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Hemodynamic responses in visual, motor, and somatosensory cortices in schizophrenia

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Abstract

Recent advances in functional neuroimaging allow comparisons between individuals with schizophrenia and control groups. Previous studies of schizophrenia have used blocked task paradigms and, more recently, "rapid event-related" designs in which stimuli of different types are presented close together in an intermixed fashion. The validity of between-group comparisons in both of these types of paradigms depends on excluding the possibility that observed functional response differences are attributable to altered hemodynamic responses in individuals with schizophrenia. The goal of the current study was to begin a systematic examination of the hemodynamic response in schizophrenia. We administered a flashing checkerboard paradigm with a motor response to 17 individuals with schizophrenia and 24 healthy controls. Both groups showed robust activation of visual, motor, somatosensory, and supplementary motor regions. For the most part, the individuals with schizophrenia demonstrated intact peak amplitude, variance, latency, and linear summation properties in regions activated by this task. We did find some evidence for increased variability in the amplitude and latency of the hemodynamic responses in the visual and somatosensory cortices, although the magnitudes of these group differences were relatively small. These results begin to validate the interpretation of functional neuroimaging studies of schizophrenia in terms of neuronal as opposed to vascular mechanisms.

Keywords: Schizophrenia; Imaging; Visual; Motor; Brain function; Hemodynamic response

Introduction

Recent developments in functional magnetic resonance imaging (fMRI) include "rapid event-related designs" (Buckner et al., 1998; Clark et al., 1998; Dale and Buckner, 1997) in which intermixed stimuli of different types are presented close together. These designs are useful to apply in understanding brain function in individuals with disorders such as schizophrenia, as they have the advantage of allowing rapid data acquisition (avoiding long scanning sessions that may be difficult for some patient populations) and the ability to isolate brain activation to specific event types (e.g., correct versus incorrect responses, which may be particularly informative in populations with overall worse performance). Research has shown that one can extract out the event-related hemodynamic response to a particular event type because the hemodynamic response in many brain areas tends to summate in an approximately linear fashion as long as the event rate is not too rapid (Bohning et al., 2003; Huettel and McCarthy, 2000, 2001; Miezin et al., 2000; Vazquez and Noll, 1996). However, in order to interpret fMRI studies of schizophrenia in terms of neuronal (as opposed to vascular) mechanisms, it is necessary to exclude population differences in the physiological

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coupling between neuronal responses and blood oxygen level-dependent (BOLD) signals, i.e., the hemodynamic response function (HDR) (Boynton et al., 1996). The relevant properties of the HDR include peak response amplitude and variance, latency, and linear summation (Buckner et al., 2000). Such factors have not been systematically examined in schizophrenia, despite the fact that either the pathophysiology of the disorder or the medications used to treat the disorder or both could impact the HDR, thereby altering the observed functional responses. Accordingly, the goal of the current study was to begin a systematic examination in patients with schizophrenia and control subjects of BOLD responses in visual, motor, somatosensory, and supplementary motor regions.

Numerous previous studies have used fMRI to examine brain activity associated with a variety of sensory, cognitive, and emotional paradigms. Studies using cognitive and emotional challenge paradigms almost always have found altered brain activity among individuals with schizophrenia, often in higher order heteromodal association regions (e.g., prefrontal cortex, temporal cortex) (Barch et al., 2002; Callicott et al., 2000; Menon et al., 2001; Stevens et al., 1998). These studies also sometimes find altered brain activity in primary sensory regions as well as (Andreasen et al., 1996; Barch et al., 2002; Callicott et al., 1998). However, most of these studies were not designed in a way that would allow one to determine whether altered brain activity in the primary sensory regions (or any region for that matter) reflect changes in basic HDR properties vs changes in the cognitive or emotional processes necessary to carry out the task.

Studies that have been specifically designed to examine the functional integrity of primary motor and somatosensory regions in schizophrenia have provided confusing and sometimes contradictory results. For example, a series of studies by Braus and colleagues (2000; 1999) suggested that functional activation in the sensorimotor cortex and supplementary motor area (SMA) is intact in neuroleptic-naïve patients with schizophrenia and that such activation shows the usual pattern of functional lateralization in the motor cortex. However, the same group also found that typical antipsychotic medications may produce a significant reduction in the BOLD responses in the sensorimotor cortex in schizophrenia and that both typical and atypical medications may reduce the BOLD response in the SMA (Braus et al., 1999). At least one other study reported intact activation of sensorimotor and SMA regions in patients with schizophrenia treated with either typical or atypical medications compared to unmedicated patients (Muller et al., 2002). Other research involving chronically medicated patients with schizophrenia has found evidence for both intact sensorimotor and SMA activation (Buckley et al., 1997) as well as reduced sensorimotor and SMA activation (Schroder et al., 1999, 1995; Wenz et al., 1994) and reduced functional lateralization (Mattay et al., 1997; Schroder et al., 1995). Of note, all of these studies used blocked paradigms that did not allow characterization of the HDR.

Studies designed to examine the integrity of functional activation in the primary visual cortex in schizophrenia have also provided mixed results. Braus and colleagues (2002), using a blocked flickering checkerboard paradigm, found intact functional activation in the primary visual cortex, but reduced thalamic, right prefrontal, and parietal lobe activation in neuroleptic-naïve individuals with schizophrenia. Other studies found enhanced activation in the visual cortex in medicated patients with schizophrenia (Renshaw et al., 1994; Taylor et al., 1997). Again, however, these studies have not examined detailed aspects of the HDR in the visual cortex in schizophrenia.

