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The BOLD onset transient: identification of novel functional differences in schizophrenia

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Blood oxygen level dependent (BOLD) signals characteristically exhibit an overshoot (transient signal increase) at the beginning of fMRI task blocks. This onset transient has often been overlooked as an independent measure of neuronal activity, but it may represent unique functional processes. We examined onset transient responses in normal subjects and individuals with schizophrenia performing three cognitive tasks. These analyses revealed a regionally specific and task specific attenuation of the onset transient in individuals with schizophrenia during performance of a working memory task. Furthermore, this attenuation was often not accompanied by a corresponding population difference in the sustained response, and is missed through conventional fMRI analysis techniques. Relevance of these findings to both an interpretation of the onset transient and the pathology of schizophrenia are discussed.

Keywords: fMRI; Overshoot; Schizophrenia

Introduction

It is well established that performance of various tasks induces regionally specific increases in cerebral blood flow that are only partially matched by increases in oxygen consumption (Fox and Raichle, 1986; Fox et al., 1988). The imbalance between increased blood flow and oxygen metabolism in the task state is the basis of the blood oxygen level dependent (BOLD) signal (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992). The BOLD signal has served as a useful, although indirect, measure of neuronal activity. A commonly observed characteristic of the BOLD response in block design studies is an initial overshoot at task onset above the signal level seen for the remainder of the task block. This overshoot has often been attributed to transient uncoupling of hemodynamic or metabolic factors before a new task–state balance is established (Buxton et al., 1998; Obata et al., 2004). Specifically, BOLD transients have been attributed to a hypothesized delay between increased cerebral blood flow and factors that attenuate the BOLD signal such as increased oxygen utilization (Davis et al., 1994; Frahm et al., 1996) or increased venous blood volume (Buxton et al., 1998; Mandeville et al., 1998). According to these accounts, transient BOLD responses do not necessarily reflect transient neuronal activity. These "overshoot" hypotheses suggest a vascular or timing delay explanation of the BOLD signal increase at task onset, rendering the onset transient of little interest as a measure of changes in underlying neuronal activity or cognitive processing.

Although the above-mentioned hypotheses are physiologically reasonable, there is evidence that overshoot mechanisms may not fully explain the onset transient. If the onset transient is simply an overshoot as the task–state balance is established, it should bear a consistent relationship to the sustained signal. In other words, higher sustained responses should be accompanied by higher task onset transients, and vice versa (Hoge et al., 1999). However, in at least one fMRI study of visual cortex, transient and sustained response magnitudes were found to vary independently and the two responses could be separately manipulated (Hoge et al., 1999). Another fMRI study demonstrated regions showing strong signal increases at task onset and offset that were distinct from regions activated by the task (Konishi et al., 2001). Studies utilizing a more direct measure of cerebral blood flow such as laser Doppler flowmetry or flow sensitive MR imaging have found that blood flow alone exhibits an onset transient matching the BOLD waveform (Hoge et al., 1999; Kruger et al., 1999; Rosengarten et al., 2002), although there are exceptions to this finding (Obata et al., 2004). An additional line of evidence comes from electro-

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physiological recordings: the local field potential (LFP) has recently been shown to correlate with the BOLD signal (Logothetis, 2003), and large transient LFP activity at task onset may relate to the appearance of a BOLD onset transient (see Figs. 1, 2 in (Logothetis, 2003)). All of these findings suggest that the onset transient could be indicative of functional or neuronal activity.

These observations raise the possibility that BOLD onset transients may represent different processes than those reflected in the sustained responses. The onset transient may therefore be modulated differently than the sustained component with task, or specifically altered in disease. Specific differences in the onset transient would be missed through conventional block design analysis, which emphasizes the sustained component of the BOLD signal. In this study, we seek to determine if directed analysis of the onset transient can reveal novel functional differences missed through more conventional approaches. Specifically, we determine if examination of the onset transient can reveal unique functional differences between normal subjects and individuals with schizophrenia during performance of a working memory task.

This study is a reanalysis of data obtained in a previously published study (Barch et al., 2002) comparing normal subjects and individuals with schizophrenia during performance of working memory, intentional encoding, and recognition tasks. While all three tasks in the original study have relevance to schizophrenia, we here emphasize the working memory task as it has been suggested that working memory may be a fundamental cognitive defect in schizophrenia (Cohen and Servan-Schreiber, 1992; Goldman-Rakic, 1991; Weinberger and Gallhofer, 1997), and the extensive literature on working memory deficits in schizophrenia provides a rich context in which to interpret our results. We make use of the other two tasks to examine task specificity of the effects observed in the working memory task. Our methods to specifically distinguish between sustained block effects and transient responses at task onset reveal regionally specific and task specific differences in the onset transient between normal subjects and individuals with schizophrenia, differences that are missed through more conventional block design analysis.

Methods

The present data were obtained in a previously reported study focused on working and long term memory in schizophrenia (Barch et al., 2002). Additional methodological details can also be found in a related publication (Barch et al., 2003a).

Subjects

Participants were 48 normal adults and 38 individuals with schizophrenia diagnosed according to DSM-IV criteria. Participants with schizophrenia were inpatients or recently released outpatients of the St. Louis Metropolitan Psychiatric center; all were medicated, 21% with typical and 79% with atypical medication. Normal subjects had a higher mean level of educational attainment than patients, but the groups did not differ significantly in age, years of parental education, gender, or handedness.

MRI data acquisition

All MR scanning was performed on a 1.5 T Siemens Vision system (Erlagen, Germany). Functional data were collected using an asymmetric spin-echo, echo-planar (EPI) sequence sensitive to blood oxygen level dependent (BOLD) contrast (TE = 50 ms, flip angle = 90°, 64 × 64 matrix, in-plane resolution 3.75 × 3.75 mm, volume TR = 2.5 s). Whole brain coverage was obtained with 16 contiguous, 8 mm thick slices. Slice tilts and offsets were prescribed parallel to the AC–PC plane on the basis of automatic atlas registration of a coarse (2 mm^3 voxel, 79 s) pre-fMRI MP-RAGE scan. Each fMRI run was comprised of 102 volumes (frames) acquired over 255 s. Structural data (for definitive atlas transformation) included a high resolution (1 × 1 × 1.25 mm) sagittal, T1-weighted MP-RAGE (TR = 10 ms, TE = 4 ms, flip angle = 8°) and a T2-weighted fast spin echo scan.

Tasks

Each participant performed three tasks: working memory, intentional encoding, and recognition memory. The working memory task required participants to indicate whether or not the current stimulus matched that presented two trials back (2-back task) and to press one of two buttons accordingly; the proportion of target to non-target stimuli was 1:3. For intentional encoding, participants were instructed to pay careful attention to each stimulus in preparation for a later memory test and to respond to each stimulus by pressing both buttons. During recognition testing, participants indicated whether the presented item had been previously seen in either the encoding or working memory task; the proportion of new to old items was 1:1.

Task blocks alternated with crosshair fixation. 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. Four additional frames were acquired to enable analysis of the fourth task block with allowance for hemodynamic delay. Stimuli were presented during task blocks at the start of each frame (2 s on time followed by a 500 ms interstimulus interval). The task type was constant within fMRI runs. Each task type was performed twice in two separate runs, once with concrete word stimuli and once with non-namable face stimuli. Thus, the memory demands and type of material (words or faces) were varied while the gross sensory and motor aspects of the task were held approximately constant.

MRI preprocessing

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 (3) rigid body correction for inter-frame head motion within and across runs. Step 3 provided a record of head position within and across all fMRI runs. Each fMRI run was intensity scaled (one multiplicative constant over all voxels and frames) to yield a whole brain mode value of 1000 (not counting the first 4 frames). We elected to 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 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). 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 main analyses, each fMRI run was transformed to atlas space and resampled to 2 mm cubic voxels.

Selective averaging

For each participant and run type, the first three task blocks together with the following fixation intervals were averaged to create 26 frame volumetric time courses. The fourth task block was not included as it was not followed by a corresponding fixation interval. In the present results, the 26 frame average response data were collapsed over material type (words and faces) because preliminary analysis showed only minor dependence on this factor. Thus, the averaging procedure generated, for each participant and memory task, volumetric (in atlas space) 26 frame time courses averaged over 6 epochs (3 each with word and face stimuli).

