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fMRI Study of Face Perception and Memory Using Random Stimulus Sequences

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Clark, Vincent P., Jose M. Maisog, and James V. Haxby. fMRI study of face perception and memory using random stimulus sequences. *J. Neurophysiol.* 79: 3257–3265, 1998. A new functional magnetic resonance imaging (fMRI) method was used to investigate the functional neuroanatomy of face perception and memory. Whole-brain fMRI data were acquired while four types of stimuli were presented sequentially in an unpredictable pseudorandom order at a rate of 0.5 Hz. Stimulus types were a single repeated memorized target face, unrepeated novel faces, nonsense scrambled faces, and a blank screen. Random stimulus sequences were designed to generate a functional response to each stimulus type that was uncorrelated with responses to other stimuli. This allowed fMRI responses to each stimulus type to be examined separately using multiple regression. Signal increases were found for all stimuli in ventral posterior cortex. Responses to intact faces extended to more anterior locations of occipitotemporal cortex than did responses to scrambled faces, consistent with previous studies of face perception. Responses evoked by novel faces were in regions of ventral occipitotemporal cortex medial to regions in which significant responses were evoked by the target face. The repeated target face stimulus also evoked activity in widely distributed regions of frontal and parietal cortex. These results demonstrate that cortical hemodynamic responses to interleaved novel and repeated stimuli can be distinguished and measured using fMRI with appropriate stimulus sequences and data analysis methods. This method can now be used to examine the neural systems involved in cognitive tasks that were previously impossible to study using positron emission tomography or fMRI.

INTRODUCTION

In many electrophysiological and psychophysical experiments of attention, perception, and memory, randomized stimulus orders are used with target stimuli presented at unpredictable times (Hillyard and Picton 1987; Regan 1989). By contrast, most previous studies of object perception and memory using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have used experimental paradigms in which trains of similar stimuli are presented in repeated blocks (e.g., Clark et al. 1996, 1997; Haxby et al. 1994, 1996; Kanwisher et al. 1997; McCarthy et al. 1997b; Puce et al. 1996; Tulving et al. 1996). In the typical blocked experimental design, the functional responses evoked by individual stimulus types presented within blocks are not resolved. Because of this limitation, responses to unpredictable presentations of individual novel stimuli cannot be discriminated from responses to familiar stimuli presented in the same sequence. This comparison is important for understanding the neural mechanisms supporting memory and recognition. The use of blocked stimulus

designs also makes it difficult to compare the results of these fMRI investigations with those of previous electrophysiological and psychophysical research that have used randomized designs. Furthermore, the specificity of functional data obtained using blocked designs may be compromised by a number of factors, including the subjects' expectancies regarding upcoming stimuli within and between blocks, and changes in subjects' attentional state and level of arousal between blocks.

Most previous attempts to overcome problems associated with blocked stimulus designs have used single trial designs with slow stimulus presentation rates to reduce the overlap of the hemodynamic response evoked by consecutive trials (Boynton et al. 1996; Buckner et al. 1996; McCarthy et al. 1997a; Zarahn et al. 1997). This method limits the number of trials that may be collected in individual experiments, and the use of long intervals without stimuli may influence subjects' level of attention and arousal. A recent paper by Dale and Buckner (1997) used stimulus presentation rates as fast as one stimulus every 2 s and showed that responses in retinotopically organized lower-order visual cortical areas of the right and left hemispheres responded selectively to stimuli positioned in the left and right visual fields, respectively. In the present study, we investigated whether differential responses in higher-order visual cortical areas to different types of stimuli presented rapidly in the same visual field location can be distinguished using fMRI.

To overcome problems associated with using blocked stimulus designs and long interstimulus intervals (ISIs), we have developed a new fMRI method to measure responses to different types of individual stimuli presented at rapid rates in pseudorandomized, interleaved sequences. We have used this method to examine the functional neuroanatomy of face perception and memory. In this experiment, three types of face stimuli (a repeated memorized target face, unrepeated novel faces, and nonsense scrambled faces) and a blank screen were presented in interleaved sequences. It was expected that differential responses to intact and scrambled faces would be similar to those of previous functional brain imaging studies, which have shown that intact faces generate responses in more anterior regions of ventral occipitotemporal cortex than do scrambled faces, specifically in the fusiform gyrus and lateral occipitotemporal sulcus (Clark et al. 1996, 1997; Haxby et al. 1994; Kanwisher et al. 1997; McCarthy et al. 1997b; Puce et al. 1996; Sergent et al. 1992). No previous PET or fMRI studies have examined responses to novel versus repeated objects presented in interleaved

sequences. A previous PET study comparing novel versus repeated objects using a blocked stimulus design (Tulving et al. 1996) found responses in medial occipitotemporal areas to novel stimuli. It was expected that the results of the present study would be consistent with these previous studies, and that the use of interleaved stimulus sequences would provide information on differential responses to novel and repeated face stimuli when presented in the same block of stimuli in an unpredictable sequence.

METHODS

Seven healthy right-handed volunteers (4 women, ages 22–32 yr) participated in this study. All subjects gave written informed consent.