As noted above, the goal of the current study was to examine basic properties of the HDR in primary sensory and motor areas in individuals with schizophrenia and demographically similar healthy controls. The behavioral paradigm involved presentation of a visual stimulus (flashing checkerboard) and recording a motor response (button press), a paradigm very similar to that used by Buckner and colleagues in healthy individuals (Buckner et al., 2000; Dale and Buckner, 1997; see also Huettel and McCarthy, 2000). We intermixed single event trials with double event trials, thereby allowing us to characterize the HDR evoked by single events and to examine the summation properties of responses to two events presented in rapid succession.

Methods

Participants

Participants were 17 outpatients with DSM-IV schizophrenia and 24 healthy controls. The participants with schizophrenia were all clinically stable outpatients recruited through an ongoing related structural imaging protocol conducted by Dr. Csernansky. Normal controls were recruited from the same community as the individuals with schizophrenia through local advertisements. Controls were excluded if they had any lifetime history of Axis I psychiatric disorder or any first order family member with a psychotic disorder. Potential participants (either patient or control) were also excluded for (1) meeting DSM-IV criteria for substance abuse (severe) or dependence (any type) at any time within the past 3 months; (2) the presence of any clinically unstable or severe medical disorder or a medical disorder that would confound the assessment of psychiatric diagnosis or make participation in the research protocol unsafe; (3) present or past head injury with documented neurological sequelae or causing loss of consciousness; and (4) DSM-IV criteria for mental retardation (mild or greater in severity). The demographic and clinical characteristics of both participant groups are shown in Table 1. All patients with schizophrenia were taking a variety of atypical antipsychotic medications. The controls had higher personal education than participants with schizophrenia ($t(39) = 3.6$, $P < 0.01$), but the groups did not differ significantly in age ($t(39) = 0.5$, $P > 0.5$), years of parent education (to match approximately for socioeconomic status) ($t(39) = 0.2$, $P >$

Table 1
Demographic and clinical characteristics

	Group			
	Healthy controls		Participants with schizophrenia	
	M	SD	M	SD
Age (in years)	42.3	10.7	39.9	11.4
Sex (% male)	54%		47%	
Parent's education (in years)	13.6	3.1	13.4	2.7
Education (in years)	15.6	2.6	12.7	2.1
Handedness (% right)	92%		100%	

0.5), gender ($\chi^2(2) = 0.2$, $P > 0.5$), and handedness (χ^2 (2) $= 2.3$, $P > 0.3$).

Schizophrenia and control diagnoses were determined using the Structured Clinical Interview for DSM-IV (SCID-IV (Spitzer et al., 1990)). The structured interviews were conducted by a MSW-level research assistant who had completed SCID-IV training and who regularly participated in ongoing diagnostic training sessions at the Metropolitan Psychiatric Center. The SCID-IV interviewer had access to all data from present and past Metropolitan Psychiatric Center hospital records, corroborative personal sources (e.g., family), and records from other hospitals. In addition, a semistructured interview was performed by an expert clinician (in most cases, J.G.C.), also using DSM-IV criteria. This expert clinician also had access to all available medical records and collaborative sources, but was blind to the results of the SCID-IV interview. The participant's final diagnosis was determined by a consensus meeting between the SCID-IV interviewer and the expert clinician.

Behavioral paradigm

The task paradigm was similar to that used by Buckner (Buckner et al., 2000). Participants were presented with a 1.25-s duration visual stimulus. Participants were asked to press a key with their right index finger at stimulus onset. The stimulus was an 8-Hz counterphase flickering black/white checkerboard centered on the fixation point subtending a 12° visual angle. Stimulus onset was controlled by the scanner via the PsyScope button box. On half the runs (2/4) this onset was synchronized to the beginning of a fMRI frame and on the other half to the midpoint of a frame. By averaging together trials in which the stimulus onset occurred at the beginning and the midpoint of the frame, this "interleaved" procedure allowed for a more robust estimate of the hemodynamic response associated with that time period (Miezin et al., 2000). Each participant completed four runs. As shown in Fig. 1, each run was constructed so that one of two types of trial occurred every eight frames (20 s). One-event trials consisted of an isolated single event. Two-event trials consisted of two events separated by 5 s. The one-event and two-event trials were pseudorandomly intermixed so that 7 of one type and 8 of the other occurred within a run. Over four runs, each subject accumulated 30 one-event trials and 30 two-event trials. For each event type, half were synchronized to frame starts and half were synchronized to frame midpoints. The single-event trials were used to extract the HDR evoked by single events presented in isolation (Buckner et al., 2000; Dale and Buckner, 1997). The two-event trials were used to examine the summation properties of the HDR.

Visual stimuli were generated by an Apple PowerMac and PsyScope (Cohen et al., 1993) and projected to participants with a Sharp LCD projector onto a screen positioned at the head end of the bore. Subjects viewed the screen through a mirror attached to the top of the MR head coil. A fiber-optic key press interfaced with the PsyScope button box was used to record participant's behavioral performance.

Scanning

All scanning was performed on the 1.5-T Vision system (Siemens, Erlanger, Germany) at the Research Imaging Center of the Mallinkrodt Institute of Radiology at the Washington University School of Medicine. For each participant, all imaging data, structural as well as functional, were obtained in one session. Structural imaging included a high-resolution ($1 \times 1 \times 1.25$ mm) sagittal MP-RAGE 3D T1-weighted scan (TR, 10 ms; TE, 4 ms; flip angle, 8°) and a T2-weighted fast turbospin echo (TSE) scan. The functional data were acquired using an asymmetric spin–echo echo–planar sequence sensitive to BOLD (T2*) contrast (TR, 2500 ms; TE, 50 ms; FOV, 24 cm; flip angle, 90°). Each functional run included 128 volumes (frames) of 2.5 s. Whole brain coverage was achieved with 19 contiguous 7-mm slices. Slice tilts and offsets were prescribed in relation to the AC–PC plane on the basis of fast automatic atlas registration of a low-resolution (2-mm cubic voxel) pre-fMRI MP-RAGE scan.