Correlation analysis and population differences

Correlation analysis (Bandettini et al., 1993) was performed on the 26 frame data using two contrasting, zero mean, reference waveforms magnitude scaled to one (Fig. 1A). The first waveform was designed to capture sustained task–fixation BOLD modulation; it was constructed as a simple boxcar right shifted 3 frames with respect to task start to account for hemodynamic delay. The second waveform was designed to capture the task onset transient; it was defined empirically on the basis of visual inspection of the BOLD signal from normal subjects in multiple brain regions. Consider, for example, the time course of the BOLD signal from a region in primary visual cortex (Fig. 1B). The onset transient is best isolated by taking its peak at frame 4 and subtracting from that the average of frames 3 and 6. The OT waveform was thus designed to perform this arithmetic operation through convolution. Since time series correlation against a fixed reference waveform is equivalent to computing a weighted sum, it is reasonable to assume that the result will be approximately normally distributed. Accordingly, voxel-wise and regional comparisons of correlation analysis results across groups and tasks were tested using the *t* statistic. For purposes of display and generating ROI (see below),

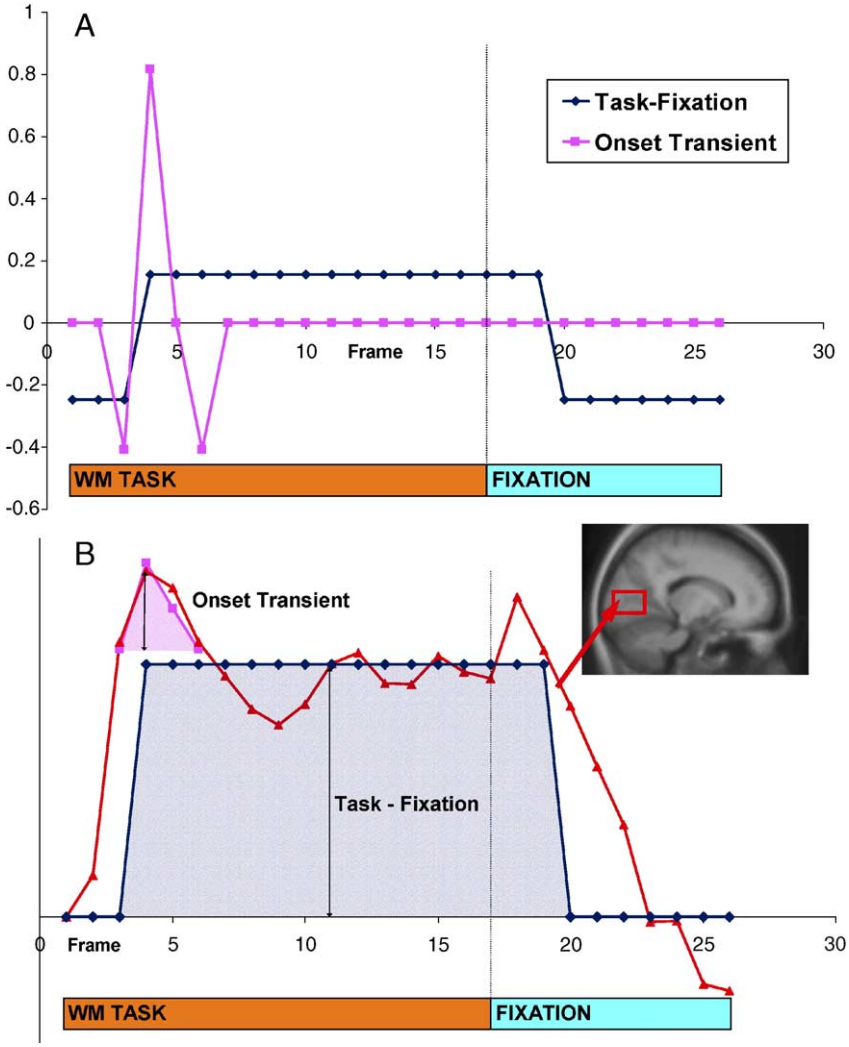

Fig. 1. (A) Reference waveforms used in the block-oriented task–fixation (blue) and onset transient (magenta) analysis. (B) BOLD signal (red line) from a region in the visual cortex (inset) during a working memory task illustrating the components of the BOLD signal isolated by each reference waveform.

the t value maps were converted to equally probable z scores. These contrast images were corrected for multiple comparisons ($P < .05$) by smoothing with a two-voxel full-width half Gaussian filter, then using Monte-Carlo correction with a threshold of 2.25 and a cluster size of 65. We also computed conventional block design t statistic images using methods based on the general linear model (Friston et al., 1994, 1995a, 1995b; Worsley et al., 1996) using an assumed hemodynamic impulse response function (Boynton et al., 1996). These conventional analyses produced statistical images very similar to those generated by voxel-wise task–fixation correlation. We here report only results obtained by correlation as this method is the most direct and uncomplicated.

Identification of regions of interest

A purely empirical strategy was used to generate ROI that were later used to evaluate the dependence of transient and sustained BOLD responses on task and patient group. Contrast images were computed as the differences between groups using both the sustained task–fixation (TF) and onset transient (OT) reference waveforms, as mentioned above. These contrast images were smoothed by convolution with a 10 mm radius hard sphere, and positive and negative peak loci exceeding a specified threshold ($z = \pm 2.25$) were identified by straightforward peak search (Mintun et al., 1989). Peak loci closer than 15 mm were consolidated by algebraic averaging to convert clusters to a single locus at the center of mass. The various parameters (smoothing radius, thresholds, and minimum distance between loci) were selected to yield a final total of 30–40 loci in both the TF and OT analyses. ROI were generated by centering 8 mm radius spheres on the peak loci. Voxels within the spherical boundaries of two loci were assigned to the nearest peak thereby ensuring no overlap between regions. Importantly, ROI voxels were masked with a smoothed version of the original contrast image corrected for multiple comparisons (FWHM 2, threshold 2.25, cluster 65, $P < .05$). The end result was a partitioning of the multiple comparisons corrected voxel-wise correlation maps (OT and TF) into discrete regions.

Regional statistics

Since regions were created by masking with a significant voxel-wise map corrected for multiple comparisons, additional regional validation of group differences is not required. However, for additional statistical rigor and to further guard against false positives, regional statistics were computed by correlation of the BOLD signal (averaged over all voxels in each ROI) against the TF and OT reference waveforms, then compared normal subjects to individuals with schizophrenia using the t statistic. These statistics were subjected to Bonferroni correction for multiple comparisons (multiplication of the raw P value by total number of regions) to obtain corrected thresholds of $P < .05$. Regions were not further considered if neither group alone showed a significant correlation effect (Bonferroni corrected $P < 0.05$) of task–fixation (for the TF analysis) or a significant effect of the onset transient (for the OT analysis). Thus, all presently reported regions showing a significant group difference were responsive to the task in at least one of the groups.

Regions were also subjected to an analysis of variance (ANOVA) using our two waveform measurements, the onset transient and task–fixation, as a within subject factor. This allows us to examine group × waveform and task × waveform interactions. A group or task by waveform interaction indicates that the two waveform variables are modulated differently with respect to group or task. We also used an ANOVA to examine the task specificity of our observed population difference in the onset transient by looking for a group × task interaction in the onset transient.

Results

Statistical contrast maps were created to illustrate the differences between normal subjects and individuals with schizophrenia in the working memory task. Fig. 2 displays these differences using task–fixation (A) and onset transient analysis (B). These images are unsmoothed and unthresholded to give the most unbiased representation of the data. A standard anatomical brain is shown for reference in panel (C). Differences between normal subjects and individuals with schizophrenia in both task–fixation and the onset transient analysis demonstrate regional specificity. Furthermore, the distributions of the differences are not the same using the two analysis approaches. For example, the left parietal cortex (gold arrow) shows a population difference using task–fixation analysis but not onset transient analysis, while the lateral orbitofrontal cortex (magenta arrow) shows an onset transient difference without a task–fixation difference. Note, however, that while the distributions are certainly different they are not mutually exclusive. The region around the dorsolateral prefrontal cortex (peach arrow) seems to exhibit both a task–fixation difference as well as a difference in the onset transient.

