Stimulus Repetition and Hemodynamic Response Refractoriness in Event-Related fMRI

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Abstract: We investigated the extent of hemodynamic recovery following the paired presentation of either identical or different faces at two different inter-stimulus intervals (ISI). Signal recovery was consistently better at an ISI of 6 sec compared to 3 sec. Significantly less signal recovery was associated with identical faces compared to different faces in bilateral mid-fusiform and right prefrontal regions but not in the calcarine and posterior fusiform regions. Repetition suppression effects contributed significantly to incomplete signal recovery in a region-specific manner. Simulations using empirically derived data suggest that experiments with shorter ISI (average 4.5–6.0 sec) are as sensitive as experiments with intermediate ISI (average 9 sec) in detecting response differences if experimental duration is equivalent. However, designs using intermediate ISI may be more appropriate if the expected difference in responses is small and if the number of suitable stimuli is limited. *Hum. Brain Mapping 20:1–12, 2003.*

Key words: event-related fMRI; repetition effects; face processing; experimental design

INTRODUCTION

Functional magnetic resonance imaging (fMRI) studies are designed to detect task or stimulus driven differences in region-specific blood oxygen level dependent (BOLD) signal change. These differences may be expressed through activation topography, magnitude of activation, temporal profile, or some combination of these characteristics. The detection of differences in response magnitude is important in uncovering the functional anatomy of cognitive processes such as priming and subsequent memory [Buckner et al., 1998; Wagner et al., 1998]. Specifically, the ability to detect subtle signal differences in as short an experiment as possible is a desirable goal and has been the subject of several methodological studies to date [Burock and Dale, 2000; Dale, 1999; Friston et al., 1999; Hagberg et al., 2001; Vazquez and Noll, 1998].

Event-related (ER) fMRI experiments are preferred to block designs when the need for stimulus randomization and concerns over habituation exist [Donaldson and Buckner, 2001]. Implementing these experiments involves a trade-off between accuracy of response magnitude estimation and time. Long inter-stimulus interval (ISI) experiments that sample the BOLD response for 18 to 20 sec following each stimulus allow a reasonably complete recovery of the hemodynamic response and require no assumptions concerning the summation of consecutive responses to test stimuli [Bandettini and Cox, 2000]. However,

Contract grant sponsor: NMRC; Contract grant number: 2000/0477; Contract grant sponsor: BMRC; Contract grant number: 014.

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Received for publication 20 March 2003; Accepted 25 April 2003
DOI 10.1002/hbm.10122

these experiments are time-inefficient and obtaining enough responses to facilitate comparisons between more than two different stimulus conditions could prove taxing to a volunteer. In addition, the long intervals between stimuli increase the likelihood of unwanted and possibly confounding cognitive processes [Binder et al., 1999].

Randomized rapid ER designs can ameliorate some of these issues by accommodating more events (engendering overlapping responses) within a shorter time span, provided the contributions of individual events can be accurately separated from the mixture of signals [Dale and Buckner, 1997; Donaldson and Buckner, 2001; Rosen et al., 1998]. In order to separate these signals, it is assumed that the hemodynamic responses to sequential events summate in a roughly linear fashion [Boynton et al., 1996; Dale and Buckner, 1997]. While it is desirable to use short ISI, there is a lower limit below which the assumption of response summation linearity breaks down [Dale, 1999; Friston et al., 1999; Huettel and McCarthy, 2000, 2001a; Vazquez and Noll, 1998]. When this occurs, responses obtained with shorter ISI may be significantly smaller than those associated with longer ISI, adding unwanted variance to the average response elicited by the conditions of interest. This in turn could compromise the detection of differences between the responses and lead to Type II errors.

Functionally linear (i.e., not completely linear, but adequately so) response summation has been demonstrated using ISI as short as 2 to 5 sec with alternating checker-board [Dale and Buckner, 1997] and simple motor tasks [Miezin et al., 2000]. However, it is at present unclear as to how appropriate these timings are for more complex stimuli or for tasks engaging higher cognitive processes. Incomplete recovery of the hemodynamic response was present with checkerboard stimuli when shorter ISI (closer to 1 sec than to 6 sec) were used [Huettel and McCarthy, 2000], and the signal attenuation was even more pronounced when complex face stimuli were presented using an identical paradigm [Huettel and McCarthy, 2001a]. These findings suggest that a minimum ISI of 6 sec may be more appropriate for event-related fMRI studies to avoid signal attenuation due to hemodynamic refractory period effects.

A limitation of the study involving faces was that the paired stimuli comprised identical faces. Invasive electrophysiological methods have revealed a "repetition suppression" effect in some neurons within the inferior temporal cortex of primates when pictures of objects were repeated [Li et al., 1993; Miller et al., 1991]. In fMRI, the repeated presentation of an identical stimulus over a short interval has also been shown to generate a compound BOLD response lower in amplitude than that obtained from presenting dissimilar visual objects [Grill-Spector et al., 1999] or words [Chee et al., 2003]. This effect has been termed "functional magnetic resonance adaptation" (fMR-A). Repeating identical faces could result in overestimating the extent of response refractoriness in short ISI experiments since most experiments that are not specifically evaluating priming or repetition effects do not involve the presentation of identical stimuli.

