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Mixed blocked/event-related designs separate transient and sustained activity in fMRI

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Abstract

Recent functional magnetic resonance imaging (fMRI) studies using mixed blocked/event-related designs have shown activity consistent with separable sustained task-related processes and transient trial-related processes. In the mixed design, control blocks are intermixed with task blocks, during which trials are presented at varying intervals. Two studies were conducted to assess the ability of this design to detect and dissociate sustained task-related from transient trial-related activity. Analyses on both simulated and empirical data were performed by using the general linear model with a shape assumed for sustained effects, but not transient effects. In the first study, simulated data were produced with sustained time courses, transient time courses, and the sum of both together. Analyses of these data showed appropriate parsing of sustained and transient activity in all three cases. For the empirical fMRI experiment, counterphase-flickering checkerboard stimuli were constructed to produce sustained, transient, and combined sustained and transient responses in visual cortex. As with the simulation, appropriate parsing of sustained and transient activity was seen in all threecases; i.e., sustained stimuli produced sustained time courses and transient stimuli produced transient time courses. Combined stimuli produced both transient and sustained time courses. Critically, transient stimuli alone did not produce spurious positive sustained responses; sustained stimuli alone produced negligible spurious transient time courses. The results of these two studies along with supplemental simulations provide strong evidence that mixed designs are an effective tool for separating transient, trial-related activity from sustained activity in fMRI experiments. Mixed designs can allow researchers a means to examine brain activity associated with sustained processes, potentially related to task-level control signals.

Introduction

The human brain is able to initiate different responses to the same set of stimuli in different situations. For example, a student taking a vocabulary test might write down the meaning of a word after hearing it. On the other hand, during a spelling test, that same student would spell the word upon hearing it. Out of the myriad possible information processing pathways, the appropriate ones must be organized to make the correct, context specific response to the situation. How does this organization take place?

One approach to this question would be to dissociate signals related to the task per se (adopting a vocabulary test "set") from signals related to lower-level task components (recalling the meaning of a specific word). The goal of this report is to describe and validate a method for dissociating these different kinds of signals based on their temporal profiles of activity.

In a laboratory setting, neural activity related to each trial of a task can be expected to occur in a similar way, producing a transient time course associated with each trial.

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Such “transient trial-related activity” would include processing specifically involved in each trial of a task.

Activity related to maintenance of the organized state or set of the system might be sustained throughout the performance of the task. The neural activity sustained across trials of a task will be referred to as “sustained” activity. This activity could be related to several different processes, including the attentional state or set of a subject during a task, or the subject’s level of arousal.

Because different time courses of activity are likely to play different roles in processing, the ability to detect and distinguish between transient trial-related activity and sustained activity should allow a more complete understanding of the functional roles of the neural activity observed.

While powerful for their own goals, two of the most commonly used functional magnetic resonance imaging (fMRI) paradigms are not suited for dissociating sustained from transient trial-related activity. Blocked designs (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992; Donaldson and Buckner, 2001) compare overall activity during a block when subjects perform one task to overall activity during a block when subjects perform a control task. In a blocked design, all activity that takes place during one task block contributes to a single estimate, potentially confounding sustained and transient trial-related activity. In contrast, event-related designs (Buckner et al., 1996; Dale and Buckner, 1997; Josephs et al., 1997; McCarthy et al., 1997; Zarahn et al., 1997a) extract only activity that is transient and associated with the event of interest (e.g., the trials of a task) ignoring sustained activity.

Several recent fMRI studies have examined sustained and transient trial-related activity by using various methods (Kato et al., 1998; Chawla et al., 1999; Fernandez et al., 1999; Mitchell et al., 2000; Otten et al., 2002). For example, a study by Donaldson and colleagues (2001) used a “mixed blocked/event-related design” to dissociate sustained and transient trial-related activity (see also complementary designs using electroencephalography and positron emission tomography by Duzel et al., 1999).

In the mixed design, trials are presented during task blocks, which are alternated with control blocks (Fig. 1A). The difference between a mixed design and a blocked design is that in a mixed design, trials are presented with different intervals between them, as in rapid event-related designs (Fig. 1B). This method allows estimation of the temporal profile of activity related to each trial (Friston et al., 1995; Buckner et al., 1996; Dale and Buckner, 1997; Josephs et al., 1997; Miezin et al., 2000). Interspersing task blocks with control blocks, as in a blocked design, allows estimation of sustained activity throughout a task block, presumably separated from transient trial-related activity.

Donaldson and colleagues’ (2001) experiment described transient trial-related activity in a recognition memory experiment as well as sustained activity related to blocks of trials. Sustained effects alone were observed in some regions, transient trial-related effects alone in others, and both were observed together in still other regions. The sensitivity and selectivity of the mixed design has not yet been tested. For example, if it were the case that the mixed design caused transient trial-related activity to be misinterpreted as sustained, then the mixed design would not be selective. The experiments described in this study examine aspects of the sensitivity and selectivity with which mixed designs can detect and dissociate sustained and transient trial-related effects. To test the sensitivity and selectivity of the design, well-characterized inputs were used to test the output of analysis by using the mixed design in two studies. The first study, on simulated data, probed whether mixed designs confound sustained and transient signals when no noise is present, or in the presence of physiologically plausible noise. However, the simulations cannot completely model the actual characteristics of fMRI data from the human brain. Therefore, an fMRI feasibility experiment was also performed.

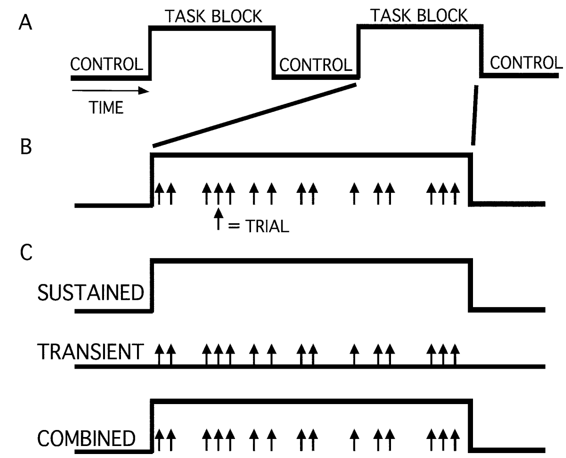


Fig. 1. Schematic of the mixed blocked/event-related design. (A) In the mixed design, as in a blocked design, blocks of performance of a control task are interspersed with blocks of performance of a task. (B) Within task blocks, individual trials (arrows) are presented with different intervals between them, as in a rapid event-related design. (C) The mixed design was tested using simulated and experimental functional magnetic resonance imaging data that included sustained activity, transient trial-related activity, or both together. Schematics of a task block for each of these conditions are shown. The Sustained condition included sustained activity throughout the task block, symbolized by the raised bar. Transient activity is that which rises to a peak and then dies down afterward. Arrows symbolize the onset of such transient activity. The Transient condition included a series of transient activity. The Combined condition included both types of activity superimposed.

In this second experiment, different durations of activity were produced in the visual cortex by using flickering checkerboard stimuli. Similar stimuli have been shown to elicit robust and well-localized hemodynamic responses (Fox et al., 1986; Boynton et al., 1996; Menon and Goodyear, 1999; Miezin et al., 2000; Ollinger et al., 2001b).

The results of the two primary studies prompted further simulations exploring conditions under which the mixed design could fail to cleanly separate transient from sustained activity.

Methods and results

The general form of the mixed design is shown in Fig. 1A. For the specific experiments described here, control blocks included 20 acquisitions of a whole brain volume (about 54 s), and task blocks included 41 acquisitions (about 110 s). Each acquisition lasted 2.5 s and will be referred to as an "MR frame." Sustained effects were assumed to occur over the entire 110 s of the task block. Transient "trials" were presented so that the time between successive stimuli varied across a block, as in rapid event-related designs (Buckner et al., 1996; Dale, 1999; Miezin et al., 2000). Twenty-five "trials" occurred in each task block. Timing between trials ranged from 1 frame to 3 frames (2.5 to 7.5 s) and was more often shorter than longer.