To better confirm these impressions, regions of interest were created separately for both the task–fixation and onset transient conditions using an automated approach (see Methods). The resulting regions are listed in Table 1. Thirty-one regions were identified with significant differences in the task-minus-fixation condition, 26 in which normal subjects demonstrated a greater task increase than individuals with schizophrenia, and 5 in which individuals with schizophrenia showed a greater increase than normal subjects (last five regions, listed in italics). Likewise, 26 regions were identified through differences in the onset transient, all 26 of which were due to a greater onset transient in normal subjects than individuals with schizophrenia. As expected, the regions identified for the task–fixation condition are very similar to those previously published on this same data set (Barch et al., 2002), and will not be elaborated upon further.

The onset transient analysis identified a distinct set of regions from the task–fixation analysis, including regions in the cerebellum, lateral orbitofrontal cortex, caudate nucleus, and prefrontal cortex. Examples of the regions identified in each analysis technique are shown in Fig. 3. In addition to regions of interest, the average time courses for some of these regions are also displayed for both normal subjects (blue time courses) and individuals with schizophrenia (magenta time courses). These time courses come directly from the 26 frame volumetric average (see Methods) and are representative of the raw data. Fig. 3A shows regions identified by task–fixation analysis with four example time courses shown above (Figs. 3: A1–A4), while 3B shows regions identified by onset transient analysis with four example time courses shown below (Figs. 3: B1–B4).

The regional time courses shown in Fig. 3 were selected to illustrate the full range of observed combinations of transient and

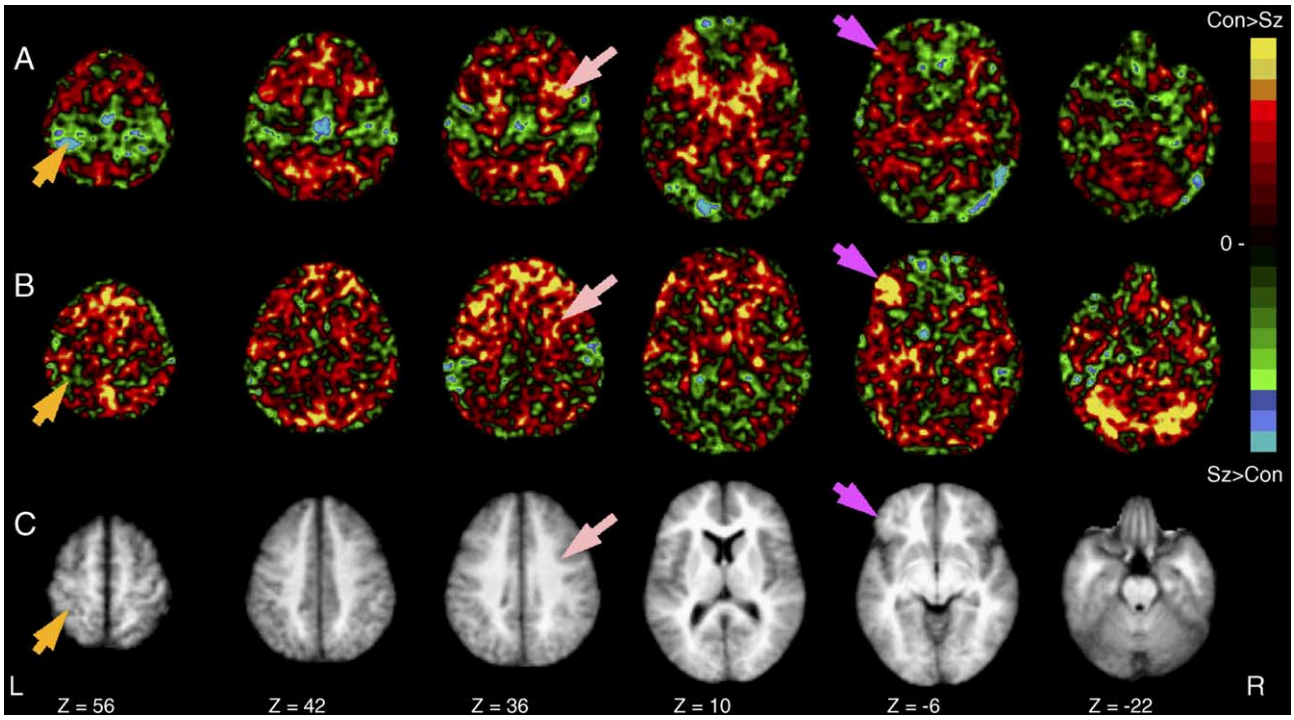

Fig. 2. Z maps illustrating differences between normal control subjects (Con) and individuals with schizophrenia (Sz) in a working memory task using conventional task–fixation analysis (A) and onset transient analysis (B). A standard anatomical brain is shown for reference in panel (C). Arrows mark some differences (gold and magenta) and similarities (peach) in the distributions.

sustained responses. For example, while all the time courses from the task–fixation regions (A1–A4) show a sustained difference across the task, the onset transient can be absent in both normal subjects and individuals with schizophrenia (A4), present in both (A3), or perhaps more prominent in normal subjects (A2). Likewise, when we consider the time courses from the onset transient regions (B1–B4) we see that the sustained activations can be the same (B2, B4), show greater average activity in normal subjects (B3), or greater average activity in individuals with schizophrenia (B1). The time courses from the non-displayed regions of interest are all similar to one of the shown examples and are available upon request.

To confirm the apparent lack of a consistent relationship between group differences in the onset transient and sustained response, we can look for a group × waveform interaction in each of our regions of interest. A significant group × waveform interaction indicates that the two waveform measurements (onset transient and task–fixation) vary differently with respect to group. All 25 of our regions identified in the onset transient analysis and 3 regions identified in the task–fixation analysis (SMA, mid. occipital gyrus, and inf. occipital gyrus) showed a significant ($P < .05$) group × waveform interaction. All of the onset transient regions whose time courses are shown in figure three showed a significant group × waveform effect ($P < .01$). This analysis demonstrates that there can be group differences in the onset transient without corresponding differences in the sustained response and vice versa.

An important question concerning our observed differences in the onset transient between normal subjects and individuals with schizophrenia is the specificity of these differences to the working memory task. In addition to further characterizing the current observations, a finding of task specificity would provide strong support for the idea that onset transient differences represent true functional differences as opposed to altered hemodynamics in individuals with schizophrenia. We examined each region identified through onset transient analysis for a group × task effect in the onset transient. The groups were normal subjects and individuals with schizophrenia while the tasks were working memory, intentional encoding, and recognition. A significant effect indicates that the group difference in the onset transient varies significantly with task. We found a significant interaction in 17 of our 25 regions (identified with "a" in Table 1) including regions in the cerebellum, lateral orbitofrontal cortex, three caudate regions, and all four DLPF cortex regions.

We next sought to determine whether this task specificity of the group difference in the onset transient was due to task differences in the onset transient in normal subjects, individuals with schizophrenia, or both, by looking for a main effect of task in the onset transient in each group. We found a significant effect of task on the onset transient in normal subjects in 15 regions (identified with "b" in Table 1), including 11 of the 17 regions showing a group × task effect such as lateral orbitofrontal cortex, cerebellum, DLPF cortex, and caudate. In contrast, only one region, the medial frontal gyrus, showed a significant task effect on the onset transient in individuals with schizophrenia.