An interleaved gradient echo, echo planar scanning sequence was used [20 axial slices, 6 mm thick; repetition time (TR) = 2,000 ms; echo time (TE) = 40 ms; flip angle = 90°; field of view = 27 cm; matrix = 64 × 64; 92 repetitions per time series] on a 1.5 Tesla Signa MRI scanner (GE, Milwaukee, WI). Five or more time series were acquired per subject. For all studies, high-resolution volume fast spoiled gradient recalled echo (FSPGR) structural images were acquired at the same locations as the echo-planar images (TR = 13.9 ms, TE = 5.3 ms, flip angle = 20°, matrix = 256 × 256).

The different stimulus types were presented in interleaved, pseudorandom sequences of 90 items. Stimulus types were a repeated target face (10% of stimuli), unrepeated novel faces (30%), scrambled faces (30%), and a blank screen (30%). Twenty scrambled face stimuli were generated by rearranging rectangular sections of the novel faces and spatially smoothing them. Stimulus duration was 1,900 ms. Stimuli were presented at a rate of 0.5 Hz, with 100 ms between stimuli. This rate of stimulus presentation was used to give subjects ample time to make a response to each stimulus before the presentation of subsequent stimuli, and was equivalent to the rates of stimulus presentation used in our previous studies of face perception (Clark et al. 1997; Haxby et al. 1996). Also, stimulus onset was synchronized to the onset of MRI data acquisition, which facilitated data analysis. Subjects were trained before scanning to make a speeded right handed button press to the target face.

Numerous random stimulus sequences were generated. Each sequence contained target faces, novel faces, scrambled face stimuli, and blanks, presented in a randomized, interleaved order. The expected neural responses to the three stimulus types were modeled separately for each sequence as a square wave with the same time course as the stimuli (on = 1, off = 0). The expected hemodynamic response for each of the three face stimulus types was modeled by convolving these three square-wave time series with a Gaussian model of the hemodynamic response function using experimentally derived values (dispersion = 1.8 s sD, delay = 4.8 s) (Friston et al. 1994; Maisog et al. 1995). Examples of predicted response waveforms for scrambled faces, novel faces, and the target face are illustrated in Fig. 1. The cross-correlations among these models of fMRI response to each stimulus type were then computed for each random stimulus sequence. Five different stimulus sequences were selected for use in this experiment that had nonsignificant correlations of predicted hemodynamic responses to target, novel, and scrambled faces ($|r| < 0.05$). Thus the predicted responses to the three types of stimuli embedded in each sequence were essentially orthogonal.

Between-scan movement was corrected with Automatic Image Registration (AIR) software (Woods et al. 1993). The statistical significance of stimulus-evoked changes in MRI signal intensity was evaluated using multiple regression (Friston et al. 1995b; Haxby et al. 1997; Maisog et al. 1996; Neter et al. 1990). For this
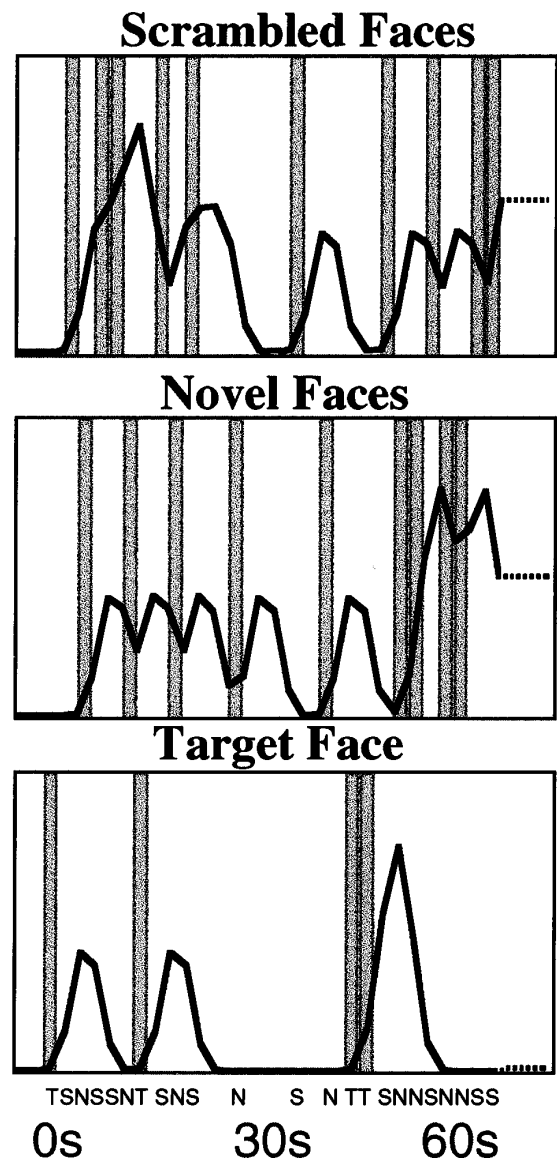

FIG. 1. Modeled hemodynamic response time series (black lines) shown for the scrambled (S), novel (N), and memorized target (T) face stimuli. The time of appearance of stimuli are indicated at the bottom of the figure, and by the location of the gray bars. Sixty seconds of 1 experimental run is shown. Amplitude of gray bars indicates asymptotic maximum of functional magnetic resonance imaging (fMRI) response. Stimulus sequences were selected for each 3-min experimental run that generated hemodynamic responses that were uncorrelated between the 3 stimulus conditions.