Data analysis

fMRI preprocessing included (1) compensation for slice-dependent time shifts (136 ms/slice), (2) elimination of odd/even slice intensity differences due to interpolated acquisition, (3) realignment of all data acquired in each subject within and across runs to compensate for rigid body motion (Ojemann, 1997), and (4) intensity normalization to a whole brain mode value of 1000. The functional data were transformed into the stereotaxic atlas space of Talairach and Tournoux (1988) by computing a sequence of affine transforms (first frame EPI to T2-weighted TSE to MP-RAGE to atlas representative target) composed by matrix multiplication. Reslicing the functional data in conformity with the atlas then involved only one interpolation. All analyses described below were conducted on the basis of atlas-transformed data resampled to 3-mm cubic voxels.

Responses evoked by each of the event types were extracted from the functional data using previously described

selective averaging technique (Buckner et al., 1998; Dale and Buckner, 1997; Maccotta et al., 2001). This method is unbiased in that it imposes no *a priori* assumption on the shape of the HDR. For each participant, we averaged all of the data for the single event trials to estimate the mean HDR over a period of eight frames (20 s). Similarly, the mean response to two-event trials was computed over a period of eight frames. These data were then analyzed as described below using appropriately designed ANOVA and *t* tests treating subject as a repeated measure. We repeated all of the analyses using a regression-based approach implemented in a general linear model framework, both with and without an assumed hemodynamic response function, with essentially identical results. To facilitate comparison with prior studies, we present here only the analyses using the selective averaging approach. We also computed, for each subject, response variability (standard deviation) for each event type at each time point.

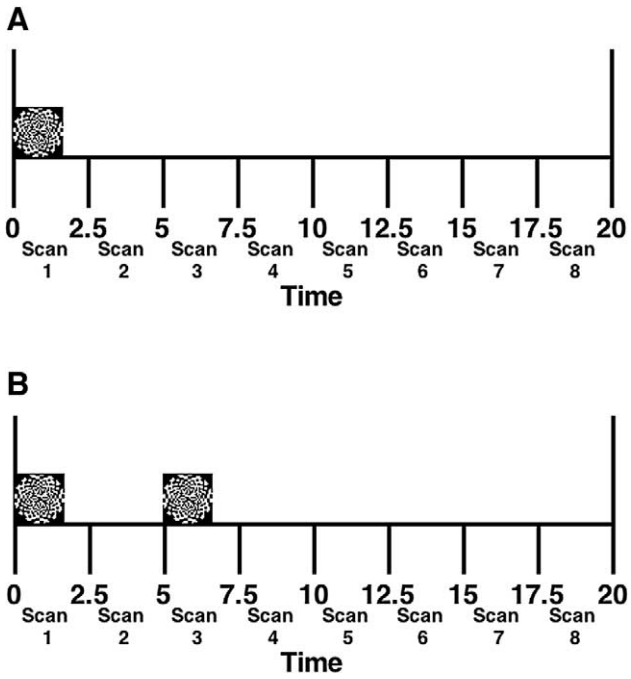

Fig. 1. Schematic of the events and timing of the single-event (A) and two-event (B) trials.

Results

Behavioral data

Motor performance was generally good and similar across groups. Only 4/17 patients missed any motor responses (1 missed 9, 1 missed 3, 1 missed 2, and 1 missed 1) and only 6/24 controls missed any motor responses (1 missed 11 and 5 missed 1). Thus, it is unlikely that any group differences in brain activity can be attributed to motor performance. Also, the majority of missed responses (24 of 31) occurred either on the single-event trials or on the first event of the two-event trials. Thus, systematic reductions in the functional responses to the second event in two-event trials (see below) cannot be explained by performance factors. We also examined reaction times to the first and second events, using an ANOVA with group as a between-subjects factor and event order (first, second) as a within-subject factor. This analysis revealed a main effect of group, $F(1,39) = 14.01$, $P < 0.001$, with the patients (first event, mean, 529, SD, 82; second event, mean, 550, SD, 87) slower than the controls (first event, mean, 433, SD, 86; second event, mean, 437, SD, 104) for both event types. There was no main effect of event type, $F(1,39) = 1.7$, $P = 0.2$, and no interaction between group and event type, $F(1,39) = 1.1$, $P = 0.3$.

Imaging data

We began by examining whether there were any group differences in the estimated movement parameters generated by the movement correction algorithms, as higher movement among the individuals with schizophrenia could increase variability and decrease the power to detect significant brain activations. As in our prior studies (Barch et al., 2001, 2002, 2003), we did not find group differences in any of the six parameters estimating absolute movement from the first frame of the first run (*X*, *Y*, *Z*, pitch, roll, yaw, all $P > 0.24$). However, unlike our prior studies (Barch et al., 2001, 2002, 2003), we also did not find significantly greater scan-to-scan movement among the individuals with schizophrenia compared to controls for any of the six parameters (*PS* ranged from 0.18 to 0.61). The fact that we did not find any significant group differences in movement in the current study may be due to the facts that the participants were all stable outpatients and that the study was relatively short (four runs).