Given that our group difference in the onset transient shows task specificity, and this specificity seems to be due to a task difference in normal subjects, we then asked if this task difference in normal subjects showed a task × waveform effect. In other words, are the two waveform measurements modulated differently with respect to task within the same population of normal subjects? Ten of our 25 onset transient regions of interest showed a significant task × waveform effect in normal subjects including

Table 1
Regions of interest isolated by task–fixation and onset transient analysis

Task–fixation analysis			Onset transient analysis		
−23 +19 +29	L dorsolateral prefrontal*	46	+35 −69 −20	R lateral posterior superior cerebellum[a,b,c,*]	
−11 +29 +26	L medial prefrontal*	32	−38 −66 −24	L lateral posterior superior cerebellum[b,c,*]	
+31 +06 +38	R dorsolateral prefrontal*	9	−25 −78 −21	L medial posterior superior cerebellum[b,*]	
+39 +32 +25	R dorsolateral prefrontal	9,46	+22 −82 −21	R medial posterior superior cerebellum[b]	
+29 +41 +15	R dorsolateral prefrontal	46	+42 −59 −36	R lateral cerebellum[a,**]	
+05 +33 +42	R medial frontal gyrus	8	−43 +34 −05	L lateral orbitofrontal[a,b,c,**]	47/11
−40 +02 +25	L inferior frontal gyrus	44	+29 +31 −11	R lateral orbitofrontal**	47/11
−41 +02 +46	L superior prefrontal	6,8	−21 −22 −08	L geniculate nuclei/PHG*	27/28
−06 +21 +46	Medial superior prefrontal	8	+23 −21 −08	R geniculate nuclei/PHG[a]	27/28
−26 +11 +11	L putamen		+13 +14 +07	R caudate head[a,b,c]	
+22 +13 +19	R BG/putamen*		−13 +14 +07	L caudate head[a,b]	
+23 −11 +29	R frontal WM*		+26 −28 +11	R caudate tail[a,b,c,*]	
−23 −13 +28	L frontal WM*		−23 −17 +17	L caudate/thalamus[b,c]	
+01 −14 +21	Interventricular septum		+43 +14 +32	R dorsolateral prefrontal[a,b,*]	44/9
+01 −23 +06	Thalamus (DM)**		−38 +16 +36	L dorsolateral prefrontal[a,b,*]	9
+16 −11 +11	R thalamus (VA)		+26 +34 +35	R dorsolateral prefrontal[a]	9
−09 −08 +09	L thalamus (VA)		−20 +32 +33	L dorsolateral prefrontal[a,b,c,*]	9
+29 −30 −06	R hippocampus*		+18 −13 +49	R medial frontal gyrus[a,*]	6
−13 −30 −13	L hippocampus	35	+01 +23 +57	Superior frontal gyrus	8
+47 −33 +02	R middle temporal gyrus	21	−46 −10 +32	L premotor cortex[a,b,c]	6
−08 −65 +43	L precuneus	7	+24 −08 +30	R frontal (WM)[a,b,*]	
+26 −63 +36	R parietal cortex**	7	−28 +00 +31	L frontal (WM)[a,b,c,*]	
−25 −61 +41	L parietal cortex	7	+48 −18 −15	R inf/mid temporal gyrus[a,c,*]	21
+30 −59 +22	R parietal/occipital sulcus*		−47 −33 −04	L middle temporal gyrus*	21
+48 −47 +24	R inferior parietal*	40	−01 −74 +46	Precuneus	7
+33 +22 +08	R operculum		−05 −45 −50	L medulla[a,*]	
−34 −39 +55	*L parietal cortex*[†,*]	40			
+03 −18 +61	*Supplementary motor area***	6			
+54 −64 −03	*R middle occipital gyrus**	19			
−16 −92 +10	*L visual cortex*	18			
+39 −85 −03	*Inferior occipital gyrus*	18			

Regions of interest isolated from differences between normal subjects and individuals with schizophrenia performing a working memory task using task–fixation and onset transient analysis. Shown are the Talairach coordinates, common names, and Brodmann areas for each region of interest.
All regions $P < 0.05$, $*P < 0.01$, $**P < 0.001$ Bonferroni corrected. WM = white matter, PHG = parahippocampal gyrus.
[†] <12 mm from L somatosensory cortex (BA5) coordinates in Barch et al., 2002.
[a] Significant group × task interaction.
[b] Significant effect of task in normal subjects.
[c] Significant task × waveform interaction in normals.

regions in lateral orbitofrontal cortex, caudate, cerebellum, and dorsolateral prefrontal cortex (identified with "c" in Table 1).

To demonstrate these various measurements of task specificity, two regions of interest identified in the onset transient analysis are illustrated in Fig. 4. We selected these two regions for illustration because they showed a significant group × task interaction, different task × waveform effects, and are relevant to the pathology of schizophrenia. The dorsolateral prefrontal cortex is the region most commonly implicated in functional imaging studies of schizophrenia, while the caudate is one of the regions showing consistent histological and anatomical abnormalities yet is usually not implicated in imaging studies of schizophrenia (see Discussion). Time courses from other regions are available upon request. The time courses from each task for the two regions are shown for normal subjects in Fig. 4A and individuals with schizophrenia in Fig. 4B. The group difference is illustrated with a simple frame by frame subtraction (normal subjects−individuals with schizophrenia) in Fig. 4C.

As mentioned previously, both regions show a group × task effect in the onset transient, seen most clearly in panel C which shows the time course of the group difference for each task. The working memory task (blue) shows a significantly greater group difference in the onset transient than either the recognition task (magenta) or the encoding task (green). Both regions show a significant effect of task on the onset transient in normal subjects (Fig. 4A) but not in individuals with schizophrenia (Fig. 4B), indicating that the task specificity in the group difference is generally due to task differences in normal subjects. Finally, the caudate shows a significant task × waveform interaction in normal subjects while the DLPF region does not. This indicates that the two waveform components are modulated differently with respect to task in the caudate, but not in this region of the DLPF cortex. This is evident from the figure (panel A), as there is a task difference in the onset transient in the caudate without an apparent difference in the sustained response, while in the DLPF there appears to be a difference in both components.

Analysis of subject movement

It is possible that participants, particularly those with schizophrenia, might move more at task onset than at any other

