

# An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia

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## Abstract

Schizophrenia is a diffuse brain disease that affects many facets of cognitive function. One of the most replicated findings in the neurobiology of schizophrenia is that the event-related potentials to auditory oddball stimuli are abnormal, effects believed to be related to abnormalities in attentional and memory processes. Although event-related potentials provide excellent resolution regarding the time course of information processing, such studies are poor at characterizing the spatial location of these abnormalities. To address this issue, we used event-related functional magnetic resonance imaging techniques to elucidate the neural areas underlying target detection in schizophrenia. Consistent with recent event-related functional magnetic resonance imaging results, target processing by control participants was associated with bilateral activation in the anterior superior temporal gyri, inferior and superior parietal lobules, and activation in anterior and posterior cingulate, thalamus, and right lateral frontal cortex. For the schizophrenic patients, selective deficits were observed in both the extent and strength of activation associated with target processing in the right lateral frontal cortex, thalamus, bilateral anterior superior temporal gyrus, anterior and posterior cingulate, and right inferior and superior parietal lobules. These findings are consistent with the evidence for abnormal processing of oddball stimuli suggested by event-related potential studies in schizophrenic patients, but provide much more detailed evidence regarding the anatomical sites implicated. These data are consistent with the hypothesis that schizophrenia is characterized by a widespread pathological process affecting many cerebral areas, including association cortex and thalamus. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* Auditory oddball task; Event-related potentials; Magnetic resonance imaging

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## 1. Introduction

Schizophrenia is one of the most enigmatic and complex disorders of the central nervous system. Its complexity is reflected in its diverse and heterogeneous clinical presentation, including symptoms of impairment in nearly all domains of mental function. Abnormalities in sensory processing, attention, and

memory stand out against a background of diffuse impairment.

Event-related potentials (ERPs) have been used successfully for over two decades to demonstrate various abnormalities of sensory and cognitive processes in patients with schizophrenia. One of the most replicated neurobiological findings in schizophrenia are abnormalities in the P3 ERP to low-probability auditory target stimuli (Ebmeier et al., 1990; Blackwood et al., 1991; Faux et al., 1993; McCarley et al., 1993; Strik et al., 1993; Ford et al., 1994a; O'Donnell et al., 1995a; Salisbury et al.,

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1998). The P3 is a large positive component of the ERP peaking about 250–500 ms following the onset of task-relevant, low-probability stimuli (Donchin and Coles, 1988). The P3 is most commonly elicited using an ‘oddball’ paradigm. In this paradigm, a participant is required to respond to (or count) infrequent target stimuli randomly interspersed among frequent non-target stimuli. The P3 is believed to be a manifestation of processes related to attention, decision-making, and memory or contextual updating (Donchin, 1981; Donchin and Coles, 1988; Johnson, 1988, 1993; Alexander et al., 1996).

P3 amplitude abnormalities to auditory stimuli have been found in first-episode psychotic patients (Salisbury et al., 1998), chronic medicated schizophrenic patients (Pritchard, 1986; Faux et al., 1988; Ebmeier et al., 1990; McCarley et al., 1993; Ford et al., 1994a), and schizophrenic patients withdrawn from medication (Faux et al., 1993; Ford et al., 1994b), and after clinical improvement (Eikmeier et al., 1992; Ford et al., 1994b; Rao et al., 1995). There are also some topographical abnormalities in the P3 response in schizophrenia, namely that the P3 amplitude reduction appears to be greater over left than right temporal lobe sites (Faux et al., 1988, 1990, 1993; McCarley et al., 1993; Glabus et al., 1994; O’Donnell et al., 1995b; Heidrich and Strik, 1997; Salisbury et al., 1998). McCarley et al. (1991) interpreted this asymmetry as evidence supporting the hypothesis that the left temporal lobe plays an important role in the pathogenesis of schizophrenia, especially in the generation of positive symptoms (McCarley et al., 1991).

Interestingly, McCarley and colleagues have shown that this P3 asymmetry is present in first-episode psychotic schizophrenic patients (Salisbury et al., 1998). Furthermore, they did not find this effect in a group of first-episode affective disorder patients. These findings suggest that the topography of the P3 might be useful in making a differential diagnosis of schizophrenia or affective disorder. Thus, ERP data on the P3 response to task-relevant auditory target stimuli have provided an improved understanding of schizophrenia that is potentially of great clinical relevance. However, the ERP methodology is limited in a number of respects, most notably in that the neural sources generating the scalp fields are difficult to localize.