In their study in which identical faces were presented in pairs, Huettel et al. [2001a] observed spatially selective, reduced signal recovery in bilateral mid-fusiform cortex. The authors suggested that this could be due to regional differences in refractory periods, or due to functional differences between cortical regions but did not evaluate further. We hypothesize that fMR-A, taking place in areas specialized for face processing, could account for the observed regional variation in signal recovery.

We sought to estimate the contribution of fMR-A to the loss of signal recovery in paired-stimulus presentation experiments and to distinguish fMR-A from other causes of incomplete hemodynamic response recovery. To achieve this, we compared the hemodynamic responses following the paired presentation of identical and different faces at two different ISI: 3 and 6 sec. Most of the parameters in this study were chosen keeping in mind the values commonly used in fMRI experiments. We acquired slices across the whole brain using a TR of 3 sec compared to 1 sec normally used in experiments investigating hemodynamic linearity and response recovery. The longer TR, used in most fMRI experiments, results in a larger MR signal compared to a shorter TR and also facilitates better coverage of the brain. To compensate for the coarser temporal sampling, we used interleaved sampling [Josephs et al., 1997].

To compare the ability of short ISI (minimum 3 sec, average 4.5–6 sec) with intermediate ISI (minimum 6 sec, average 9 sec) ER-fMRI experiments to detect differences in signal magnitude between stimulus conditions, we performed simulations based on empirical data.

SUBJECTS AND METHODS

Eight healthy right-handed participants (three women) aged between 20 and 25 gave informed consent for this study. Colored photographs of unfamiliar

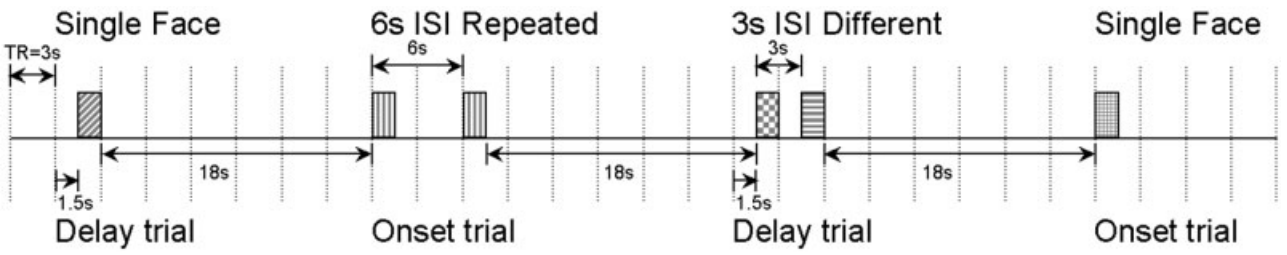

Figure 1.
Exemplars of the sequence and timing used in different trial types.

human faces were presented for 1,500 msec (Fig. 1). The participants viewed one of five trial types: a single face, a pair of identical faces presented at ISI of 3 and 6 sec, and a pair of different faces presented at ISI of 3 and 6 sec. None of the faces shown was repeated across trials. After each trial, a white cross was shown on a black background for 18 sec to allow for recovery of the hemodynamic response. For each trial type, half the stimuli were presented at the onset (Onset trials) of image acquisition. The remaining stimuli (Delay trials) were presented after a delay of 1,500 msec (TR/2). Twenty trials were presented for each trial type (10 delay and 10 onset trials). All five trial types were randomly intermixed within each of the five experimental runs, each of which lasted 477 sec. To encourage attentiveness to the presented faces, participants were asked to indicate the gender of the faces they viewed by pressing appropriate buttons on a response box.

The visual stimuli were rear-projected (Epson EMP 7250) onto a silk screen placed at the rear of the magnet bore. Participants viewed the stimuli via an angled mirror fastened to the head coil. A bite-bar was used to reduce head motion.

Imaging and image analysis

Imaging was performed in a Siemens 3T Allegra system equipped with a head coil (Siemens Allegra, Erlangen, Germany). Thirty-two oblique axial slices were acquired approximately parallel to the AC-PC line using a T2* weighted gradient-echo EPI sequence (TR = 3000 msec; effective TE = 30 msec; matrix = 64 × 64; FOV = 192 × 192 mm; 3.0 mm thickness, 0.3-mm gap). A set of T2 weighted images was acquired in an identical orientation to the functional MR data. High-resolution anatomical reference images were obtained using a three-dimensional MP-RAGE T1-weighted sequence.

The functional images from each subject were preprocessed and analyzed using BrainVoyager 2000 v. 4.7 (Brain Innovation, Maastricht, Holland). Mean intensity normalization was performed prior to motion correction. Alternating axial slices were realigned in time using sinc interpolation. In the spatial domain, data was smoothed with a Gaussian smoothing kernel of 4 mm FWHM. A temporal high pass filter with a period of 157 sec, equivalent to of 3 cycles (per run) in time, was applied following linear trend removal. The functional images were aligned to co-planar high-resolution images and the image stack was then aligned to a high-resolution 3-D image of the brain. The resulting realigned data set was transformed into Talairach space [Talairach and Tournoux, 1988].