Next we tested for significant group differences in functional responses to the one-event or two-event trials. To do so, we computed voxelwise ANOVAs with group as a between-subjects factor and both trial type (fixation, single-event trial, two-event trial) and time point (frames 1–8 within each response) as within-subject factors. We thresholded the resulting statistical maps for significance using a cluster-size algorithm (Forman et al., 1995) that protects against an inflation of the false-positive rate with multiple comparisons. A cluster-size threshold of eight contiguous voxels and a per-voxel α of 0.0001 was chosen, which corresponds to a corrected whole brain false-positive rate of approximately 0.05. This algorithm revealed no regions with significant group $\times$ time point interactions and no significant group $\times$ time point $\times$ trial type interactions. A second analysis with the per-voxel false-positive criterion (α) decreased to 0.001 again showed no significant group differences. Nonetheless, the absence of significant interactions with group does not necessarily imply that the two groups showed similar patterns of brain activity. Thus, to determine whether the two groups did indeed display the same pattern of task-related brain activity, we conduced

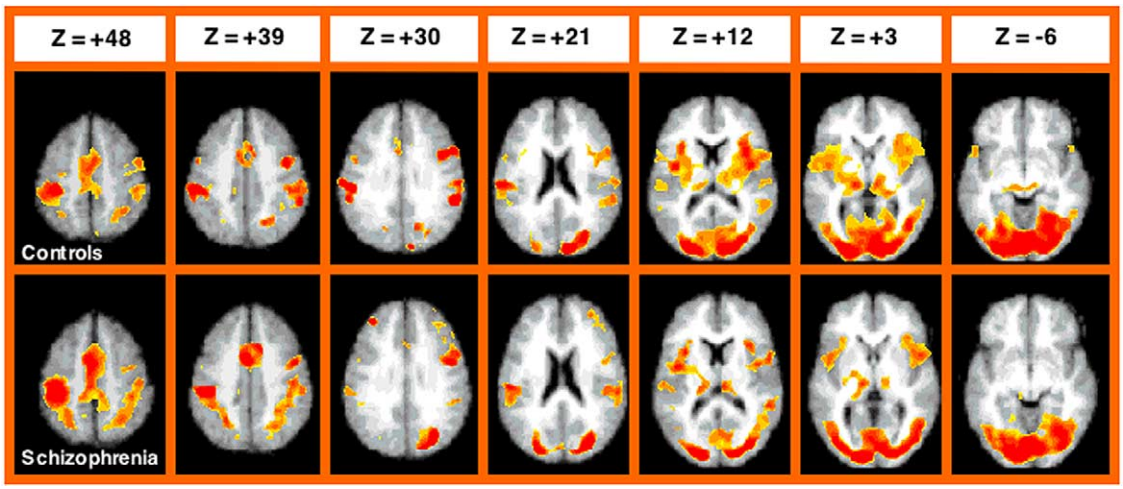

Fig. 2. Brain regions demonstrating significant task-related activation in healthy controls and participants with schizophrenia. The right side of the image is the right side of the brain, and the left side of the image is the left side of the brain.

voxelwise ANOVAs in each group separately taking both trial type and time point as within-subject factors. As shown in Fig. 2, the healthy controls and the patients with schizophrenia demonstrated very similar patterns of brain activation. In particular, both groups showed robust activation in visual, motor, somatosensory, and SMA regions in response to the visual and motor demands of the task.

We next examined the properties of the hemodynamic responses in visual, motor, somatosensory, and SMA cortices. First, we generated regions of interest (ROI) centered on peaks of activation in the main effect of time point maps (collapsing across groups and across the single- and two-event trials) generated by ANOVA analysis as described above. A peak was identified as a region that exceeded the cluster-size threshold, was centered in a region with at least 15 contiguous voxels, and was separated by at least 15 mm from other peaks. We note that similar results were found as presented below when peaks of activation were identified separately for each group, rather than for the groups combined. As shown in Fig. 3, we identified three peaks in the visual cortex, including a midline region in BA 17 ($X = +2$, $Y = -84$, $Z = -3$) and both right ($X = +26$, $Y = -81$, $Z = +9$) and left ($X = -23$, $Y = -90$, $Z = +9$) regions in BA 18. We also identified one peak in the motor cortex ($X = -41$, $Y = -27$, $Z = +54$), one in the somatosensory cortex ($X = -32$, $Y = -48$, $Z = +54$), and one in the SMA ($X = -5$, $Y = -15$, $Z = +51$).

We extracted the mean time course for each subject in each ROI for the one-event and two-event trials. To examine the summation properties of the hemodynamic response we subtracted the time courses for the one-event trials from the two-event trials in each ROI. This gives an estimate of the added contribution of the second event on top of the first. For each subject, ROI, and trial type, we identified response peaks as the frame (of 2–8) that showed the greatest increase in fMRI signal relative to frame 1. Each such peak yielded a measure of amplitude (percentage of signal change relative to frame 1) and latency (in increments of 2.5 s). We then conducted ANOVAs for each of the ROIs with group as a between-subjects factor and event (first, second) as a within-subject factor and peak amplitudes as the dependent variable. As can be seen in Fig. 4, the two groups did not differ in peak amplitudes for either the first or second event for any of the ROIs (all main effects of

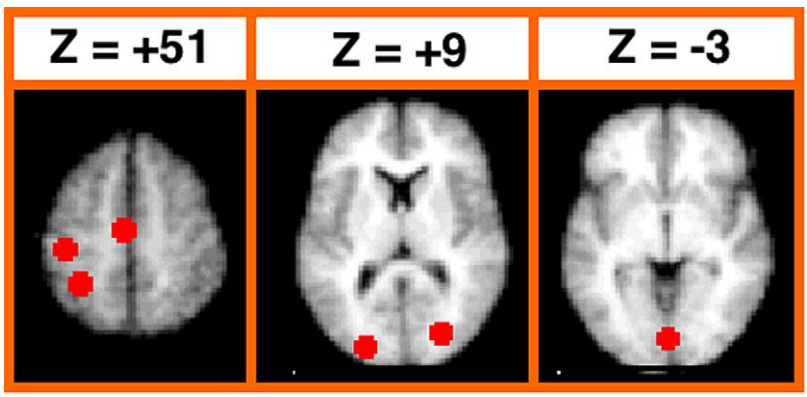

Fig. 3. Regions of interest in primary motor, somatosensory, supplementary motor, and primary visual cortex regions, identified as described in the text.