Analyses on data collected by using the mixed design were performed using the general linear model (GLM) as implemented with in-house software (Miezin et al., 2000; Ollinger et al., 2001a,b). Transient effects were coded in the GLM by delta function regressors for each of the seven frames following trial onset. Seven frames were examined because they span about 15 s, roughly the time it takes for the hemodynamic response to decay to baseline (Boynton et al., 1996; Miezin et al., 2000). This method does not assume a response shape (Miezin et al., 2000). A sustained effect was coded into the GLM as a single regressor with an assumed shape. This shape has a graded rise to a sustained value and a decline to zero at termination, modeled as a "gamma" function convolved with a boxcar function of width equal to the assumed duration of neuronal firing (Boynton et al., 1996).

Experiment 1: simulation of sustained and transient signals

Simulation methods

Simulated data were created by using the Bay Zero simulation software (Buckner et al., 1998; Burock et al., 1998; Kelly et al., 2002). This software linearly sums simulated responses to create data sets that vary over time in a manner similar to fMRI data. Simulated data were created according to the following three experimental design conditions as seen in Fig. 1C: Sustained (only), Transient (only) and Combined (Sustained and Transient) conditions. Each transient response was simulated to have the shape of a "gamma" function (Boynton et al., 1996):

$$H = \left(\frac{t - \text{delay}}{\tau}\right)^2 e^{-\left(\frac{t-\text{delay}}{\tau}\right)}$$

where t is time. The delay was 2 s, the time constant (τ) was 1.25 s, and the maximum amplitude of the response was 0.6% change from baseline. Simulated parameters were chosen to be similar to experimental data.

The sustained condition was simulated to rise slowly at onset to a sustained amplitude of 0.6% and decline slowly after 41 frames (gamma function convolved with a boxcar function). The Combined condition was simulated as the sum of the Sustained and Transient conditions.

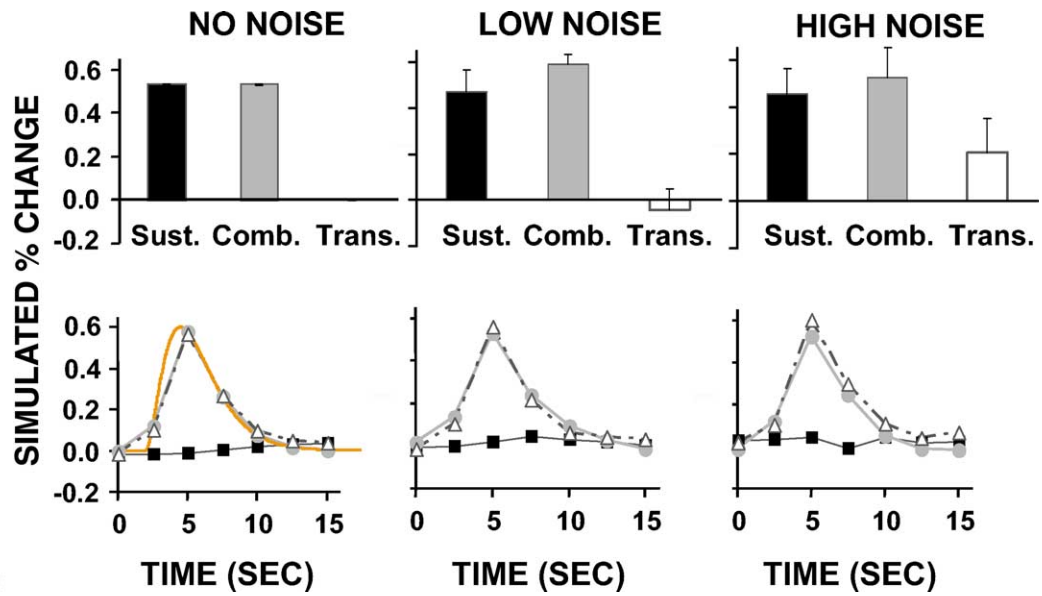
Table 1
Noise parameters[a]

	Low noise	High noise
White noise variance	0.0	0.4
Autocorrelated noise variance	1.5	9.0
Temporal correlation	0.5	0.9

[a] Noise parameters extracted from analysis of functional magnetic resonance imaging data with an autocorrelated plus white noise model (Purdon and Weisskoff, 1998). These noise parameters were used to simulate physiologically plausible noise.

Data from 13 simulated subjects were generated based on three "runs" of data for each subject, for each of three conditions. Each run consisted of two task blocks and three control blocks as in Fig. 1A. Data for each condition were analyzed by using the same GLMs. Regressors were included for sustained and transient effects (as in the Combined condition) whether or not those effects had been simulated in the data. This tested whether transient activity is misapplied to the sustained effects and vice versa. Analyses included two additional regressors for each run, i.e., one for the baseline signal and one for the slope, or linear drift, in the MR signal.

Noise model. The same simulation was performed on data that included physiologically reasonable amounts of noise. Several papers (Zarahn et al., 1997b; Purdon and Weisskoff, 1998) have shown that noise in the human brain is temporally autocorrelated ("$1/f$ noise"). To determine what parameters of noise were relevant for the scanner used in this experiment, fMRI data from Experiment 2 were analyzed to determine their noise characteristics. Spherical regions of interest of 1 cm in diameter were defined in the insula (at Talairach coordinates $+-41$, -9,0) and in the inferior frontal gyrus ($+-47$, 39,0) (Talairach and Tournoux, 1988). BOLD data in these regions that were not correlated to the visual stimuli presented ("residual signal") were extracted by subtracting the modeled signal from the measured BOLD signal (see Experiment 2). Using the noise model of Purdon and Weisskoff (1998), the white noise component, autocorrelated component, and degree of correlation of noise from these regions was determined. The magnitude of noise differed across the brain; i.e., noise in the insula was small relative to the rest of the brain, while the magnitude of noise in the inferior frontal gyrus was relatively large. Table 1 shows the estimated values of these noise parameters. Bay Zero was used to create "high noise" simulations with parameters like those in the inferior frontal gyrus and "low noise" simulations with parameters like those in the insula. These noisy simulated data were analyzed just as simulated data for the no noise conditions.



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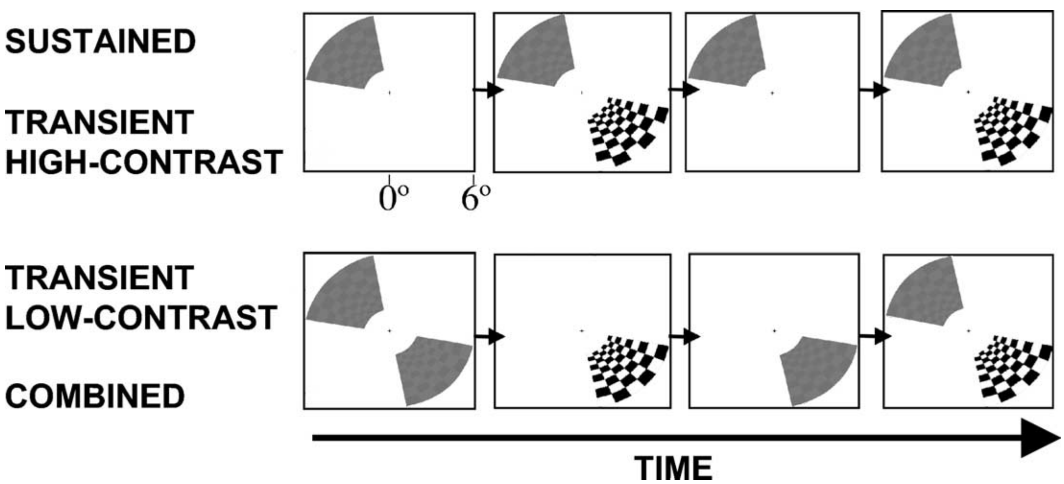


Fig. 2. Results of analysis of simulated data with mixed design. Simulated data were created according to the temporal profiles in Fig. 1C. Three levels of noise were used. The three conditions of data were analyzed identically. Magnitudes of sustained regressors are shown in the top half of the figure, error bars show standard error of the mean. Extracted transient activity is shown in bottom half of figure. No Noise condition also shows shape of modeled effect in orange. Sustained (Sust.), black squares; Combined (Comb.), gray circles; Transient (Trans.), white triangles.

