

Transient BOLD responses at block transitions

Michael D. Fox,^{a,*} Abraham Z. Snyder,^{a,d} Deanna M. Barch,^b
Debra A. Gusnard,^{a,c} and Marcus E. Raichle^{a,d}

^aDepartment of Radiology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 4525 Scott Ave., St. Louis, MO 63110, USA

^bDepartment of Psychology, Washington University in St. Louis, MO 63130-4899, USA

^cDepartment of Psychiatry, Washington University in St. Louis, MO 63110, USA

^dDepartment of Neurology, Washington University in St. Louis, MO 63110, USA

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Block-design fMRI responses include sustained components present for the duration of each task block as well as transient components at the beginning and end of each block. Almost all prior block-design fMRI studies have focused on the sustained response components while the transient responses at block transitions have been largely ignored. These transients, therefore, remain poorly characterized. We here present a systematic study of block-transition transient responses obtained using four widely divergent tasks. We characterize transient response topography and examine the extent to which these responses vary across different tasks and between block onset and offset. Our analysis reveals that certain regions show transient responses regardless of task or transition type. However, our analysis also shows that specific task state transitions give rise to transient responses with unique spatial profiles. Relevance of the current findings to studies of exogenous attention, task shifting, and the BOLD overshoot is discussed.

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Introduction

Block design fMRI involves administering blocks of contrasting experimental conditions, for example task vs. rest, over epochs typically 25–40 s in duration. Conventionally, block design analyses evaluate signal modulation attributable to condition contrast *assuming that the neuronal response is constant across each block*. These techniques effectively collapse across time, thus discarding information in the temporal response profile. This analysis strategy dates back to the earliest functional neuroimaging studies based on positron emission tomography (PET) in which response modulations necessarily had to be measured over a

sustained task period, usually about 1 min (Raichle et al., 1983). The greatly improved temporal resolution afforded by fMRI makes it possible to detect transient responses at block onset and offset in addition to sustained responses. Just as examination of the sustained response has provided insight into cognitive operations occurring throughout a task block, examination of transient responses could provide important information about functional processes occurring specifically at the beginning or end of a task block (block transitions). This idea is reinforced by recent work indicating that transient BOLD responses at block transitions can be specifically modified by clinical state (e.g., diagnosis of schizophrenia) (Fox et al., 2005). Such data highlight the need for an increased understanding of transient BOLD responses at block transitions.

Transient phenomena at the onset of the task-related BOLD response have been noted for many years but, in the preponderance of extant studies, have been attributed to transient mismatch between neuronal metabolic demand (assumed to be constant within task blocks) and various components of the vascular response (Buxton et al., 1998; Obata et al., 2004). In other words, BOLD transients at block transitions have generally not been viewed as reflecting transient neuronal activity. A notable exception is the study by Konishi et al. (2001), which found that intentional encoding task block transients exhibited a spatial distribution distinct from that of the sustained response, suggesting that transient and sustained components of the BOLD signal might reflect distinct functional processes. Their study, however, was limited to a single task paradigm and made no distinction between the transient response at task onset vs. offset (Konishi et al., 2001). We here present a meta-analysis of BOLD transient responses distinguishing between task onset and offset using four very different task conditions: 2-back working memory, visual scene analysis, overt word reading, and simple visual fixation. We address four major questions:

1. Can transient vs. sustained components in block design fMRI experiments be reliably distinguished and localized?

* Corresponding author. Fax: +1 314 362 6110.

E-mail address: foxm@npg.wustl.edu (M.D. Fox).

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2. Which regions exhibit the largest transient responses on average? Are there regions that always show transient responses at task state transitions?
3. To what extent do transient BOLD responses depend on task? Are these responses different at block onset and offset within the same task?
4. How do these empirical observations constrain our interpretation of the functional role of transient activity at block transitions?

It should be noted that the current study is an analysis of transient BOLD responses at the onset and offset of a task block. This is different from recently published analyses which examine state and item effects (sometimes referred to as BOLD transients) within a task block (Velanova et al., 2003; Visscher et al., 2003).

Methods

The current analysis is based on data acquired in four previous block design fMRI studies not originally focused on block transition transients. These data were selected to include a broad range of cognitive activities. A summary listing of task and control conditions, subject number, stimuli, scanning parameters, and original sources of these data is given in Table 1.

Tasks, subjects, and imaging parameters

2-back working memory task

The working memory data were obtained in a previously published study of memory in schizophrenic vs. normal participants (Barch et al., 2002). Only the normal volunteer data are included here. All subjects ($n = 48$) were right handed. Participants were instructed to determine whether or not serially presented items matched those presented two trials back (2-back task) and to press one of two buttons accordingly using the right hand. The stimuli were concrete nouns or non-namable faces shown on a video screen. Each participant completed one fMRI run in which the stimulus type (nouns or faces) was constant. Each run began with 4 frames of crosshair fixation (discarded from the analyses)

followed by four 40 s (16 frame) task blocks separated by three 25 s (10 frame) fixation blocks. The fourth task block was discarded from the analysis as it was not followed by a complete fixation block. The current analysis collapsed across stimulus type (words and faces) to increase the signal to noise ratio.

Word reading task

The reading data were obtained in a previously published study on reading vs. verb generation (Kerr et al., 2004). Only the word reading data are used here. Normal, right-handed participants ($n = 15$) read aloud common English nouns presented on a video screen for 150 ms every 1.6 s. Subjects completed 10 fMRI runs consisting of three 32 s task blocks alternating with three 32 s fixation blocks (6 blocks per run). The same word list was used in each run (60 words/run) with the word order pseudorandomly varied.

Opening eyes (visual fixation) task

Normal, right handed ($n = 10$) volunteers alternately opened and closed their eyes in response to pre-recorded verbal instructions delivered through acoustically shielded head-phones (Resonance Technologies Inc., Los Angeles, CA). The scanner room ambient illumination was kept at a low level. In the eyes open condition, subjects were asked to stare at a small fixation cross. The eyes closed condition was not otherwise specified in the subject instructions. Subjects completed 6 runs, each consisting of four 40 s blocks of eyes open and four 40 s blocks of eyes closed. Half the runs began with the eyes open condition and half with the eyes closed condition. In the current analysis, only full epochs starting with an eyes open block followed by an eyes closed block were used. Each run thus produced three usable eyes open/eyes closed epochs.

