., Kwong, K.K., Jiang, H., Kennedy, W.A., Ledden, P.J., Brady, T.J., Rosen, B.R., and Tootell, R.B.H. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. Proc. Natl. Acad. Sci. USA *92*, 8135–8139.

Miller, E.K., and Desimone, R. (1994). Parallel neuronal mechanisms for short-term memory. Science *263*, 520–522.

O'Craven, K.M., Rosen, B.R., Kwong, K.K., Treisman, A., and Savoy, R.L. (1997). Voluntary attention modulates fMRI activity in human MT-MST. Neuron *18*, 591–598.

Petrides, M., Alivisatos, B., Evans, A.C., and Meyer, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. Proc. Natl. Acad. Sci. USA *90*, 873–877.

Raichle, M.E., Fiez, J.A., Videen, T.O., MacLoed, A.-M.K., Pardo, J.V., Fox, P.T., and Petersen, S.E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. Cerebral Cortex *4*, 8–26.

Reese, T.G., Davis, T.L., and Weisskoff, R.M. (1995). Automated shimming at 1.5 T using echo-planar image frequency maps. J. Magn. Reson. Imag. *5*, 739–745.

Riches, I.P., Wilson, F.A., and Brown, M.W. (1991). The effects of visual stimulation and memory on neurons of the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of the primate. J. Neurosci. *11*, 1763–1779.

Roediger, H.L., III, Weldon, M.S., and Challis, B.H. (1989). Explaining dissociations between implicit and explicit measures of retention: a processing account. In Varieties of Memory and Consciousness: Essays in Honor of Endel Tulving, H.L. Roediger and F.I.M. Craik, eds. (Hillsdale, NJ: Erlbaum), pp. 2–41.

Rolls, E.T., Baylis, G.C., Hasselmo, M.E., and Nalwa, V. (1989). The effect of learning on the face selective responses of neurons in the cortex in the superior temporal sulcus of the monkey. Exp. Brain Res. *76*, 153–164.

Rosen, B.R., Buckner, R.L., and Dale, A.M. (1998). Event related fMRI: past, present, and future. Proc. Natl. Acad. Sci. USA, in press.

Savoy, R.L., Bandettini, P.A., O'Craven, K.M., Kwong, K.K., Davis, T.L., Baker, J.R., Weisskoff, R.M., and Rosen, B.R. (1995). Pushing the temporal resolution of fMRI: studies of very brief visual stimuli, onset variability and asynchrony, and stimulus-correlated changes in noise. Proc. Soc. Magn. Reson. Sci. Meet. Exhib. *3*, 450.

Schacter, D.L. (1992). Understanding implicit memory: a cognitive neuroscience approach. Am. Psychol. *47*, 559–569.

Schacter, D.L., and Buckner, R.L. (1998a). Priming and the brain. Neuron *20*, this issue, 185–195.

Schacter, D.L., and Buckner, R.L. (1998b). On the relations among priming, conscious recollection, and intentional retrieval: evidence from neuroimaging research. Neuro. Learn. Mem., in press.

Schacter, D.L., Alpert, N.M., Savage, C.R., Rauch, S.L., and Albert, M.S. (1996). Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. Proc. Natl. Acad. Sci. USA *93*, 321–325.

Schacter, D.L., Buckner, R.L., Koutstaal, W., Dale, A.M., and Rosen, B.R. (1997). Late onset of anterior prefrontal activity during true and false recognition: an event-related fMRI study. Neuroimage *6*, 259–269.

Schacter, D.L., Chiu, C.-Y.P., and Ochsner, K.N. (1993). Implicit memory: a selective review. Annu. Rev. Neurosci. *16*, 159–182.

Sereno, M.I., Dale, A.M., Reppas, J.B., Kwong, K.K., Belliveau, J.W., Brady, T.J., Rosen, B.R., and Tootell, R.B.H. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science *268*, 889–893.

Shulman, G.L., Corbetta, F.M., Buckner, R.L., Raichle, M.E., Fiez, J.A., Miezin, F.M., and Petersen, S.E. (1997). Top-down modulation of early visual cortex. Cerebral Cortex *7*, 193–206.

Smith, E.E., and Jonides, J. (1997). Working memory: a view from neuroimaging. Cogn. Psych. *33*, 5–42.

Squire, L.R., Ojemann, J.G., Miezin, F.M., Petersen, S.E., Videen, T.O., and Raichle, M.E. (1992). Activation of the hippocampus in normal humans: a functional anatomical study of memory. Proc. Natl. Acad. Sci. USA *89*, 1837–1341.

Talairach, J., and Tournoux, P. (1988). Co-planar Stereotaxic Atlas of the Human Brain. (New York: Thieme Medical Publishers).

Tootell, R.B.H., Reppas, J.B., Kwong, K.K., Malach, R., Born, R.T., Brady, T.J., Rosen, B.R., and Belliveau, J.W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. J. Neurosci. *15*, 3215–3230.

Tootell, R.B.H., Dale, A.M., Sereno, M.I., and Malach, R. (1996). New images from human visual cortex. Trends Neurosci. *19*, 481–489.

Ungerleider, L.G. (1995). Functional brain imaging studies of cortical mechanisms for memory. Science *270*, 769–775.

Van Essen, D.C., and Drury, H.A. (1997). Structural and functional analyses of human cerebral cortex using a surface-based atlas. J. Neurosci. *17*, 7079–7102.

Wagner, A.D., Buckner, R.L., Koutstaal, W., Schacter, D.L., Gabrieli, J.D.E., and Rosen, B.R. (1997). An fMRI study of within- and across-task item repetition during semantic classification. Cogn. Neurosci. Soc. Annu. Meet. *4*, 68.

Wagner, A.D., Desmond, J.E., Glover, G.H., and Gabrieli, J.D.E. (1998). Conceptual repetition priming effects with picture stimuli. J. Cognit. Neurosci., in press.

Zarahn, E., Aguirre, G., and D'Esposito, M. (1997a). A trial-based experimental design for fMRI. Neuroimage *6*, 122–138.

Zarahn, E., Aguirre, G.K., and D'Esposito, M. (1997b). Empirical analyses of BOLD fMRI statistics: I. Spatially unsmoothed data collected under null-hypothesis conditions. Neuroimage *5*, 179–197.