analysis, the delayed and smoothed time series computed for the three stimulus types were used as regressors. Multiple regression finds the weighted sum of these regressors that best fits the obtained fMRI time series, using a least-squares test of fit. Insofar as overlapping responses are approximately additive (Boynton et al. 1996; Dale and Buckner 1997), significant responses evoked by any combination of the three stimulus types can be identified within the same voxel location. However, because the regressors were uncorrelated, significant activity evoked by one stimulus condition could not be modeled using any linear combination of the other stimuli's regressors, and thus could only reach significance for the regressor representing the response to that stimulus. Additional regressors were included in the analysis to partial out variance due to baseline shifts between time series and linear drift within time

series. The significance of the regression weight for each stimulus type was tested using the extra sums of squares test, which generated a Wilks' Λ map (Neter et al. 1990). The Wilks' Λ map was then converted to an *F*-test map by an exact transformation (Rencher 1995). The *F* ratio gives the ratio of the magnitude of signal variance explained by the statistical model to the magnitude of the unexplained signal variance. A *Z* statistic was then formed from the *F* ratio, using a probability integral transformation (Friston et al. 1991). To form the *Z* statistic, the magnitude of the *F* ratio and the degrees of freedom in the denominator of the *F* ratio were multiplied by an experimentally derived correction factor (0.42) (Maisog et al. 1995) to correct for temporal autocorrelations due to the smoothness of the hemodynamic response. Regions of interest (ROIs) were located by identifying clusters of three or more contiguous voxels where MRI signal increased in response to a stimulus condition and that were significant at $P < 0.05$.

ROIs were also located by identifying clusters of three or more contiguous voxels where MRI signal increased in response to a specific combination of stimulus conditions. ROIs were spatially normalized using SPM96 (Friston et al. 1995a) for use in subsequent multisubject comparisons.

After data from each individual subject were analyzed using multiple regression, the statistical results of these analyses were compared across subjects using two different methods. *1*) The overlap of significant activity across subjects was assessed for each stimulus type and combination of stimulus types within individual voxels. This was performed by identifying the number of subjects with significant activity for the same stimulus type or combination of stimulus types in the same spatially normalized voxel location. Clusters of voxels that showed the same pattern of signal change and overlapped for at least three subjects were analyzed for volume, anatomic center of mass, and Brodmann's area (BA) based on the
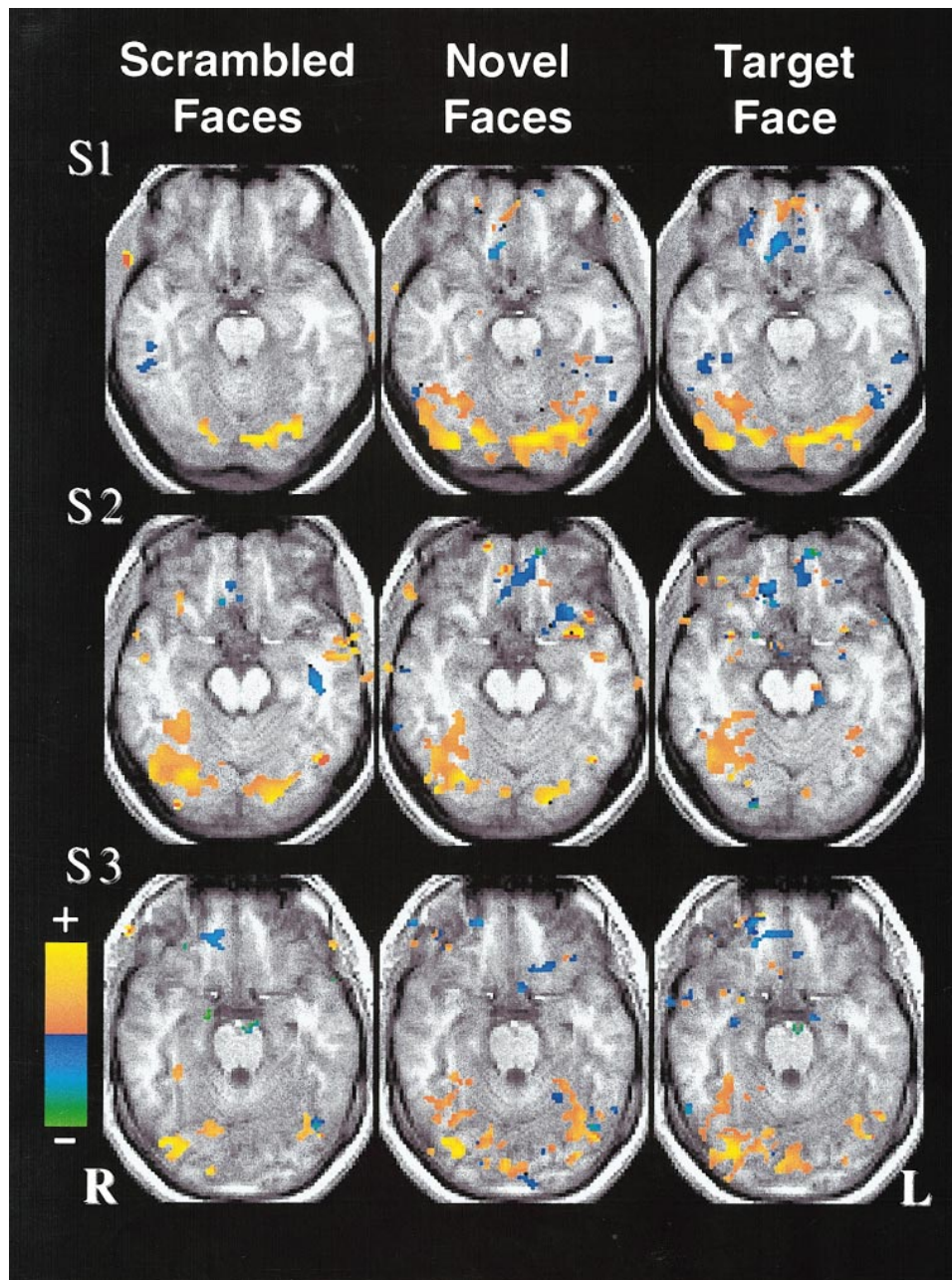