Using positron emission tomography (PET) and

single photon emission computed tomography (SPECT) to measure regional blood flow during oddball tasks, researchers have shown that the bilateral lateral frontal cortex, anterior cingulate, and posterior occipital/temporal/parietal junction are involved in oddball processing (Ebmeier et al., 1995; Shajahan et al., 1997a). Furthermore, SPECT studies have demonstrated that there is reduced frontal activation in schizophrenia during oddball tasks (Shajahan et al., 1997a). Blackwood et al. (1994) observed that the latency of the P3 correlated with resting regional blood flow in the cingulate, left fronto-temporal regions and left parietal regions. However, event-related studies are impractical with PET and SPECT, and therefore, the hemodynamic response associated with individual events (e.g. target stimuli) cannot be selectively resolved. Thus, these studies do not demonstrate unambiguously that the observed effects are selective to target processing. Moreover, the exact relevance of these latter data to P3 abnormalities in schizophrenia remains unclear.

Other methods have been used to localize the neural sources involved in target processing during oddball tasks. These methods include topographical and ERP source localization techniques (Potts et al., 1998), depth electrode recordings (Halgren, 1980; Baudena et al., 1995; Halgren et al., 1995a,b, 1998), and studies of patients with focal brain lesions (Knight, 1984; Knight et al., 1989; Paller et al., 1992; Yamaguchi and Knight, 1995). These studies have implicated areas within the frontal, temporal, and parietal lobes as being involved in oddball processing.

Recent developments in functional magnetic resonance (fMRI) imaging have shown that it is possible to measure the hemodynamic response for distinct events. Event-related fMRI (erfMRI), as it has been coined, has opened new avenues of research for hemodynamic imaging (Josephs et al., 1997; Rosen et al., 1998). Several groups of investigators have performed erfMRI studies of cerebral activity associated with processing low-probability stimuli. McCarthy et al. (1997) found that low-probability visual stimuli elicited activation in the middle frontal gyrus, inferior parietal lobe and posterior cingulate. Menon et al. (1997) found that target stimuli in the auditory modality generated activity in the inferior parietal lobe, thalamus and anterior cingulate (see also Opitz et al., 1999). Using an MR pulse sequence that allowed

imaging of the entire brain, we found that low-probability task-relevant target visual (Kiehl et al., 2000a) and auditory (Kiehl et al., in press) stimuli elicit activation in bilateral anterior superior temporal gyri, thalamus, inferior and superior parietal lobules, anterior and posterior cingulate and lateral frontal cortex. These same cerebral sites are active whether participants are responding manually or silently counting the visual (Kiehl and Liddle, 1999c) or auditory target stimuli (Kiehl and Liddle, 1999b). We have shown recently that these sites are activated when participants respond to target stimuli with either their right or left hand (Kiehl and Liddle, 1999a). We have also demonstrated that neural activity in these sites is reproducible after 6 weeks in a test–retest study in healthy participants (Kiehl and Liddle, 1999h).

Polich and colleagues have shown that the P3 has a similar morphology and topography during three-tone auditory oddball tasks, two-tone auditory oddball tasks, and infrequent single-tone auditory target detection tasks (Katayama and Polich, 1996; Polich and Margala, 1997). Similarly, we have demonstrated that target processing during each of these paradigms activates the bilateral anterior superior temporal gyri, thalamus, inferior and superior parietal lobules, anterior and posterior cingulate and right lateral frontal cortex (Kiehl and Liddle, 1999d,f). Thus, the observation that the same cerebral sites are activated during paradigms used to elicit a P3 suggests that these sites are involved in the generation of the P3 response to target stimuli. We note that in the former studies, it was not possible to determine precisely whether the observed hemodynamics reflect generators specific to the P3 and/or to other electrical components such as the N1, a negative potential observed approximately 100 ms after low-probability task relevant target stimuli. To address this issue, we recently performed a ‘gap’ detection study in which participants were asked to detect a missing stimulus in a stream of auditory stimuli. ERP studies have shown that detecting the missing stimulus elicits a strong P3 response with little or no early N1 component (Sutton et al., 1967; Friedman, 1984). Consistent with our previous research, gap detection was associated with activation in the bilateral anterior superior temporal gyri, thalamus, inferior and superior parietal lobules, anterior and posterior cingulate and right lateral frontal cortex,

providing strong evidence that these neural areas are related to the scalp recorded P3 response (Kiehl and Liddle, 1999g).

The purpose of the present study was to elucidate the cerebral sites activated during auditory target detection in schizophrenic patients and control participants. We employed an identical experimental methodology as in our previous studies of auditory oddball target detection (Kiehl and Liddle, 1999a,b, d–h; Kiehl et al., in press). We hypothesized that we would replicate in this new sample of healthy participants the same pattern of activation for target stimuli as we have observed in previous studies. Based on the extensive literature demonstrating P3 amplitude abnormalities in schizophrenia, we predicted that there would be underactivity at some or all of the multiple sites implicated in oddball detection in healthy subjects.

