

Abnormal Hemodynamics in Schizophrenia During an Auditory Oddball Task

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Background: Schizophrenia is a heterogeneous disorder characterized by diffuse brain abnormalities that affect many facets of cognitive function. One replicated finding in schizophrenia is abnormalities in the neural systems associated with processing salient stimuli in the context of oddball tasks. This deficit in the processing of salience stimuli might be related to abnormalities in orienting, attention, and memory processes.

Methods: Behavioral responses and functional magnetic resonance imaging data were collected while 18 patients with schizophrenia and 18 matched healthy control subjects performed a three-stimulus auditory oddball task.

Results: Target detection by healthy participants was associated with significant activation in all 38 regions of interest embracing distributed cortical and subcortical systems. Similar reproducibility was observed in healthy participants for processing novel stimuli. Schizophrenia patients, relative to control subjects, showed diffuse cortical and subcortical hypofunctioning during target detection and novelty processing, including bilateral frontal, temporal, and parietal cortices and amygdala, thalamus, and cerebellum.

Conclusions: These data replicate and extend imaging studies of target detection in schizophrenia and present new insights regarding novelty processing in the disorder. The results are consistent with the hypothesis that schizophrenia is characterized by a widespread pathologic process affecting many cerebral areas, including cortical, subcortical, and cerebellar circuits.

Key Words: Schizophrenia, fMRI, P3, P300, auditory, oddball, target detection, novel, novelty detection

Patients diagnosed with schizophrenia exhibit impairments in executive control and working memory that stand out against a background of diffuse cognitive abnormalities (Dickinson et al 2004; Liddle 2001). One method to examine updating of working memory and cognitive control is to assess the neural systems associated with processing target stimuli in the context of oddball tasks. In a typical oddball target detection task, the target stimulus ("oddball") occurs much less frequently (i.e., 10%) than the background regular stimuli (i.e., 90%). Successful performance of the oddball task (by correctly responding to the target stimuli) requires contextual updating and working memory (Donchin and Coles 1988). It has long been known that the detection of low-probability target stimuli is associated with sequences of time-locked event-related potentials (ERPs), the most prominent of which is a positive deflection occurring at approximately 300 msec poststimulus (P300 or P3; Sutton et al 1965, 1967). Over the last 30 years, reduced amplitude in the ERPs associated with processing target stimuli in oddball tasks has become one of the most replicated findings in schizophrenia research (Ford et al 1999; Levitt et al 1973; McCarley et al 1991a, 1991b; van der Stelt et al 2004); however, ERP measures are limited because scalp electrical potentials are modified by conduction of electrical current through the volume of the brain, making it difficult to obtain precise information regarding the spatial distribution of the neural activity that is responsible for generation of these electrical potentials (Halgren and Marinkovic 1996; Halgren et al 1998). It might be that more precise informa-

tion regarding the spatial distribution of neural sources involved with target detection might yield more accurate information as to the brain regions implicated in schizophrenia and other disorders (e.g., depression) characterized by abnormal P3.

A number of groups have examined the hemodynamic correlates of target detection by using event-related functional magnetic resonance imaging (fMRI) (Ardekani et al 2002; Casey et al 2001; Clark et al 2000; Horovitz et al 2002; Huettel and McCarthy 2004; Kiehl and Liddle 2003; Kiehl et al 2001a, 2001b; Linden et al 1999; Madden et al 2004; Stevens et al 2000; Strange and Dolan 2001; Strange et al 2000). In general, these studies found that target detection in the context of auditory oddball tasks is associated with activation in spatially distributed cortical and subcortical sites. The sites implicated include bilateral inferior frontal gyrus, bilateral middle and superior temporal gyrus, bilateral inferior and superior parietal lobule, and bilateral amygdala, thalamus, and cerebellum.

There has been one event-related fMRI study of target detection during an auditory oddball task in schizophrenia (Kiehl and Liddle 2001). It was observed that schizophrenic patients, relative to healthy comparison subjects, exhibited reduced activation in multiple frontal, temporal, parietal, and subcortical sites during target detection. Patients also showed excessive target-related activity in right posterior superior temporal gyrus relative to healthy subjects. These data were interpreted as supporting the model that schizophrenia is associated with fronto-temporal disconnection (see also Friston 1999). In a subsequent study, independent component analysis was used to characterize functional connectivity in patients with schizophrenia during an auditory oddball task (Calhoun et al 2004a). Aberrant patterns of connectivity in bilateral temporal lobes were found to reliably differentiate patients with schizophrenia from healthy control subjects at the level of individual participants. In one sample, 97% of subjects were correctly classified into patient or healthy control groups. To test the reliability of the procedure, an additional cohort of patients and control subjects was examined, and it was determined that 94% of participants were correctly classified into patient or healthy control groups. These data suggest that hemodynamic measures during oddball tasks might help to delineate the relevant brain disturbances in schizophrenia.

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The purpose of the present study was to replicate and extend the results of auditory oddball task abnormalities in schizophrenia (Kiehl and Liddle 2001). Previously, only 10 regions of interest were examined for target detection in schizophrenia. Recent large-scale ($n = 100$) fMRI studies have identified nearly 40 distinct cortical and subcortical brain regions in auditory target detection (Kiehl et al, *in press*). This raises the possibility that other brain regions might be implicated in schizophrenia during target detection than were observed in the initial study. Also, in the previous study a three-stimulus auditory oddball task was used (target, novel, and standard stimuli), and group comparisons were only reported for target detection. Studies have shown that novelty processing elicits a P3 ERP with a more fronto-central distribution (i.e., P3a) than the parietally distributed canonical P3 (i.e., P3b) elicited by target stimuli (Courchesne et al 1975). Evidence suggests that the P3a is abnormal in schizophrenia (Grillon et al 1990; Schall et al 1999; van der Stelt et al 2004); however, no studies have examined the underlying hemodynamics associated with novelty processing in oddball paradigms in schizophrenia. Functional MRI studies have identified 35 regions of interest associated with novelty processing in the context of the three-stimulus auditory oddball task in healthy control subjects (Kiehl and Liddle 2003; Kiehl et al 2001a, 2001b, *in press*). In the present study, a larger sample size was used, as well as more advanced image processing analyses, than in the initial study.