Scene analysis task

The scene analysis data were acquired in a previously published study of self-referential vs. non self-referential judgment (Gusnard et al., 2001). Here, we used only the non self-referential data. Right handed participants ($n = 24$) judged whether photographic scenes displayed on a video monitor were indoors (right index finger button press), outdoors (right middle finger button press), or ambiguous

Table 1

Summary of task and control conditions, subject number, stimuli, scanning parameters, and original sources of the data for the four studies included in the present analysis

Task block type	Working memory	Read	Eyes open	Scene analysis
Task type duration	40 s	32 s	40 s	36 s
Control block type	Fixation	Fixation	Eyes closed	Fixation
Control block duration	25 s	32 s	40 s	36 s
Subject number (female)	48 (26 F)	15 (8 F)	10 (7 F)	24 (12 F)
Subject age (range, mean)	36.2	1924, 21.4	2334, 27.5	2035, 24
Stimulus type	Faces/Words	Simple nouns	Fixation cross	IAPS pictures
Stimulus duration	2 s	150 ms	Constant	500 ms
Stimulus ISI	2.5 s	1.6 s	NA	3.6 s
Behavioral response	R hand BP	Verbal	None	R and L hand BP
Scanner	1.5 T	3 T	3 T	1.5 T
BOLD TR	2.5 s	2.0 s	2.5 s	2.16 s
BOLD TE	50 ms	25 ms	30ms	50 ms
BOLD flip	90°	90°	90°	90°
BOLD resolution	3.75 × 3.75 × 8 mm	3.2 × 3.2 × 3.2 mm	4 × 4 × 4 mm	3.75 × .75 × 8 mm
Publication	Barch et al. (2002)	Kerr et al. (2004)	Unpublished	Gusnard et al. (2001)

BP = button press, F = female, ISI = inter-stimulus interval from onset of one stimulus to the next.

(left index finger button press). All pictures were from the International Affective Picture System (IAPS) (Lang et al., 1997) and were presented for 500 ms every 3.6 s. Subjects completed 6 fMRI runs. Each run began with 10 s of fixation (discarded from analysis) followed by three 36 s task blocks alternating with three 36 s fixation blocks. Each task block included 10 pictures.

MRI scanning

All MR scanning was performed at Washington University Medical center in St. Louis, MO using either a 1.5 T Siemens Vision system (Erlangen, Germany) or 3 T Siemens Allegra system (Erlangen, Germany) (Table 1). Functional data were collected using an asymmetric spin-echo, echo-planar (EPI) sequence sensitive to blood oxygen level dependent (BOLD) contrast. All studies included whole brain coverage with contiguous slices. Structural data (for definitive atlas transformation) included a high resolution sagittal, T1-weighted MP-RAGE and a T2-weighted fast spin echo scan. Scanning parameters for individual studies are listed in Table 1.

fMRI preprocessing

For all the above studies, fMRI preprocessing steps included (1) compensation of systematic, slice dependent time shifts, (2) elimination of systematic odd-even slice intensity differences due to interleaved acquisition, and (3) rigid body correction for inter-frame head motion within and across runs. Each fMRI run (excluding the first four frames) was intensity scaled (one multiplicative constant over all voxels and frames) to a yield a whole brain mode value of 1000. We standardize the *mode* (as opposed to the *mean*) intensity because this statistic is clearly determinable by analysis of the distribution of fMRI voxel values, which is always sharply unimodal. This strategy avoids problems in computing whole brain mean intensity in EPI images attributable to the fact that the location of the brain edge is ambiguous in the presence of susceptibility artifacts and relatively low spatial resolution (Ojemann et al., 1997).

Atlas registration was achieved by computing affine transforms (9-parameter) connecting the fMRI run first frame (averaged over

all runs after cross-run realignment) with the T2- and T1-weighted structural images (Ojemann et al., 1997). Each subject's MP-RAGE was registered to the atlas template using a 12 parameter affine transform. Our atlas representative template includes MP-RAGE data from 12 normal individuals and was made to conform to the Talairach atlas (Talairach and Tournoux, 1988) according to the SN procedure of Lancaster et al. (1995). To prepare the BOLD data for the present analyses, each fMRI run was transformed to atlas space and resampled to 2 mm cubic voxels.

Coding of sustained and transient effects

For each participant and study, the functional data were averaged to create a volumetric time series representing the mean BOLD response averaged over one task block followed by one control block. These averages were spatially smoothed (FWHM 4.0 mm Gaussian blur) and then analyzed using the general linear model (GLM) (Friston et al., 1994, 1995a,b; Worsley et al., 1996). Our GLM used ordinary least squares with the assumption that the noise was independent and identically distributed with zero mean and constant variance. For subsequent statistical inference, we assumed a Gaussian noise distribution.

Our linear model included three response components, a sustained component present throughout the task block, a transient component at task block onset, and a transient component at task block offset (Fig. 1). As in conventional block design analyses, we modeled the sustained component by convolving a canonical hemodynamic impulse response function with a rectangular waveform of duration equal to the task block (Boynton et al., 1996). The transient component at task block onset was modeled by independently estimating the response at each frame for the first 15 s after the start of the task block. Similarly, the offset transient was modeled by independently estimating the response at each frame for the first 15 s after the end of the task block. Thus, the block transition transients were estimated without any assumptions regarding waveform (except for limited duration) (Ollinger et al., 2001a,b). Fig. 1 provides an example of the general linear model estimates for a region in the right temporal–parietal junction for the working memory task.

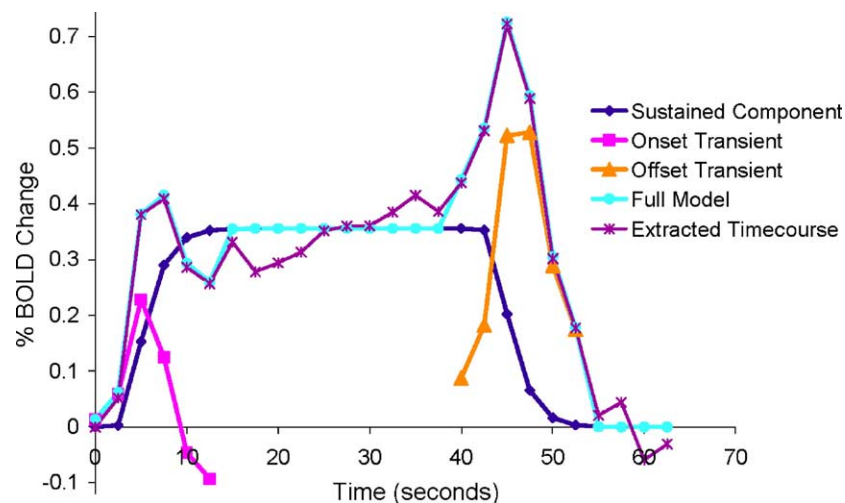


Fig. 1. Example of the general linear model estimates for block transient and sustained components from a region in the right temporal–parietal junction during the working memory task. Shown are the three modeled components (sustained, onset transient, and offset transient), the linear summation of these three components (full model), and the extracted time course for this region.