## 2. Methods

### 2.1. Participants

Eleven schizophrenic out-patients, currently in complete or partial remission, and 11 healthy control participants volunteered for the study. Schizophrenia was diagnosed according to the criteria in the DSM-IV on the basis of clinical interview and review of the case file. The National Adult Reading Test (NART) was employed to assess pre-morbid intelligence (Nelson and O’Connell, 1978; Sharpe and O’Carroll, 1991), and Quick Test was used to assess current intellectual functioning (Ammons and Ammons, 1962). Healthy participants, and their first-degree relatives, were free of any Axis I disorder. There were equal numbers of males and females in the two groups (six males; five females). There were no differences between the two groups in age [mean age: controls, 27.0 (S.D. 8.2); patients, 26.6 (S.D. 8.5)], NART scores [mean percentage correct: controls, 72.7 (S.D. 11.0); patients, 73.0 (S.D. 12.7)], Quick scores [mean percentage correct: controls, 86.3 (S.D. 6.9); patients, 85.3 (S.D. 8.9)] or Hollingshead criteria for socio-economic status [mean score averaged across parents: controls: 3.2 (S.D. 1.15); patients 2.68 (S.D. 1.25)], as evaluated by *t*-tests (all *P*s > 0.32). All schizophrenic patients were receiving

treatment with atypical antipsychotic medication. Nine patients were receiving olanzapine (mean dose 13.5 mg/day, range 10–25 mg/day), one patient was receiving risperidone (3 mg/day), and one patient was receiving clozapine (200 mg/day).

All participants provided written informed consent and were screened for MRI compatibility before entry into the scanning room. All experimental procedures met with University and Hospital ethical approval.

## 2.2. Procedure

Two runs of 244 stimuli were presented to the participant using a custom visual and auditory presentation package (VAPP; <http://www.psychiatry.ubc.ca/sz/nlab/software/vapp/>) using a MRI compatible auditory sound system (Magnacoustics, Inc.) with noise-attenuating (25 dB) headphones with insert ear phones. The stimulus runs consisted of non-target stimuli (1000 Hz tones), target stimuli (1500 Hz tones), and non-repeating random digital noises (e.g. tone sweeps, whistles). These latter stimuli formed the novel stimulus category. All stimuli were presented at approximately 80 dB. All participants reported that they could hear the stimuli and discriminate them from the background scanner noise (see the results of the behavioral data). The target and novel stimuli each occurred with a probability of 0.125; the non-target stimuli occurred with a probability of 0.75. The stimulus duration was 200 ms with a 2000 ms inter-stimulus interval (ISI). Target and novel stimuli were always preceded by at least three non-target stimuli (range 3–5). The intervals between stimuli of interest were allocated in a pseudo-random manner in the range 6–10 s so as to ensure that these stimuli had an equal probability of occurring at 0, 1, and 2 s after the beginning of a 3 s image-acquisition period. By varying the phase of the stimulus presentation relative to the acquisition time, we were able to effectively sample the hemodynamic response to the stimuli of interest uniformly at 1 s intervals (see Josephs et al., 1997; Friston et al., 1998; Kiehl et al., in press).

Participants were instructed to respond as quickly and as accurately as possible with their right index finger every time the target tone occurred and not to respond to the non-target tones or the novel stimuli. A commercially available MRI compatible fiber-optic

response device (Lightwave Medical, Vancouver, BC) was used to acquire behavioral responses. Reaction times were computed on trials for which the participant responded correctly within 1200 ms post-stimulus. Omission errors included any missed target tones or any response with a latency of greater than 1200 ms following the onset of the target stimulus. Errors of commission were defined as responses following the non-target or novel stimuli within 1200 ms of stimulus onset. Prior to entry into the scanning room, each participant performed a practice block of 10 trials to ensure an understanding of the instructions.

## 2.3. Imaging parameters

Imaging was implemented on a standard clinical GE 1.5 T system fitted with a Horizon Echo-speed upgrade. The participant's head was firmly secured using a custom head holder. Conventional spin-echo T<sub>1</sub> weighted sagittal localizers were acquired to view the positioning of the participant's head in the scanner and to graphically prescribe the functional image volumes. Functional image volumes were collected with a gradient-echo sequence (TR/TE 3000/40 ms, flip angle 90°, FOV 24 × 24 cm, 64 × 64 matrix, 62.5 kHz bandwidth, 3.75 by 3.75 mm in plane resolution, 5 mm slice thickness, 29 slices) covering the entire brain (145 mm). This sequence is sensitive to blood-oxygen-level-dependent (BOLD) contrast (see review by D'Esposito et al., 1999). The two stimulus runs consisted of 167 time points, prefaced by a 12 s rest session that was collected to allow for T<sub>1</sub> effects to stabilize. The images collect in the first 12 s were not included in any subsequent analyses.