FIG. 2. Color-coded percentage change maps from 3 subjects demonstrating the response to scrambled, novel, and target face stimuli, plotted onto coplanar normalized coronal structural images of right hemisphere located at $-20z$ mm in the Talairach coordinate system (Talairach and Tournoux 1988). The right side of the brain is displayed on the *left,* and left on the *right*. Areas showing increased MR signal during face-matching relative to control are shown in red and yellow, and areas showing decreased signal are shown in blue and green. Color intensity ranges from $+0.8$ to -0.8%, representing average percentage change in response to a single stimulus.
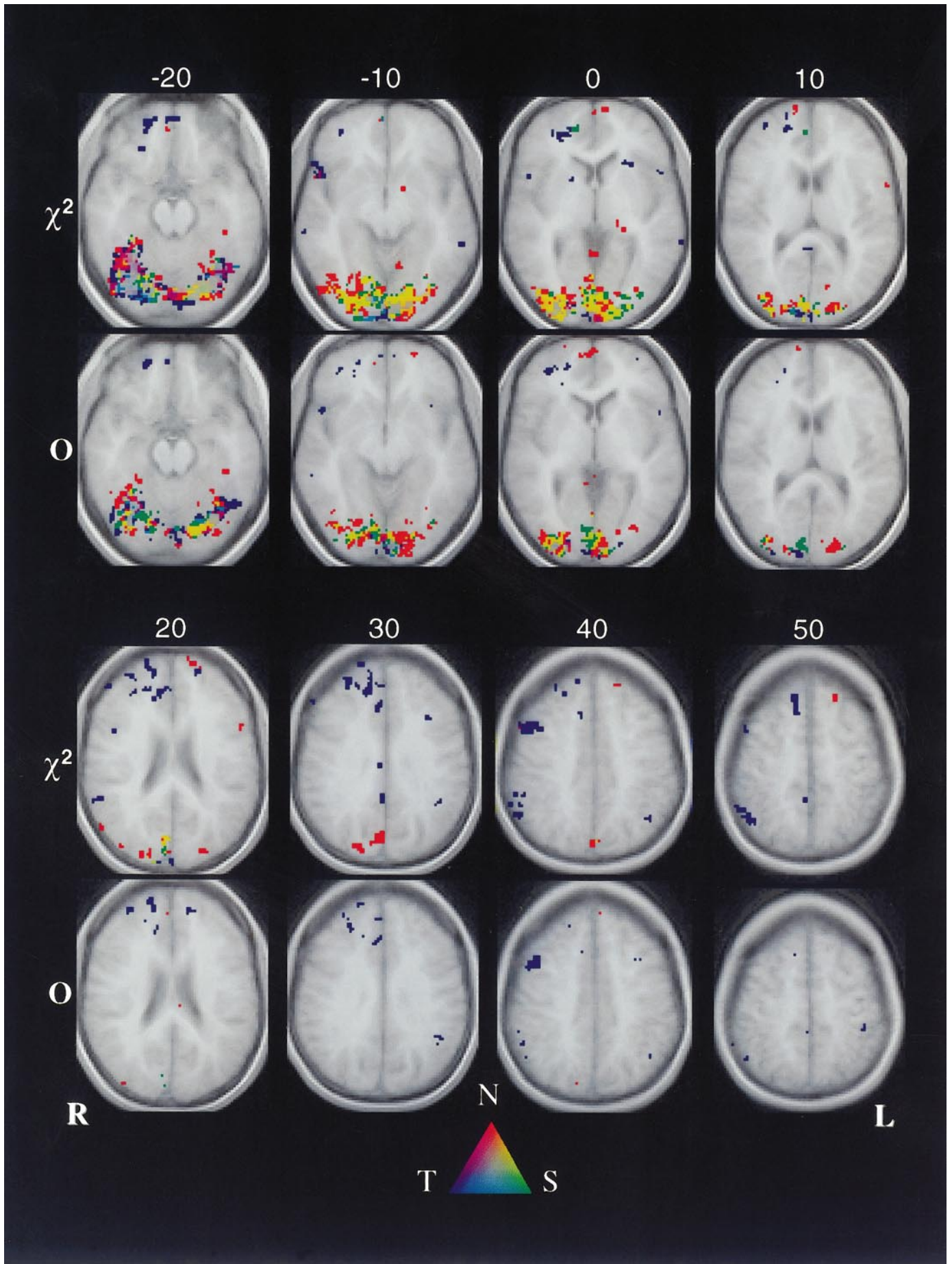
atlas of Talairach and Tournoux (1988). 2) χ^2 distribution maps were obtained for each stimulus condition separately by obtaining the sum of the squares of all seven subjects' Z score probability maps, which had been thresholded to include only voxels with positive signal change. The sum of squared Z score values has been shown to have a χ^2 distribution (Hugill 1985; Papoulis 1991). This was done separately for the statistical probability maps of the responses to scrambled faces, novel faces, and the target face. These three group χ^2 maps were then thresholded at $P < 0.05$ (df = 7).