Voxel-by-voxel statistical analysis was performed using a general linear model (GLM) with finite impulse response (FIR) predictors. In accordance with the method used by Ollinger et al. [2001a,b], single face trials were treated as "partial trials" and trials involving face-pairs were treated as "compound trials." Hemodynamic responses to single faces and the first face in every pair were estimated using the same set of predictors, labeled "First Stimulus." Four sets of predictors were used to estimate the hemodynamic responses to the second faces in the four paired trial types: "3s ISI Repeated," "3s ISI Different,", "6s ISI Repeated," and "6s ISI Different." The two sets of predictors, the first involving Onset trials and the second involving the Delay trials (totaling 12 predictors), were interleaved, allowing the entire signal time course to be estimated at a resolution of TR/2 or 1.5 sec.

Seven regions-of-interest (ROI), which showed consistent activations across all subjects, were functionally defined for each individual. These ROI lay in the calcarine cortex (between Talairach y coordinate −100 and −86 mm), posterior fusiform (between Talairach y coordinate −85 and −69 mm), mid-fusiform regions

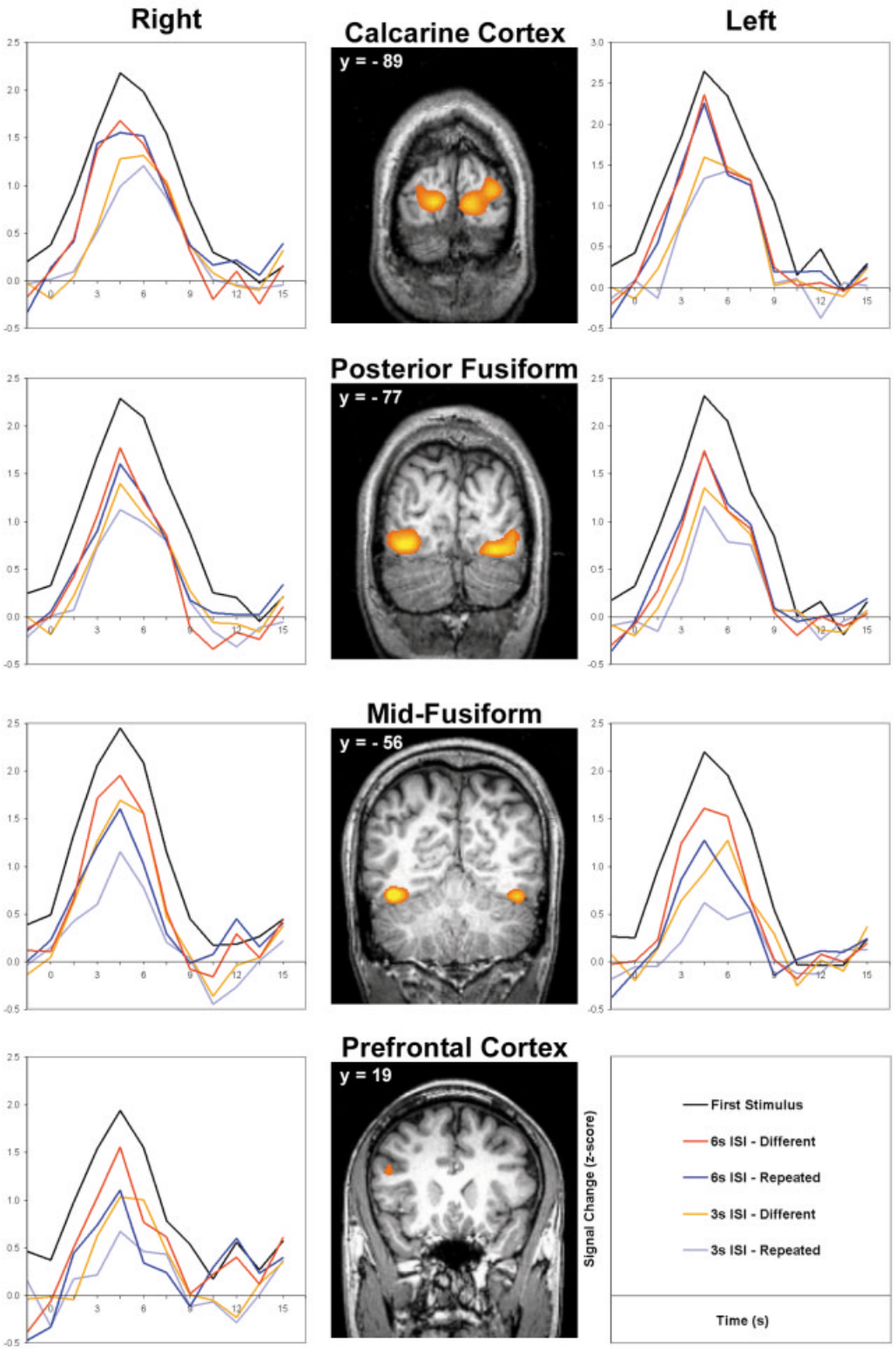
Right
Calcarine Cortex
y = - 89
Left
Posterior Fusiform
y = - 77
Mid-Fusiform
y = - 56
Prefrontal Cortex
y = 19
First Stimulus
6s ISI - Different
6s ISI - Repeated
3s ISI - Different
3s ISI - Repeated
Signal Change (z-score)
Time (s)

Figure 2.