## 2.4. Image processing

Functional images were reconstructed offline, and the two runs were separately realigned using the procedure by Friston et al. (1996) as implemented in Statistical Parametric Mapping (SPM97; Friston et al., 1995b). Translation and rotation corrections did not exceed 2.5 mm and 2.5°, respectively, for any of the participants. A mean functional image volume was constructed for each participant for each run from the realigned image volumes. This mean image volume was then used to determine parameters for spatial normalization into the modified Talairach

space employed in SPM97 using the procedure of Friston et al. (1995a). In this space, coordinates are expressed relative to a rectangular coordinate frame with the origin at the midpoint of the anterior commissure and the y-axis passing through the posterior and anterior commissures. The normalization parameters determined for the mean functional volume were then applied to the corresponding functional image volumes for each participant. During the latter procedure, the normalized images were re-sampled into isotropic 4 mm voxels. The normalized functional images were then smoothed with an 8 mm full width at half-maximum Gaussian filter.

For the primary analyses, we identified regions of interest using the following strategy. We identified the locations of peak activation with z-scores greater than 5.4 (corresponding to a probability level of  $P < 0.001$  corrected for multiple comparisons) in our initial study (Kiehl et al., in press) of auditory target detection in control participants (i.e. different healthy participants from those used in the present study). We defined cubic regions (with 20 mm sides) centered on these locations. We excluded peaks in vicinity of primary auditory cortex and also premotor cortex, sensorimotor cortex and supplementary motor area since these areas are likely to be directly related to motor response rather than target detection. Wherever two peaks were within 20 mm, we omitted the lesser peak, except in the thalamus where the mean location of the peaks in the left and right thalamus was taken as the center of a single thalamic region of interest. Table 1 lists the 10 regions of interest identified using this procedure. For each of the 22 participants, an individual statistical parametric map (SPM) was created by determining the z-value representing the goodness of fit between the observed hemodynamic response and a model hemodynamic response for each type of event for each voxel. Event-related responses to the target and novel stimuli were modeled using a synthetic hemodynamic response function composed of two gamma functions (see Josephs et al., 1997 for a mathematical model, and Friston et al., 1998 for an illustration). The first gamma function modeled the hemodynamic response using a peak latency of 6 s. The second gamma function was used to model the small 'overshoot' of the hemodynamic response on recovery. Variations in peak latency of the hemodynamic response were adjusted using the respective

temporal derivatives of the two gamma functions. The variance associated with low-frequency noise was modeled and removed using a high-pass filter (cut-off period of 89 s; Holmes et al., in press). Noise associated with alternations of the applied radio frequency field was modeled and removed using a notch filter (period of 6 s). In order to control for between-subject variation in image intensity, all images were scaled to a mean of 100 (arbitrary units) for all analyses. Within each region of interest in the SPM(Z) for the target stimuli for each participant, the following measurements were determined: (1) the number of significant voxels exceeding a z-score of 1.65 (corresponding to a probability level less than 0.05, uncorrected for multiple comparisons) and (2) the peak amplitude of the hemodynamic response. These measurements correspond to the extent of activation and magnitude of response, respectively. These measurements were then analyzed using separate 2 Group (control, patient)  $\times$  10 Site (see Table 1 for list of sites) repeated-measures ANOVAs. We then performed planned comparisons for each measurement in each of the regions of interest. In order to control for a Type I error, we only discuss regions of interest in which the results indicated that both measurements significantly differentiated between the two groups at the  $P < 0.05$  level. Although both target and novel stimuli were modeled, the purpose of the present experiment was to examine the hemodynamics to target stimuli. The results of the novel stimuli are presented in a separate report (Kiehl and Liddle, 1999e). Analyses of the behavioral data indicated that there were no group differences in accuracy for target or novel stimuli (see below). In addition, there were too few error trials to allow robust modeling of the hemodynamic response to errors of commission or omission (see Kiehl et al., 2000b). For these reasons, error trials were not modeled separately.

In addition to the 10 regions of interest, we also searched a region corresponding to the peak activation in motor cortex from our previous study (Kiehl et al., in press; see Table 1 for coordinate locations). This latter region of interest was included as an internal physiological standard to confirm that our experimental procedure and analyses strategy produced reliable activation in both groups of participants, as recommended by Callicott et al. (1998).

Table 1  
Summary statistics for all analyses for the region of interests examined for auditory oddball stimuli<sup>a</sup>