The primary hypotheses were that patients with schizophrenia would show diffuse impairments in hemodynamic activity associated with target detection and novelty processing in multiple frontal, temporal, parietal, and subcortical sites relative to matched control subjects. It was hypothesized that patients with schizophrenia would exhibit excessive target-related activity in right posterior superior temporal gyrus. It was also hypothesized that patients with schizophrenia would show hemodynamic activity at levels similar to those observed in healthy control subjects in motor regions, consistent with the fact that participants were required to indicate the presence of target stimuli with a button press, using their right index finger. This latter "internal physiological standard" is useful in that if patients activate some brain areas at levels similar to those of control subjects it is likely that the differences in brain activation in other areas are regional effects and are not due to methodologic issues, such as performance or image quality (for more on this issue, see Callicott et al 1998).

Methods and Materials

Participants

Twenty-one medicated outpatients with schizophrenia and 21 healthy matched control subjects provided written informed consent and volunteered for the study (10 other patients were approached to participate but declined). Schizophrenia was diagnosed on the basis of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al 1997). The National Adult Reading Test (NART) was used to estimate premorbid intelligence (Nelson and O'Connell 1978; Sharpe and O'Carroll 1991), and the Quick Test was used to estimate current intellectual functioning (Ammons and Ammons 1962, 1979). Healthy participants and their first-degree relatives were free of any Axis I disorder, as assessed with the SCID screening device (First et al 2002). No patient or control subject met criteria for drug or alcohol abuse or dependence. Three patients were excluded for either poor performance on the auditory oddball task or exces-

sive head motion (greater than one voxel rotation or translation). The respective matched control subjects were excluded to preserve equal sample sizes. The remaining sample of 18 patients with schizophrenia and 18 healthy control subjects comprised equal numbers of men and women in the two groups (14 men). One patient refused cognitive assessment. There were no differences between the two groups in terms of age (mean [SD]: control subjects, 36.06 [11.5] years; patients, 34.83 [11.1] years) or Quick scores (control subjects, 116.6 [5.73]; patients, 110.5 [9.9]); however, control subjects had slightly higher NART scores than patients [control subjects, 116.4 (6.35); patients, 109.2 (11.4); $t(33) = -2.2, p < .04$]. All of the schizophrenic patients were receiving treatment with atypical antipsychotic medication, seven patients were also taking mood stabilizers, and six were taking antidepressants. Two patients admitted to being noncompliant with their medications. All participants were right handed (Annett 1970), and all reported normal hearing. All experimental procedures met with the Institute of Living/Hartford Hospital institutional ethical approval.

Symptomology

On the day of scanning, a trained staff member evaluated the symptoms experienced by the patients with schizophrenia during the preceding week, using the Signs and Symptoms of Psychotic Illness (SSPI) interview schedule (Liddle et al 2002). The SSPI comprises 20 symptom items scored 0 to 4 according to the severity of the symptom. Syndrome (i.e., symptom cluster) scores were calculated from the items based on the factor loadings described for the SSPI in Liddle et al (2002). The mean syndrome scores for Reality Distortion, Disorganization, and Psychomotor Poverty were 4.4, 1.6, and 4.6, respectively.

Procedure, Task, and Stimuli

The auditory oddball task was nearly identical to that used in our previous event-related fMRI studies in health and psychopathology (Kiehl and Liddle 2001, 2003; Kiehl et al 2001a, 2001b). Two runs of stimuli were presented to the participant by a computer-controlled auditory sound system that delivers the auditory stimuli with insert earphones embedded within 30-dB sound-attenuating MR-compatible headphones. The standard stimulus was a 500-Hz tone (80% of trials), the target stimulus was a 1000-Hz tone (10% of trials; 48 total events), and the novel stimuli (10% of trials; 48 total events) were nonrepeating random digital noises (e.g., tone sweeps, whistles). All stimuli were presented at approximately 80 dB for 200 msec. All participants reported that they could hear the stimuli and discriminate them from the background scanner noise.

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 standard tones or the novel stimuli. Before beginning the task, each participant performed a practice block of 10 trials to ensure understanding of the instructions. A commercially available MRI-compatible fiber-optic response device (Lightwave Medical, Vancouver, British Columbia, Canada) was used to acquire behavioral responses. Reaction times were computed on trials for which the participant responded correctly within 1500 msec poststimulus. Omission errors included any missed target tones or any response with a latency of greater than 1500 msec after the onset of the target stimulus. Errors of commission were defined as responses after the frequent standard or novel stimuli within 1500 msec of stimulus onset.

Imaging Parameters

Imaging was implemented on a standard clinical GE 1.5-T system (GE Medical Systems, Milwaukee, Wisconsin). Functional image volumes were collected with a gradient-echo sequence (repetition time/echo time 3000msec/40 msec, flip angle 90°, field of view 24 × 24 cm, 64 × 64 matrix, 62.5-kHz bandwidth, 3.75 × 3.75-mm in-plane resolution, 5-mm slice thickness, 29 slices) covering the entire brain (145 mm). The two stimulus runs consisted of 167 time points, prefaced by a 12-sec rest period that was collected to allow for T1 effects to stabilize. These initial four images were not included in any subsequent analyses.

Functional images were reconstructed off-line and reoriented approximately to the anterior commissure–posterior commissure plane. Functional image runs were realigned with INRIAlign, a motion-correction algorithm unbiased by local signal changes (Freire and Mangin 2001; Freire et al 2002). After realignment, a mean functional image was computed for each run. The mean echo planar imaging (EPI) image was matched to the EPI template provided with Statistical Parametric Mapping 2 (SPM2; Wellcome Department of Imaging Neuroscience). The spatial transformation into standard Montreal Neurological Institute (MNI) space was determined with a tailored algorithm with both linear and nonlinear components (Friston et al 1995). This transformation was then applied to the corresponding functional images that were resliced into 4 × 4 × 4-mm resolution in MNI space. The normalized data were smoothed (12 mm full width at half maximum), and a fifth-order infinite impulse response Butterworth low-pass filter of .16 Hz was applied to remove any high-frequency noise. The data were then analyzed with a canonical hemodynamic response and temporal derivative in SPM2. The modeled composite hemodynamic response for each run was derived by extracting stimulus-onset timings for only those events that each participant responded to correctly (e.g., targets with correct button-presses within 1500 msec poststimulus, or correctly ignored standard and novel stimuli within this 0–1500-msec window). Thus, every participant had an fMRI time series model specific to his or her behavioral response patterns. To reduce the impact of spatially varying hemodynamic delays and delays due to slice timing differences, the true amplitude of the hemodynamic response, which is a function of both the nonderivative and derivative terms, was calculated (Calhoun et al 2004b). A high-pass filter (cutoff period, 116 sec) was incorporated into the model to remove noise associated with low-frequency confounds (e.g., respiratory artifact, scanner drift). Importantly, no within-session scaling (also called proportional scaling) was used to avoid the well-known artifacts that it can produce (see Aguirre et al 1998; Desjardins et al 2001). Standard stimuli were modeled and used as baseline for all group comparisons. To assess the stability of the standard stimuli as baseline, we also report the hemodynamic activity associated with processing the standard stimuli in both groups. For both groups, contrasts were specified that evaluated the effects of 1) target stimuli relative to the standard baseline; 2) novel stimuli relative to the standard stimulus baseline; and 3) standard stimuli relative to the implicit baseline. The images containing these amplitudes were then entered into the second-level analyses (i.e., random-effects analyses). A priori hypotheses were tested in 38 and 35 regions of interest associated with target detection and novelty processing, respectively. The regions of interest were 8-mm spheres centered on the center of the coordinate of the region of interest. For purposes of comparison with an fMRI study of oddball detection in schizophrenia (Kiehl and Liddle 2001), we report uncorrected *p* values for all comparisons; however, the search volume