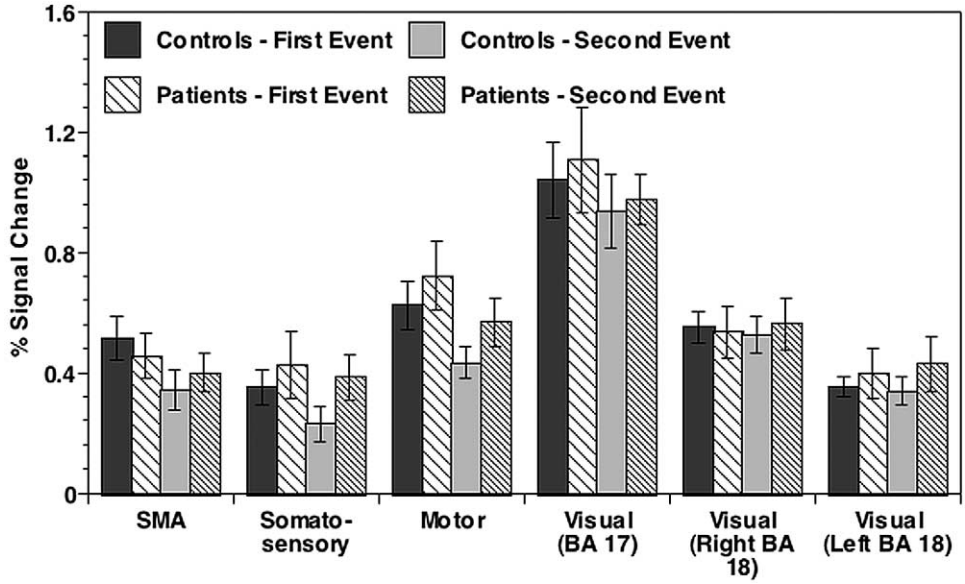

Fig. 4. Graph demonstrating the mean peak amplitudes for each group for each of the ROIs in motor, somatosensory, SMA, and visual regions, separately for the single-event trials and for the two-event trials (with the single-event trial subtracted out).

group, $P > 0.15$, all group by event interactions, $P > 0.4$). Also, as can be see in Fig. 4, the peak amplitudes for the first and second events for both groups were very similar for all of the visual regions, replicating previous findings of roughly linear summation of the hemodynamic responses in the visual cortex across multiple events (all $P > 0.36$). This

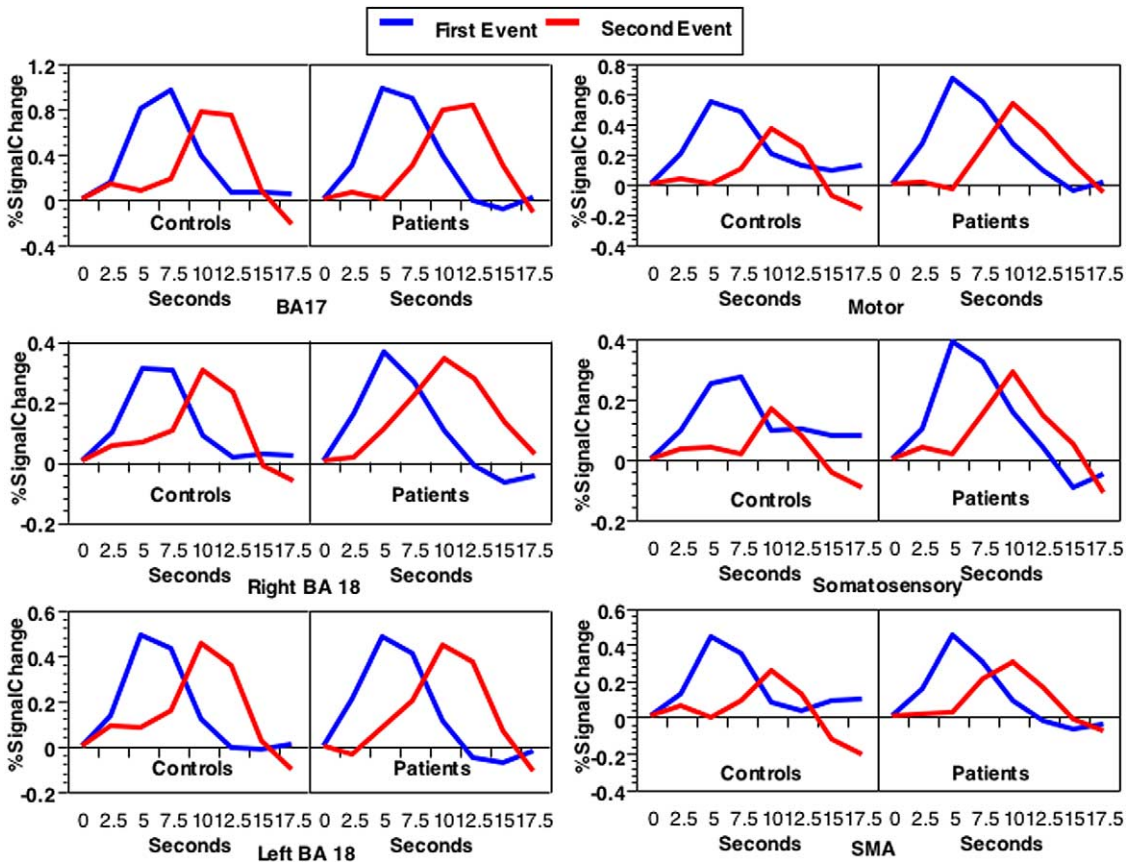

Fig. 5. Graphs plotting the time course of activation in each of the three visual regions for healthy controls and patients with schizophrenia. The blue lines represent the time course of activity for the single-event trials. The red lines represent the time course of activity for the two-event trials, with the time course for the single-event trials subtracted out.