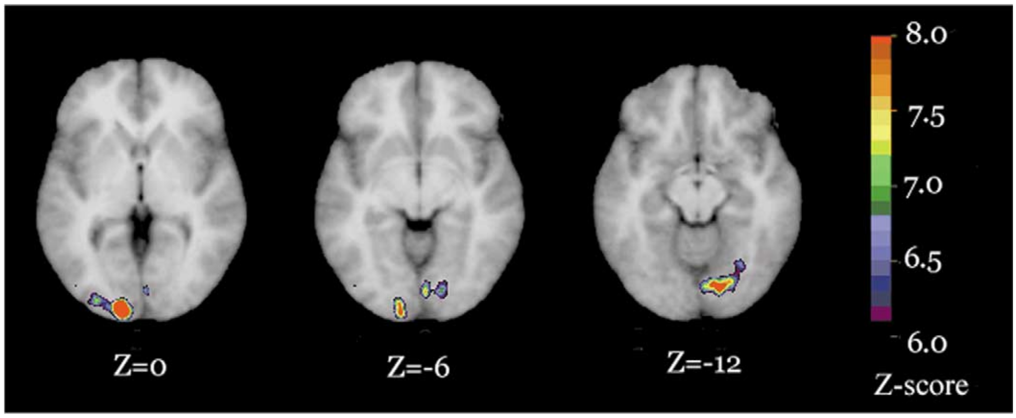
Fig. 3. Stimuli used in the functional magnetic resonance imaging experiment. The first row shows selected frames from a block during which a Sustained stimulus condition was presented in the left hemifield while a high-contrast Transient stimulus condition was presented in the right hemifield. Note that during the Sustained condition, the low-contrast stimulus is present at all times. During Transient stimulus conditions, however, stimuli are shown only intermittently and for 1.25 s at a time. The second row shows selected frames from a block during which a low-contrast Transient stimulus condition was presented in the left hemifield while a Combined condition was presented in the right hemifield. Note that the Combined condition stimuli consist of (sustained) low-contrast stimuli intermittently replaced with high-contrast transient stimuli.

Simulation results

Fig. 2a and b show the sustained and transient effects that were obtained from analyses of data simulated with and without noise. The mixed design analysis extracted effects appropriately; activity was not found that had not been simulated. These data show that it is possible in principle (given relative linearity of signals) to extract sustained and transient signals from fMRI data, even in the case of physiologically plausible ranges of noise. However, actual fMRI data may include nonlinearities and unmodeled noise sources that could confound this paradigm.

Experiment 2: fMRI study of sustained and transient visual stimuli

To test the mixed design in the context of actual fMRI signals and noise sources, an fMRI experiment was performed by using stimuli that produced sustained, transient, and a combination of sustained and transient responses in visual cortex.



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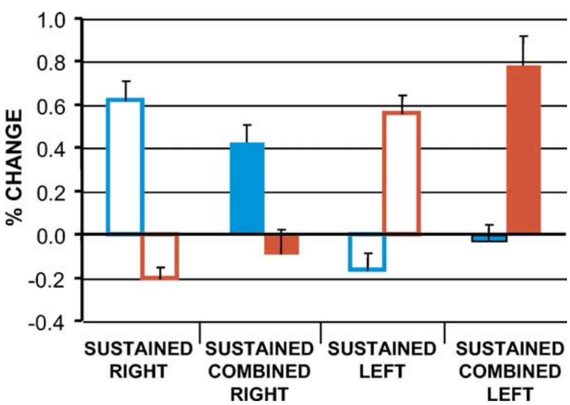

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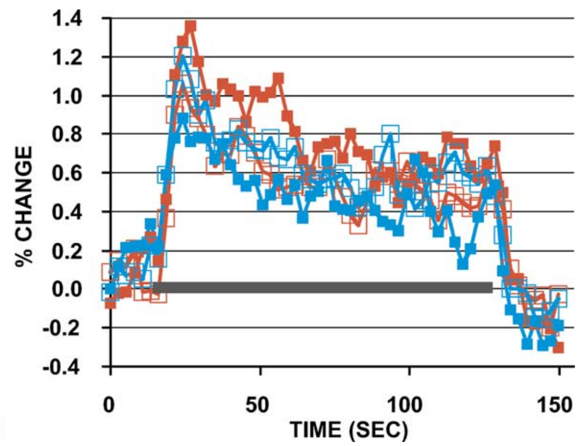

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Fig. 4. Statistical image is superimposed on the averaged anatomical image for all 13 subjects. Pseudocolor scale shows significance in units of standard deviation (Z-score). Transverse slices are shown in Talairach space at $z = 0$, -6, and -12 mm. Note that activity in the left visual cortex is superior to activity in the right visual cortex, consistent with the fact that stimuli in the right visual field were in the lower quadrant, and stimuli in the left visual field were in the upper quadrant.

Fig. 5. Sustained effects extracted from Analysis 1. Open bars represent effects for the Sustained conditions. Filled bars represent effects for the Combined conditions. Effects extracted from the left hemisphere region are in light blue (left bar of each pair), and those from the right hemisphere region are in dark red (the right bar of each pair). The left side of the figure represents stimuli in the right visual field; the right side of the figure represents stimuli in the left visual field. Error bars represent standard error of the mean. Note that only the effects in the visual field contralateral to the stimulus (left/blue bars on the left half of the figure, right/red bars on the right) are large and positive.

Fig. 6. Sustained time courses extracted from Analysis 1. Again, red represents effects extracted from the right hemisphere region of interest, while blue represents effects extracted from the left region of interest. Only data from the region of interest contralateral to the stimulus are shown (same as the large positive bars in Fig. 5). Effects from the Sustained conditions are plotted with open squares. Effects from the Combined conditions are plotted with filled squares. Note that there is a slow decay over time in the sustained signal. The thickened bar on the *x*-axis represents the time during which the sustained stimuli were present.

Subjects

Thirteen subjects (6 male; mean age, 24 years; range, 19–30 years) participated in return for payment. Subjects were screened by using a questionnaire to ensure that they were neurologically normal, right-handed, that they had good vision without contact lenses or glasses, and that they were eligible to be scanned with MRI. Informed consent was obtained from each subject according to the guidelines of the Washington University Human Studies Committee.

Equipment

Visual stimuli were presented to subjects by projecting (Epson 500C LCD projector) the image generated from a Macintosh G3 (Apple, Cupertino, CA) using Psyscope software (Cohen et al., 1993) onto a screen at the back of the magnet bore. Subjects viewed the screen through a mirror attached to the headcoil. Subjects responded to the behavioral task by using a fiber-optic key press whose output was recorded by Psyscope.

Subjects' eye movements were monitored by using hardware and software by Applied Science Laboratories (Model 504 LRO, Bedford, MA). A dim infrared light was reflected by a small mirror attached to the headcoil onto the subject's left eye. A video camera sensitive to infrared light monitored the subject's eye throughout the scan.