examined included multiple voxels, and thus we also report *p* values corrected for multiple comparisons for the small volume examined (Worsley et al 1996).

Results

Behavioral Data

There were no significant behavioral differences between groups for percentage of correct hits (patients 96.2 [8.7]; control subjects 99.9 [4.9]), percentage of novel stimuli correctly rejected (patients 92.6 [9.0]; control subjects 96.3 [6.0]), or percentage of standard stimuli correctly rejected (patients 99.1 [3.28]; control subjects 99.9 [1.13]; all *p* > .10). Control subjects responded to target stimuli faster than did patients [$t(34) = 3.63, p < .001$]. The mean (SD) reaction times were 377.0 (85.0) msec and 512.7 (133.8) msec for control subjects and patients, respectively.

Imaging Data

Healthy Control Subjects: Areas of Activation for Target Stimuli Relative to Standard Stimuli. Consistent with the hypotheses, control participants demonstrated highly significant (*p* < .0001) activation in all regions of interest associated with processing of target stimuli (see Table 1, Figure 1). In the frontal lobes, these regions included bilateral middle and inferior frontal gyrus, anterior and posterior cingulate, medial frontal gyrus, insula, and precentral gyrus. In the parietal lobe, significant activation was observed for target detection in postcentral gyrus, inferior and superior parietal lobule, posterior cingulate, and cuneus. Consistent with the modality of stimulus presentation, extensive activation was observed in bilateral inferior, middle, and superior temporal gyrus. Strong activity was also observed in bilateral amygdala, thalamus, putamen, and cerebellum, and in midbrain.

Schizophrenia Patients: Areas of Activation for Target Stimuli Relative to Standard Stimuli. Patients with schizophrenia exhibited weak, but nevertheless suprathreshold, activity in many of our a priori regions of interest for target detection. Suprathreshold activity was observed in bilateral inferior frontal gyrus, anterior cingulate, right insula, bilateral inferior and superior parietal lobule, left superior temporal gyrus, right middle and inferior temporal gyrus, right amygdala, bilateral lingual gyrus, bilateral thalamus, and bilateral cerebellum. Patients failed to demonstrate significant hemodynamic activity in bilateral middle frontal gyrus, left insula, posterior cingulate, precuneus, left middle and inferior temporal gyrus, left amygdala, and bilateral putamen. Consistent with previous work, patients demonstrated highly significant activity in left precentral gyrus, medial frontal cortex, and right cerebellum, consistent with the fact that target detection was associated with a right index finger button press.

Group Comparisons: Target Stimuli. Consistent with prior work, control subjects demonstrated significantly larger hemodynamic responses for target stimuli than patients with schizophrenia in left middle frontal gyrus, left inferior parietal lobule, posterior cingulate, right middle temporal gyrus, thalamus, and cerebellum. Group differences in bilateral parietal lobule reached only trend levels (left, *p* < .14; right *p* < .10) after correcting for the search region examined (both regions were significant at the same threshold used in Kiehl and Liddle 2001). Additional regions that were found to be reduced in schizophrenia patients relative to control subjects during target detection include right middle frontal gyrus, bilateral insula, left postcentral

Table 1. Summary Results of the Comparison of Target Stimuli Versus the Standard Stimulus Baseline