Statistical parametric maps for the sustained and transient responses were computed for each of the four tasks. Sustained response significance maps were evaluated by voxel-wise *t* tests of modeled response magnitudes (Holmes and Friston, 1998). Transient response significance maps were created separately for block onset and offset using voxel-wise analysis of variance (ANOVA) tests for a main effect of time (Braver et al., 1997; Shulman et al., 1999), i.e., BOLD modulation within the transient epoch (15 s) not otherwise modeled and not attributable to noise. All statistical maps were converted to equally probable *z* scores and thresholded ($z > 3.0$) to correct for multiple comparisons on the basis of Monte-Carlo simulations. The final maps show areas of significant BOLD response (false discovery rate 5%) for contiguous clusters of size of 49 (*t* test) or 51 (ANOVA) voxels. Fig. 2 shows examples of such maps corresponding to the onset transient, sustained component, and offset transient for the working memory task. Straightforward conjunction analyses were performed to determine the extent of spatial overlap between various response component pairs. These results were computed as the number of voxels showing a significant response for both components divided by the number of voxels showing a significant response for either component.

Comparison across tasks and block onset and offset

Having computed statistically reliable maps for each of the eight transient responses considered separately, the next set of questions concerned similarities and differences. As the data were acquired in separate studies differing in methodological detail (Table 1), it was not possible to directly analyze within-group task-dependent contrasts. Nevertheless, a strategy more systematic than visual inspection of the maps was needed.

First, to address the question of response commonalities, the *z* maps were combined using a fixed effects analysis (Bosch, 2000), i.e., adding *z* scores and dividing by the square root of the number of contributing studies ($n = 8$). The resulting *z* statistic map shows

regions with the most significant transient responses *on average*, collapsing across task and transition type (onset vs. offset). It should be emphasized that the fixed effects analysis strategy was not required to achieve statistical significance; each of the eight analyses independently produced its own statistical map. A conjunction analysis was performed by setting all voxels showing a significant transient response in each individual transition equal to one, and then adding the distributions. Thus, voxels with a conjunction map value of 8 were significant in all eight examined transitions.

Identification of regions of interest (ROI)

Second, to facilitate comparison of transient responses across task paradigms, temporal response profiles were examined in fixed regions of interest (ROI). Regions were created using an empirical strategy starting with the map obtained by the fixed effects analysis. Peak loci exceeding a selected threshold ($z = 15.5$) were identified by straightforward peak search (Mintun et al., 1989). Loci closer than 12 mm were consolidated by algebraic averaging of coordinates to create a single locus at the center of mass. The peak search parameters (*z* threshold and consolidation distance) were chosen to yield approximately 20 consolidated peak loci. Regions of interest were generated by centering spheres (8 mm radius) on the consolidated peak loci. Voxels within the spherical boundaries of two loci were assigned to the nearest peak thereby ensuring no overlap between regions. ROI voxels not meeting a selected criterion ($z = 15.0$) in the original image were eliminated. The result was a partitioning of the average transient map into 18 non-overlapping regions centered on loci of peak significance, including only voxels meeting a conservative statistical criterion. The atlas coordinates of these 18 regions of interest are listed in Table 2.

Transient responses at task onset and offset within a task were compared on a regional basis using an analysis of variance (ANOVA). The results were Bonferroni corrected for multiple comparisons (multiplication of *P* values by 18) and are shown in Table 2.

Table 2
“Transient” regions of interest showing the most significant transient responses averaged across tasks

Name	Coordinates			<i>z</i> score	Onset vs. offset transient ANOVA			
	<i>X</i>	<i>Y</i>	<i>Z</i>		WM	Read	Eyes	SA
R TPJ	52	46	18	19.75	0.0774	13.32	3.42	17.1
R ant. cingulate	6	6	43	19.43	0.864	3.78	0.081	0.000036
L ant. cingulate	−7	7	37	19.14	0.18	0.774	0.252	0.000146
R mid. frontal gyrus	41	1	34	18.38	9.18E−06	13.14	0.0198	0.045
SMA	−6	−7	51	17.97	0.0324	0.000396	1.008	4.5E−12
R frontal operculum/insula	31	15	8	17.96	0.00018	2.52	0.63	0.00414
R post. precuneus	14	72	37	17.81	0.108	10.62	0.00306	0.918
R precuneus	10	37	43	17.80	0.432	14.76	2.16E−05	0.198
L frontal operculum/insula	33	10	8	17.44	0.001512	0.198	4.68	0.0702
R post. parietal	30	57	44	17.38	0.00468	3.24	0.01296	3.78
R thalamus	10	21	5	17.24	8.28E−07	0.000864	9.18	0.0432
L precuneus	13	37	41	16.89	0.774	8.28	0.0252	0.00063
Post. cingulate	−1	34	26	16.80	5.22E−05	9.72	5.22E−05	1.296
R precuneus	10	58	43	16.69	4.86	16.74	0.00702	5.4E−09
R fusiform gyrus	24	54	11	16.57	1.8	0.504	0.0972	5.76E−25
L post. precuneus	11	75	36	16.14	0.612	7.38	0.00036	11.34
R sup. frontal gyrus	30	39	32	15.93	2.7	3.24	16.02	0.252
L fusiform gyrus	26	70	11	15.56	0.0972	0.0846	13.86	2.88E−19

Shown for each region are the Talairach coordinates, the peak *z* score value from the fixed effects analysis, and the *P* value results of an ANOVA comparing transient responses at task block onset and offset for each task (WM = working memory, SA = scene analysis). ANOVA results have been Bonferroni corrected by multiplying each *P* value by the number of regions (18); statistically significant results ($P < 0.05$) are shown in bold.