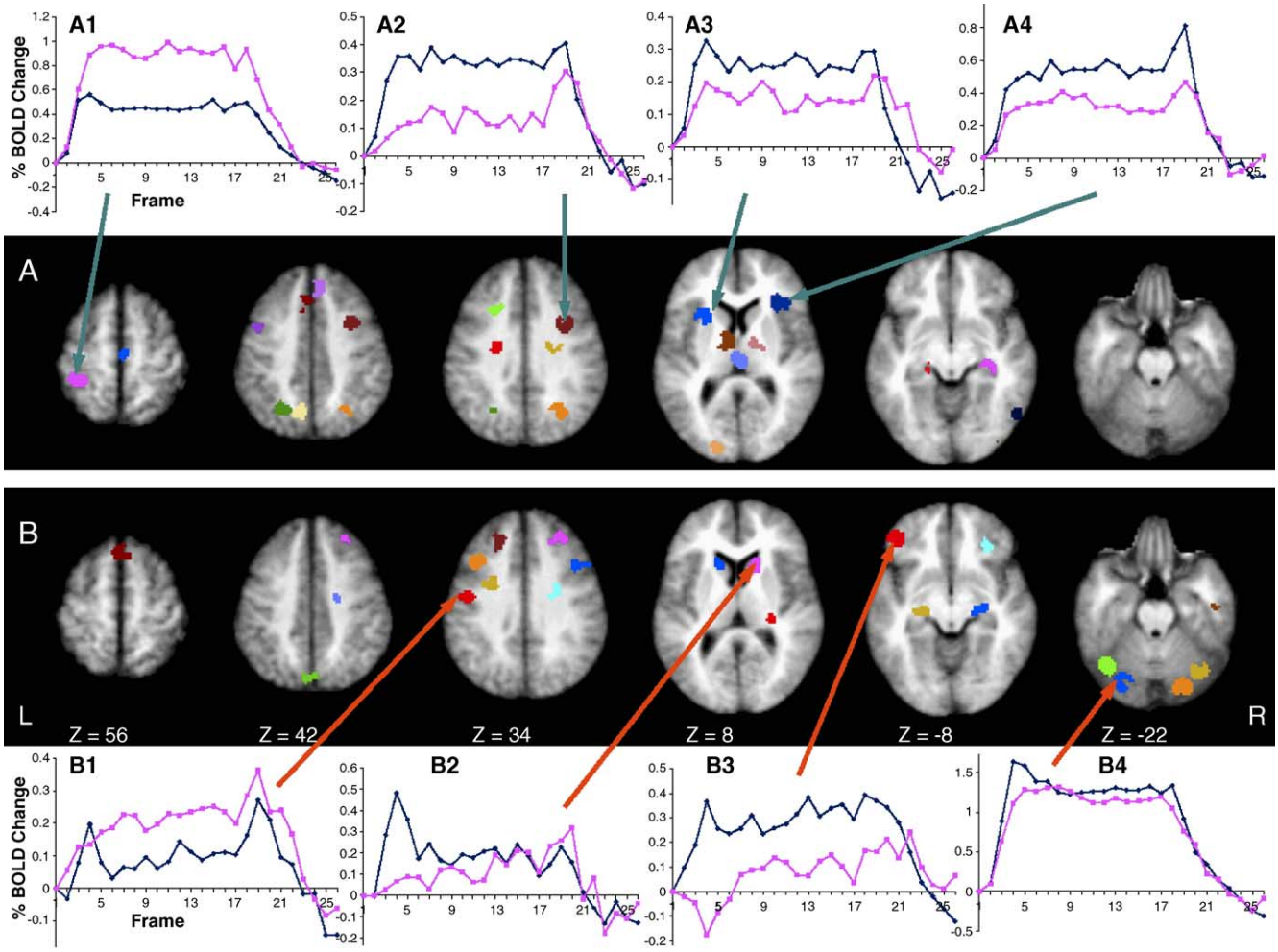

Fig. 3. Regions of interest generated from differences between normal subjects and individuals with schizophrenia in a working memory task using task–fixation analysis (A) and onset transient analysis (B). Single-block average time courses for normal subjects (blue time course) and individuals with schizophrenia (magenta time course) are shown for some regions. Task–fixation regions with illustrated time courses are: A1: L parietal cortex; A2: R dorsolateral prefrontal cortex; A3: L putamen; A4: R operculum. Onset transient regions with illustrated time courses are B1: L premotor cortex; B2: R caudate head; B3: L lateral orbitofrontal cortex; B4: L medial posterior superior cerebellum.

time during the task, and that this increased movement contributes to the absence of the onset transient in individuals with schizophrenia. The average incremental movement for a 26 frame block (16 task frames followed by 10 fixation frames) for both normal subjects (blue time course) and individuals with schizophrenia (magenta time course) is shown in Fig. 5. Fig. 5A shows the average translational motion (by averaging the x, y, and z directions) while Fig. 5B shows the average rotational motion (by averaging pitch, roll, and yaw). The gray box denotes the period during which the onset transient is observed. While individuals with schizophrenia do move slightly more throughout the entire block, there is certainly not a sudden increase in movement during the time of the onset transient in either group.

Analysis of anatomical differences

One potential confound that must be addressed is anatomical variability between individuals with schizophrenia and normal subjects. In both the task–fixation and the onset transient analysis, we observe statistically significant differences between normal subjects and individuals with schizophrenia that localize to periventricular white matter regions. While these regions pass our statistical analysis, and do show significant modulation in at least one group, we believe these differences are more likely due to anatomical changes among the individuals with schizophrenia, such as enlarged lateral ventricles, than true functional abnormalities, but we report them nonetheless. If we observe periventricular white matter differences, however, we must address the finding of periventricular differences in other regions such as the caudate nucleus. It is possible that the observed onset transient difference in the caudate is due to the region of interest being centered on gray matter in the normal subjects but ventricle in the individuals with schizophrenia. To examine this issue, we used the average anatomy from the T1-weighted scans of the individuals with schizophrenia to create a region of interest centered on each head of the caudate nucleus. Special care was taken to avoid the ventricular border of the caudate. This region of interest is shown in Fig. 6 (red outline) overlayed on the average anatomy for both normal subjects (A) and individuals

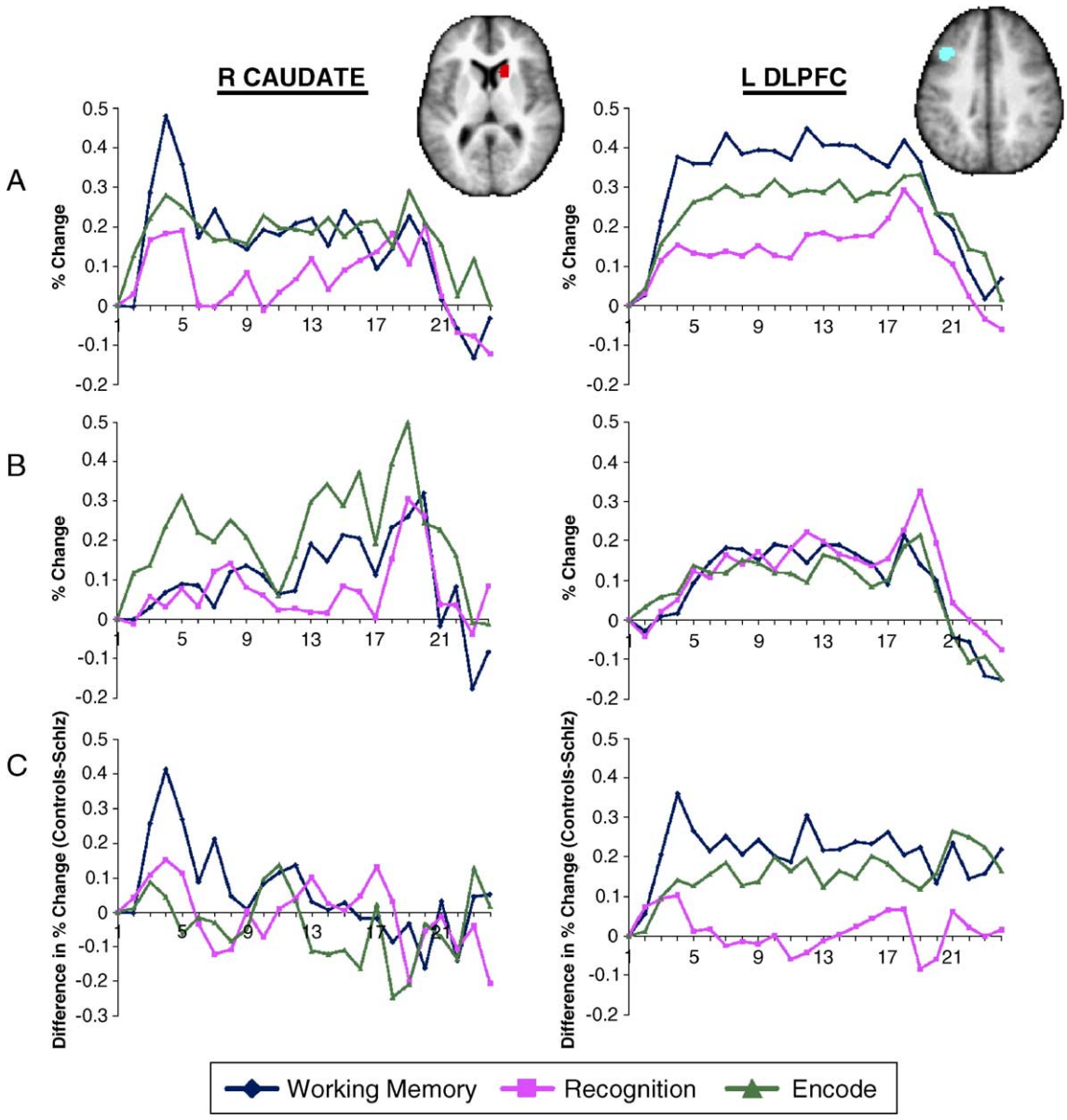

Fig. 4. Time courses comparing working memory (blue), recognition (magenta), and encoding (green) tasks in the right caudate and left dorsolateral prefrontal cortex for normal subjects (A) and individuals with schizophrenia (B). The time course differences between normal subjects and individuals with schizophrenia for each task are shown in the bottom row (C).

with schizophrenia (B). The time courses from this region for both normal subjects (blue) and individuals with schizophrenia (magenta) are shown in Fig. 5C. The difference in the onset transient persists in the caudate ($P < .01$), even when the average anatomy from individuals with schizophrenia is used to define the region.

Performance

A subset of controls ($N = 30$) and individuals with schizophrenia ($N = 30$) were compared that were performance matched for accuracy ($P = 1.00$) and did not vary significantly in reaction time ($P = .564$). Of the 31 task–control regions identified, all remained significant ($P < .05$) except for one of the regions in the R dorsolateral prefrontal cortex (29,41,15). Of the 25 regions differing in the onset transient, all remained significant in the performance matched subsets ($P < .05$).