Anatomic Region	x	y	z	Healthy Control Subjects	Schizophrenia Patients	Control Subjects vs. Schizophrenia Patients
Frontal Lobes				(<i>t</i> = 17)	(<i>t</i> = 17)	(<i>t</i> = 34)
1 R superior/middle frontal gyrus (26, 52, 30; <i>p</i> < .001)	24	52	28	7.67582 (<i>p</i> < .00000) un (<i>p</i> < .00001) fw	2.51944 (<i>p</i> < .01097) un (<i>p</i> < .11561) fw	3.24454 (<i>p</i> < .00132) un (<i>p</i> < .02206) fw
2 Anterior cingulate gyrus (0, 16, 40; <i>p</i> < .01)	0	16	40	8.72042 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	4.25777 (<i>p</i> < .00027) un (<i>p</i> < .00763) fw	1.65555 (<i>p</i> < .052100) un (<i>p</i> < .292800) fw
Parietal Lobes						
3 L inferior parietal/supramarginal gyrus (−56, −41, 30; <i>p</i> < .01)	−56	−40	32	12.12951 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	4.68638 (<i>p</i> < .00011) un (<i>p</i> < .00350) fw	3.08136 (<i>p</i> < .00203) un (<i>p</i> < .03085) fw
4 L superior parietal oobule (−38, −48, 60; ns)	−36	−48	60	12.08447 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	5.6386 (<i>p</i> < .00001) un (<i>p</i> < .00049) fw	2.18695 (<i>p</i> < .01770) un (<i>p</i> < .14728) fw
5 R superior parietal lobule (24, −60, 55; <i>p</i> < .01)	24	−60	56	7.65288 (<i>p</i> < .00000) un (<i>p</i> < .00001) fw	3.93078 (<i>p</i> < .00054) un (<i>p</i> < .01314) fw	2.45691 (<i>p</i> < .00959) un (<i>p</i> < .09714) fw
6 R inferior parietal/supramarginal gyrus (64, −34, 25; <i>p</i> < .001)	64	−32	24	8.58437 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	5.774 (<i>p</i> < .00001) un (<i>p</i> < .00037) fw	1.93034 (<i>p</i> < .03050) un (<i>p</i> < .20775) fw
7 Posterior cingulate gyrus (0, −30, 30; <i>p</i> < .05)	0	−28	28	6.90455 (<i>p</i> < .00000) un (<i>p</i> < .00004) fw	2.40897 (<i>p</i> < .01372) un (<i>p</i> < .13373) fw	3.87612 (<i>p</i> < .00023) un (<i>p</i> < .00543) fw
Temporal Lobes						
8 L superior temporal gyrus (−56, 11, −15; <i>p</i> < .001)	−52	12	−16	10.09554 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	4.84481 (<i>p</i> < .00008) un (<i>p</i> < .00250) fw	3.79618 (<i>p</i> < .00029) un (<i>p</i> < .00654) fw
9 R superior/middle temporal gyrus (52, 19, −15; <i>p</i> < .01)	52	−20	−12	9.96183 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	3.36447 (<i>p</i> < .00184) un (<i>p</i> < .03304) fw	3.99159 (<i>p</i> < .00017) un (<i>p</i> < .00414) fw
Deep Gray						
10 R thalamus (3, −17, 5; <i>p</i> < .001)	8	−16	8	6.56676 (<i>p</i> < .00000) un (<i>p</i> < .00008) fw	3.54878 (<i>p</i> < .00123) un (<i>p</i> < .02458) fw	3.99281 (<i>p</i> < .00017) un (<i>p</i> < .00413) fw
Motor Areas						
11 L postcentral gyrus (−26, −44, 65; ns)	−24	−44	64	10.39021 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	4.29963 (<i>p</i> < .00024) un (<i>p</i> < .00711) fw	2.85212 (<i>p</i> < .00366) un (<i>p</i> < .04828) fw
Additional Regions from Kiehl et al (Unpublished Data)						
Frontal Lobes						
12 L superior/middle frontal gyrus	−28	48	28	6.87617 (<i>p</i> < .00000) un (<i>p</i> < .00004) fw	2.97386 (<i>p</i> < .00425) un (<i>p</i> < .06047) fw	3.77671 (<i>p</i> < .00031) un (<i>p</i> < .00684) fw
13 L middle frontal gyrus	−40	40	24	11.01741 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	2.88557 (<i>p</i> < .00512) un (<i>p</i> < .06896) fw	2.64227 (<i>p</i> < .00616) un (<i>p</i> < .07086) fw
14 L inferior frontal gyrus (1984 cm ³ ; 31 voxels)	−60	8	24	5.86085 (<i>p</i> < .00001) un (<i>p</i> < .00029) fw	5.0046 (<i>p</i> < .00005) un (<i>p</i> < .00168) fw	Nonsignificant
15 L inferior frontal gyrus	−56	−24	12	10.1238 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	6.26916 (<i>p</i> < .00000) un (<i>p</i> < .00014) fw	2.87118 (<i>p</i> < .00349) un (<i>p</i> < .04657) fw
16 R inferior frontal gyrus	56	12	24	5.9832 (<i>p</i> < .00001) un (<i>p</i> < .00024) fw	3.93921 (<i>p</i> < .00053) un (<i>p</i> < .01296) fw	2.07075 (<i>p</i> < .02276) un (<i>p</i> < .17321) fw
17 L precentral gyrus	−36	−24	64	9.50054 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	6.83335 (<i>p</i> < .00000) un (<i>p</i> < .00005) fw	Nonsignificant

Table 1. (continued)

Anatomic Region	x	y	z	Healthy Control Subjects	Schizophrenia Patients	Control Subjects vs. Schizophrenia Patients
18 L precentral gyrus	-36	-32	64	10.50705 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	6.58351 (<i>p</i> < .00000) un (<i>p</i> < .00008) fw	1.80391 (<i>p</i> < .03926) un (<i>p</i> < .24140) fw
19 R precentral gyrus	36	-4	60	5.51131 (<i>p</i> < .00002) un (<i>p</i> < .00063) fw	3.46666 (<i>p</i> < .00147) un (<i>p</i> < .02806) fw	Nonsignificant
20 Medial frontal gyrus	0	-8	56	8.71341 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	4.45072 (<i>p</i> < .00018) un (<i>p</i> < .00553) fw	1.83857 (<i>p</i> < .03667) un (<i>p</i> < .23197) fw
21 L insula	-40	20	-12	10.09625 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	2.28848 (<i>p</i> < .01744) un (<i>p</i> < .15575) fw	3.69434 (<i>p</i> < .00039) un (<i>p</i> < .00825) fw
22 R insula	44	24	-12	6.8596 (<i>p</i> < .00000) un (<i>p</i> < .00005) fw	4.04894 (<i>p</i> < .00042) un (<i>p</i> < .01080) fw	4.81042 (<i>p</i> < .00002) un (<i>p</i> < .00050) fw
Parietal Lobes						
23 L postcentral gyrus	-56	-20	20	11.01741 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	6.89179 (<i>p</i> < .00000) un (<i>p</i> < .00004) fw	2.77188 (<i>p</i> < .00448) un (<i>p</i> < .05609) fw
24 R postcentral gyrus	64	-20	24	7.9999 (<i>p</i> < .00000) un (<i>p</i> < .00001) fw	5.92571 (<i>p</i> < .00001) un (<i>p</i> < .00027) fw	2.49355 (<i>p</i> < .00880) un (<i>p</i> < .09143) fw
25 Precuneus	0	-44	52	7.46548 (<i>p</i> < .00000) un (<i>p</i> < .00002) fw	2.31056 (<i>p</i> < .01669) un (<i>p</i> < .15154) fw	3.55365 (<i>p</i> < .00057) un (<i>p</i> < .01132) fw
Temporal Lobes						
26 L middle temporal gyrus (2,048 cm ³ ; 32 voxels)	-60	-56	4	5.83558 (<i>p</i> < .00001) un (<i>p</i> < .00032) fw	2.45562 (<i>p</i> < .01248) un (<i>p</i> < .12584) fw	2.75032 (<i>p</i> < .00472) un (<i>p</i> < .05835) fw
27 L inferior temporal gyrus	-52	-16	-16	4.01352 (<i>p</i> < .00045) un (<i>p</i> < .01253) fw	Nonsignificant	2.95214 (<i>p</i> < .00284) un (<i>p</i> < .03985) fw
28 R inferior temporal gyrus (2,048 cm ³ ; 32 voxels)	56	-64	4	5.00114 (<i>p</i> < .00005) un (<i>p</i> < .00180) fw	4.03873 (<i>p</i> < .00043) un (<i>p</i> < .01099) fw	2.98471 (<i>p</i> < .00261) un (<i>p</i> < .03739) fw
29 L amygdala/parahippocampal gyrus	-16	-4	-20	8.49763 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	3.12748 (<i>p</i> < .00306) un (<i>p</i> < .04787) fw	3.04288 (<i>p</i> < .00225) un (<i>p</i> < .03333) fw
30 R amygdala/parahippocampal gyrus	20	-4	-20	9.37928 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	3.58492 (<i>p</i> < .00114) un (<i>p</i> < .02318) fw	2.49492 (<i>p</i> < .00877) un (<i>p</i> < .09122) fw
Occipital Lobe						
31 L lingual gyrus/cuneus	-12	-72	4	9.01995 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	3.89792 (<i>p</i> < .00058) un (<i>p</i> < .01388) fw	6.50833 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw
32 R lingual gyrus/cuneus	20	-72	8	6.7667 (<i>p</i> < .00000) un (<i>p</i> < .00005) fw	3.29309 (<i>p</i> < .00214) un (<i>p</i> < .03699) fw	3.34264 (<i>p</i> < .00101) un (<i>p</i> < .01793) fw
Deep Gray						
33 L thalamus	-8	-20	4	7.53456 (<i>p</i> < .00000) un (<i>p</i> < .00001) fw	3.63596 (<i>p</i> < .00102) un (<i>p</i> < .02134) fw	2.93822 (<i>p</i> < .00294) un (<i>p</i> < .04094) fw
34 L putamen/globus pallidus	-36	0	-4	8.92523 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	3.19621 (<i>p</i> < .00264) un (<i>p</i> < .04304) fw	2.93972 (<i>p</i> < .00293) un (<i>p</i> < .04082) fw
35 R putamen/globus pallidus	24	0	0	7.97216 (<i>p</i> < .00000) un (<i>p</i> < .00001) fw	2.50632 (<i>p</i> < .01126) un (<i>p</i> < .11766) fw	3.72714 (<i>p</i> < .00035) un (<i>p</i> < .00766) fw