(between Talairach y coordinate −65 and −44 mm) in each cerebral hemisphere and in the inferior frontal gyrus of the right prefrontal cortex (between Talairach y coordinate 16 and 25 mm) (Fig. 2). The first six regions lie in the ventral visual pathway that participates in face processing. The right prefrontal region chosen was activated when non-famous faces were presented for encoding [Chee and Caplan, 2002; Kelley et al., 1998].

Statistical maps were generated for individual participants. Voxels were defined as significantly activated if the peak of the modeled hemodynamic response (corresponding to 4.5 and 6.0 sec from stimulus onset) for the "First Stimulus" exceeded a threshold of $F(2,720) > 12$ ($P < 10^{-6}$, uncorrected). Signal time-courses were obtained from active voxels within each ROI. This yielded five sets of response estimates corresponding to each of the five conditions of interest.

These estimates were then fitted to a Gaussian function [Rajapakse et al., 1998] with three parameters, amplitude α, time-to-peak μ, and dispersion σ. Nonlinear least-squares fitting of the fMRI responses using Matlab (*lsqcurvefit.m*) provided estimates of the model parameters.

$$G(t;\alpha,\mu,\sigma) = \alpha \frac{1}{\sqrt{2\pi\sigma^2}} e^{\frac{-(t-\mu)^2}{2\sigma^2}} \quad (1)$$

To examine the effect of ISI and stimulus repetition on the recovery of the hemodynamic response across cortical regions, the estimated peak amplitude for the BOLD response to the second face was expressed as a fraction of the estimated peak amplitude of the response to the first face for each ROI. This "normalized signal recovery" could take a value between 0 and 1, where 1 denotes complete recovery and 0 represents no recovery.

Simulated experiments

For the simulations, we selected an averaged hemodynamic response from the right mid-fusiform gyrus from the empirical study and used this as the canonical impulse response. TR was chosen to be 3 sec to keep the timing consistent with that used in the empirical study. The simulations comprised two conditions that differed in response magnitude. Effect size was expressed as a fraction, in which the difference between the two responses was the numerator and the larger response was the denominator. The effect size between the two conditions was systematically increased from 0.05 to 0.35 in steps of size 0.02 to 0.05. Based on results from the empirical study, we set a 40% drop in signal magnitude at 3 sec and 20% at 6 sec ISI for the second of a pair of stimuli. For ISI greater than 6 sec, full recovery of hemodynamic response was assumed. We also assumed that the incomplete recovery of hemodynamic response is only affected by the immediately prior stimulus.

Stimulus presentation sequences were generated using three different presentation paradigms. In the first paradigm, the two conditions were distributed at ISI of 3, 6, and 9 sec using a uniform distribution, which has been shown in simulations to provide high response estimation efficiency [Hagberg et al., 2001]. In rapid ER experiments, three or more inter-stimulus intervals are used to provide sufficient simultaneous equations for estimating the hemodynamic response without making prior assumptions about its shape [Josephs et al., 1997; Miezin et al., 2000; Ollinger et al., 2001a]. The length of the experiment was incremented from 140 scans (30 events per condition and 20 baseline scans) to 210 (45 events per condition and 30 baseline scans), creating two different simulations. The second paradigm was identical to the first except that the events from the two conditions were uniformly distributed at slightly longer ISI of 6, 9, and 12 sec.

In the third set of simulations, baseline (fixation) events were randomly mixed with the two test conditions, and an event from one of these "three" conditions was presented at each scan (the total number of events of each condition was balanced across the whole experimental run). Therefore, the average ISI between the two conditions-of-interest is 4.5 sec. Two different simulated time-series of length 140 (40 events of each condition, 40 non-events, and 20 baseline scans) and 210 (60 events of each condition, 60 non-events, and 30 baseline scans) were generated. The inclusion of random baseline events introduced temporal jitter for the conditions of interest, providing sufficient equations to solve for the hemodynamic response.

Stationary white Gaussian noise was added to the simulated time-series [Press et al., 1987]. The standard deviation of the noise was varied between 3.2 and 4 leading to signal-to-noise ratios (SNR, ratio of the mean of the MR signal to the standard deviation of the noise [Huettel and McCarthy, 2001b]) of approximately 210,

Figure 2.
Coronal sections showing areas activated for face processing from an individual participant, with the *y*-coordinate in Talairach space indicated on the top left corner of each slice. Adjacent panels show the estimated BOLD signal change in *Z* scores for different conditions in each ROI, averaged across all participants.