Drug effect

Only a study of drug naive or drug free individuals with schizophrenia can determine if our observed effects are due to antipsychotic medication. However, we can perform a useful analysis comparing individuals with schizophrenia on two different types of medication, typical and atypical. While these two classes of medication share certain properties such as dopamine blockade, they are known to differ in their anticholinergic and antiserotonergic properties. There were no significant differences in the onset transient in any region between individuals with

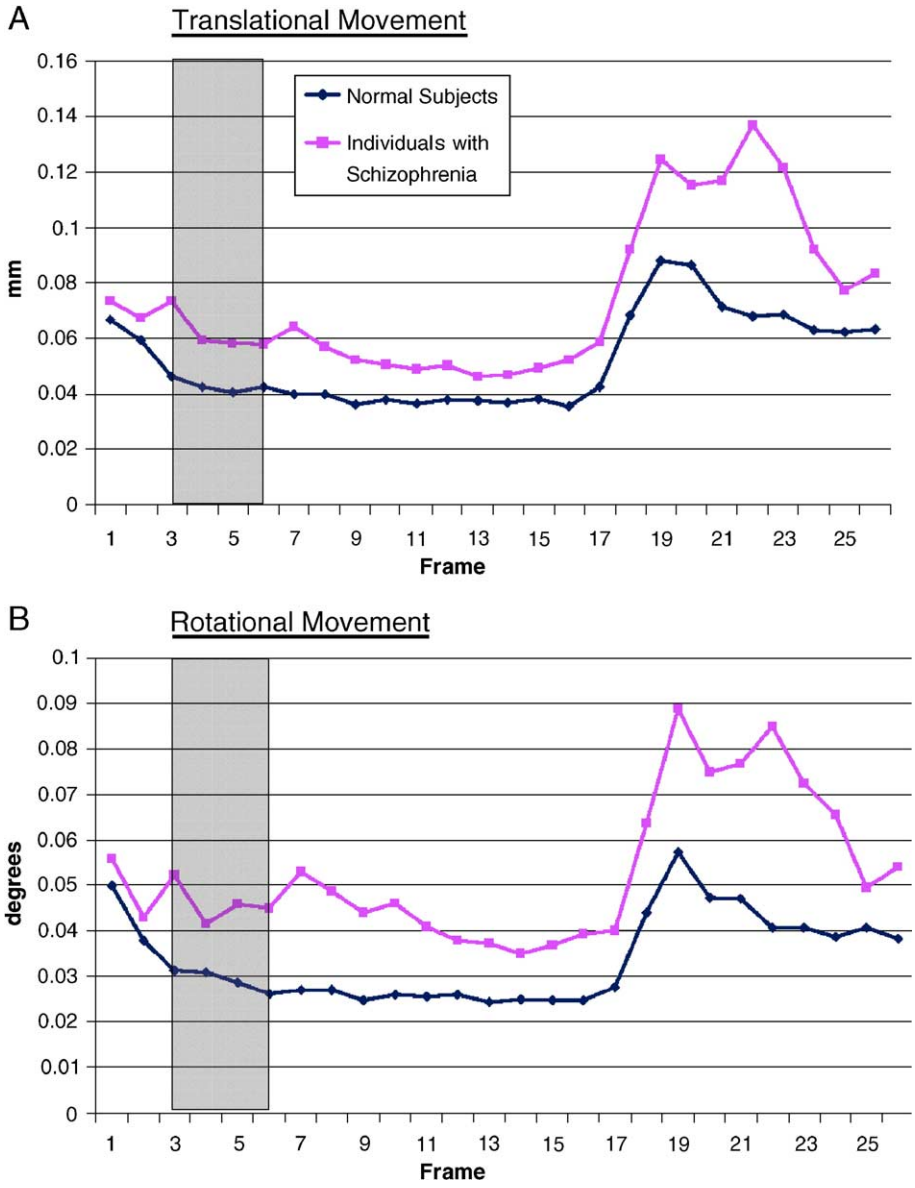

Fig. 5. Incremental movement across a block for average translational movement (A) and rotational movement (B) for both normal subjects (blue time course) and individuals with schizophrenia (magenta time course). The gray box illustrates the time of the onset transient.

schizophrenia on atypical medication (N = 30) and those on typical medication (N = 8), yet both medication groups were independently significantly different from normal subjects in numerous (>10) regions.

Discussion

The goal of this study was to determine if analysis of the BOLD onset transient could reveal unique functional differences not isolated through conventional block-design analysis techniques. We have demonstrated a regionally specific attenuation of the onset transient in individuals with schizophrenia when compared to normal subjects in a working memory task, a difference missed through task–fixation analysis. Furthermore, this difference in the onset transient is regionally and task specific.

Potential confounds

We have examined a number of potential confounds that could affect our results including movement, anatomical variation, performance, and drug effects. With regards to movement, individuals with schizophrenia do move slightly more throughout the entire task block which could cause a general signal reduction, therefore the confound of movement cannot be ruled out. However, the lack of a selective increase in movement during the time of the onset transient makes it highly unlikely that movement could be responsible for a selective attenuation of the onset transient in individuals with schizophrenia.

We can also make some conclusions about anatomical variability, performance, and drug effects. Our analysis which addressed anatomical variability, such as enlarged ventricles in individuals with schizophrenia, showed that anatomical differences between the two groups cannot explain the attenuation of the onset

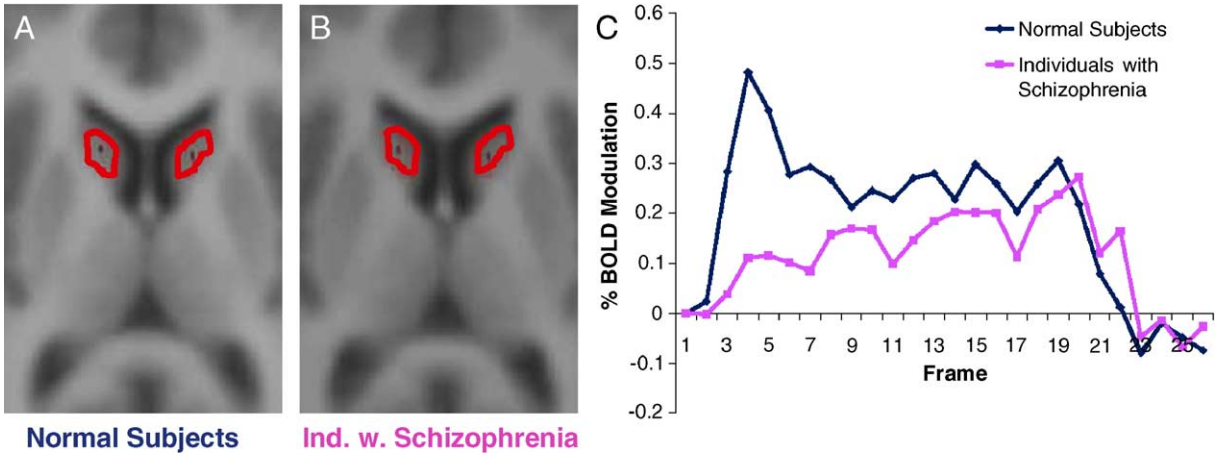

Fig. 6. Region of interest (in red) over the head of the caudate nucleus created using the average schizophrenic anatomy (B). The average anatomy for normal subjects is shown in panel (A) and the regional time courses for both normal subjects (blue) and individuals with schizophrenia (magenta) are shown in panel (C).

transient in the caudate nucleus. In our analysis of drug effects, we found no difference between individuals with schizophrenia on typical and atypical classes of medication. This suggests that our results might not be due to a drug effect or due to an effect that both classes of medication share such as dopamine blockade. Our subdivision of controls and individuals with schizophrenia into performance matched subgroups showed that performance cannot account for our observed population differences.

A final confound that should be discussed is the possibility of differences in basic hemodynamic coupling in individuals with schizophrenia. Population differences in the hemodynamic response would weaken our claim that analysis of the onset transient reveals interesting functional differences between the two populations. While it might be possible for differences in the hemodynamic response to be altered in a regionally specific manner in schizophrenia, it is highly unlikely that it could be altered in a task specific manner. In addition, previous work on the basic BOLD response in individuals with schizophrenia has demonstrated essentially normal hemodynamic responsiveness (Barch et al., 2003a), making differences in cerebrovascular physiology or hemodynamic coupling an unlikely source of the observed differences in the onset transient.