Stimuli

Stimuli from the peripheral visual field are almost exclusively processed in the contralateral visual cortex in early visual regions (Inouye, 1909; Holmes and Lister, 1916;

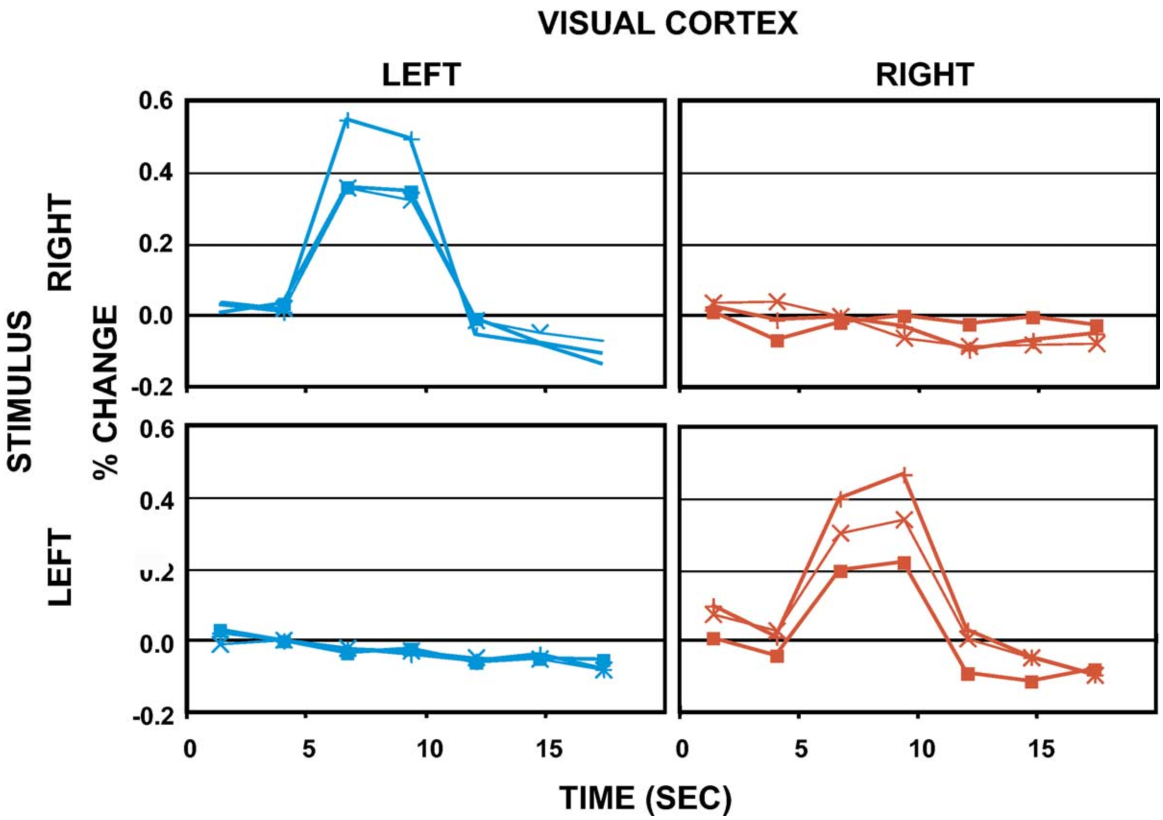

Fig. 7. Transient effects extracted from Analysis 1. Transient effects extracted from left visual cortex are plotted on the left side of the figure in blue; right visual cortex on the right in red. Effects for stimuli in the right visual field are in the first row, left visual field are in the second row. High-contrast transient effects are denoted by +; low-contrast transient effects are shown with the x symbol, and transient effects in the combined condition are shown by filled squares. Note that only the effects in visual field contralateral to the stimulus (upper left and lower right panels) are large and positive.

Daniel and Whitteridge, 1961; Hubel and Wiesel, 1962; Fox et al., 1986; Sereno et al., 1995; Tootell et al., 1998). Therefore, we presented stimuli in both left and right hemifields simultaneously, and treated responses in left and right visual cortex regions separately.

Counterphase 8-Hz flickering checkerboard wedges spanning a 70-degree arc whose eccentricity spanned 2 to 6 degrees were presented in the upper-left or lower-right quadrant of the visual field. Sample stimuli are shown in Fig. 3. The low-contrast stimulus had less than 10% contrast and the high-contrast stimulus had 98% contrast. Both the high-contrast and low-contrast checkerboards had alternating high-luminance and low-luminance squares. Though it may be difficult to distinguish high- and low-luminance squares in the figure for the low-contrast condition, they were distinct when seen at full size. Stimuli were shown on a gray background equal in luminance to the light blocks of the low-contrast stimuli, though for clarity in Fig. 3 the background is shown in white.

The approximate timing of each functional MR run is shown in Fig. 1A. Each run consisted of 62 s (23 MR frames) of fixation, followed by a 110-s (41 MR frames) stimulus block, followed by 54 s (20 MR frames) of fixation, a 110-s stimulus block, and 56 s (21 MR frames) of fixation.

Stimulus conditions. During each stimulus block, one of four stimulus conditions was presented in the upper-left visual field, while either the same or a different stimulus condition was presented in the lower-right visual field. The "Sustained" stimulus condition (Fig. 1C) consisted of a low-contrast checkerboard stimulus flickering continuously

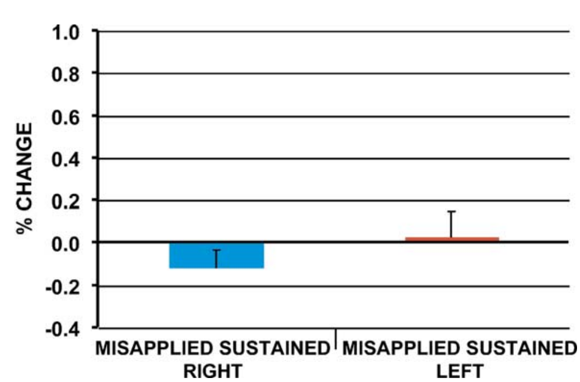

Fig. 8. Misapplied sustained effects from Analysis 2. Misapplied sustained effects coded for during low-contrast Transient conditions and high-contrast Transient conditions are averaged together. Effects in the contralateral visual cortex are shown for stimuli that occurred in the right visual field (blue, since the effect was extracted from the left visual cortex), and the left visual field (in red). Error bars represent standard error of the mean. Neither value is significantly positive.

Table 2
Stimulus conditions and associated visually evoked effects: Analysis 1[a]

	Stimulus condition	Effect(s) modeled	Stimulus duration (s)	No. of regressors	*P* value	
					Contra	Ipsi
Left visual field	Sustained	sustained	110	1	<0.0005	0.059
	High-ctst transient	high-ctst transient	1.25	7	<0.00001	0.0063
	Low-ctst transient	low-ctst transient	1.25	7	<0.00001	0.047
	Combined	sustained/combined	110	1	<0.0005	0.71
		transient/combined	1.25	7	<0.00001	0.028
Right visual field	Sustained	sustained	110	1	<0.0005	0.003
	High-ctst transient	high-ctst transient	1.25	7	<0.00001	0.067
	Low-ctst transient	low-ctst transient	1.25	7	<0.00001	0.0061
	Combined	sustained/combined	110	1	<0.0005	0.44
		transient/combined	1.25	7	<0.00001	—

[a] Stimulus conditions and associated visually evoked effects from Analysis 1. The first column lists all stimulus conditions (in the left and right visual field). The second column shows the name of the effects modeled for each condition. The duration of the stimulus associated with each effect is given in the third column. The number of regressors for each effect is 1 for all sustained effects (since only their magnitudes are estimated by the GLM) and 7 for all transient effects (since their time courses over 7 frames are estimated). The last two columns report significance values (*P* value) for each effect in the visual cortex region contralateral to and ipsilateral to the stimulus.

at 8 Hz for the entire 110-s stimulus block. Two "Transient" stimulus conditions consisted of flickering checkerboard stimuli of either high or low contrast presented for 1.25 s. During the Transient stimulus conditions, these stimuli were presented 25 times in 110 s. Intervals between transient stimuli varied as in a rapidly presented event-related paradigm as in the simulation ("Transient," Fig. 1C). Each of four presentation timing sequences occurred equally often for blocks of each condition. Another type of stimulus set combined transient with sustained stimuli (Fig. 1C). For "Combined" stimulus sets, high-contrast flickering checkerboards were presented with the same duration and timing sequences as in the transient blocks described above. Additionally, low-contrast flickering checkerboards were present at all times during the block when high-contrast checkerboards were not present.

Transient or Combined conditions occurring in different hemifields during the same block never shared the same presentation sequence, so that the different transient effect types could be separated.