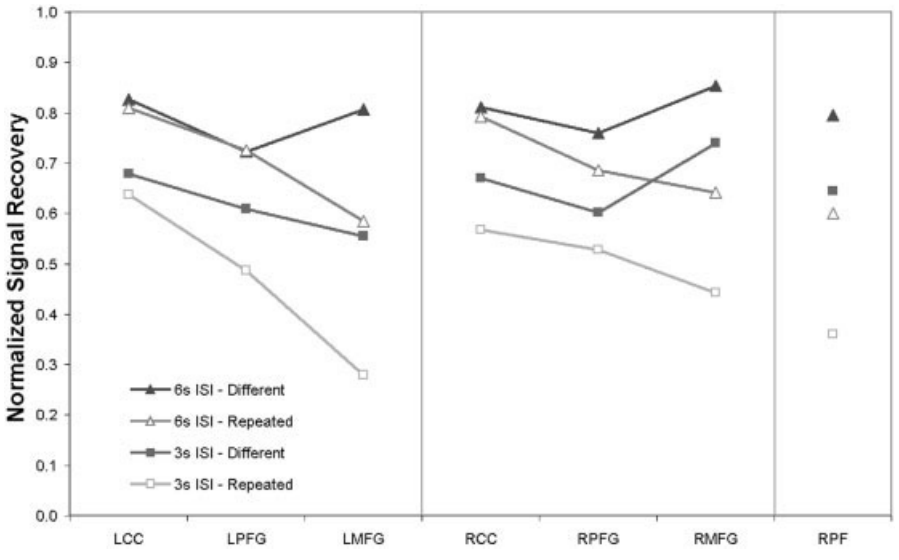

Figure 3.
The "normalized signal recovery" values for the Different and Repeated trials at 3 and 6 sec ISI for each of the seven ROI.

190, and 170 in three different variations of each simulated time-series. All resulting simulated time-series data were analyzed using general linear model with FIR predictors, identical to analysis of the empirical data.

RESULTS

All eight participants showed consistent activation in seven ROI: bilateral calcarine sulcus, bilateral posterior fusiform gyrus, bilateral mid-fusiform gyrus, and right prefrontal cortex.

Estimated BOLD response to a second face at different ISI, with and without face repetition

The signal recovery was less at 3 sec than at 6 sec ISI (Figs. 2 and 3) in all ROI. At 3 sec ISI, the normalized signal recovery averaged across ROI was 0.47 (S.D. 0.12) for the repeated faces, and 0.64 (S.D. 0.06) for different faces. At 6-sec ISI, signal recovery values were 0.69 (S.D. 0.09) for repeated faces and 0.80 (S.D. 0.04) for different faces.

A four-factor ANOVA was used to evaluate the normalized signal recovery as a function of ISI (3 or 6 sec), fMR-A (Repeated or Different), cortical region (calcarine cortex, posterior fusiform gyrus and mid-fusiform gyrus), and hemisphere. There was significantly less signal recovery at 3 sec than at 6 sec ISI [$F(1,7) = 23.45$, $P < 0.005$]. Signal recovery was also significantly higher with different faces [$F(1,7) = 12.92$, $P < 0.01$]. There was no interaction between ISI and the cortical region [$F(2,6) < 1$]. In contrast, fMR-A differed by cortical region [interaction: $F(2,6) = 7.12$, $P < 0.05$]. No other significant effect was found.

Separate *t*-tests performed at each ROI showed that fMR-A was significant in both left and right mid-fusiform areas at 3 sec ISI [left: $t(7) = 3.62$, $P < 0.01$; right: $t(7) = 5.74$, $P < 0.001$] and 6 sec ISI [left: $t(7) = 3.37$, $P < 0.05$; right: $t(7) = 2.42$, $P < 0.05$]. fMR-A was not significant in the calcarine cortex and the posterior fusiform areas bilaterally. fMR-A was also significant in the right prefrontal region at both 3 sec ISI [$t(7) = 2.35$, $P < 0.05$] and 6 sec ISI [$t(7) = 2.45$, $P < 0.05$].

The contribution of fMR-A to decreasing signal recovery was determined by subtracting the normalized signal recovery for repeated faces from that of different faces at each ISI (Fig. 4). Prominent fMR-A was present in the mid-fusiform region bilaterally and in the right prefrontal region. The size of effect appeared to be lower at 6 sec ISI but the difference did not reach statistical significance.

Simulations

Most of the simulated designs identified an effect size greater than 0.25 as "statistically significant" (Table I). As expected, increasing the number of events per condition improved sensitivity, as did a higher SNR. Keeping the number of events per condition fixed, designs with an average ISI of 9 sec were capa-

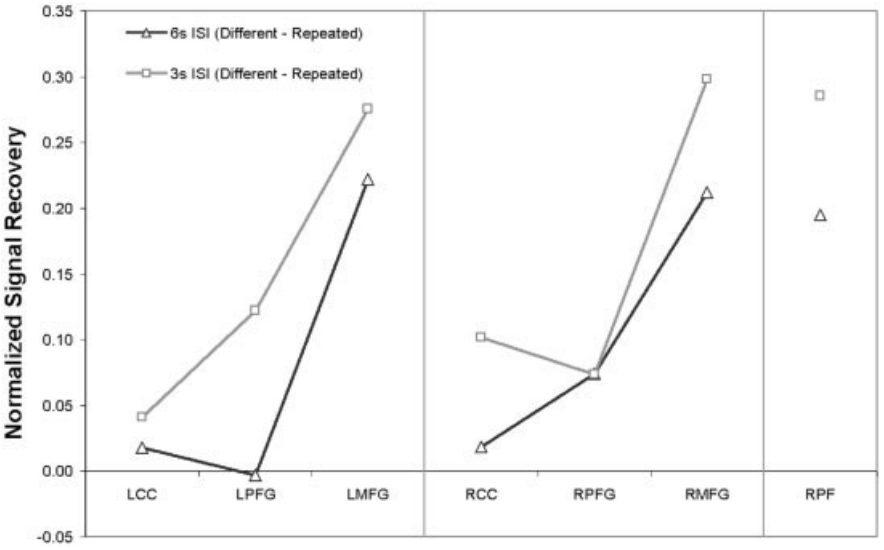

Figure 4.
The fMR-A effect for different ROI at ISI of 3 and 6 sec. The largest fMR-A effects were seen in bilateral mid-fusiform and right prefrontal regions.

ble of detecting effect sizes as low as 0.13 ($P < 0.05$) while corresponding designs with average ISI of 6 and 4.5 sec only detected effect sizes greater than 0.18 and 0.25, respectively.