Results

Separation of onset transient, sustained, and offset transient responses

For each of the four tasks, voxel-based maps of significant onset transient, sustained, and offset transient responses were created. Results for one of the tasks, the working memory task, are shown in Fig. 2. To illustrate face validity of the GLM based procedure for separation of transient and sustained components, single-slice square regions of interest (not to be confused with the ROIs listed in Table 2) are shown overlaid on the distributions. The time courses for a single epoch (40 s task followed by 25 s fixation) for each ROI are displayed to the right. The blue time

course corresponds to the blue region of interest in each row while the green time course corresponds to the green region of interest in each row. ROIs were chosen to demonstrate the close relationship between the distribution maps and the volumetric time courses.

Consider, for example, the blue ROI over the right basal ganglia in the first row ($z = 8$). By examining the placement of this ROI on each of the three distributions, we see that the region overlies a large onset transient response, a medium sustained response, but little to no offset transient response. When we then examine the time course for this region to the right (blue time course), we see a large onset transient, a medium sustained effect, and little to no offset transient. This procedure can be repeated for each ROI shown in Fig. 2, demonstrating a close correspondence between the

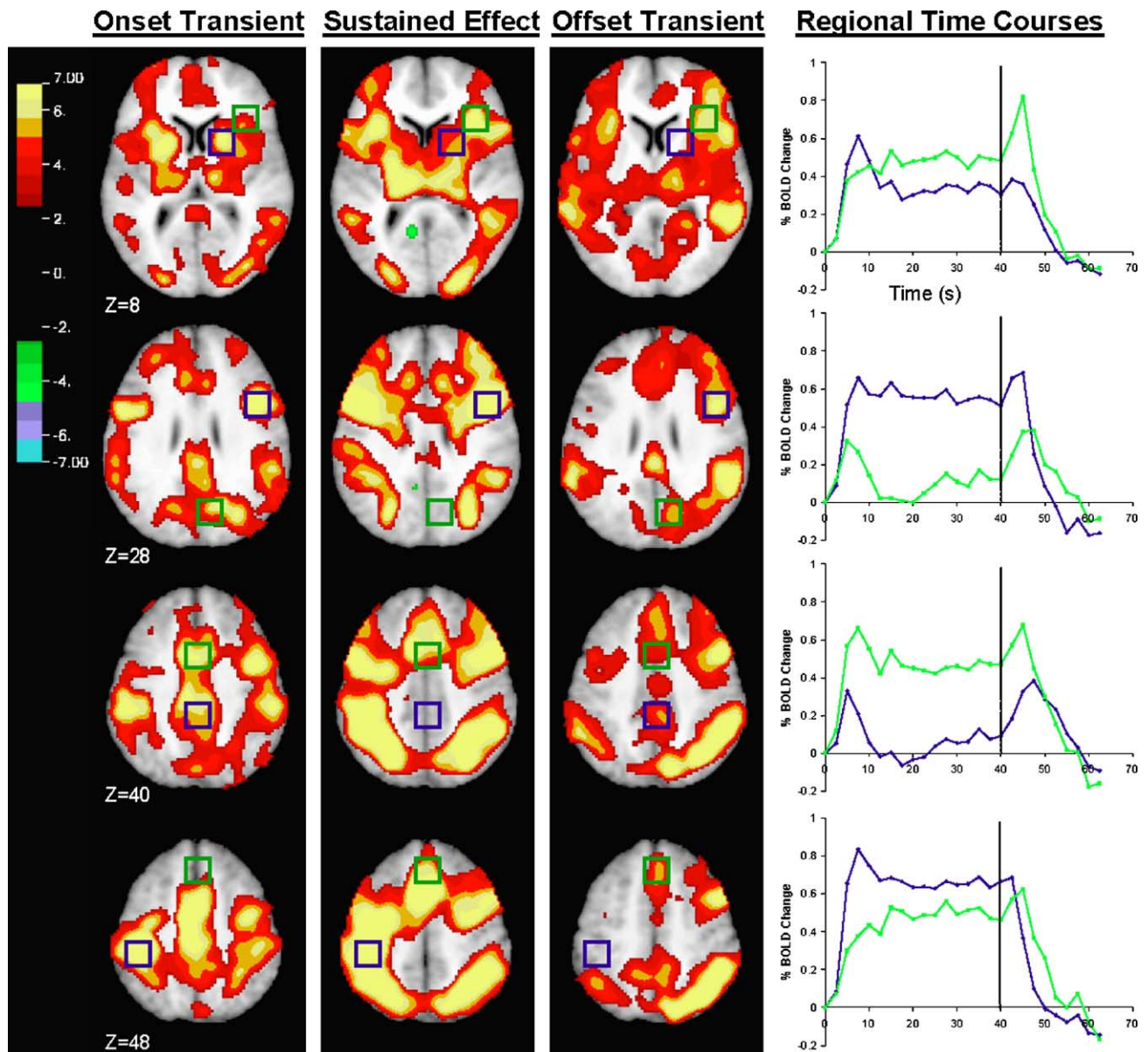


Fig. 2. Correspondence between GLM-based distributions of transient and sustained responses and the volumetric time courses for one of the four tasks (2-back working memory). Images are z score distributions of the significant transient response at task block onset, sustained response present throughout the task block, and transient response at task block offset for the working memory task. Single-slice square regions of interest (not to be confused with ROIs listed in Table 2) and the corresponding color-coded time courses for each region are shown to the right. The dotted line at 40 s denotes the time of task offset (the transition from task to fixation).

maps of transient and sustained responses and the raw time courses. This process was repeated for each of the four studies to insure that our GLM-based technique for localizing transient and sustained components accurately reflects these components in the volumetric time courses.

Several observations can be made upon analysis of Fig. 2. First, the topographies of the three components show commonalities as well as differences. This impression was quantified by computing the percent overlap between the distributions. For the working memory task (Fig. 2), the overlap between the distribution of the onset transient and sustained response was 35%. In other words, 35% of the voxels showing a significant onset transient response or a significant sustained response were significant for both components. The percent overlap for the working memory task between the onset transient and offset transient was 31%, and between the sustained response and offset transient was 40%. Across all four tasks, the average percent overlap between the onset transient and sustained was 24%, onset and offset transient was 40%, and sustained and offset transient was 20%.

The finding of different distributions of significant sustained and transient responses is further supported by the observation of different combinations of transient and sustained components in the regional time courses (Fig. 2). Transient responses at task onset and offset can be seen in the absence of a sustained effect (e.g., R precuneus; green ROI; $z = 28$). Similarly, we can observe a transient response at task onset without a transient response at task offset and vice versa (e.g., R operculum; green ROI; and R basal ganglia; blue ROI; $z = 8$).