Functional interpretation of the onset transient

The results of the current study strongly support a functional or neuronal interpretation of the onset transient in the BOLD signal as opposed to an overshoot or hemodynamic phenomenon as the task–state balance is established. We have shown that the onset transient is different between individuals with schizophrenia and normal subjects. This difference is regionally specific, task specific, and demonstrates independence from sustained, task-related signal changes. These findings are difficult to reconcile with an overshoot explanation of the onset transient based on hemodynamic or timing delay factors, and suggest that the onset transient should be interpreted as representative of underlying functional or neuronal activity.

The concept of functionally relevant activity at state transitions is not new, and is well represented in the literature. Transient BOLD activity increases have been found to accompany state transitions in fMRI studies of *task shifting* (Braver et al., 2003; Dove et al., 2000; Kimberg et al., 2000; Sohn et al., 2000), *set shifting* (Konishi et al., 1998, 1999; Nagahama et al., 1999), and *block transitions* (Konishi et al., 2001). In addition, more direct studies of neuronal activity using event related potentials (Karayanidis et al., 2003) or local field potentials (Logothetis, 2003) have shown transient activity at state transitions.

Implications for schizophrenia

In addition to demonstrating the utility of the onset transient for identification of functional differences and providing evidence for a functional interpretation of the onset transient, the current study presents new findings relevant to schizophrenia. Many of the regions identified through our onset transient analysis including the dorsolateral prefrontal (DLPF) cortex, lateral orbitofrontal cortex, caudate, and cerebellum are components of anatomically defined closed looped circuits linking the frontal lobe to subcortical nuclei (Alexander et al., 1986, 1990). A similar cortico–thalamic–cerebellar circuit has also been identified linking the cerebellum to the prefrontal cortex (Middleton and Strick, 2000; Wiser et al., 1998).

Many of the components of these frontal–subcortical circuits identified through onset transient analysis have been previously implicated in schizophrenia (Shenton et al., 2001). The most frequently identified component of these circuits is the dorsolateral prefrontal (DLPF) cortex in which anatomical, functional, histological, and biochemical differences in individuals with schizophrenia have been shown (Bunney and Bunney, 2000; Callicott et al., 2003; Manoach, 2003). Studies of the caudate in medication-naive individuals with schizophrenia have found decreased volume (Corson et al., 1999; Keshaven et al., 1998; Shihabuddin et al., 1998), decreased glucose metabolism (Buchsbaum et al., 1992), and increased choline levels (Bustillo et al., 2002), suggesting an intrinsic abnormality in the caudate nucleus of individuals with schizophrenia. Decreased size of the lateral orbitofrontal cortex has also been occasionally observed in individuals with schizophrenia (Shenton et al., 2001). Damage to the lateral orbitofrontal cortex has been associated with preservative errors of behavioral set shifting (Butters et al., 1973; Iversen and Mishkin, 1970), a commonly observed behavioral abnormality in schizophrenia

(Riehemann et al., 2001; Smith et al., 1998; Taylor, 1996; but see also Manoach et al., 2002).

Although less well established, abnormalities in the function and structure of the cerebellum have also been implicated in schizophrenia (Rapoport et al., 2000; Wiser et al., 1998). Many studies, but not all, have identified decreased cerebellar volume in individuals with schizophrenia, especially in the posterior superior lobe (Okugawa et al., 2003). Postmortem analysis has also reported histological abnormalities in the cerebellum of individuals with schizophrenia (Reyes and Gordon, 1981; Tran et al., 1998).

Although structural and histological abnormalities have been reported in many components of the frontal–subcortical circuits identified through onset transient analysis, not all regions have been equally implicated in functional imaging studies of individuals with schizophrenia. The DLPFC has been found to exhibit a functional imaging abnormality during working memory tasks in patients with schizophrenia (Bunney and Bunney, 2000; Callicott et al., 2003; Manoach, 2003) much more consistently than regions such as the caudate, cerebellum, and lateral orbitofrontal cortex. The current study offers a partial explanation for this failure of functional imaging to detect changes in such brain areas putatively involved in schizophrenia. We demonstrate that through standard task–fixation analysis, only the DLPF exhibits a difference between normal subjects and individuals with schizophrenia (see also Barch et al. 2003b), whereas analysis of the onset transient identifies a much more comprehensive list of circuit components including the DLPF cortex, lateral orbitofrontal cortex, caudate nucleus, and cerebellum. The current findings demonstrate the utility of using an analysis of the onset transient to identify meaningful functional differences that are missed through standard task–fixation analysis. Furthermore, the difference in the onset transient localizes to a specific set of regions previously implicated in the pathology of schizophrenia, and appears to be most evident in working memory, a task hypothesized to be the primary functional deficit in schizophrenia (Cohen and Servan-Schreiber, 1992; Goldman-Rakic, 1991; Weinberger and Gallhofer, 1997).

Analysis techniques

In future studies of the onset transient with fMRI, several technical issues should be considered. Task-minus-fixation and onset transient analysis of the differences between individuals with schizophrenia and normal subjects identify different regions of interest, and one analysis often fails to isolate regions identified by the other. A potential solution to this problem is to not assume any response, and examine the group by time effect across all time points using an analysis of variance (ANOVA). When this analysis was run on the current data set, however, it produced a distribution almost identical to that of the task–fixation analysis, and failed to isolate regions differing only in the onset transient. Studies that analyze data using a group by time ANOVA, therefore, will likely fail to identify short transient differences just as the task–fixation analysis did. An analysis specifically designed to isolate differences in the onset transient, such as the one presented in this study, appears to be essential. An approach similar to our current analysis, and implemented in a previous study of transients at block transition (Konishi et al., 2001), is to use a general linear model to assume both the sustained (task–fixation) and the onset transient responses. This analysis was applied to the current data set, and produced similar results to those currently presented.

Conclusion

The goal of this study was to determine if the onset transient could be used as a distinct functional entity to find novel differences among tasks and between populations. We have demonstrated differences in the onset transient between individuals with schizophrenia and normal subjects during performance of a working memory task. These differences show task specificity and localize to areas previously implicated in the pathology of schizophrenia. We have also demonstrated task differences within the same population of normal subjects. These differences in the onset transient are independent of corresponding differences in the sustained response and are missed through standard task–fixation analysis. Our results demonstrate the utility of using the onset transient for the identification of novel functional differences among tasks and between populations, and strongly support a functional interpretation of the onset transient.

Acknowledgments

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References

Alexander, G.E., Delong, M.R., et al., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Alexander, G.E., et al., 1990. Basal ganglia–thalamocortical circuits: parallel substrates for motor, oculomotor, prefrontal and limbic functions. Prog. Brain Res. 85, 119–146.

Bandettini, P.A., Wong, E.C., et al., 1992. Time course EPI of human brain function during task activation. Magn. Reson. Med. 25, 390–397.

Bandettini, P.A., Jesmanowicz, A., et al., 1993. Processing strategies for time-course data sets in functional mri of the human brain. Magn. Reson. Med. 30, 161–173.

Barch, D.M., Csernansky, J.G., et al., 2002. Working and long-term memory deficits in schizophrenia: is there a common prefrontal mechanism? J. Abnorm. Psychol. 111 (3), 478–494.

Barch, D.M., Mathews, J.R., et al., 2003a. Hemodynamic responses in visual, motor, and somatosensory cortices in schizophrenia. NeuroImage 20, 1884–1893.

Barch, D.M., Sheline, Y.I., et al., 2003b. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol. Psychiatry 53, 376–384.

Boynton, G.M., Engel, S.A., et al., 1996. Linear systems analysis of functional magnetic resonance imaging in human V1. J. Neurosci. 16 (13), 4207–4221.

Braver, T.S., Reynolds, J.R., et al., 2003. Neural mechanisms of transient and sustained cognitive control during task switching. Neuron 39, 713–726.

Buchsbaum, M.S., Haier, R.J., et al., 1992. Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. Arch. Gen. Psychiatry 49, 935–942.

Bunney, W.E., Bunney, B.G., 2000. Evidence for a compromised dorsolateral prefrontal cortical parallel circuit in schizophrenia. Brain Res. Rev. 31, 138–146.