An advantage of using shorter ISI is that more events can be sampled within a particular experimental timeframe giving a potential increase in statistical power. To determine if this increase in power can overcome the increased variability of signal magnitude arising from incomplete response recovery following shortly separated sequential stimuli, we compared results keeping the experimental duration constant. Under the condition of equivalent experimental time, designs with an average ISI of 6 and 4.5 sec yielded comparable sensitivity to effect size differences when compared to designs with an average ISI of 9 sec, indicating that increasing the number of events can compensate for the variability arising due to incomplete signal recovery at shorter ISI.

Effect size in previous studies on human memory

A brief review of the literature was conducted to determine the effect sizes reported by several well-known publications in the field of memory [Brewer et al., 1998; Buckner et al., 2001; Kirchhoff et al., 2000; Otten and Rugg, 2001; Wagner et al., 1998, 2000] and the results are summarized in Table II. The "normalized effect size" was expressed as a fraction where the difference in signal change between conditions was the numerator and the magnitude of the larger response was the denominator, identical to the method used in the simulations. In most studies, the reported effect size was greater than 0.25. This effect size is large enough to be detected with the use of short ISI designs given signal stability comparable to that used in the present experiment.

DISCUSSION

The main findings of the present study are summarized as follows: The signal recovery at 6 sec was higher than at 3 sec and the recovery at both 3 and 6 sec ISI was greater when using different faces compared to identical faces. When identical faces were presented, the incomplete signal recovery showed regional variation along the ventral visual-processing pathway. However, when different faces were presented, the incomplete signal recovery no longer showed significant region specific variation. Finally, the results from the simulations suggest that for the same experimental time, experimental designs using short and intermediate ISI show comparable sensitivity in contrast detection.

Region specific contribution of fMR-A to incomplete signal recovery

For repeated faces, there was significantly lower recovery in the mid-fusiform areas than in the posterior fusiform or calcarine areas, at both 3 and 6 sec ISI. Huettel et al. [2001] reported similar results at 1 sec ISI. The present study suggests that this may be due to

TABLE I. Simulation results showing sensitivity of different protocols in detecting different effect sizes

	4.5 ISI*				6.0 ISI				9.0 ISI			
	140 scans**		210 scans		140 scans		210 scans		210 scans		280 scans	
	40 events***		60 events		30 events		45 events		30 events		45 events	
Simulated Effect	Effect size	t(127)	Effect size	t(197)	Effect size	t(127)	Effect size	t(197)	Effect size	t(197)	Effect size	t(267)
SNR = 210												
0.05	0.00	0.06	0.05	0.96	0.00	−0.03	0.04	0.79	0.04	0.91	0.10	2.75[b]
0.08	0.03	0.47	0.08	1.49	0.03	0.41	0.04	0.80	0.04	1.02	0.11	3.08[c]
0.10	0.02	0.35	0.11	2.06[a]	0.09	1.21	0.08	1.47	0.05	1.20	0.14	3.72[d]
0.13	0.07	1.22	0.14	2.54[a]	0.10	1.47	0.10	2.09[a]	0.10	2.33[a]	0.17	4.72[d]
0.15	0.09	1.60	0.15	2.94[c]	0.13	1.85	0.15	2.90[c]	0.15	3.34[c]	0.19	5.27[d]
0.18	0.10	1.69	0.17	3.26[c]	0.17	2.42[a]	0.19	3.63[d]	0.17	3.83[d]	0.22	6.16[d]
0.20	0.16	2.77[b]	0.20	3.92[d]	0.18	2.69[b]	0.21	4.07[d]	0.18	4.34[d]	0.25	6.82[d]
0.25	0.19	3.34[c]	0.24	4.69[d]	0.23	3.46[d]	0.24	4.95[d]	0.22	5.28[d]	0.29	7.93[d]
0.30	0.22	3.88[d]	0.30	5.96[d]	0.31	4.58[d]	0.29	5.94[d]	0.30	7.03[d]	0.36	9.97[d]
0.35	0.29	5.02[d]	0.35	6.59[d]	0.39	5.77[d]	0.35	7.22[d]	0.34	7.82[d]	0.40	11.05[d]
SNR = 190												
0.05	0.00	0.03	0.04	0.64	0.01	0.12	0.02	0.33	0.02	0.48	0.10	2.47[a]
0.08	0.04	0.56	0.07	1.24	0.04	0.51	0.06	1.06	0.06	1.23	0.12	2.89[c]
0.10	0.02	0.29	0.10	1.76	0.08	1.00	0.10	1.75	0.09	1.95	0.14	3.39[d]
0.13	0.08	1.19	0.11	1.85	0.11	1.44	0.11	2.01[a]	0.10	2.03[a]	0.15	3.69[d]
0.15	0.07	1.12	0.15	2.63[b]	0.12	1.55	0.13	2.29[a]	0.13	2.75[b]	0.18	4.15[d]
0.18	0.10	1.55	0.18	3.08[c]	0.18	2.32[a]	0.18	3.21[c]	0.16	3.35[d]	0.21	5.11[d]
0.20	0.11	1.77	0.18	3.12[c]	0.16	2.06[a]	0.21	3.87[d]	0.19	4.05[d]	0.25	6.22[d]
0.25	0.17	2.64[b]	0.26	4.54[d]	0.26	3.36[c]	0.24	4.40[d]	0.22	4.69[d]	0.28	6.79[d]
0.30	0.23	3.47[d]	0.30	5.29[d]	0.32	4.37[d]	0.30	5.50[d]	0.27	5.55[d]	0.35	8.64[d]
0.35	0.28	4.39[d]	0.36	6.23[d]	0.36	4.80[d]	0.37	6.99[d]	0.32	6.94[d]	0.39	9.43[d]
SNR = 170												
0.05	−0.01	−0.14	0.05	0.84	−0.01	−0.09	0.02	0.35	0.00	0.04	0.12	2.59[a]
0.08	0.02	0.33	0.06	0.85	0.06	0.72	0.06	1.02	0.05	0.90	0.14	3.08[c]
0.10	0.01	0.20	0.09	1.38	0.06	0.68	0.07	1.13	0.08	1.59	0.15	3.28[c]
0.13	0.04	0.57	0.13	2.10[a]	0.09	1.01	0.12	1.94	0.11	2.15[a]	0.17	3.65[d]
0.15	0.06	0.87	0.13	2.07[a]	0.14	1.74	0.13	2.22[a]	0.12	2.21[a]	0.18	3.85[d]
0.18	0.10	1.35	0.18	2.81[b]	0.16	1.96	0.17	2.80[b]	0.18	3.38[d]	0.23	5.20[d]
0.20	0.12	1.75	0.21	3.40[d]	0.22	2.68[b]	0.17	2.80[b]	0.15	2.85[c]	0.23	5.16[d]
0.25	0.18	2.55[a]	0.26	4.23[d]	0.24	2.87[c]	0.23	3.77[d]	0.24	4.48[d]	0.29	6.43[d]
0.30	0.21	3.03[c]	0.31	5.01[d]	0.34	4.24[d]	0.29	4.89[d]	0.26	4.86[d]	0.34	7.39[d]
0.35	0.27	3.76[d]	0.36	5.79[d]	0.39	4.89[d]	0.35	6.00[d]	0.34	6.63[d]	0.41	9.16[d]