Effect types included in the GLM. The four stimulus conditions describe five different visually evoked effect types (Table 2). The Sustained condition is modeled by a sustained effect. The high-contrast Transient condition is modeled by a high-contrast transient effect. The low-contrast Transient condition is modeled by a low-contrast transient effect. The Combined condition is modeled by two effects: a sustained/combined effect and a transient/combined effect. Since each of these five effects can follow from stimulus conditions in the left and right hemifields, there were a total of 10 different visually evoked effects.

Behavior

During all scans, subjects were instructed to keep their gaze on a fixation cross in the center of their field of view and to ignore the checkerboard stimuli. To maintain attention at the center of gaze as well as possible, subjects were instructed to press a button as soon as they could when the fixation cross changed from black to gray. The fixation cross dimmed at random times during the scan (on average 7 times per scan) for 250 ms. This task was difficult, as the change in luminance of the fixation was small. Subjects responded correctly 83% of the time, with a reaction time of 640 ms. Subjects' accuracy and reaction time were not significantly different during control and task blocks (paired two-tailed *t* test; percent correct: $T_{12} = 0.22$, $P = 0.83$; reaction time: $T_{12} = 0.0062$, $P = 0.995$), indicating that their attention to the task probably did not differ greatly between control periods and stimulus blocks.

MRI data acquisition

fMRI data were acquired on a Siemens 1.5-T Vision system (Erlangen, Germany). Subjects' heads were stabilized using pillows and a thermoplastic face mask. Structural images were acquired first, using a sagittal MP-RAGE sequence (repetition time TR = 9.7 ms, echo time TE = 4 ms, flip angle = 12°, inversion time TI = 300 ms, voxel size 1 × 1 × 1.25 mm). Functional images were acquired parallel to the anterior-posterior commissure plane in each subject, after manually defining that plane in the MP-RAGE image. Functional images were acquired by using an asymmetric spin-echo-planar sequence sensitive to Blood Oxygenation Level Dependent (BOLD) Contrast (Kwong et al., 1992; Ogawa et al., 1992). Sequence parameters were: T2* evolution time = 50 ms, flip angle = 90°, voxel size = 3.75 × 3.75-mm in-plane resolution, 8-mm slices (Conturo et al., 1996). One volume was acquired every 2.678 s, or one MR "frame." Subjects performed up to 12 functional runs. During each run, 146 frames of 16 contiguous axial slices were acquired. The first four frames of each run were discarded to allow stabilization of longitudinal magnetization.

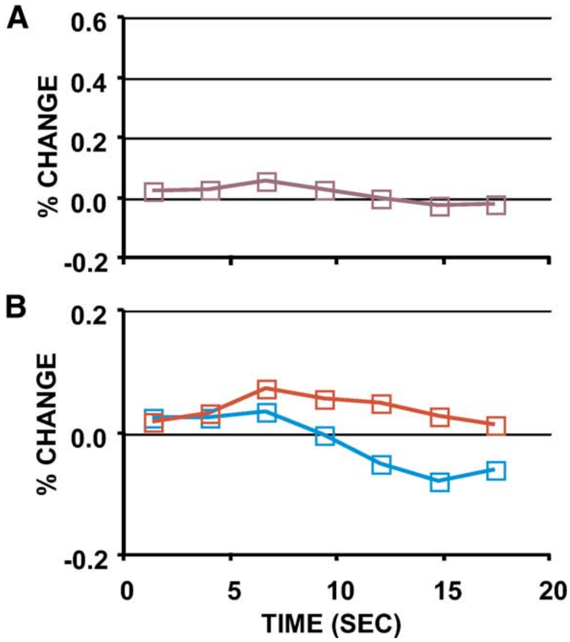

Fig. 9. Misapplied Transient effect from Analysis 3. (A) Time course of misapplied transient effect estimated during Sustained conditions. These data are averaged from data in the region of interest contralateral to the sustained stimulus, collapsed over left and right visual field. (B) Misapplied transient effects separated into those extracted for the misapplied Transient left effect, in the contralateral (right) hemisphere region of interest (shown in red) and the misapplied Transient right effect in the left hemisphere region of interest (shown in light blue). Time courses are plotted on an expanded scale so that the small changes in magnitude can be seen. Notice that the time course for the misapplied transient right effect shows a decrease over time ($P < 0.0001$). The misapplied transient left effect did not change significantly over time ($P = 0.9042$).

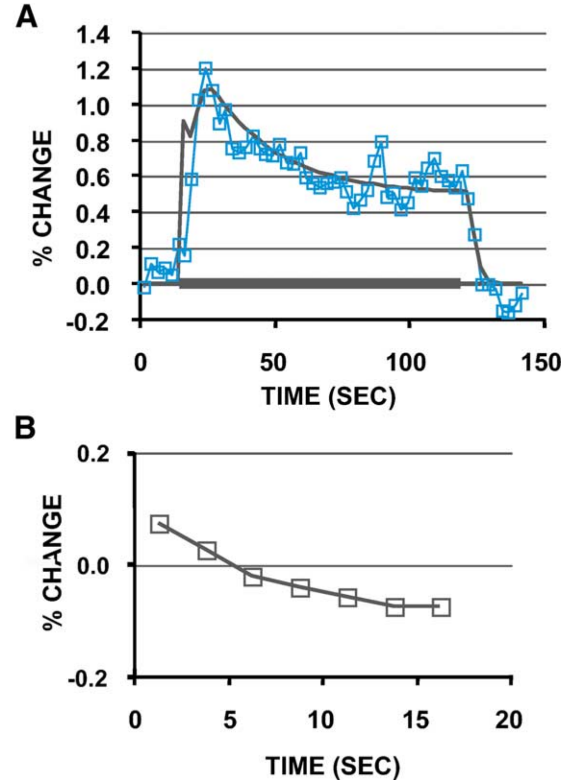

Fig. 10. Simulation of decreasing sustained effects. Based on the empirical observations that the time courses of the sustained effects decreased over time and that one of the misapplied transient effects had a significant decrease over time, another simulation was performed. Sustained effects were simulated as in the simulation of Fig. 2, and summed with a function that decreased steadily over time ($e^{-t/25s}$). This resulting "decreasing sustained" function is plotted in A along with the time course of the sustained effect for the Sustained condition in the right hemifield from Fig. 6. When these data were analyzed using a model that included sustained and transient effects, the transient effects extracted decreased over time as shown in B.

Data analysis

Functional images were preprocessed to remove artifacts. Each volume was corrected to account for intensity differences due to order of slice acquisition. Volumes were then motion corrected using a rigid-body rotation and translation correction (Lancaster et al., 1995; Snyder, 1996). Then each slice was temporally realigned using sinc interpolation to account for between-slice timing differences induced by their acquisition order.

Runs in which a subject's root mean square movement was more than 1 mm were excluded from further analysis. Twelve runs of data were included for each of 11 subjects, 11 runs for one subject, and 8 runs for one subject.

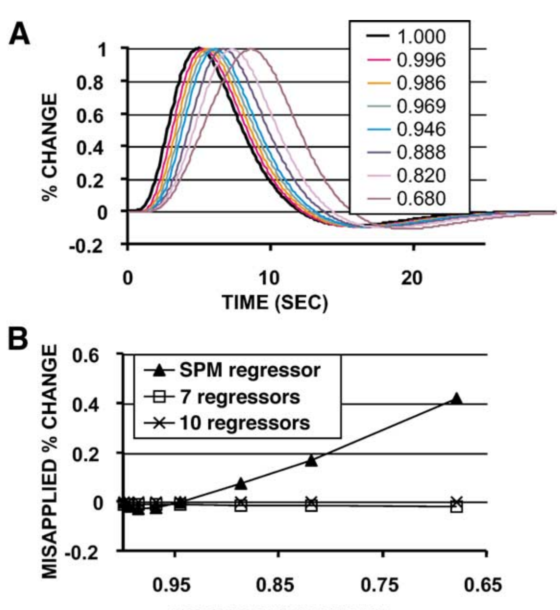

Fig. 11. (A) SPM canonical waveform convolved with increasingly long boxcars has decreasing correlation to the original waveform. Key shows correlation with basic SPM shape for each curve. (B) When a mixed design is used and a shape is assumed for transient activity, as correlation to the SPM canonical waveform decreases, activity is misapplied to the sustained regressor. When the transient activity is modeled by 7 regressors, there is much less misapplication of sustained activity, and even less when 10 regressors are used.