Comparison of transient responses across tasks

The distributions of significant onset and offset transient responses for each of the four tasks are shown for a single slice ($z = 10$) in Fig. 3. While there are similarities in the distributions (see below), each transition is associated with a unique spatial distribution of the transient response.

In order to determine which voxels exhibited the most significant average transient activity across tasks, maps of the onset transient and offset transient from all four studies (8 transitions total) were combined with a fixed effects analysis. The resulting z statistic

image is shown in Fig. 4A. A conjunction analysis was also performed to determine which voxels exhibited a significant transient response across all transitions (Fig. 4B). The voxel value in Fig. 4B indicates the number of transitions in which the voxel showed a significant transient. Features evident in Figs. 4A and B include a right lateralization of the transient responses. Fig. 4B also demonstrates that a large portion of the brain shows a significant transient response in at least one task, and several voxels exhibit a significant transient response in all eight of the examined transitions.

Using the map of the average transient from the fixed effects analysis, regions of interest were created using an automated process (see Methods). While the region showing the greatest average transient response was in the right temporal–parietal junction (TPJ), we also see a large transient response in the anterior and posterior cingulate, right and left frontal operculum/insula, precuneus, supplementary motor area (SMA), thalamus, right posterior parietal, fusiform gyri, and right middle and superior frontal regions (Table 2).

Transient responses between onset and offset within the same task and between the four different tasks were compared for each region listed in Table 2. Transient responses at task block onset and offset within the same task were statistically contrasted using an ANOVA (Table 2). A significant P value ($P < 0.05$, Bonferroni corrected for 18 regions) indicates a significant difference between the transient response at task block onset and offset for a particular task. For comparison of transient responses across tasks, time courses for all regions listed in Table 2, or their homologous region in the opposite hemisphere, are shown in Figs. 5 and 6, and Supplementary Fig. 1. It is notable that transient responses are present across studies despite different tasks, subject groups, TRs, and different scanners. While these factors prohibit quantitative comparisons of the magnitude of transient activity between tasks, informative qualitative observations can be made.

Fig. 5 shows regions including the right TPJ, right precuneus, and posterior cingulate that exhibit pronounced transient responses regardless of the task or transition. Despite large differences between the different task paradigms, these regions display a prominent transient response at both task onset and offset for each task. It should be noted that while these regions exhibit a transient response for each transition, the magnitude of the response can be

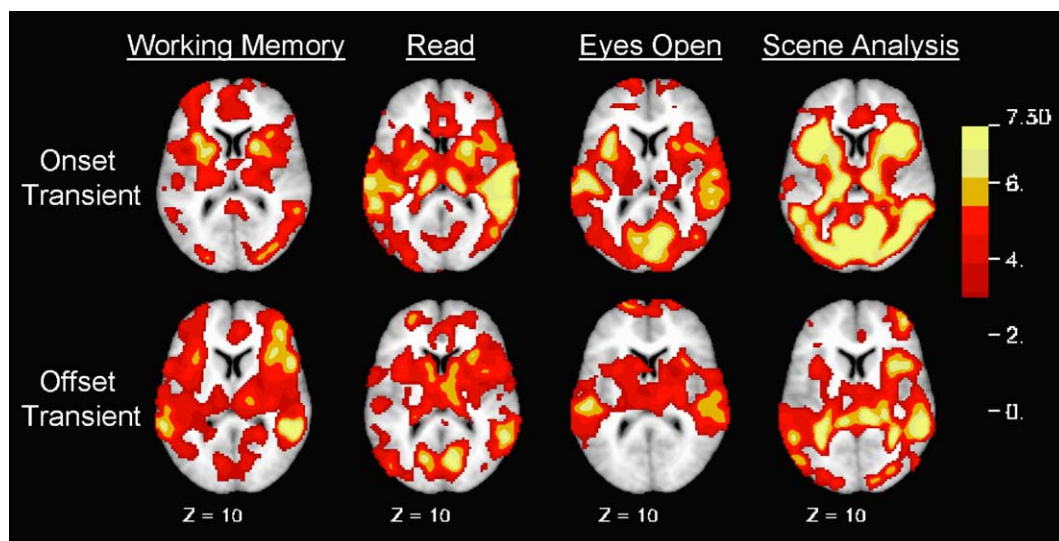


Fig. 3. Z score distributions of significant onset and offset transient responses for each of the four tasks, shown for a single slice ($z = 10$).

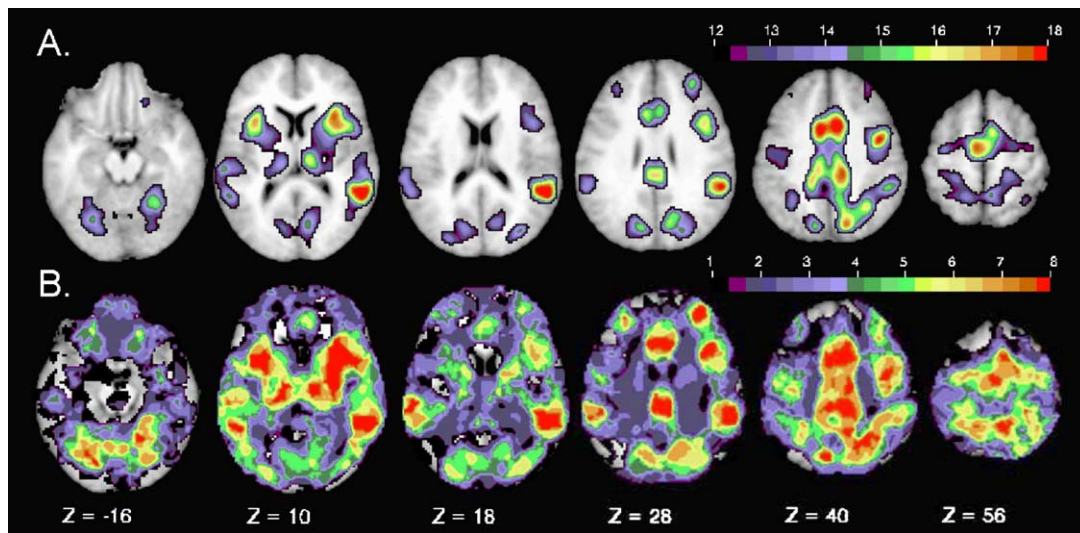


Fig. 4. Combination of transient responses across four tasks. (A) Z score distribution from a fixed effects analysis showing the most significant transient response collapsing across task type and block onset and offset. (B) Conjunction analysis showing the number of transitions (of 8 transitions examined) in which each voxel exhibited a significant transient response.

different depending on the particular task and whether the transition is task onset or offset. For example, the right precuneus and right posterior precuneus show a difference in the transient

response between task onset and offset in the eyes open/fixation task ($P < 0.05$, Table 2), but approximately equal responses at onset and offset in all other tasks ($P > 0.05$, Table 2).