* ISI given as average (in seconds)
** Scans refer to experiment length.
*** Events per condition
[a] $P < 0.05$; [b] $P < 0.01$, [c] $P < 0.005$; [d] $P < 0.001$.

fMR-A in the mid-fusiform gyrus, rather than regional differences in hemodynamic refractory properties. The relative contribution of fMR-A to incomplete signal recovery was inferred by the difference in signal recovery elicited by identical and different faces, assuming that hemodynamic factors were identical in the two stimulus conditions. In bilateral mid-fusiform and right prefrontal regions, fMR-A contributed to about half of the reduction in signal recovery.

As our volunteers were asked to note the gender of the faces shown, they may have paid less attention to the repeated faces, leading to reduced activation. Selective attention to faces can modulate activation in the fusiform area [Wojciulik et al.,

TABLE II. "Normalized effect size" in selected memory studies

Reference	Contrast	Normalized effect size
Brewer et al., 1998	Remembered-Forgotten	0.26
	Remembered-Forgotten	0.23
	Remembered-Forgotten	0.20
Wagner et al., 1998	Remembered-Forgotten	0.32
	Remembered-Forgotten	0.35
	Remembered-Forgotten	0.26
	Remembered-Forgotten	0.19
	Remembered-Forgotten	0.14
Otten and Rugg, 2001	Remembered-Forgotten	0.49
	Remembered-Forgotten	0.72
	Remembered-Forgotten	0.65
	Remembered-Forgotten	0.90
	Remembered-Forgotten	0.51
Kirchhoff et al., 2000	Words: Novel-Repeated	0.78
	Words: Novel-Repeated	0.34
	Words: Novel-Repeated	0.44
	Pictures: Novel-Repeated	0.87
	Pictures: Novel-Repeated	0.42
	Pictures: Novel-Repeated	0.32
	Words: Novel-Repeated	0.69
	Words: Novel-Repeated	0.68
	Pictures: Novel-Repeated	0.77
	Pictures: Novel-Repeated	0.50
	Pictures: Novel-Repeated	0.47
Wagner et al., 2000	Long Lag-Short Lag	0.31
	Long Lag-Short Lag	0.16
Buckner et al., 2001	Remembered-Forgotten	0.35
	Remembered-Forgotten	0.36
	Remembered-Forgotten	0.22

1998]. However, if this were so, we might expect similar differences in signal to be observed in the primary visual areas as well, since selective attention has also been shown to modulate the activity of the primary visual cortex [Huk and Heeger, 2000]. The lack of modulation of activation in the primary visual cortex supports the notion that the different responses to identical and different faces cannot be attributed to differences in attention alone.