Table 1. (continued)

Anatomic Region	x	y	z	Healthy Control Subjects	Schizophrenia Patients	Control Subjects vs. Schizophrenia Patients
Cerebellum						
36 L cerebellum	-20	-64	-24	10.23544 ($p < .00000$) un ($p < .00000$) fw	4.65268 ($p < .00011$) un ($p < .00376$) fw	3.93633 ($p < .00019$) un ($p < .00472$) fw
37 R cerebellum	20	-52	-28	14.27947 ($p < .00000$) un ($p < .00000$) fw	6.66164 ($p < .00000$) un ($p < .00007$) fw	3.8503 ($p < .00025$) un ($p < .00577$) fw
Brainstem						
38 Brainstem	0	-24	-24	6.87617 ($p < .00000$) un ($p < .00004$) fw	4.53745 ($p < .00015$) un ($p < .00478$) fw	5.77158 ($p < .00000$) un ($p < .00003$) fw

Results are presented for all 38 regions of interest identified as associated with target detection in healthy control subjects (Kiehl and Liddle 2003; Kiehl et al 2001a, 2001b, in press). For comparison purposes, the first 10 regions of interest listed are from our initial functional magnetic resonance imaging study of target detection in schizophrenia (Kiehl and Liddle 2001). Original Montreal Neurological Institute (MNI) coordinates and p values from the comparison in which patients showed reduced amplitude of the hemodynamic response for target detection compared with control subjects in the initial study are listed in The "Anatomic Region" column. For all regions of interest, the columns depict anatomic region, MNI coordinates (x, y, z), and t scores for comparisons of healthy control subjects versus baseline (see also Figure 1, left panel), patients with schizophrenia versus baseline (Figure 1, left middle panel); and the comparison in which healthy control subjects showed greater hemodynamic activity for target detection than did patients with schizophrenia (Figure 1, right middle panel). Two p values are reported under the respective t scores. The first p value (un) is an uncorrected p value identical to that used in our initial schizophrenia study of target detection (Kiehl and Liddle 2001). Also reported is a p value (fw) after correcting for the search volume examined using the family-wise error rate as implemented in Statistical Parametric Mapping 2. Note that the size (cubic millimeters and number of $4 \times 4 \times 4$ -mm voxels) of each region of interest was 2112 cm^3 (33 voxels) unless otherwise specified. In some cases the region of interest was reduced due to the overlap with non-brain voxels, R, right; L, left.

gyrus, precuneus, bilateral superior, middle, and inferior temporal gyrus, left amygdala, bilateral lingual gyrus, putamen, cerebellum, and brainstem (see Table 1).

There was also subtle evidence of excessive target-related activity in schizophrenia patients relative to control subjects in bilateral precentral gyrus and bilateral inferior lateral frontal gyrus (see Figure 1); however, these latter effects were nonsignificant after correcting for searching the entire brain.

Healthy Control Subjects: Areas of Activation for Novel Stimuli Relative to Standard Stimuli. Novelty processing elicited significant activation in nearly all a priori regions of interest. One region, left anterior cingulate, reached only trend levels ($p < .056$). These data are illustrated in Figure 2 and summarized in Table 2.

Schizophrenia Patients: Areas of Activation for Novel Stimuli Relative to Standard Stimuli. Novelty processing in patients with schizophrenia was associated with suprathreshold activity in bilateral postcentral gyrus, bilateral superior temporal gyrus,

right middle temporal gyrus, bilateral inferior frontal gyrus, and bilateral lingual gyrus. Patients failed to show significant activity in bilateral frontal cortex, anterior cingulate, some temporal lobe sites, and thalamus.

Group Comparisons: Novel Stimuli. Patients with schizophrenia showed significantly smaller hemodynamic response for novel stimuli than was observed in control subjects in right inferior frontal gyrus, left insula, bilateral postcentral gyrus, right superior temporal gyrus, left middle temporal gyrus, bilateral inferior temporal gyrus, left lingual gyrus, bilateral thalamus, bilateral inferior parietal lobule, and left cerebellum (Table 2).