| Regions of interest           | Talairach coordinates |     |     | Kiehl et al. (in press) z-score | Control group z-score | Control extent |        | Patient extent |        | Control magnitude |        | Patient magnitude |        | Statistical results |
|-------------------------------|-----------------------|-----|-----|---------------------------------|-----------------------|----------------|--------|----------------|--------|-------------------|--------|-------------------|--------|---------------------|
|                               | x                     | y   | z   |                                 |                       | Mean           | (S.D.) | Mean           | (S.D.) | Mean              | (S.D.) | Mean              | (S.D.) |                     |
| <b>Frontal</b>                |                       |     |     |                                 |                       |                |        |                |        |                   |        |                   |        |                     |
| 1. R superior frontal gyrus   | 26                    | 52  | 30  | 7.41***                         | 5.57**                | 15.73          | (15.2) | 2.82           | (7.8)  | 0.71              | (0.26) | 0.35              | (0.20) | ***; ***            |
| 2. R anterior cingulate gyrus | 0                     | 16  | 40  | 8.26***                         | 7.97***               | 48.64          | (27.4) | 2.82           | (19.7) | 1.03              | (0.35) | 0.62              | (0.21) | **;                 |
| <b>Parietal</b>               |                       |     |     |                                 |                       |                |        |                |        |                   |        |                   |        |                     |
| 3. L supramarginal gyrus      | -56                   | -41 | 30  | 8.30***                         | 7.27***               | 31.18          | (24.5) | 14.73          | (17.1) | 0.83              | (0.30) | 0.51              | (0.18) | *; **               |
| 4. L superior parietal lobule | -38                   | -48 | 60  | 7.94***                         | 8.55***               | 48.91          | (23.2) | 23.91          | (25.0) | 1.13              | (0.54) | 0.91              | (0.70) | **;                 |
| 5. R superior parietal lobule | 24                    | -60 | 55  | 5.78***                         | 4.72*                 | 12.82          | (12.2) | 4.45           | (10.1) | 0.68              | (0.19) | 0.35              | (0.32) | ***; **             |
| 6. R inferior parietal lobule | 64                    | -34 | 25  | 8.05***                         | 7.05***               | 37.73          | (23.2) | 11.27          | (17.1) | 0.90              | (0.26) | 0.46              | (0.14) | *; ***              |
| 7. Posterior cingulate gyrus  | 0                     | -30 | 30  | 7.43***                         | 6.02***               | 13.55          | (18.0) | .91            | (1.3)  | 0.80              | (0.35) | 0.49              | (0.24) | **;                 |
| <b>Temporal</b>               |                       |     |     |                                 |                       |                |        |                |        |                   |        |                   |        |                     |
| 8. L superior temporal gyrus  | -56                   | 11  | -15 | 8.12***                         | 8.20***               | 29.82          | (19.5) | 9.00           | (14.4) | 1.25              | (0.59) | 0.71              | (0.18) | ***; **             |
| 9. R superior temporal gyrus  | 52                    | 19  | -15 | 8.29***                         | 8.50***               | 37.27          | (19.1) | 9.00           | (13.7) | 1.41              | (0.60) | 0.75              | (0.31) | ***; **             |
| <b>Deep grey</b>              |                       |     |     |                                 |                       |                |        |                |        |                   |        |                   |        |                     |
| 10. Mean thalamus             | 3                     | -17 | 5   | 7.79***                         | 6.18***               | 19.64          | (25.1) | 1.55           | (3.7)  | 0.97              | (0.35) | 0.41              | (0.25) | *; ***              |
| <b>Motor areas</b>            |                       |     |     |                                 |                       |                |        |                |        |                   |        |                   |        |                     |
| 11. L postcentral gyrus       | -26                   | -44 | 65  | 8.03***                         | 8.23***               | 53.09          | (27.5) | 42.91          | (26.1) | 1.02              | (0.39) | 0.84              | (0.19) | n.s.; n.s.          |

<sup>a</sup> Mean and standard deviations (S.D.) are reported for the healthy control participants and the schizophrenic patients for both the extent and magnitude of activation observed for processing the target stimuli. Data from Kiehl et al. (in press) and from a separate analyses of the control group are reported (see Section 2). In the statistical results column, 'E' and 'M' refer to the results of the extent and magnitude analyses, respectively. \*\*\*  $P \leq 0.001$ ; \*\*  $P \leq 0.01$ ; \*  $P \leq 0.05$ ; n.s.: non-significant.