General linear model. Preprocessed data were analyzed on a voxel-by-voxel basis using the GLM (Friston et al., 1994, 1995; Worsley and Friston, 1995; Josephs et al., 1997; Miezin et al., 2000; Donaldson et al., 2001). The distinguishing feature of the mixed design is that both sustained and transient effects are coded in the GLM, as described above.

Analyses included all functional runs that passed movement criteria. All analyses included two additional regressors, i.e., one for the baseline signal and one for the slope, or linear drift, in the MR signal. All effects are described in terms of percentage of the average baseline term estimated across all runs.

Images in atlas space were interpolated to isotropic voxels 2 mm on a side. For analysis of data between subjects, each subject's data was placed in standardized stereotaxic atlas space (Talairach and Tournoux, 1988; Lancaster et al., 1995; Snyder, 1996) and smoothed with a gaussian filter with full width at half maximum of two voxels of $2 \times 2 \times 2$ mm^3.

Notes regarding all analyses. As noted, the sustained effects were modeled by using a single regressor. This does not allow extraction of time profiles of the sustained effect. Instead, time profiles of sustained effects were obtained by using the portion of the fMRI temporal signal variance that was not explained by the model (that is, the residual). The residual signal plus the signal associated with the modeled magnitude of a sustained effect was computed for each frame of each subject's data for a region of interest. This estimate was averaged over all occurrences of the effect for one subject, then averaged across subjects. This estimate based on the residual is reported as the time course of the sustained effect.

Three separate analyses were performed on these data. For purposes of clarity, the results of each analysis will be presented after the description of that analysis.

All regional analyses were performed by using the regions of interest defined in Analysis 1 so that the different analyses may be compared.

Analysis 1

Methods: Analysis 1—visually evoked effects

GLMs that coded for each of the 10 effect types related to visual stimuli (Effects modeled, Table 2) were created for each subject. The omnibus F-statistic was calculated for each voxel in each subject's image. This is a measure of (explained variance)/(unexplained variance) for the whole GLM (Draper and Smith, 1966), including all effect types but excluding the baseline and linear drift regressors. Omnibus F-statistic maps for each subject were transformed to stereotaxic space and maps for all subjects were averaged (Fig. 4). A peak search algorithm (Mintun et al., 1989) identified the location of the two largest F-value peaks in this image, as well as the average F-value in a 7-mm-radius sphere around those points. This average value was used as a threshold. Regions of interest were defined as the collection of all voxels that could be connected to the peak in a chain of face-contiguous voxels whose activation exceeded this threshold.

Significance values for all sustained effects were calculated by using a two-tailed t test where the null hypothesis is that the effect's magnitude is zero. Significance values for all transient effects were calculated by using a one-factor analysis of variance (ANOVA) with time as the factor. These values for transient effects were then corrected for sphericity (Box, 1954; Ollinger and McAvoy, 2000). All values are shown in Table 2. Corrected values that do not meet a criterion of $P < 0.05$ are listed as "—."

Results: Analysis 1—visually evoked effects

Fig. 4 shows a statistical map averaged over all subjects highlighting voxels that showed a good fit to the model of all visually evoked effects in Analysis 1. The two most significant peaks were in the left and right occipital cortex respectively. Note that the peak in the left visual cortex is located superiorly to the peak in the right visual cortex. This is to be expected, since the stimuli in the right visual field appeared in the lower quadrant and so should project to the left visual cortex superior to the calcarine sulcus (Inouye, 1909; Holmes, 1918; Daniel and Whitteridge, 1961; DeYoe et al., 1996). The left visual cortex region of interest defined from this map was made up of 101 voxels; right visual cortex region of interest was made up of 119 voxels.

Sustained (Fig. 5 and 6) and transient (Fig. 7) effects for flickering checkerboard stimuli were large in the contralateral hemisphere and very small in the ipsilateral hemisphere. For all figures, effects in the left visual cortex region of interest are shown in light blue while effects in the right region of interest are in red. Significance values for each effect over contralateral and ipsilateral regions of interest are shown in Table 2.

Note in Fig. 5 that in the contralateral region of interest, the magnitudes of sustained effects have no consistent relationship between the Sustained (only) and Combined conditions. A three-factor ANOVA (Ipsilateral vs. Contralateral Stimuli; Sustained (only) vs. Combined Conditions; Left vs. Right visual cortex regions of interest) was performed on the data for the sustained effects. There was a very significant effect of Ipsilateral vs. Contralateral stimuli ($F_{1,12}$ = 146.65, $P < 0.0001$). The only other significant effect was the interaction of all three factors ($F_{12,1} = 8.586$, $P = 0.0126$). Despite the significance of the interaction, post hoc comparisons showed no systematic relationship of hemisphere and condition.

The sustained effects for ipsilateral stimuli do not show positive activity. They appear slightly negative, but reach significance for only one of the four sustained effects (Fig. 5 and Table 2, right visual field, sustained condition).

Time courses for the sustained effects (calculated as described in the data analysis section) are shown in Fig. 6.

Note that these time courses show higher activity at the beginning of the sustained stimulus than near the end.

Transient effects in the contralateral region of interest showed highly significant changes over time and, as can be seen in Fig. 7, had time courses that followed the typical rise and fall of a hemodynamic response (Boynton et al., 1996). Four of the six transient effects in the ipsilateral region of interest were significant at the $P < 0.05$ level. However, the time course of these effects showed a steady decrease over time, as seen in Fig. 7; this will be discussed below.

Analysis 2

Methods: Analysis 2—misapplied sustained effects

A second analysis was performed to examine whether the mixed design misapplies variance to sustained effects when only transient activity is present. In this analysis "misapplied sustained" effects were coded in the model each time a Transient (only) stimulus condition occurred during a task block.

A separate set of GLMs was created that coded for each of the 10 visually evoked effects (Analysis 1), as well as for two additional effects. The first of these effects, called "misapplied sustained high-contrast left," was coded for during each block that contained the high-contrast Transient stimulus condition in the left hemifield. A second effect, called "misapplied sustained low-contrast left," was coded for during each block that contained the low-contrast Transient stimulus condition in the left hemifield. A different set of GLMs was created that coded for the 10 visually evoked effects as well for effects that modeled two misapplied sustained effects in the right hemifield, i.e., the "misapplied sustained high-contrast right" effect and the "misapplied sustained low-contrast right" effect. If positive deflections of activity caused by the transient stimuli are misapplied to the sustained effect by the mixed design, then these misapplied sustained effects should be significant and positive.

Only activations in the region of interest contralateral to the presentation of the relevant transient effect were included in the analysis. A two-factor ANOVA was performed with contrast level and stimulus hemifield as factors.

Results: Analysis 2—misapplied sustained effects

Results of the two-factor ANOVA showed no significant main effects or interactions, indicating that any potential misapplied sustained effect was indistinguishable between hemifields or contrasts. The main effect of hemisphere showed a trend level of significance, however ($F_{1,12} = 3.51$, $P = 0.0854$). Because of this trend, we examined left and right regions of interest separately. Fig. 8 shows the magnitudes of the misapplied sustained effects for sustained stimuli in the left and right hemifields. *T* tests showed that the misapplied sustained left effect in the right hemisphere was not significant ($T_{25} = 0.363$, $P = 0.72$). The misapplied sustained right effect in the left hemisphere showed a negative mean (-0.114) with a trend level of significance ($T_{25} = 2.02$, $P = 0.055$).

Analysis 3

Methods: Analysis 3—misapplied transient effects

A third analysis was performed to examine whether the mixed design gives rise to misapplied transient effects. In this analysis, a set of "misapplied transient" effects was coded during each block containing a Sustained (only) stimulus condition.