Healthy Control Subjects: Areas of Activation for Standard Stimuli Relative to Implicit Baseline. Standard stimuli, the baseline for the above comparisons, elicited activity in bilateral primary auditory cortex.

Schizophrenia Patients: Areas of Activation for Standard Stimuli Relative to Implicit Baseline. Standard stimuli elicited activity in bilateral primary auditory cortex.

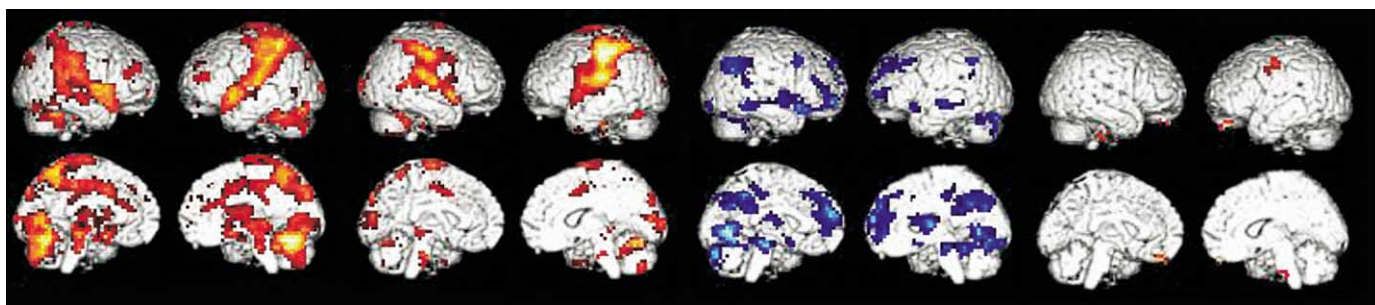


Figure 1. Hemodynamic activity elicited by auditory target stimuli in 18 schizophrenia patients and 18 matched healthy control subjects. The panels illustrate the areas of activation for target processing relative to standard stimulus baseline for healthy control subjects (far left) and schizophrenia patients (middle left). Areas where schizophrenia patients exhibit diminished activity relative to control subjects are illustrated in blue color maps (middle right); regions where patients exhibit excessive activity relative to control subjects are shown in the far right panel. The threshold for the far left panel is $p < .000001$; left middle, $p < .001$; right middle, $p < .001$; far right, $p < .05$. Complete statistical results are presented in Table 1.

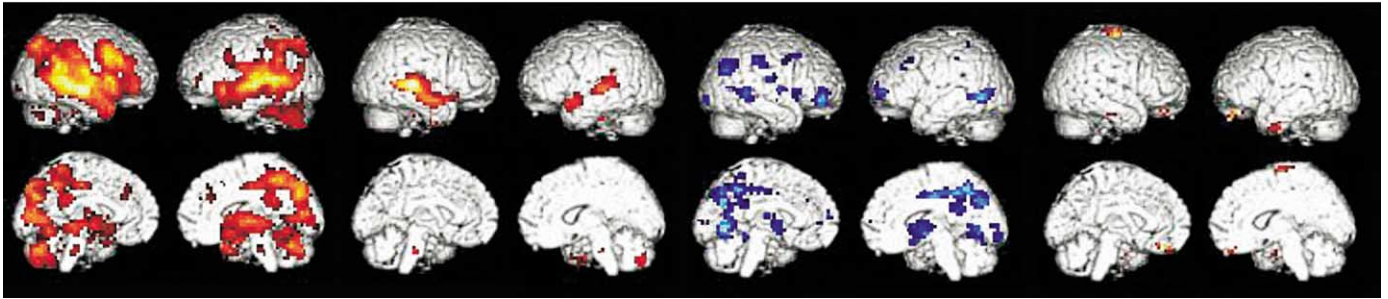


Figure 2. Hemodynamic activity elicited by auditory novel stimuli in 18 schizophrenia patients and 18 matched healthy control subjects. The panels illustrate of the areas of activation for target processing relative to standard stimulus baseline for healthy control subjects (far left) and schizophrenia patients (middle left). Areas where schizophrenia patients exhibit diminished activity relative to control subjects are illustrated in blue color maps (middle right); regions where patients exhibit excessive activity relative to control subjects are shown in the far right panel. The threshold for the far left panel is $p < .001$; left middle, $p < .001$; right middle, $p < .001$; far right, $p < .05$. Complete statistical results are presented in Table 2.

Group Comparisons: Standard Stimuli. There were no group differences, even at conservative uncorrected thresholds, in hemodynamic activity for the standard stimuli.

Discussion

This study was designed to replicate and extend previous results of abnormal hemodynamic activity during auditory target detection in patients with schizophrenia. In accordance with the hypotheses, schizophrenia was associated with reductions in the magnitude of the hemodynamic response to target stimuli in multiple frontal, temporal, parietal, subcortical, and cerebellar sites. Previously, one fMRI study (Kiehl and Liddle 2001), which examined a limited number of brain regions, identified nine sites in which patients showed reduced hemodynamic activity compared with control subjects during target detection. As illustrated in Figure 1 and reported in Table 1, all nine of these regions of interest were found to show reduced hemodynamic activity for target detection in patients relative to control subjects in the current sample, replicating prior research (Kiehl and Liddle 2001). It should be noted, however, that when a stringent correction for multiple comparisons was performed, only six of the nine sites remained significant. The regions that showed highly consistent reductions in hemodynamic activity across samples include right lateral frontal cortex, left supramarginal gyrus, posterior cingulate, bilateral anterior superior temporal gyrus, and thalamus. Subsequent research of target detection has identified nearly 40 brain regions that show reliable activation for target detection in healthy control subjects (Kiehl and Liddle 2003; Kiehl et al 2001a, 2001b, in press). Examination of these additional sites revealed more brain regions in which patients with schizophrenia showed reduced hemodynamic activity for target detection than did healthy participants. These regions included left inferior and superior frontal gyrus, bilateral insula, bilateral inferior temporal gyrus, left amygdala, precuneus, brainstem, and bilateral lingual gyrus, putamen, and cerebellum (see lower section of Table 1). Thus, these results replicate and extend our previous fMRI study of target detection deficits in schizophrenia (Kiehl and Liddle 2001) and support the notion that schizophrenia is characterized by diffuse brain abnormalities in multiple frontal, temporal, parietal, cerebellar, and subcortical sites. These results also suggest that fMRI studies of target detection are useful probes of the integrity of these multiple brain regions in psychopathology in general and schizophrenia in particular.