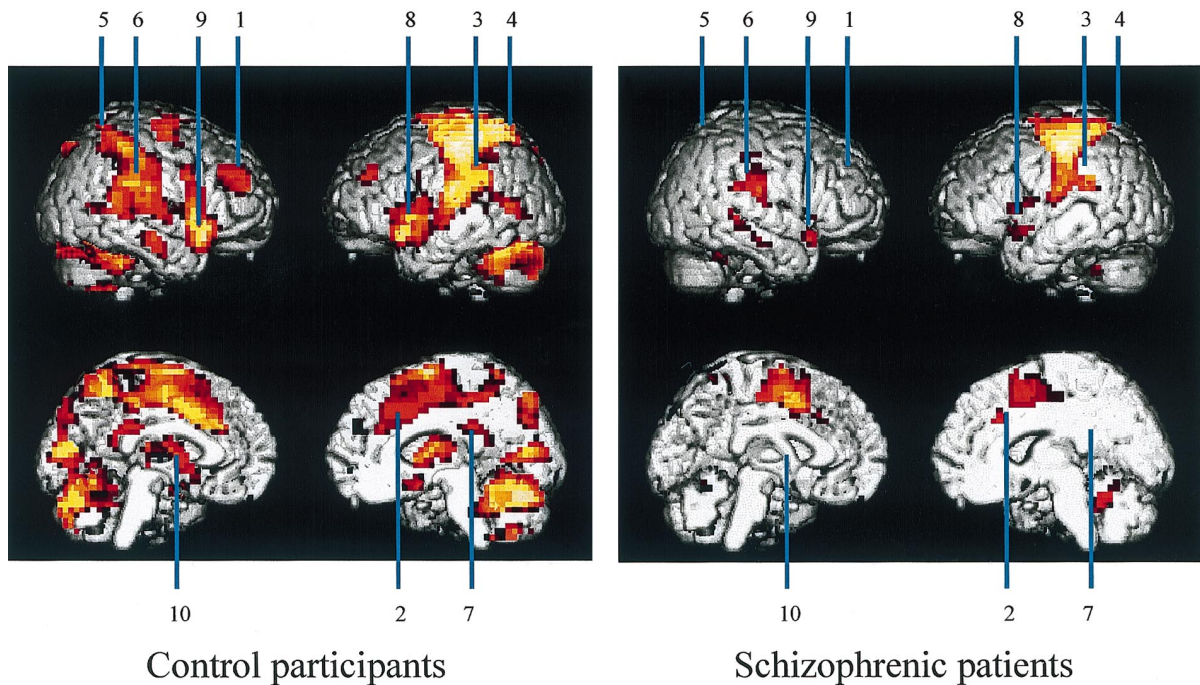


Fig. 1. Cortical surface rendering of the areas of activation for target processing for the control participants (left) and the schizophrenic patients (right). Schizophrenic patients exhibit less activation at 10 cortical sites implicated in oddball discrimination: right lateral frontal cortex (1); anterior cingulate gyrus (2); left supramarginal gyrus (3); left superior parietal lobule (4); right superior parietal lobule (5); left inferior parietal lobule (6); posterior cingulate cortex (7); left superior temporal gyrus (8); right superior temporal gyrus (9); and thalamus (10). Both groups exhibit strong activation of motor cortex. All illuminated voxels have a  $P$  value greater than  $P < 0.001$ , corrected for multiple comparisons.

We also performed a group SPM analysis for all the healthy control participants to confirm the results from our previous study. The parameters for this latter analysis was identical to those employed for the single-subject analyses and those in our previous studies (Kiehl et al., in press)

### 3. Results

#### 3.1. Behavioral data

There were no significant behavioral differences between groups for percentage of correct hits [patients 97.2 (S.D. 6.1); controls 99.6 (S.D. 0.8)], errors of omission [patients 1.0 (S.D. 1.8), controls 0.2 (S.D. 0.4)], or errors of commission [patients 2.1 (S.D. 3.1), controls 1.4 (S.D. 1.1), all  $P$ s  $> 0.16$ ]. Controls responded to target stimuli faster than did patients [ $t(20) = 3.49$ ,  $P < 0.002$ ]. The mean (and standard

deviation) reaction time was 633 (164.0) ms and 445 (73.0) ms for patients and controls, respectively.

#### 3.2. Imaging data

The results of the repeated-measures ANOVAs revealed that patients significantly differed from controls in both the extent and magnitude of activation for target stimuli [main effect of Group, extent,  $F(1, 20) = 23.76$ ,  $P < 0.000092$ ,  $MSE = 1559.3$ ; magnitude,  $F(1, 20) = 23.57$ ,  $P < 0.0001$ ,  $MSE = 3660.2$ ]. Planned comparisons revealed that patients showed significantly smaller and less extensive activation than controls bilaterally in the anterior superior temporal gyrus, left supramarginal gyrus, right superior and inferior parietal lobule, anterior and posterior cingulate, thalamus, and right lateral frontal cortex (see Table 1 for results; Figs. 1 and 2 for illustration).