Time-locked averaging was performed to confirm the results of statistical tests. To obtain average evoked fMRI response time series, time-locked averages were obtained for each stimulus type separately. These were computed by selectively averaging all echo-planar images volumes that were collected at the same point in time relative to the onset of each instance of the same stimulus type. These time-locked averages were computed separately for 12 sequential time points, ranging from 4 s before stimulus onset to 18 s after stimulus onset. Evoked time series were then averaged across groups of contiguous voxels with statistically significant responses to the same stimulus type or combinations of stimulus types. The percentage change of activity for each time point was computed relative to a prestimulus baseline (-2 s to 0 s).

RESULTS

The mean accuracy for detection of the memorized target face was 95%. The average reaction time for the correct detection was 641 ± 103 ms.

Different patterns of response to scrambled faces, novel faces, and the memorized target face were observed in data obtained from individual subjects, as shown in Fig. 2. The response evoked by scrambled faces was more posterior and smaller in volume than the response evoked by intact faces (novel or target faces). Intact faces evoked activity in regions that overlapped with regions that responded to scrambled faces, but extended more anteriorly and laterally in all subjects to include bilateral ventrolateral occipital cortex in the inferior occipital sulcus and ventral occipitotemporal cortex in the fusiform gyrus, lateral occipitotemporal sulcus, and inferior temporal gyrus.

The consistency of this pattern of response across subjects was examined by analysis of the overlap maps and the group χ^2 maps. Both analyses confirmed that the different patterns of response to each stimulus type were consistent across subjects, as can be seen in Fig. 3, but areas of overlap and significant χ^2 were less extensive than areas of activation found in results of individual subjects. As the overlap analysis proved to be more conservative than the χ^2 analysis, the overlap maps were examined for volume, anatomic center of mass, and BA.

The analysis of overlap showed that all stimuli evoked significantly increased signal in the same voxel location of individual subjects near the posterior end of the calcarine fissure ($-4x$, $-95y$, $-16z$) and in the fusiform gyrus bilaterally ($32x$, $-74y$, $-19z$ and $-36x$, $-74y$, $-19z$). Additional regions in posterior occipital cortex (posterior to $-80y$) were found that responded to scrambled and novel faces, but not to the target face. Some voxels were found in individual subjects that responded to scrambled and target faces, but not to novel faces. However, none of these voxels overlapped across subjects.

Regions of individual subjects that responded to both the target and novel faces were only found to overlap significantly across multiple subjects in the right hemisphere ($39x$, $-56y$, $-22z$). This is nearby to foci found in many other studies of face perception using a blocked stimulus design (Clark et al. 1996: $37x$, $-55y$, $-10z$; Haxby et al. 1994: $38x$, $-58y$, $0z$; Kanwisher et al. 1997: $40x$, $-55y$, $-10z$; McCarthy et al. 1997b: $40x$, $-59y$, $-22z$; Sergent et al. 1992: $37x$, $-55y$, $-11z$). Activity evoked by novel faces in anterior ventral occipitotemporal cortex (anterior to $-60y$) was situated medially to activity evoked by the target face in both the left hemisphere [$-35x$ for novel faces vs. $-41x$ for target face, $t = 7.7$, df(1,28), $P < 10^{-5}$] and the right hemisphere [$38x$ for novel faces vs. $49x$ for target face; $t = 5.8$, df(1,99), $P < 10^{-7}$].

Activity that was evoked by novel faces alone (with no significant response to other stimulus types) was observed in many regions of occipital, temporal, and frontal cortex. ROIs included the left cuneus (BA 18), left lingual and bilateral fusiform gyri (BA 18, 19, 37), right inferior and middle occipital gyri (BA 18, 19), right inferior temporal gyrus (BA 37), right superior temporal gyrus (BA 22), left middle temporal gyrus (BA 35, 36), and bilateral dorsal and superior frontal gyri (BA 6 in the left hemisphere, BA 10 in the right). Regions that responded only to the target face were located over a wider range of brain regions than those that responded only to novel faces, but were less extensive in posterior cortical areas. This included the right cuneus (BA 18), right lingual and bilateral fusiform gyri (BA 18, 19, 37), bilateral inferior parietal gyri (BA 7, 40), right superior parietal gyrus (BA 7), bilateral dorsal frontal gyri (BA 6, 8, 9, 32), bilateral inferior frontal gyri (BA 9, 44, 45), right middle frontal gyrus (BA 6, 8, 9, 10, 47), and right superior frontal gyrus (BA 6, 9, 10). The target face evoked a larger volume of activity in right frontal cortex (3.4 cm³ total volume) than in the left (0.5 cm³), according to the overlap criteria used.