Patients also demonstrated abnormal hemodynamic activity during processing of low-probability, task-irrelevant novel stimuli. Deficits in hemodynamic activity for processing novel stimuli were observed in patients with schizophrenia, relative to control subjects, in multiple frontal regions, including right middle and inferior frontal gyrus, bilateral inferior parietal lobule, posterior cingulate, left inferior temporal gyrus, right middle temporal gyrus, bilateral thalamus, and cerebellum. Taken collectively with the findings of auditory target detection, these data suggest that schizophrenia is associated with disturbances in hemodynamic activity in diffuse cortical and subcortical sites during processing of salient target and novel stimuli. Target detection and novelty processing are classically associated with a host of cognitive processes. Target detection, for example, includes sensory processing, attention, working memory, contextual updating, response selection, response monitoring, and motor control. Processing of novel stimuli requires sensory processing, attention, working memory, response selection, and response inhibition. There is a substantial literature on these latter processes in schizophrenia illustrating abnormalities.

Processing of target and novel stimuli are also known to engage an "orienting reflex" or "orienting processes" (Sokolov 1963). The orienting reflex is associated with an increase in the level of arousal, including electroencephalogram desynchronization, skin conductance increases, and heart rate modulations (Mesulam 2000). Sokolov (1963) postulated that the orienting reflex required an interaction between neocortical and brainstem reticular components. These latter circuits are commonly referred to as the ascending reticular activating system, which is a system that is believed to interact with nearly all regions of the brain. Indeed, nearly 40 distinct brain regions show time-locked hemodynamic activity for processing salient target stimuli (Kiehl et al, in press). More than 30 regions, often overlapping with areas implicated in target detection, are associated with novelty detection. One interpretation of these hemodynamic data is that they might be the neural manifestation of the orienting reflex; however, this interpretation might be too simplistic.

It was Halgren and colleagues who identified many of the neural regions associated with target detection and novelty processing by using intracranial electrical recording techniques in patients about to undergo neurosurgery for the treatment of intractable epilepsy (Baudena et al 1995; Clarke et al 1999a, 1999b; Halgren 1980; Halgren et al 1995a, 1995b). These studies observed that target detection and novelty processing were associated with time-locked electrical activity in nearly all brain

Table 2. Summary of the Significant Areas of Activation for the Comparison of Novel Stimuli Versus the Standard Baseline

Anatomic Region	x	y	z	Healthy Control Subjects	Schizophrenia Patients	Control Subjects vs. Schizophrenia Patients
Frontal Lobes						
1 L middle/inferior frontal gyrus (2,048 cm ³ ; 32 voxels)	-56	16	24	4.54268 (<i>p</i> < .00014) un (<i>p</i> < .00461) fw	2.127 (<i>p</i> < .02389) un (<i>p</i> < .21150) fw	Nonsignificant
2 R middle/inferior frontal gyrus	52	16	24	8.26455 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	2.92054 (<i>p</i> < .00476) un (<i>p</i> < .07548) fw	3.18926 (<i>p</i> < .00153) un (<i>p</i> < .02713) fw
3 L inferior frontal gyrus/insula	-36	16	-8	5.58356 (<i>p</i> < .00002) un (<i>p</i> < .00054) fw	2.31021 (<i>p</i> < .01671) un (<i>p</i> < .17106) fw	1.92049 (<i>p</i> < .03111) un (<i>p</i> < .22418) fw
4 R inferior frontal gyrus/insula	36	24	-8	6.5498 (<i>p</i> < .00000) un (<i>p</i> < .00008) fw	2.84034 (<i>p</i> < .00564) un (<i>p</i> < .08474) fw	2.84504 (<i>p</i> < .00373) un (<i>p</i> < .05333) fw
5 Medial frontal gyrus	0	24	48	4.02888 (<i>p</i> < .00044) un (<i>p</i> < .01287) fw	Nonsignificant	Nonsignificant
6 L anterior cingulate gyrus	-4	8	36	3.10385 (<i>p</i> < .00322) un (<i>p</i> < .05628) fw	Nonsignificant	2.58538 (<i>p</i> < .00707) un (<i>p</i> < .08485) fw
7 R anterior cingulate gyrus	4	28	32	4.10129 (<i>p</i> < .00037) un (<i>p</i> < .01142) fw	Nonsignificant	2.25331 (<i>p</i> < .01528) un (<i>p</i> < .14376) fw
8 L insula	-40	-4	4	5.46301 (<i>p</i> < .00002) un (<i>p</i> < .00069) fw	Nonsignificant	Nonsignificant
9 R precentral gyrus	40	8	28	6.28461 (<i>p</i> < .00000) un (<i>p</i> < .00014) fw	2.83316 (<i>p</i> < .00572) un (<i>p</i> < .08561) fw	3.20679 (<i>p</i> < .00146) un (<i>p</i> < .02617) fw
Parietal Lobes						
10 L postcentral gyrus	-60	-20	20	7.43397 (<i>p</i> < .00000) un (<i>p</i> < .00002) fw	3.20977 (<i>p</i> < .00257) un (<i>p</i> < .04896) fw	2.81804 (<i>p</i> < .00399) un (<i>p</i> < .05608) fw
11 L postcentral gyrus	64	-20	20	9.01576 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	4.87012 (<i>p</i> < .00007) un (<i>p</i> < .00237) fw	3.96743 (<i>p</i> < .00018) un (<i>p</i> < .00485) fw
12 R postcentral gyrus	-52	-40	36	4.92361 (<i>p</i> < .00006) un (<i>p</i> < .00212) fw	1.76706 (<i>p</i> < .04647) un (<i>p</i> < .30365) fw	3.00738 (<i>p</i> < .00246) un (<i>p</i> < .03908) fw
13 L superior parietal lobule	56	-36	48	5.86933 (<i>p</i> < .00001) un (<i>p</i> < .00031) fw	2.65505 (<i>p</i> < .00830) un (<i>p</i> < .10976) fw	3.5561 (<i>p</i> < .00057) un (<i>p</i> < .01240) fw
14 R posterior cingulate gyrus	4	-36	24	6.11282 (<i>p</i> < .00001) un (<i>p</i> < .00019) fw	Nonsignificant	3.91254 (<i>p</i> < .00021) un (<i>p</i> < .00551) fw
15 L inferior parietal lobe	-40	-52	44	6.04741 (<i>p</i> < .00001) un (<i>p</i> < .00022) fw	Nonsignificant	3.24475 (<i>p</i> < .00132) un (<i>p</i> < .02419) fw
16 R inferior parietal lobe	36	-64	44	8.1786 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	2.0726 (<i>p</i> < .02651) un (<i>p</i> < .22447) fw	3.82933 (<i>p</i> < .00026) un (<i>p</i> < .00669) fw
Temporal Lobes						
17 L superior temporal gyrus (2,048 cm ³ ; 32 voxels)	-64	-36	8	8.38135 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	5.27049 (<i>p</i> < .00003) un (<i>p</i> < .00100) fw	2.67041 (<i>p</i> < .00575) un (<i>p</i> < .07322) fw
18 R superior temporal gyrus	48	20	-16	6.14403 (<i>p</i> < .00001) un (<i>p</i> < .00018) fw	3.96653 (<i>p</i> < .00050) un (<i>p</i> < .01462) fw	2.82638 (<i>p</i> < .00391) un (<i>p</i> < .05522) fw
19 L middle temporal gyrus	56	-40	24	8.43712 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	2.25782 (<i>p</i> < .01853) un (<i>p</i> < .18209) fw	2.99402 (<i>p</i> < .00255) un (<i>p</i> < .04011) fw