A follow-up analysis of the area of activation

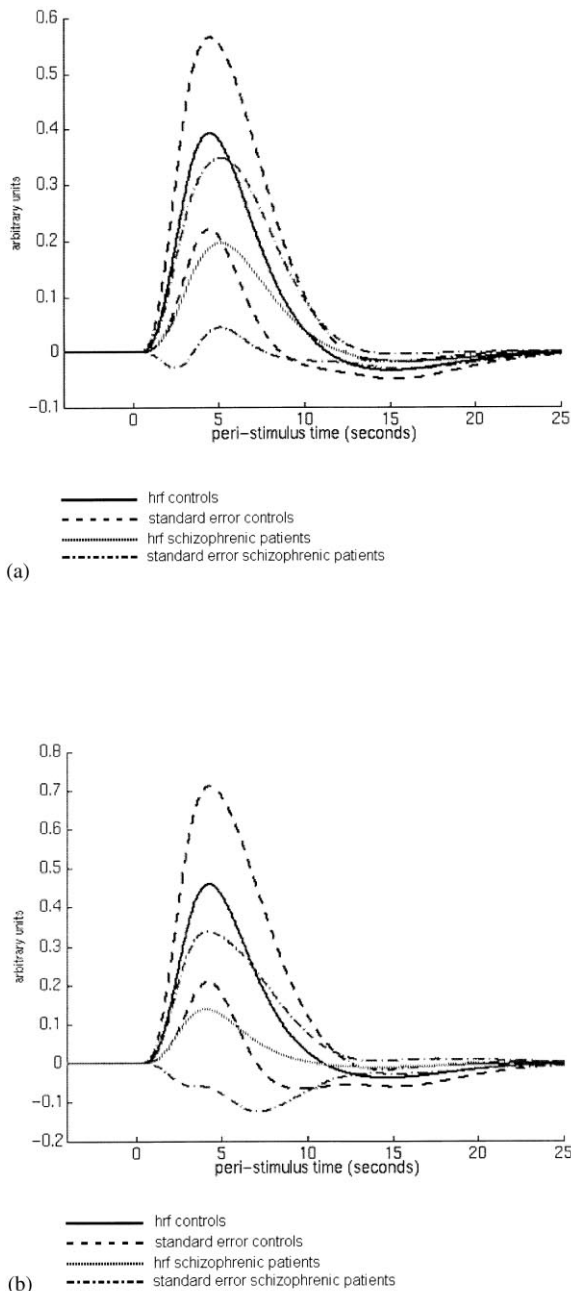


Fig. 2. Grand mean (solid line) and standard error (dashed lines) event-related hemodynamic response function (amplitude in arbitrary units vs. peri-stimulus time) from a voxel located (a) in the right lateral frontal cortex and (b) in the thalamus for control participants (blue) and schizophrenic patients (red). The response is significantly larger for controls than for patients in both regions (see Table 1).

related to motor processing (i.e. left postcentral gyrus) revealed that there were no group differences in the extent or magnitude of activation in the left motor cortex ( $P_s > 0.60$ ).

The results of the group analyses for the controls revealed a significant activation associated with target processing in all 10 cerebral sites that we have previously shown to be activated in another cohort of healthy participants. These results are summarized in Table 1.

#### 4. Discussion

This study was designed to identify the cerebral sites involved with auditory target detection in schizophrenic patients and healthy control participants and to elucidate any abnormalities that may be present in the schizophrenic patients. In accordance with our hypothesis, we observed that there were reductions in both the extent and magnitude of the hemodynamic response to target stimuli for schizophrenic patients, relative to control participants, bilaterally in the anterior superior temporal gyri, inferior parietal lobules, right superior parietal lobule, thalamus, anterior and posterior cingulate, and right lateral frontal cortex. Importantly, there were no group differences in the pattern of activation in left motor cortex (see Fig. 1 for illustration). This latter effect suggests that schizophrenic patients are able to produce activation in motor areas similar in extent and magnitude to that observed in control participants and indicates that the failure to produce activation in the other regions of interest is unlikely to be due to differences in quality of the images between patients and controls.

The observed abnormalities in the schizophrenic patients are consistent with the ERP literature on auditory oddball tasks reporting abnormalities in the P3 response to target stimuli.

A number of ERP studies have implicated the temporal lobes in the generation of the abnormal P3 in schizophrenia (see McCarley et al., 1991 for review). Although we did not observe any hemispheric asymmetries in the hemodynamic response to target stimuli in the temporal lobes, our data are consistent with the notion that temporal lobe abnormalities are present in schizophrenia and that these abnormalities are implicated in generation of the

abnormal P3 response. The regions of interest in the anterior temporal lobes embraced Brodmann areas 38, 21 and 47. Many studies have implicated these regions in working memory and other memory-related processes (recently reviewed by Smith and Jonides, 1997) suggesting that the working memory or contextual updating component of oddball detection may be related to neural activity in these regions. This interpretation is supported by data that show that the reduced amplitude of the P3 response target stimuli in schizophrenia, an effect believed to be related to temporal lobe dysfunction, is correlated with working memory deficits (Shajahan et al., 1997b).

However, the abnormalities in schizophrenic patients embraced many areas. Robust differences between groups were also found in the thalamus, anterior and posterior cingulate and right lateral frontal cortex. Each of these sites has been linked to systems involved with attentional processes (Knight, 1984; Devinsky et al., 1995; Carter et al., 1997; McCarthy et al., 1997; Knight and Nakada, 1998). The electrocortical response to oddball stimuli has long been considered to be related to attentional processes (Donchin, 1981; Donchin and Coles, 1988; Johnson, 1988, 1993; Alexander et al., 1996). In particular, oddball detection requires both sustained attention and selective attention. Both of these aspects of attention are impaired in schizophrenia (see Benes, 1996, for a review). While the localization of different aspects of attention in the brain is still a subject of debate, evidence indicates that anterior cingulate plays an important role in selective attention (Pardo et al., 1990; Vogt et al., 1992; Devinsky et al., 1995). Furthermore, the right lateral frontal cortex has been implicated in sustained attention (Foster et al., 1994). Therefore, the observed abnormalities in these areas potentially reflect the attentional demands of oddball detection.