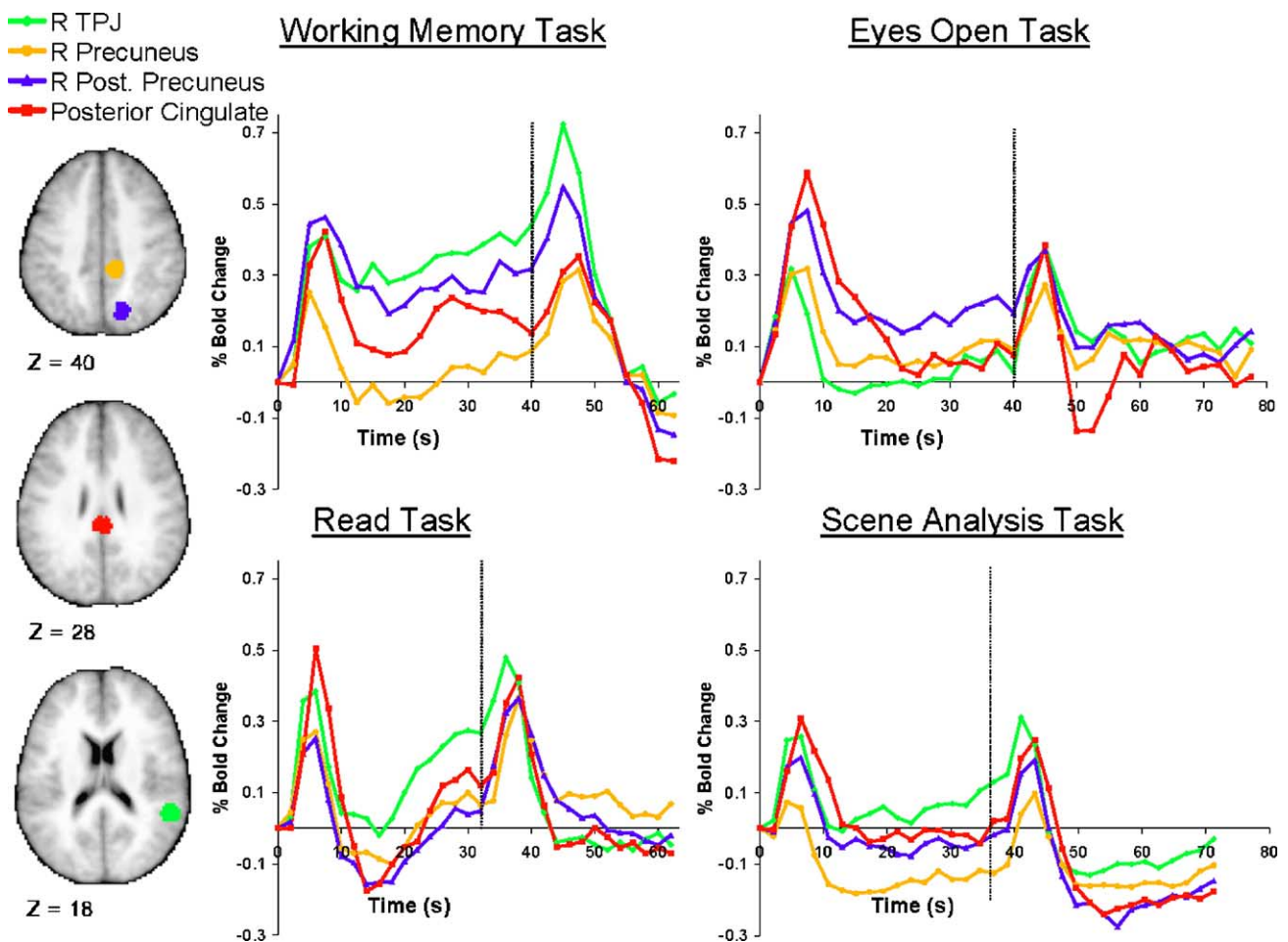


Fig. 5. Average time courses for each task from transient regions of interest showing pronounced transient responses at all transitions (task onset and offset in all four tasks). Time courses are color matched to their corresponding region. The dotted line represents the time of task offset in each study.