The regional specificity of fMR-A in relation to repeated presentation of identical faces relates to the role of the mid-fusiform region in face recognition. Initially suggested by clinical studies of prosopagnosia [Bodamer, 1947], evidence for face-selective processing in this region was provided by intra-operative evoked potential [Allison et al., 1994, 1999; McCarthy et al., 1999] and fMRI [Kanwisher et al., 1997; Puce et al., 1995] studies. Repeated presentation of faces has been shown to elicit a reduced response in second and subsequent presentations [Henson et al., 2000; Huettel and McCarthy, 2001a; Puce et al., 1999].

Repetition suppression in response to repeated presentation of objects detected by direct electrophysiological recordings in primate inferior temporal cortex [Miller et al., 1991, 1993] has been suggested as a possible neural basis for fMR-A [Grill-Spector and Malach, 2001]. Notably, the delayed match to sample experiments involved explicit memory and the suppression response was immediate [Miller et al., 1993]. The immediate suppression suggests a bottom-up or perceptual feature driven response of inferior temporal neurons to stimulus repetition. However, decreased firing could also result from top-down modulation of neuronal activity. With intra-operative ERP recordings, passive face repetition effects are not seen in the early (N200) face-specific component but are clearly evident in responses arising after 250 msec [Puce et al., 1999], suggesting that top-down modulation may account for fMR-A. It is presently unclear which mechanism predominates [Henson and Rugg, 2003].

Repetition priming effects have been demonstrated when pictorial stimuli are repeated after 3 days, with multiple intervening images involving different categories of items [van Turennout et al., 2000]. It is not known if priming invokes the same neural mechanisms as the "fMR-A" seen with immediate repetition without intervening stimuli, even though reduced responses occur in both settings.

Instead of repetition suppression, repetition enhancement has also been reported. While repetition suppression for famous faces was observed, Henson et al. [2000] also reported repetition enhancement for unfamiliar faces. In the present study, we presented unfamiliar faces but did not find any region that showed repetition enhancement. The difference in results might be due to the different repetition lags used in the two studies. In the previous study, the first and repeat presentations of a face were separated by many intervening stimuli and a long time lag. In contrast, the present study involved face repetition without intervening stimuli and a very short time lag. It is possible that repetition effects at different repetition lags may reflect distinct neural or psychological mechanisms.

Contribution of hemodynamic refractoriness to incomplete signal recovery

With respect to closely spaced pictorial stimuli, it could be argued that the categorical similarity between different faces could still yield some repetition suppression effect, and that a comparison between faces and houses could further reduce the contribution of neural factors to the observed signal attenuation. However, a significant component of the reduction in signal observed when different faces were presented sequentially may still be reasonably attributed to hemodynamic coupling or vascular effects. The importance of hemodynamic factors underlying reduced signal recovery is suggested by a study showing overestimation of the BOLD response even after weighting a linearly predicted fMRI response using simultaneous, empirically derived visual evoked responses to alternating checkerboards [Janz et al., 2001]. This study showed that hemodynamic effects occur *in addition* to neural habituation effects. The use of optical imaging in human somatosensory cortex has shown that hemodynamic response refractoriness can also occur *in the absence* of demonstrable refractory effects in cortical evoked potentials [Cannestra et al., 1998].

In theory, knowing the underlying mechanisms to incomplete signal recovery at short ISI could afford the formulation of weighting functions to compensate for decreased signal recovery at these shorter ISI [Robson et al., 1998]. This would reduce the variance in responses gathered from an event-related study design that uses a mixture of short and long ISI. This may not yet be feasible. The present study reveals the potential contribution of fMR-A to regional differences in signal recovery. The various stimulus specific repetition effects alluded to above may involve different underlying mechanisms that have different time constants.

Design implications of the present findings

The simulations suggest that, given the same experimental time, experiments with shorter ISI (minimum 3 sec, average 4.5–6 sec) are as sensitive in detecting contrasts between conditions as those utilizing intermediate ISI (minimum 6 sec, average 9 sec). With shorter ISI, greater variance in the signal is expected as, depending on the timing of prior event(s), individual hemodynamic responses may be attenuated by up to 40%, compared to attenuation of up to 20% for intermediate ISI. This higher variance is compensated by the increase in power due to the larger number of events [Friston et al., 1998].

When differences in response magnitude between the conditions of interest is relatively large (>25%), experimental time can be reduced significantly by using a shorter ISI. Alternatively, working with a particular experimental duration, more conditions, or more events per condition, can be accommodated. Event-related designs allow for post-hoc sorting of experimental events according to behavioral responses, for example, correct vs. erroneous judgments, or subsequently recognized vs. forgotten stimuli. As the distribution of events per condition is not known a priori, some condition(s) of interest may end up with disproportionately few events. By increasing the total number of events, the number of events for each condition should also increase, so that sufficient events will be available for accurate response estimation.

Conversely, when response differences between the conditions of interest are small, the use of intermediate ISI is more appropriate. Compared to shorter ISI experiments, intermediate ISI experiments are associated with lower variance and larger average magnitude of BOLD signal change (due to better signal recovery). In theory, this would afford the detection of regions that show biologically meaningful but subtle differences in response magnitude. The greater sensitivity of intermediate ISI experiments might also prove useful for experiments where the availability of adequate numbers of suitable stimuli is limited. This could arise when multiple psychologically important factors have to be controlled for.

ACKNOWLEDGMENTS

We are grateful to S.A. Huettel and S. Graham for their helpful comments.

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