The present study employed a medicated patient population, raising the possibility that some of the observed differences between groups may be due to the effects of medication. Previous ERP observations indicating that the abnormal neuronal activity associated with oddball detection in schizophrenia is at least partially independent of medication (Eikmeier et al., 1992; Faux et al., 1993; Ford et al., 1994b; Rao et al., 1995) suggest it is likely that at least some of the abnormalities in regional cerebral activity

during oddball detection, observed in this study, are independent of medication status. It is important to note that the patients were slower to respond to target stimuli than were control participants. This raises the possibility that some of the observed hemodynamic differences may be due to this behavioral effect. One might hypothesize that long reaction times in patients may lead to delayed and/or more variable hemodynamic responses than that observed in control participants. Such an effect is seen in single-trial ERP studies of the P3 in schizophrenia (Ford et al., 1994a). However, it would be expected that longer reaction times would have a less marked effect on hemodynamic response because the hemodynamic response occurs over a longer time scale. In our data, a difference in delay in the hemodynamic response would be reflected in a group difference in the temporal derivative term in the modeled response function. We did not observe any significant group differences in this term.

The results from the healthy control participants replicated the results from our previous event-related fMRI studies of auditory oddball processing (Kiehl and Liddle, 1999a,b,d,f,g,h; Kiehl et al., in press). In each of the studies, we observed activation for target processing in the left and right anterior superior temporal gyri, inferior and superior parietal lobules, thalamus, anterior and posterior cingulate, and right lateral frontal cortex. These data strongly suggest that the neural sources underlying the target detection during oddball tasks can be reliably associated with activation in these 10 sites. Extensive activation of association cortex during oddball detection in healthy participants potentially reflects the possibility that it is advantageous to prepare for a flexible response to oddball stimuli (Halgren et al., 1998). Our data indicate that schizophrenic patients do not show this flexibility but tend to activate only the minimal number of areas essential for the performance of the task. This observation is consistent with the hypothesis that schizophrenic patients have difficulty coordinating activity at diverse brain sites. In light of evidence from other studies using different paradigms indicating abnormalities of early processing of auditory signals in schizophrenia (Javitt et al., 1997, 1998), it would potentially have been of interest to examine primary auditory cortex in this study. However, we made no a priori predictions regarding differences in activation

of primary auditory cortex between patients and healthy participants because activation of the primary auditory cortex was not always observed in our previous fMRI studies of auditory oddball processing in healthy participants. None the less, we did perform a supplementary analysis comparing activity in primary auditory cortex in patients and controls and found no significant differences (after correction for multiple comparisons).

The results of this study are consistent with the findings from previous studies that have reported abnormalities of the P3 ERP component in schizophrenia but provide much more detailed information about the locations of abnormal cerebral function. In particular, virtually all of the areas of association cortex that are involved in oddball stimulus detection in healthy subjects, as well as the thalamus, are underactive in the schizophrenic patients. This finding raises the question of whether the observed underactivity at an extensive network of sites arises from a widespread pathological process affecting association cortex and thalamus or, alternatively, from a focal failure at a cardinal site in a network. Other functional imaging studies employing a variety of tasks have revealed abnormal function at diverse sites. For example, schizophrenic patients have been reported to exhibit underactivity in lateral frontal cortex during the Wisconsin Card Sorting test (Weinberger et al., 1988), during word generation (Yurgelun-Todd et al., 1996; Curtis et al., 1998) and during self-selected movements (Spence et al., 1998), underactivity of medial frontal lobe during the Tower of London problem-solving task (Andreasen et al., 1992), underactivity of lateral temporal cortex while monitoring self-generated speech (McGuire et al., 1995), underactivity of parietal cortex during self-selected movements (Spence et al., 1997), and underactivity of frontal cortex, thalamus and cerebellum during memory tasks (Andreasen et al., 1996). Studies of cerebral structure have reported localized abnormalities in medial lobe (Suddath et al., 1989), lateral temporal lobe (Shenton et al., 1992), frontal cortex (Raine et al., 1992) and thalamus (Andreasen et al., 1994), while other studies have reported widespread diminution in gray-matter volume (Zipursky et al., 1992, 1994, 1998). Overall, the balance of the evidence from structural and functional imaging studies supports the hypothesis for a widespread

pathological process affecting many cerebral areas, especially association cortex and thalamus, in schizophrenia. Despite the relative simplicity of the oddball detection task employed in this study, it succeeds in demonstrating abnormalities at many of the sites that have been implicated in the pathophysiology of schizophrenia.

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