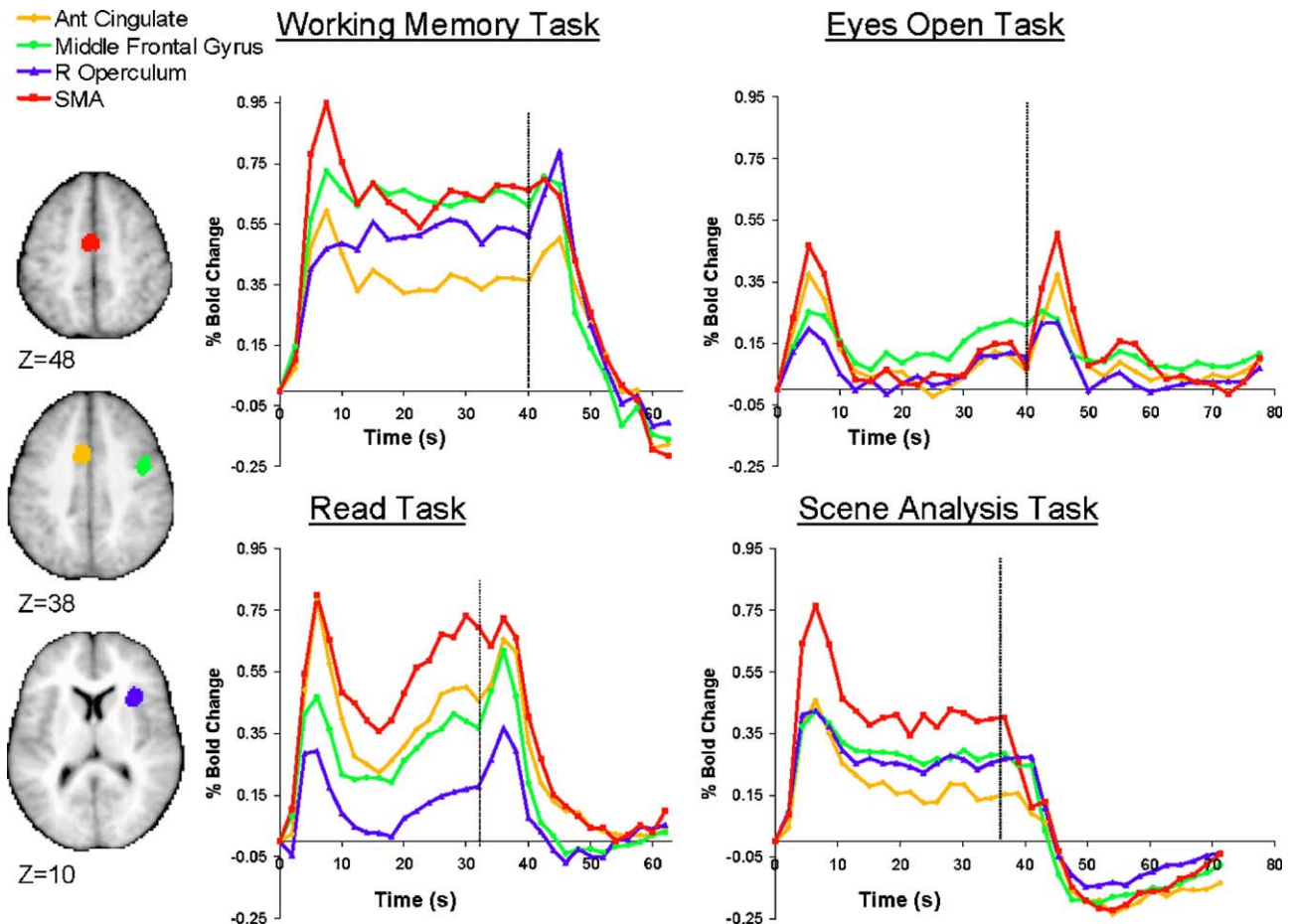


Fig. 6. Average time courses for each task from transient regions of interest showing transient responses dependent on the particular transition. Time courses are color matched to their corresponding region. The dotted line represents the time of task offset in each study.

Fig. 6 displays additional regions from Table 2, but in contrast to the regions shown in Fig. 5, these regions do not show an obvious transient response at each transition. Instead, the transient responses from these regions seem to depend greatly on the particular task or transition. For example, the SMA shows striking qualitative differences between the onset and offset transients for the working memory, scene analysis, and to a lesser extent for the read task, yet equal transient responses at task onset and offset for the eyes open task. In the right frontal operculum/insula, we observe a greater offset transient than onset transient in the working memory task, greater onset transient than offset transient in the scene analysis task, and approximately equal transient responses at onset and offset in both the eyes open and read tasks. Note that qualitative observations regarding differences in the transient response between task onset and offset within a task are supported through quantitative comparisons using an ANOVA (Table 2).

The time courses for additional regions of interest listed in Table 2 such as thalamus, posterior parietal, superior frontal, and fusiform gyri can be found in online supplemental material (Supplementary Fig. 1). Between Figs. 5 and 6, and Supplementary Fig. 1, all regions listed in Table 2 or a homologous region in the opposite hemisphere are illustrated.

It should be emphasized that transient responses are not limited to the regions reported in Table 2. A supplemental analysis examined additional anatomically defined regions of interest in primary visual and motor cortices (Supplementary Fig. 2).

Pronounced transient responses are apparent at task onset in primary motor cortices and at both task onset and offset in primary visual cortex. Transient responses in these anatomically defined regions show dependence on both task onset vs. offset as well as the specific task paradigm.

Discussion

Separation of transient and sustained components

We have presented a GLM-based approach for analysis of transient and sustained responses in block design studies. In addition to the sustained BOLD increases measured in most conventional block-design analysis strategies, the current technique can be used to localize significant transient responses at block transitions. Importantly, the current technique obtains an estimate of the transient without assuming the shape of the response. We demonstrated face validity of our technique by showing close correspondence between our voxel-based maps of transient and sustained responses and the time courses they are meant to represent (Fig. 2). We acknowledge that our models of the sustained and transient components are not numerically orthogonal, and indeed the underlying biological phenomena may not be orthogonal. Therefore, a linear model will not permit perfect assignment of variance to the different components in the presence

of noise. However, our technique does provide a useful and practical means of separating transient and sustained responses.

The current results demonstrate significant transient responses at block onset and offset in all paradigms examined. We note a topographical dissociation between transient and sustained responses, as has been previously observed (Konishi et al., 2001), as well as topographical differences between transient responses at task block onset and offset. Conventional block design analysis techniques that collapse across time combine both block transient and sustained effects, obscuring important functional information about task-relevant processes.

In addition to direct relevance for processing of block-design data, the current findings have implications for *event-related* analyses (Buckner et al., 1996; Josephs et al., 1997; Rosen et al., 1998). It is possible that, in event-related studies with widely spaced trials, some of the event-related activation is due to the transient responses reported here. Similarly, in any event-related paradigm, it is possible that responses to the first few events (during the time of the onset transient) will include components different from those observed for later events.

Transient regions of interest

Collapsing across task and transition generated a map illustrating the topography of regions most associated with transient responses at block transitions (Fig. 4). This distribution is highly similar to previous results obtained using an encoding task (Konishi et al., 2001). The region showing the largest average transient response is the right temporal–parietal junction (TPJ); similarly, organized but lower amplitude transient responses were also seen in the anterior and posterior cingulate, frontal operculum/insula bilaterally, precuneus, supplementary motor area (SMA), thalamus, right posterior parietal cortex, fusiform gyri, and right middle and superior frontal regions (Table 2).

Similar regions to those currently reported (Table 2) have been implicated in exogenous attention, novelty detection, termination of a state of readiness, task switching, and set shifting (Dove et al., 2000; Kimberg et al., 2000; Sohn et al., 2000; Corbetta and Shulman, 2002; Shulman et al., 2002; Braver et al., 2003). Perhaps the most striking topographic correspondence between previous results and the current study concerns the exogenous or ventral attention system as conceived by Corbetta, Shulman, and colleagues (Corbetta and Shulman, 2002). Right lateralization is a prominent feature of both data sets, and regional similarities include the insula/operculum, middle frontal gyrus, and the right TPJ. The ventral attention system is involved in detection of behaviorally relevant, novel, and unexpected stimuli. It is activated, along with the anterior cingulate, by changes in sensory stimuli regardless of presentation modality (Downar et al., 2000). The same set of regions has been shown to be active at the end of a trial, an effect thought to be related to terminating a state of readiness (Corbetta and Shulman, 2002; Shulman et al., 2002).