GLMs were created that coded for effects related to the 10 visually evoked effects (Table 2) as well as for two sets of regressors that mimicked the timing of transient trials. The "misapplied transient left" effect was coded in the GLM during each block in which the Sustained (only) stimulus condition was presented in the left visual field. During each block in which the Sustained (only) stimulus condition was presented in the right visual field, a set of "misapplied transient right" effects were coded. These "misapplied" transient effects were coded as if they occurred at varied intervals in a timing sequence like those used for the visually presented transient stimuli. For each block, choice among the four timing sequences for the misapplied transient effects was random, but with the constraint that they never shared the same timing as the visually evoked effect during the same block for stimuli presented in the opposite hemifield.

For this analysis, significance values quoted are based on a one-factor repeated measures ANOVA with time as the factor. Data were collapsed across hemifield (in effect, doubling the number of samples) to allow the analysis greater power to detect a misapplied transient effect if it exists. This means that time courses in both right and left hemisphere were included in the ANOVA.

Results: Analysis 3—misapplied transient effects

Fig. 9 shows the time courses for the misapplied transient effects. Fig. 9A shows activity in the contralateral visual cortex averaged for the misapplied transient effects due to stimuli in left and right hemifields. This effect was not significantly different from zero (repeated measures ANOVA; $F_{6,150} = 2.099$, $P = 0.057$).

Although the significance of this effect did not reach the criterion level of $P = 0.05$, it showed a trend level of significance, so the misapplied transient effect was explored further. Fig. 9B shows the time course for the misapplied transient effects broken down into misapplied transient effects associated with sustained stimuli in the left and right hemifields. The misapplied transient left effect was not significant in the region of interest contralateral to its presentation (repeated measures ANOVA; $F_{6,72} = 0.356$, $P = 0.9042$). On the other hand, the misapplied transient right effect was highly significant (repeated measures ANOVA; $F_{6,72} = 7.28$, $P < 0.0001$). This indicates that the marginal significance of the combined effect is driven by the highly significant misapplied transient right effect. As can be seen from Fig. 9B, the misapplied transient right effect (in light blue) does not show a normal transient hemodynamic time course, but rather shows a general decreasing trend over time. Note that the scale of Fig. 9B has been magnified so that this small difference can be seen.

Supplemental simulations

Supplemental simulations were performed to examine what situations might cause the mixed design to fail to dissociate sustained from transient activity. These simulations addressed situations where sustained activity might be misapplied to the transient regressors and situations where transient activity might be misapplied to the sustained regressor. Also investigated was the question of whether variations in the timing of blocks and trials can affect the mixed design's power to detect transient and sustained signals.

Sustained activity misapplied to the transient regressor

The decreasing trend of the misapplied transient effect, coupled with the result of decreasing sustained time courses seen in Analysis 1, led to a question: Could the apparent significance of the decreasing transient effect be caused by the decreasing sustained time course? A test of this hypothesis was performed by using Bay Zero. A "decreasing sustained" effect, which rose to a peak and gradually decreased over the time of one task block, was simulated. The function simulated was the sum of the sustained shape assumed in the analysis (gamma function convolved with a boxcar function) and a function that is large at onset and decays over time ($e^{-t/25\text{ s}}$, where $t =$ time in seconds from onset of stimulus). This function is shown in Fig. 10A alongside empirical data showing the time course obtained for the Sustained condition in the right hemifield (these data are also shown in Fig. 6). The simulated data were analyzed by using a GLM that coded for both a sustained effect that rose to a constant amplitude during the task block and a series of transient effects (like the GLMs in the other simulations). Although there was no transient trial-related activity in the simulation, the results of the model showed transient effects with a decreasing temporal profile as seen in Fig. 10B. This temporal profile shows a small response magnitude similar to that seen for the misapplied transient right effect (see results of Analysis 3, Fig. 9B).

Transient activity misapplied to the sustained regressor

Misapplied sustained effect due to assumptions of transient activity shape. One possible way to eliminate these nonhemodynamic but "significant" transient time courses would be to assume a hemodynamic shape for the transient effects in the GLM. Then only regions whose activity approximated this shape would be extracted from the analysis. However, there is a potential problem with this method. If the transient response shape does not fit the assumed response shape, activity corresponding to the difference between the true activity and the modeled shape could be misapplied to the sustained regressor. To test this hypothesis, another simulation was performed by using MATLAB. Simulated data were created with transient trial-related activity [as in Fig. 1C, Transient (only)] that had the shape of the statistical parametric mapping (SPM) canonical hemodynamic function (Friston et al., 1995). The timing of the trial-related activity was identical to that used for the previous simulations. Two runs of data were simulated, composed of four blocks, with the four different timings of trials each represented. To parametrically vary the shape of the simulated MR response, the canonical function was convolved with boxcars of the following seven time lengths: 0.5, 1, 1.5, 2, 3, 4, and 6 s. As the boxcar length increased, the correlation between the SPM canonical response and the simulated response decreased. The shapes and correlations are shown in Fig. 11A. This procedure is consistent with the work of others (Boynton et al., 1996) looking at variations in hemodynamic response shape. These data were analyzed using the GLM by including one regressor for a sustained response as well as one regressor for the transient response that assumed the basic SPM canonical shape for this activity. Fig. 11B shows the result of this simulation; as the simulated transient signal deviated from the assumed shape, more and more of the transient trial-related activity became misapplied to the sustained regressor. This indicates that assuming a shape for the hemodynamic response in the GLM can cause misapplication of activity to the sustained effect.

For comparison, the same simulated data were analyzed by using the methods used in Experiment 1 (transient responses modeled as 7 regressors). As the transient response extends further than 7 frames in length, this 7-regressor analysis method causes a very small negative misapplied sustained response as late activity (the "undershoot") is misapplied to the sustained regressor. With the addition of more regressors to cover the entire response (see 10-regressor data in Fig. 11), the model once again accurately parses sustained and transient activity.

Saturation of transient activity. The effects of saturation of transient activity on sustained responses were examined by using Bay Zero. Transient (only) activity was simulated just as above, using a gamma function (see equation above) with a peak amplitude of 0.6%. No noise was included in the simulation, but the total activity was assumed to saturate so that for any initial value of the signal (Y_i), the saturated value of the signal (Y_s) was given by $Y_s = \dfrac{S \times Y_i}{S + Y_i}$.
When S is not very large with respect to the signal Y_i, the saturated signal is attenuated relative to the original signal. Dale and Buckner (1997) and Huettel and McCarthy (2000) calculated the visual cortical response to two visual stimuli that were closely spaced in time. Both found slight attenuation in the response to the second stimulus. The largest attenuation found in either of these two papers was consis-

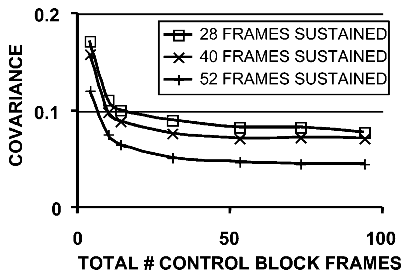

Fig. 12. Relative variability of the estimate for the sustained effect versus the number of total control block frames. Note that the covariance does not change much after about 31 control block frames are included.

tent with a value for S of about 7. When saturation with this magnitude was introduced, transient time courses peaked on average at about 0.5% change, and a very small spurious sustained response (0.03% change) was obtained. When more saturation was introduced, this spurious response did not increase considerably, and when less saturation was introduced, the spurious response decreased. This change is too small to reliably detect statistically, and no effect of saturation was observed during strong visual cortical activity. Therefore, we find it reasonable to assume that saturation should not pose a problem in cognitive experiments

Modifying the timing of the design to increase power. The variance attributed to any particular effect in a GLM depends on both the timing of the stimuli and also the amount of noise in the MR signal. Under the assumption that the signal noise is uncorrelated, the variance for an effect will be directly proportional to signal noise variance with the proportionality constant determined by the design matrix. Thus, the relative variance of any two effects can be determined simply by using the design matrix of the GLM. Specifically, the on-diagonal elements of the covariance matrix give a measure of relative variance for each regressor in the model (Draper and Smith, 1966). By comparing this measure across different design matrices, one can choose a design with relatively less variance for a particular effect.