The time series obtained by computing the averaged evoked fMRI responses to each stimulus type showed that response waveforms differed between stimulus types in a manner consistent with the results of the statistical analyses, as illustrated in Fig. 4. The peak response latency was very consistent across stimulus types and regions, falling within a limited range of 4–6 s. Response amplitudes varied across

FIG. 3. For all slices, regions of significantly increased signal evoked by scrambled faces (S; green), novel faces (N; red), and the target face (T; blue) are shown. Results are plotted onto coplanar axial structural images. The location of the images along the z dimension in Talairach space (ranging from -20 to $+50$ mm) are shown. The right side of the brain is displayed on the *left,* and left on the *right.* Rows marked ''O'' show regions with a significant overlap of response, defined as a minimum of 3 subjects showing a significant response for the same condition in the same normalized voxel location. Voxel color determined by relative number of subjects showing significant response to each condition at that normalized voxel location. Rows marked ''χ^2'' show regions with a significant χ^2 amplitude, obtained by summing the squared Z score values across subjects. Voxel color determined by relative amplitude of χ^2 test of each condition at that normalized voxel location.
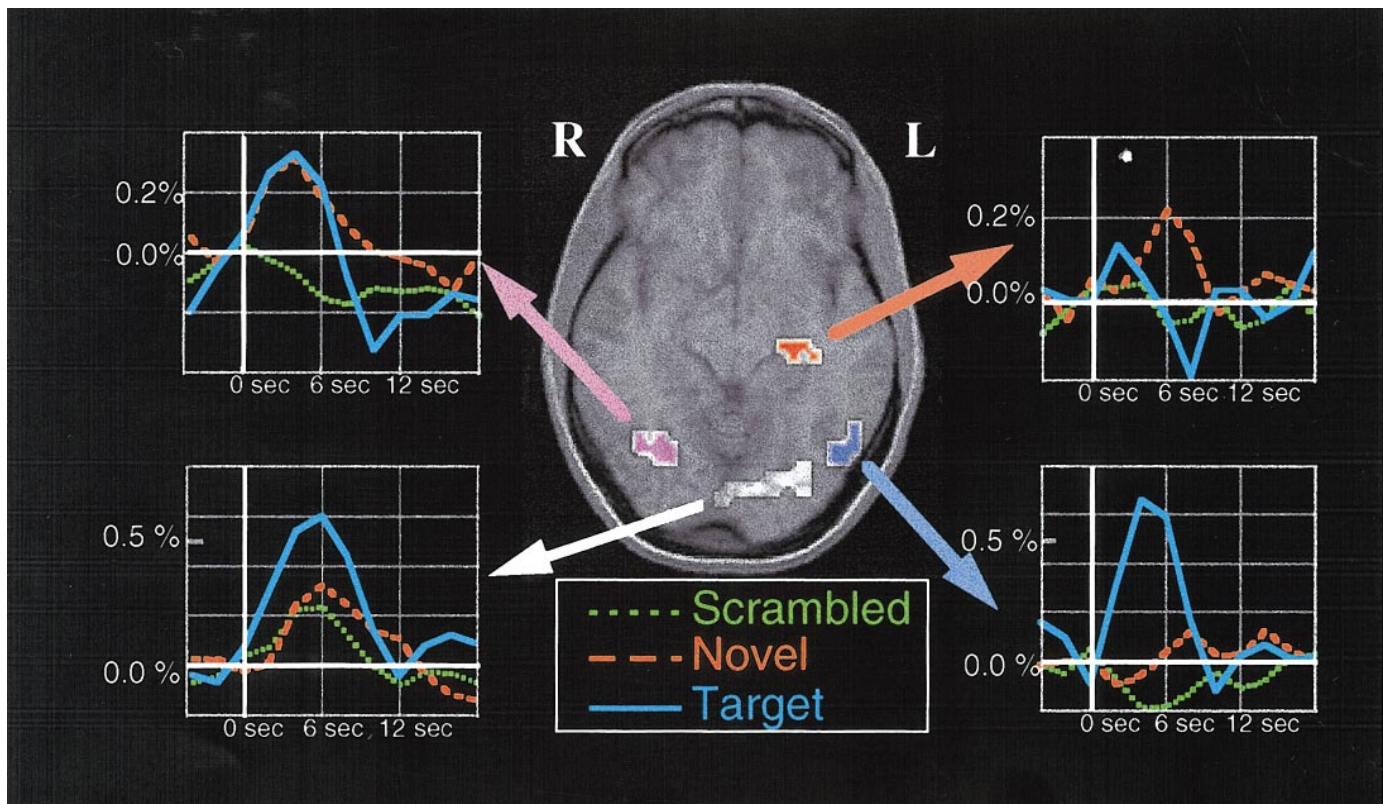
FIG. 4. Stimulus locked average time series are shown for 4 groups of contiguous voxels of 1 subject. The white region was found to respond significantly to all 3 stimulus types, the purple region responded to novel and target faces, but not the scrambled face, the red region responded only to novel faces, and the blue region responded only to the target face. Averaged evoked fMRI time series responses to scrambled faces are shown in green, responses to novel faces shown in red, and responses to target face shown in blue. Time series plotted from 4 s before stimulus onset to 18 s after stimulus onset. Amplitude of percentage change relative to prestimulus baseline is shown.

regions and were typically larger for the target face than for the other stimulus types. This may have resulted from the greater proportion of scrambled and novel face stimuli then target stimuli occurring at pre- and poststimulus time points, which decreased the relative change in evoked response amplitude.