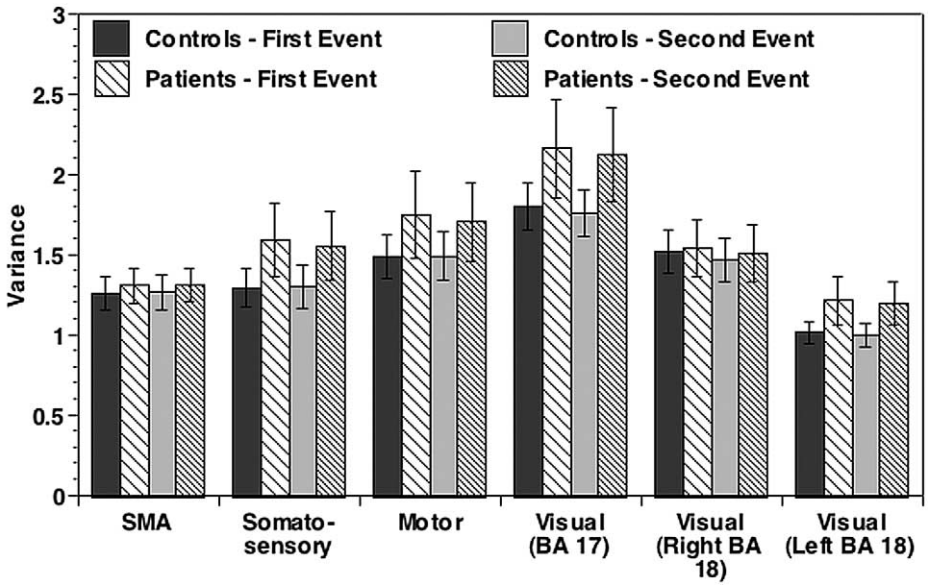

Fig. 6. Graph showing the variance in the fMRI signal for each group for each of the regions in motor, somatosensory, SMA, and visual regions, separately for the single-event trials and for the two-event trials.

is best illustrated by plotting the time courses across all frames for the single-event and the two-event trials (with the time course for the one-event trials subtracted out). As can be seen in Fig. 5, these time courses in the visual cortex look highly similar, except for a shift of 5 s in the start of the signal rise. However, both groups showed a significantly smaller peak amplitude for the second event in the motor cortex, $F(1,39) = 5.4$, $P < 0.05$, and a trend toward a reduced peak to the second event in SMA, $F(1,39) = 3.2$, $P = 0.08$. The peak amplitudes for events one and two did not differ significantly in the somatosensory cortex, $F(1,39) = 2.3$, $P > 0.1$. Again, this effect is clearly illustrated in the time courses for the motor, somatosensory, and SMA regions in Fig. 5.

We next examined whether the variance of the raw fMRI signal differed across groups. As shown in Fig. 6, variance estimates did not differ significantly between the two groups for any of the ROIs (all $P > 0.18$). We next examined whether the variance in the peak amplitude differed between the groups, using Levene's Tests for Equality of Variances. There were no significant group differences in the variance of the peak amplitude estimates for the single-event trials, though there were trends in some regions for the patients to have higher variance. As can be seen by the standard deviation bars in Fig. 4, this trend was most apparent in the right visual cortex, $F(1,39) = 3.4$, $P = 0.07$, and in the motor cortex, $F(1,39)$ 3.6, $P = 0.06$. There were two significant group differences in the variance for the peak amplitudes across groups for the second event: BA 17, $F(1,39) = 6.6$, $P < 0.05$, and the somatosensory cortex, $F(1,39) = 4.0$, $P = 0.05$.

We next examined whether there were any group differences in latency of the BOLD response peak, measured as described above. There were no significant differences in peak latency (see Table 2) between groups for any of the ROIs, for either the first event (all $P > 0.10$) or the second event (all $P > 0.2$). Last, we examined whether the variance (standard deviation, see Table 2) of the latency measures differed across the two groups using Levene's Test for Equality of Variances. For the first event, the variance of the latency measure was significantly greater in patients than controls in BA 17, $F(1,39) = 4.2$, $P < 0.05$, and there was a trend in the same direction in the somatosensory cortex, $F(1,39) = 3.2$, $P = 0.08$. For the second event, there also was a trend for greater variance of latency in patients in the somatosensory cortex, $F(1,39) = 3.4$, $P = 0.07$.