To determine generally how many frames of the control task are optimal, GLMs were created that were similar in every respect but the total number of frames during control blocks. These GLMs were created as in Fig. 1, with two task blocks. Task blocks were 28, 40, or 52 frames long. An average of 5 trials occurred in every 10 frames during the task blocks. The number of frames in the second and third control blocks were equal. The first control block contained between 0 and 8 fewer frames than the second and third control blocks. The total number of control block frames ranged from 4 to 94 frames. This total is the sum of all frames in all three control blocks. Fig. 12 shows that for small number of control block frames, the estimates for sustained regressors are poor. However, once the total number of control block frames exceeds approximately 31 frames, the benefit to adding more control block frames is small. This was true for all choices of task block length, indicating that it is not the ratio of control block frames to task block frames, but the absolute number of control block frames that gives rise to this effect. Analyses of this type are useful for choosing between several different possible experimental designs.

Discussion

The experiments presented here suggest that the mixed design can extract effects with sustained and transient temporal profiles from fMRI data and dissociate them from each other. Though the evidence implies that sustained activity is most often not misapplied to the transient effect, some evidence suggests that it may be misapplied in certain situations. These findings place constraints on the application of mixed designs, which will be discussed in the "Constraints on the use of the mixed design" section.

Mixed designs can accurately extract transient and sustained signals

Both the simulation and the fMRI experiment showed robust sustained signals in the Sustained and Combined conditions, and robust transient signals in the Transient and Combined conditions. Conversely, little or no misapplication of activity from one effect to another was found.

Nonetheless, some of the results outlined potential spurious effects that were examined further. There was a slight trend for misapplied sustained activity to have a negative mean. This is consistent with other studies that have shown neural activity decreases during stimulation of another part of visual cortex (Shmuel et al., 2002).

Decreasing temporal profile of sustained activity

In the data examined here, there was a trend (Fig. 6) for all of the sustained effects to decrease gradually over time. This decreasing trend is likely to be due to physiological factors external to the mixed design we are testing. Contrast adaptation is known to occur in early visual cortical areas in cats and in primates (Sclar et al., 1989; Carandini and Ferster, 1997; Heinrich and Bach, 2001). Such adaptation could contribute to the decrease in activity seen in response to the stimuli of sustained contrast (Bandettini et al., 1997; Miller et al., 2001).

The decreasing temporal profile of sustained activity may explain a finding regarding the transient effects. Analysis 1 of the visually evoked effects found that several of the transient time courses in the ipsilateral visual field changed significantly over time (Table 2, Ipsilateral). Inspection of Fig. 7 shows that their time courses have a generally decreasing trend, rather than the typical rise and fall of a hemodynamic response. This result was also found in the misapplied transient time courses of Analysis 3. In this case, the misapplied transient time course in the left visual cortex region of interest decreased significantly over time.

An explanation of these decreasing transient effects can be given as follows. Both cases involve coding for transient effects during blocks when sustained stimuli are present. In the case of Analysis 3, the misapplied transient effects are modeled only during the Sustained conditions. In the case of the decreasing time courses in the ipsilateral visual cortex to transient stimuli in Analysis 1, sustained stimuli were present in the visual field opposite to transient stimuli half of the time (two of the four conditions involved sustained stimuli). The sustained activity due to these sustained stimuli was not constant, as was assumed in the analysis, but decreased over time (Fig. 6). Since the regressor for the first frame of a transient effect always precedes the last frame, it always occurs when the sustained activity is at a slightly larger value. It follows that there is a consistent and significant difference between these two points.

In this way, the effects related to the transient conditions might "absorb" some of the variance due to the decreasing sustained effect. In fact, simulations using Bay Zero (Fig. 10) show that decreasing transient time courses would be detected as a result of "sustained" activity that decreased over time if the activity was modeled as if it had the same magnitude throughout.

The decreasing time courses for transient effects do not show the typical hemodynamic response, and can be explained by the decreasing sustained effects. These results indicate that use of the mixed design should not lead to misinterpretation of sustained activity to transient effects, assuming that experimenters examine the time courses resulting from their analyses as well as the statistical images generated.

Constraints on the use of the mixed design

Although the mixed design does separate sustained and transient activity in general, the simulations performed here highlight several constraints on its use. First, to prevent nonhemodynamic responses from being interpreted as transient neural responses, time courses of transient effects must be examined along with statistical maps. As discussed in the previous paragraph, misestimation of the time course of sustained activity could cause variance from the sustained effect to be misapplied to the transient effect, giving rise to transient signals that "change in time" significantly, but are not hemodynamic in nature. The wrong conclusion (transient trial-related response in ipsilateral visual field) might have been assumed if the statistical image had been analyzed alone.

One might try to get around this problem by assuming a shape for the transient hemodynamic response in the GLM. This method gives rise to its own problems, since small misestimation of the time course of transient activity can cause spurious sustained activity (as seen in Fig. 11). Therefore, a second constraint is that transient responses should not be modeled in the GLM with assumed shapes. An alternative is to filter out nonhemodynamic looking responses in analyses subsequent to the GLM.

A third constraint must be placed on the interpretation of time courses for sustained effects. The mixed design, as implemented here, cannot distinguish between residuals due to consistently graded responses to subsequent trials, and residuals due to continuously varying sustained effects. This is because with the current mixed design, sustained effects are modeled with an assumed shape in the GLM and therefore information about their shapes comes from residuals of the model. Transient trial-related activity related to the same stimulus type are modeled in the GLM as if they have the same amplitude. Therefore, if the amplitude of the transient trial-related activity depends on time, the residual will depend on time. The residual's time dependence could be misinterpreted as a change over time in the sustained effect. Other methods of extracting the time course of sustained activity could be used, such as modeling many frames of the sustained response in the GLM, or modeling the sustained signal with a decreasing shape. However, by increasing the number of modeled effects, the statistical power of the analysis is decreased. Further optimization of the mixed design may allow better estimation of the time course of sustained effects.

Finally, a critical consideration is that the ability of the mixed design to extract sustained state-related activity depends on the consistent induction of that psychological state. If an experimental design fails to induce a consistent cognitive state, the neural correlates of such a state cannot be extracted or interpreted. For example, if too few trials are included in a block of trials, or large gaps between trials occur, it is unlikely that the relevant behavioral state will be induced or maintained. "Too few" must be defined psychologically, here. This places a fourth constraint on the use of mixed designs that applies to any experimental paradigm. When designing fMRI experiments in general, and mixed design experiments in particular, the psychological consequences of the design cannot be ignored.

Potential uses of the mixed design

This study has shown that the mixed design can be used to examine sustained task-related activity and transient trial-related activity in fMRI data. The ability to dissociate these two different types of activity should allow researchers to explore questions involving slowly varying neural responses related to the state of a subject. To date, these sustained signals are largely unexplored, barring a few examples. These examples imply that sustained activity exists in the brain and is present during memory retrieval (Donaldson et al., 2001), memory encoding (Kato et al., 1998; Fernandez et al., 1999; Mitchell et al., 2000; Otten et al., 2002), and attention to attributes of visual stimuli (Chawla et al., 1999). Psychological interpretation of such effects should be more constrained when two or more different task types are compared in the same group of subjects.

The brain, being composed of a large number of processing pathways, must organize those pathways to get any one particular task (for example, taking a vocabulary test) accomplished. Some of the signals related to this organization are likely to have a temporal profile that is sustained. The ability to observe activity with sustained temporal profiles should greatly expand the range of cognitive processes for which the study of fMRI activity can be useful.

Conclusion

The mixed design represents an important expansion of the repertoire of fMRI tools available for exploring neural information processing. Neural activity related to task state can be distinguished from activity related to individual trials. This dissociation of effects with different temporal profiles should allow researchers a means to better determine what functions are served by particular activations. This may allow better understanding of processes that are related to the state of a subject, as separate from processing performed for each trial.

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