Bustillo, J.R., Rowland, L.M., et al., 2002. High choline concentrations in the caudate nucleus in antipsychotic-naive patients with schizophrenia. Am. J. Psychiatry 159, 130–133.

Butters, N., Butter, C., et al., 1973. Behavioral effects of sequential and one-stage ablations of orbital prefrontal cortex in the monkey. Exp. Neurol. 39, 204–214.

Buxton, R.B., Wong, E.C., et al., 1998. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magn. Reson. Med. 39, 855–864 (June).

Callicott, J., Mattay, V., et al., 2003. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. Am. J. Psychiatry 160, 2209–2215.

Cohen, J.D., Servan-Schreiber, D., 1992. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol. Rev. 99, 45–77.

Corson, P.W., Nopoulos, P., et al., 1999. Caudate size in first-episode neuroleptic-naive schizophrenic patients measured using an artificial neural network. Biol. Psychiatry 46, 712–720.

Davis, T.L., Weisskoff, R., et al., 1994. Temporal aspects of fMRI task activation; dynamic modeling of oxygen delivery. Proceedings of the 2nd Annual Meeting of the ISMRM San Francisco, p. 69.

Dove, A., Pollmann, S., et al., 2000. Prefrontal cortex activation in task switching: an event related fMRI study. Cogn. Brain Res. 9, 103–109.

Fox, P.T., Raichle, M.E., 1986. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc. Natl. Acad. Sci. U. S. A. 83, 1140–1144.

Fox, P.T., Raichle, M.E., et al., 1988. Nonoxidative glucose consumption during focal physiologic neural activity. Science 241, 462–464.

Frahm, J., Kruger, G., et al., 1996. Dynamic uncoupling and recoupling of perfusion and oxidative metabolism during focal brain activation in man. Magn. Reson. Med. 35, 143–148.

Friston, K., Jezzard, P., et al., 1994. Analysis of functional MRI time-series. Hum. Brain Mapp. 1, 153–171.

Friston, K., Holmes, A., et al., 1995a. Analysis of fMRI time series revisited. NeuroImage 2, 45–53.

Friston, K., Holmes, A., et al., 1995b. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.

Goldman-Rakic, P.S., 1991. Prefrontal cortical dysfunction in schizophrenia: the relevance of working memory. In: Carroll, B.J., Barrett, J.E. (Eds.), Psychopathology and the Brain. Raven, New York, pp. 1–23.

Hoge, R.D., Atkinson, J., et al., 1999. Stimulus-dependent BOLD and perfusion dynamics in human V1. NeuroImage 9, 573–585.

Iversen, S.D., Mishkin, M., 1970. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Exp. Brain Res. 11, 376–386.

Karayanidis, F., Coltheart, M., et al., 2003. Electrophysiological correlates of anticipatory and poststimulus components of task switching. Psychophysiology 40, 329–348.

Keshaven, M.S., Rosenburg, D., et al., 1998. Decreased caudate volume in neuropleptic-naive psychotic patients. Am. J. Psychiatry 155, 774–778.

Kimberg, D.Y., Aguirre, G.K., et al., 2000. Modulation of task-related neural activity in task-switching: an fMRI study. Cogn. Brain Res. 10, 189–196.

Konishi, S., Nakajima, K., et al., 1998. Transient activation of inferior prefrontal cortex during cognitive set shifting. Nat. Neurosci. 1 (1), 80–84.

Konishi, S., Kawazu, M., et al., 1999. Contribution of working memory to transient activation in human inferior prefrontal cortex during performance of the Wisconsin card sorting test. Cereb. Cortex 9, 745–753.

Konishi, S., Donaldson, D.I., et al., 2001. Transient activation during block transition. NeuroImage 13, 364–374.

Kruger, G., Kastrup, A., et al., 1999. Simultaneous monitoring of dynamic changes in cerebral blood flow and oxygenation during sustained activation of the human visual cortex. NeuroReport 10 (14), 2939–2943.

Kwong, K.K., Belliveau, J.W., et al., 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc. Natl. Acad. Sci. U. S. A. 89, 5675–5679.

Lancaster, J.L., Glass, T.G., et al., 1995. A modality-independent approach to spatial normalization of tomographic images of the human brain. Hum. Brain Mapp. 3, 209–223.

Logothetis, N.K., 2003. The underpinnings of the BOLD functional magnetic resonance imaging signal. J. Neurosci. 23, 3963–3971.

Mandeville, J.B., Marota, J.J.A., et al., 1998. Dynamic functional imaging of relative cerebral blood volume during rat forepaw stimulation. Magn. Reson. Med. 39, 615–624.

Manoach, D.S., 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr. Res. 60, 285–289.

Manoach, D.S., Lindgren, K.A., et al., 2002. Schizophrenic subjects show deficient inhibition but intact task switching on saccadic tasks. Biol. Psychiatry 51, 816–826.

Middleton, F.A., Strick, P.L., 2000. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res. Rev. 31, 236–250.

Mintun, M.A., Fox, P.T., et al., 1989. A highly accurate method of localizing regions of neuronal activation in the human brain with positron emission tomography. J. Cereb. Blood Flow Metab. 9 (1), 96–103.

Nagahama, Y., Okada, T., et al., 1999. Transient neuronal activity in the medial superior frontal gyrus and precuneus time locked with attention shift between object features. NeuroImage 10, 193–199.

Obata, T., Liu, T.T., et al., 2004. Discrepancies between BOLD and flow dynamics in primary and supplementary motor areas: application of the balloon model to the interpretation of BOLD transients. NeuroImage 21, 144–153.

Ogawa, S., Tank, D.W., et al., 1992. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc. Natl. Acad. Sci. 89, 5951–5955.

Ojemann, J.G., Akbudak, E., et al., 1997. Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. NeuroImage 6, 156–167.

Okugawa, G., Sedvall, G., et al., 2003. Smaller cerebellar vermis but not hemisphere volumes in patients with chronic schizophrenia. Am. J. Psychiatry 160, 1614–1617.

Rapoport, M., Van Reekum, R., et al., 2000. The role of the cerebellum in cognition and behavior: a selective review. J. Neuropsychiatry Clin. Neurosci. 12, 193–198.

Reyes, M.G., Gordon, A., 1981. Cerebellar vermis in schizophrenia. Lancet, 700–701.

Riehemann, S., Volz, H., et al., 2001. Hypofrontality in neuroleptic naive schizophrenic patients during the Wisconsin card sorting task—a fMRI study. Eur. Arch. Psychiatry Clin. Neurosci. 251, 66–71.

Rosengarten, B., Osthaus, S., et al., 2002. Overshoot and undershoot: control system analysis of hemodynamics in a functional transcranial Doppler test. Cerebrovasc. Dis. 14, 148–152.

Shenton, M.E., Dickey, C.C., et al., 2001. A review of MRI findings in schizophrenia. Schizophr. Res. 49, 1–52.

Shihabuddin, L., Buchsbaum, M.S., et al., 1998. Dorsal striatal size, shape, and metabolic rate in never-medicated and previously medicated schizophrenics performing a verbal learning task. Arch. Gen. Psychiatry 55, 235–243.

Smith, G.L., Large, M.M., et al., 1998. Further evidence for a deficit in switching attention in schizophrenia. Biol. Psychiatry 107, 390–398.

Sohn, M.H., Ursu, S., et al., 2000. The role of the prefrontal cortex and parietal cortex in task shifting. Proc. Natl. Acad. Sci. U. S. A. 97, 13448–13453.

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

Taylor, S.F., 1996. Cerebral blood flow activation and functional lesions in schizophrenia. Schizophr. Res. 19, 129–140.

Tran, K.D., Smutzer, G.S., et al., 1998. Reduced Purkinje cell size in the cerebellar vermis of elderly patients with schizophrenia. Am. J. Psychiatry 155, 1288–1290.

Weinberger, D., Gallhofer, B., 1997. Cognitive function in schizophrenia. Int. Clin. Psychopharmacol. 12 (4), S29–S36.

Wiser, A.K., Andreasen, N.C., et al., 1998. Dysfunctional cortico–cerebellar circuits cause 'cognitive dysmetria' in schizophrenia. NeuroReport 9, 1895–1899.

Worsley, K.J., Marrett, S., et al., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. Hum. Brain Mapp. 4, 58–73.