The flashing checkerboard paradigm with motor response was originally intended to study visual, motor, and somatosensory cortices (Buckner et al., 2000). However, a number of other brain regions are also activated by this task, many of which are likely to be engaged in tasks with more complex cognitive and emotional requirements (Huettel and McCarthy, 2001). Accordingly, we also explored the properties of the hemodynamic response in a number of additional regions activated by the task. Specifically, we identified peaks in the right ($X = +14$, $Y = -27$, $Z = +3$) and left ($X = -26$, $Y = -15$, $Z = +6$) thalamus, left parietal ($X = +-53$ $Y = -27$, $Z = +24$), cingulate ($X = +2$ $Y = +6$, $Z = +42$), right BA 44/6 ($X = +44$, $Y = 0$, $Z = +33$), and left BA 44/6 ($X = -38$, $Y = +6$, $Z = +9$). We then examined the peak amplitudes across the groups for the first event (single stimulus trial) and the second event, using ANOVAs for each of the ROIs with group as a between-subjects factor and event (first, second) as a within-subject factor and peak amplitudes as the dependent variable. As can be seen in Fig. 7, the two groups did not differ in peak amplitudes for either the first or second event for ROIs in the thalamus, parietal cortex, cingulate, and left BA 44/6 (all main effects of group, $P > 0.39$, all group by event interactions, $P > 0.29$). There was a trend for a group by event

Table 2
Peak amplitude timing across regions and groups

	Group							
	Healthy controls				Participants with schizophrenia			
	First event		Second event		First event		Second event	
	M	SD	M	SD	M	SD	M	SD
Primary motor cortex	6.1	1.4	10.7	1.4	5.2	1.4	10.3	1.7
Somatosensory cortex	6.4	1.9	10.7	3.5	6.8	2.1	10.6	2.3
Supplementary cortex	5.7	1.9	9.7	2.7	5.7	1.7	9.4	2.4
BA 17	7.0	1.5	11.0	1.3	6.0	2.2	11.6	1.8
Right BA 18	6.2	1.5	10.4	2.2	6.0	2.0	10.3	2.5
Left BA 18	6.4	1.6	10.7	1.6	6.3	1.6	10.9	2.2
Right thalamus	6.4	1.9	9.2	2.5	6.3	2.2	9.4	2.7
Left thalamus	6.9	2.0	10.3	2.9	6.2	2.7	9.3	3.2
Left parietal	6.6	1.6	10.8	2.4	6.2	1.8	10.9	2.8
Cingulate	6.4	1.8	9.8	2.5	5.6	1.4	10.3	2.8
Right BA 44/6	6.2	2.3	9.8	2.5	6.3	2.2	10.2	2.9
Left BA 44/6	5.9	1.8	10.7	2.4	6.0	2.8	9.7	3.5

interaction in right BA 44/6, $F(1,39) = 3.5$, $P = 0.07$, reflecting the fact that peak amplitudes were somewhat lower for the first event among patients, but not for the second event. Of interest, however, the peak amplitude for the second response was significantly lower than the peak amplitude for the first responses for the right thalamus ($F(1,39) = 3.3$, $P < 0.05$), left thalamus ($F(1,39) = 4.1$, $P < 0.05$), and cingulate ($F(1,39) = 5.2$, $P < 0.05$) for both patients and controls. This effect was not significant in the left parietal or in either of the BA 44/6 regions (all $P > 0.18$).

We next examined the variance in the MR signal in these regions, using ANOVAs with group as a between-subjects factor and trial type (single event, two event) as a within-subject factor. Again, there were no significant differences in the variance of the MR signal, either for the one event trials or the two event trials (all main effects of group $p > .22$; all group by event type interaction $p > .21$). We then examined whether there were any group differences in the variance of the peak amplitude across groups, using Levene's test for Test for Equality of Variances. There were no significant group differences in peak amplitude variance, either for the first event (all $p > .23$) or the second event (all $P > 0.09$) in all ROIs. A similar analysis of response latency (see Table 2) showed no significant group differences either for the first event (all $p > .15$) or the second event (all $p > .21$) in any ROI. The was only one marginal group difference in the variance (standard deviation; see Table 2) of the latency measure in cingulate cortex ($F(1,39 = 3.9$, $P = 0.06$; all other $P > 0.12$). There were no significant group differences in the variance of the latency measure for the second event (all $P > 0.45$).

Discussion

The primary goal of the current study was to examine whether the amplitude, shape, timing, and summation properties of the evoked hemodynamic response in primary motor, somatosensory, and visual regions among individuals with schizophrenia were similar to those of healthy controls. We found activation of motor, somatosensory, and visual cortex in our patients with schizophrenia who were medicated with atypical medications that was similar to that observed in healthy controls. Specifically, we found no significant group differences in response peak amplitude or latency in motor, somatosensory, and visual regions. Most importantly, we found that, compared to healthy controls, the individuals with schizophrenia displayed similar HDR

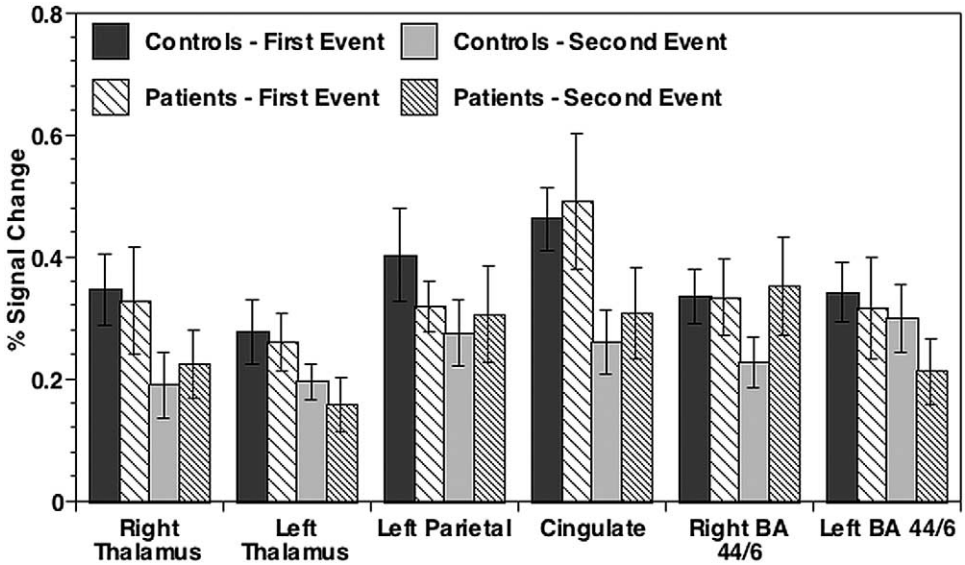

Fig. 7. Graph demonstrating the mean peak amplitudes for each group for each of the regions in the thalamus and parietal, cingulate, and prefrontal cortices, separately for the single-event trials and for the two-event trials (with the single-event trial subtracted out).