The present topography is also concordant with previous studies focused on switching between tasks or cognitive sets. Regions responding to task switching include lateral prefrontal cortex, insula, SMA, precuneus, posterior cingulate, posterior parietal, and thalamus (Dove et al., 2000; Kimberg et al., 2000; Sohn et al., 2000; Braver et al., 2003). Regions implicated in studies of set shifting (e.g., the Wisconsin card sorting task) include inferior frontal areas, the middle frontal gyrus, and the precuneus (Konishi et al., 1998; Konishi et al., 1999; Nagahama et

al., 1999; Konishi et al., 2001). Integrating our findings with previously reported results suggests that processes giving rise to transient responses at task onset and offset likely include change detection, task shifting, and termination of a previous task state.

Unique distributions of transient activity

Notwithstanding that some regions respond always or nearly always at block transitions, the majority of regions show at least some dependence on transition type (block onset vs. offset) and specific task. This is true despite the fact that our region identification procedure was biased against finding such specificity. The meta-analysis character of the present study precludes directly testing the statistical significance of contrasts depending on task; a within-subject study would be needed. Nevertheless, the data strongly suggest that particular transitions give rise to unique spatial response profiles, which implies that a unique combination of functional processes may be involved in mediating each specific transition. Thus, whereas change detection would seem to be a feature of all transitions, other processes such as termination of state of readiness and initiation of motor activity are likely to depend on the particular transition in question. This observation has implications for studies of task and set shifting, which so far have tended to examine direction-nonspecific transitions between similar tasks.

Relation to the BOLD overshoot

Transient increases in the BOLD signal at block transitions have often been explained as “overshoot” attributable to transient uncoupling of hemodynamic or metabolic factors (Buxton et al., 1998; Obata et al., 2004). Specifically hypothesized mechanisms include delay between increased cerebral blood flow and factors that attenuate the BOLD signal such as increased oxygen utilization (Davis and Kwong 1998; Frahm et al., 1996) or increased venous blood volume (Buxton et al., 1998; Mandeville et al., 1998).

Several of the current findings are difficult to reconcile with a hemodynamic or metabolic mismatch model. First, we show that the relationship between transient and sustained components varies regionally across the brain as well as between tasks within the same brain region. Second, no hemodynamic or metabolic mismatch model has been proposed that can account for both onset and offset transient responses in the absence of any sustained response, a robust observation especially in the eyes open/eyes closed paradigm. Finally, our transient responses occur in regions of the brain that have been implicated in transient neuronal functions such as task switching and change detection. While only a combined study of electrical activity and BOLD imaging can conclusively determine the extent to which BOLD transients represent transient neuronal activity, the current results join a growing body of evidence against a purely hemodynamic explanation of transient BOLD responses at block transitions (Hoge et al., 1999; Kruger et al., 1999; Konishi et al., 2001; Rosengarten et al., 2002; Fox et al., 2005).

Relation to electrophysiology

Additional support for a neuronal origin for the BOLD transient response comes from electrophysiological studies. The local field potential (LFP) has recently been shown to correlate with the BOLD signal (Logothetis, 2003). Accordingly, it is reasonable to

propose that transient LFP activity observed at task onset may relate to a corresponding BOLD phenomenon as shown by Logothetis and colleagues in a direct comparison of BOLD and electrophysiology (see Figs. 1 and 2 in (Logothetis, 2003)).

Numerous event-related potential (ERP) studies have noted transient electrical responses at state transitions (Barcelo et al., 2002; Barcelo, 2003; Karayanidis et al., 2003). Perhaps most notable among such responses is the P300 potential. The P300 potential is typically elicited by sensory oddball or novelty paradigms, but is also prominent in set shifting. The P300 is thought to represent updating of context information in working memory (Donchin and Coles, 1988; Knight and Scabbini, 1998; Jeon and Polich, 2003). By means of intercranial recordings, correlational studies with fMRI, and lesion studies, the P300 potential has been attributed to generators in a widely distributed network of brain regions including SMA, anterior cingulate, middle and superior frontal cortex, insula/operculum, posterior parietal cortex, and most prominently, the TPJ (McCarthy and Wood, 1987; Knight and Scabbini, 1998; Horn et al., 2003; Mulert et al., 2004). This localization corresponds well with the regions most strongly associated with BOLD transients at block transitions. Perhaps even more intriguing is the recent finding of attenuated block onset transients in individuals with schizophrenia (Fox et al., 2005), given that an attenuated P300 potential has been one of the most consistent empirical findings in schizophrenia over the past 30 years (Roth and Cannon, 1972; Jeon and Polich, 2003).

Implications of transient responses for the understanding of cognitive states

Analyzing activity at block transitions offers insight into how the brain switches between states as well as the neuronal organization of these states. We have made the observation that regions showing transient responses at block transitions are also implicated in task and set switching. This suggests that task “onsets” and “offsets” may be better understood as state transitions. It should be emphasized that visual fixation is itself a task during which the brain remains active. From a cerebral energetics perspective, the difference in energy utilization during complex cognitive task performance vs. rest or visual fixation is very small (Raichle and Gusnard, 2002). Along these lines, electrophysiological studies show that brain states may differ in the temporal coding or pattern of neuronal firing rather than the average spike rate (Lauritzen and Gold, 2003). These observations support the view that the difference between states is better conceptualized in terms of a *reorganization* rather than an activation. If this is so, one might expect broadly distributed increases in metabolic demand as the brain reorganizes from one state to another. Likewise, reorganization processes would likely depend both on the current task state and the state being transitioned into. Transient BOLD increases at block transitions are both broadly distributed and, at least to some degree, specific with respect to particular transitions. Allowing that BOLD responses only indirectly reflect neuronal activity, these characteristics are consistent with a role in reorganization at state transitions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuroimage.2005.06.025.

Note added in proof

After online publication of the manuscript we became aware of relevant work with similar methodology examining transient versus sustained BOLD responses in the auditory cortex (Giraud et al., 2000; Seifritz et al., 2002; Harms et al., 2002; Harms et al., 2003; Harms et al., 2005). These studies provide further support for the present conclusion that transient BOLD responses at block transitions are likely indicative of underlying transient neuronal activity.

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