Group averages of the evoked time series were obtained to examine the mean response latency of the hemodynamic response. The evoked time series of significant voxels were averaged together across subjects depending on their location relative to the origin of Talairach stereotaxic space, defined by the position of the AC-PC line. Group average evoked responses to the target face stimulus of eight brain sectors are shown in Fig. 5 (right and left ventral posterior, right and left dorsal posterior, right and left ventral anterior, and right and left dorsal anterior). Analysis of these time series revealed that responses in all brain regions had the same latency-to-peak amplitude, falling near 6 s poststimulus onset.

DISCUSSION

These results demonstrate that fMRI can be used to detect and discriminate the responses to different types of stimuli presented in randomized, interleaved sequences with rapid rates of stimulus presentation. Nonspecific responses to all stimuli were found in posterior occipital cortex. The presentation of intact faces (target and novel faces) evoked activity in more anterior locations of occipitotemporal cortex. This

general pattern of response topography was consistent across the seven subjects studied and agrees with previous fMRI experiments of face perception using a blocked stimulus design (Clark et al. 1996, 1997; Kanwisher et al. 1997; McCarthy et al. 1997b; Puce et al. 1996).

In addition, a number of differences were found in the responses to novel faces versus the memorized target face. Greater responses to novel faces were found in medial portions of ventral temporal cortex (anterior to $-60y$), whereas greater responses to the memorized target face were found in lateral portions of ventral temporal cortex. This difference in response topography suggests that stimulus evoked responses in anterior occipitotemporal cortex may be segregated depending on stimulus familiarity or behavioral relevance. This conjecture is consistent with the work of Tulving et al. (1996), who found a temporal/limbic ''novelty detection'' region in a PET study of novel versus previously seen complex pictures. This is also consistent with other studies where stimulus novelty was examined using single word stimuli (Kapur et al. 1995) and for auditorily presented sentences (Tulving et al. 1994). The finding of more lateral activity evoked by the target face is consistent with lesion studies in nonhuman primates, which have shown that lesions in ventrolateral extrastriate cortex, near or within area TEO, greatly decreased performance on discrimination learning tasks where fine visual discriminations must be made (Iwai and Mishkin 1968, 1969; Kikuchi and Awai
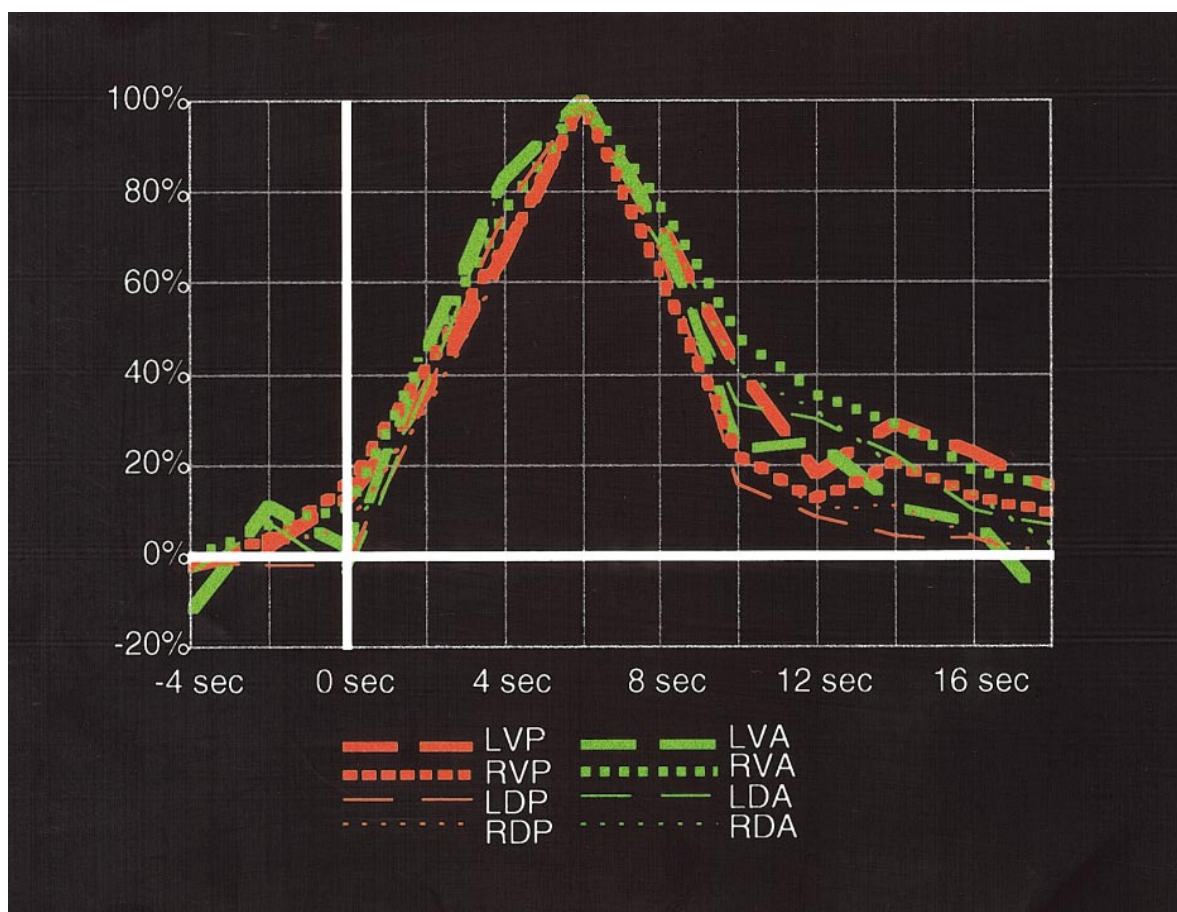
FIG. 5. Group mean evoked fMRI responses to the target face stimulus, normalized to the peak response amplitude. Mean response waveforms were averaged across subjects for 8 separate regions, determined by location relative to the AC-PC line. This included right hemisphere (R, dotted line) vs. left hemisphere (L, dashed line), dorsal (D, thin line) vs. ventral (V, thick line), and anterior (A, green line) vs. posterior (P, red line). Voxels from all brain regions peaked at the same time (6 s).