summation properties in the same ROIs. This result is somewhat at odds with prior research by Braus and colleagues (1999), who found reduced BOLD responses in the somatosensory cortex in individuals taking atypical medications, and with prior research showing enhanced visual activation in schizophrenia (Renshaw et al., 1994; Taylor et al., 1997). However, a number of other previous studies have found intact activation of primary motor, somatosensory, and visual regions (Buckley et al., 1997; Muller et al., 2002), and the vast majority of cognitive activation studies do not report abnormalities in primary motor, somatosensory, or visual regions. Thus, our study joins a growing literature suggesting that functional brain activation responses in sensorimotor and visual regions are intact in individuals with schizophrenia when the cognitive and strategic demands of the task are minimal. We did find some evidence for increased variability among patients with schizophrenia, in terms of both the variance in the peak magnitude and the timing of the peak. However, this increased variance was significant for only a few regions and the differences were relatively small. Nevertheless, this result suggests that it will be important in future studies to include variance measures in studies of group differences in peak amplitude and latency. Increased variance as well as reductions in peak amplitudes can lead to reduced effect sizes in estimates of functional brain activation; both effects can contribute to group differences in significance maps.

As in many previous studies, the evidence for approximately linear summation of the hemodynamic response was most apparent in visual cortex, for both patients and controls (Buckner et al., 2000; Dale and Buckner, 1997; Huettel and McCarthy, 2000). This finding makes sense in that one can have the most confidence that the state of the participant and their processing of the visual stimulus is likely to have been stationary, especially given an objective measurement of attention to the task (i.e., a button press), confirming that they saw the onset of the visual stimulus. In addition, our intertrial interval of 5 s was similar to that used in prior studies that have found near linear summation. For example, Huettel and McCarthy (2000) noted a roughly 90% recovery in visual cortex at a 6-s intertrial interval. We did not observe similarly impressive linear summation of the hemodynamic response in the motor, somatosensory, and SMA regions in either the patients or the controls. For example, in Buckner et al. (2000) the amplitude of the peak response to the second event was about 98% of that of the first event in motor regions. In the current study, our values in the motor cortex were closer to 70%. Of note, Miezin et al. (2000) did find lower values for the motor cortex when comparing a mean intertrial interval of 5 s to one of 20 s. (The peak amplitude for 5 s was approximately 75% of the peak value for 20 s.) Nonetheless, these results for sensorimotor cortices are somewhat surprising given that participants were equally likely to respond to the second event as to the first event, and reaction times to the first and second events were not significantly different. We did find that the variance for reaction times to the second event compared to the first was somewhat higher in both patients and controls. If the timing and execution of the motor response to the second event was more variable than that for the first event, this could lead to a modest reduction in the estimate of the peak amplitude for the second event. This would be especially likely to occur if the timing of the peak amplitude varied across trials within participants more for the second than for the first event. Regardless of the reason for this result, the most important point for the purposes of the current study is that the patients and controls showed the same degree of linear summation across the sensorimotor and visual cortices, despite the fact that the hemodynamic response did not summate in a fully linear fashion in the motor and somatosensory cortices. Evidence of near linear summation in the visual cortex is consistent with preserved hemodynamic coupling in schizophrenia. The variability across regions is an interesting topic for future investigations (Huettel and McCarthy, 2000).

Most studies of the validity of using rapid event-related paradigms have only examined activation in primary sensory, motor, and visual regions. However, as we noted above, many other brain regions are active even in these simple paradigms. Our results suggest that activation in regions such as the parietal cortex and BA 44/6 also show summation properties that are again very similar in patients and controls, with near linear summation in several regions. However, in both groups, thalamic ROIs and the cingulate cortex showed significantly reduced peaks for the second event compared to the first in both groups. In seems unlikely that differences in vasculature across various regions of the brain account for inconsistent linear summation. Rather, it may be that the psychological functions subserved by these regions change in nature for the second compared to first events in a series. For example, if these regions were somehow involved in orienting attention to the onset of a stimulus, these processes may be either less needed or occur faster to a second event that follows rapidly after a first. Clearly, this is an area that will require examination in future research.

In summary, the results of the current study provide strong support for the hypothesis that basic properties of the hemodynamic response (peak amplitude, latency, and linear summation) are intact in medicated patients with schizophrenia. This is true in primary motor, somatosensory, and visual regions, as well as the thalamus, parietal cortex, cingulate, and prefrontal cortex. We did find some evidence for increased variability in the amplitude and latency of the hemodynamic response in the visual and somatosensory cortices, although the magnitudes of these group differences were relatively small. As noted above, increased variability can lead to reduced estimates of brain activation in populations such as individuals with schizophrenia. It is possible that this increased variability may be even more apparent in regions serving higher cognitive functions and thus should be examined closely in future studies. Nonetheless, the results suggest that it is valid and feasible to use both blocked design and rapid event-related paradigms in indi-

viduals with schizophrenia and that abnormalities in the coupling of the hemodynamic response to neural activation will not be a major confound in the interpretation of the results of such studies.

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