1980). Many regions of frontal and parietal cortex responded to the target face but did not respond to the other stimuli. These results and those of McCarthy et al. (1997a) and Menon et al. (1997) suggest that the detection of infrequent target stimuli evokes activity in a number of widely distributed cortical regions.

The target face stimulus comprised only 10% of total stimuli and therefore was less frequent than the scrambled and novel face stimuli, which each comprised 30% of stimuli. As with all other neuroimaging methods where signal averaging is employed (e.g., PET, event related potentials, etc.), the sensitivity of signal detection is reduced when fewer sums are obtained. However, a large volume of cortex was found that responded to the target face, indicating that the number of target face stimuli presented was sufficient to obtain a significant response.

Previously, the temporal dispersion of the hemodynamic response detected by fMRI has made it difficult to distinguish functional responses to different types of stimuli presented sequentially in rapid sequences. Recently described methods used to derive independent responses to different stimuli presented in series have mostly used stimulus presentation rates much slower than those used in the present study (Boynton et al. 1996; Buckner et al. 1996; McCarthy et al. 1997a; Zarahn et

al. 1997). Although useful for some applications, the use of slow rates of stimulus presentation limits the number of stimuli that can be presented within a single experiment and may influence subjects' level of attention and arousal. Also, this makes it difficult to compare findings with previous electrophysiological and psychophysical studies, which have typically used more rapid rates of stimulus presentation (Hillyard and Picton 1987; Regan 1989). Dale and Buckner (1997) used stimulus presentation rates that ranged between 1 stimulus per 20 s and 1 stimulus per 2 s, using a simple reversing checkerboard stimulus presented sequentially in the right and left visual fields. This study employed the careful use of stimulus randomization, so that when time-locked averaging was employed, the number of each stimulus type occurring at each relative time point before and after the stimuli of interest were approximately equal throughout the epoch. This ensured that the other stimulus types did not contribute to the average evoked response of the stimulus of interest. This study showed that responses to left and right field stimuli could be distinguished in retinotopically organized lower order visual areas. This study also showed that stimuli presented in a series evoked hemodynamic activity that was nearly identical to the linear addition of activity evoked by individual stimuli, which was also found in the study of Boynton et al. (1996).

The present study investigated whether fMRI can be used to distinguish responses in higher-order cortical areas to different types of randomly presented stimuli based on differences in stimulus form and familiarity. In contrast to the method of stimulus randomization used by Dale and Buckner (1997), the method employed here produced orthogonal response waveforms between the three stimulus types used, but did not require constraints in the relative proportions of different stimulus types required for time-locked averaging. The multiple regression analysis did not require that the response to each individual stimulus be examined, but it instead examined the summed response across all stimuli of the same type within individual runs. Because the fMRI signal is additive and varies in amplitude with variations in stimulus density over the preceding 8–10 s, the methods presented here could be used to examine responses to stimuli presented using any combination of stimulus presentation rate and ISI. This is true given that an accurate model of neural and hemodynamic responses to the stimuli can be constructed, and the stimulus sequences can be arranged such that orthogonal regressors for each stimulus type can be obtained for use in the multiple regression analysis.

The present study was designed such that the predicted functional response to each stimulus type was uncorrelated with the responses to other stimuli. Because of this, the response to each stimulus type was essentially orthogonal from the responses to other stimulus types and could be identified independently using multiple regression. The finding of distinct, anatomically segregated responses to different stimulus types agrees with previous research, suggesting that the model of the hemodynamic response and the assumption of linear additivity are valid to a close approximation. Other studies have suggested that there may be regional differences in the latency of the hemodynamic response (Buckner et al. 1996). Such differences could reduce the sensitivity of this method, as the response waveforms would be shifted in time relative to the regressors. However, differences in response latency were analyzed across a range of brain regions and were not found to vary by more than a small amount. Future improvements in the modeling of the neural and hemodynamic responses to stimuli will serve to reduce statistical error and improve signal detection.

This method can now be used to examine responses to cognitive tasks that require the use of random stimulus sequences, which could not be studied previously using PET or fMRI. This includes tasks that examine responses to frequent target and nontarget stimuli presented in an unpredictable sequence or that examine responses to multiple types of nontarget stimuli presented in an interleaved series.

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