Table 2. (continued)

Anatomic Region	x	y	z	Healthy Control Subjects	Schizophrenia Patients	Control Subjects vs. Schizophrenia Patients
20 R middle temporal gyrus (1,920 cmm; 30 voxels)	-56	8	-20	5.79752 (<i>p</i> < .00001) un (<i>p</i> < .00032) fw	5.736 (<i>p</i> < .00001) un (<i>p</i> < .00036) fw	1.72145 (<i>p</i> < .04604) un (<i>p</i> < .28012) fw
21 L inferior temporal gyrus	-56	-20	-8	10.01158 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	3.73651 (<i>p</i> < .00082) un (<i>p</i> < .02127) fw	3.56206 (<i>p</i> < .00056) un (<i>p</i> < .01224) fw
22 R inferior temporal gyrus	64	-20	-12	12.38284 (<i>p</i> < .00000) un (<i>p</i> < .00000) fw	5.2386 (<i>p</i> < .00003) un (<i>p</i> < .00110) fw	3.07971 (<i>p</i> < .00204) un (<i>p</i> < .03387) fw
Occipital Lobe						
23 L lingual gyrus/cuneus	-8	-80	8	5.56013 (<i>p</i> < .00002) un (<i>p</i> < .00057) fw	Nonsignificant	3.03315 (<i>p</i> < .00230) un (<i>p</i> < .03715) fw
24 R lingual gyrus/cuneus	12	-76	16	5.50797 (<i>p</i> < .00002) un (<i>p</i> < .00063) fw	2.37157 (<i>p</i> < .01478) un (<i>p</i> < .15871) fw	2.70718 (<i>p</i> < .00526) un (<i>p</i> < .06860) fw
Deep Gray						
25 L thalamus/caudate	-12	0	8	5.02983 (<i>p</i> < .00005) un (<i>p</i> < .00170) fw	Nonsignificant	4.52618 <i>p</i> < .00004) un (<i>p</i> < .00116) fw
26 R thalamus/caudate	16	-12	8	5.42188 (<i>p</i> < .00002) un (<i>p</i> < .00076) fw	Nonsignificant	4.02676 (<i>p</i> < .00015) un (<i>p</i> < .00422) fw
27 L amygdala	-24	0	-20	5.48242 (<i>p</i> < .00002) un (<i>p</i> < .00067) fw	3.00194 (<i>p</i> < .00400) un (<i>p</i> < .06698) fw	2.15745 <i>p</i> < .01888) un (<i>p</i> < .16486) fw
28 R amygdala	28	0	-24	6.15811 (<i>p</i> < .00001) un (<i>p</i> < .00017) fw	3.50762 (<i>p</i> < .00135) un (<i>p</i> < .03073) fw	2.44632 (<i>p</i> < .00983) un (<i>p</i> < .10684) fw
Cerebellum						
29 L cerebellum	-16	-80	-36	5.67881 (<i>p</i> < .00001) un (<i>p</i> < .00045) fw	4.15712 (<i>p</i> < .00033) un (<i>p</i> < .01068) fw	2.13827 <i>p</i> < .01969) un (<i>p</i> < .16930) fw
30 R cerebellum	20	-80	-36	4.25739 (<i>p</i> < .00027) un (<i>p</i> < .00877) fw	4.16955 (<i>p</i> < .00032) un (<i>p</i> < .01046) fw	2.42534 (<i>p</i> < .01032) un (<i>p</i> < .11049) fw
31 L cerebellum	-20	-72	-28	6.11339 (<i>p</i> < .00001) un (<i>p</i> < .00019) fw	4.15712 (<i>p</i> < .00033) un (<i>p</i> < .01068) fw	2.49429 (<i>p</i> < .00878) un (<i>p</i> < .09882) fw
32 R cerebellum	20	-72	-28	5.43587 (<i>p</i> < .00002) un (<i>p</i> < .00073) fw	3.51691 (<i>p</i> < .00132) un (<i>p</i> < .03028) fw	3.19478 (<i>p</i> < .00151) un (<i>p</i> < .02682) fw
Brainstem						
33 Brainstem	0	-28	-36	4.7641 (<i>p</i> < .00009) un (<i>p</i> < .00297) fw	4.42218 (<i>p</i> < .00019) un (<i>p</i> < .00615) fw	Nonsignificant

Results are reported for regions of interest identified in prior studies (Kiehl et al 2001b, in press). Columns depict anatomic region, Montreal Neurological Institute coordinates (x, y, z), and *t* scores for comparisons of healthy control subjects versus baseline (see also Figure 2, left panel), patients with schizophrenia versus baseline (Figure 2, left middle panel), and the comparison in which healthy control subjects showed greater hemodynamic activity for novelty processing than did patients with schizophrenia (Figure 2, right middle panel). Both uncorrected (un) and corrected (fw) *p* values are reported. Corrected *p* values use the family-wise error rate for the small search volume examined as implemented in Statistical Parametric Mapping 2. Note that the size (cubic millimeters and number of 4 × 4 × 4-mm voxels) of each region of interest was 2112 cm³ (33 voxels) unless otherwise specified. In some cases the region of interest was reduced due to the overlap with non-brain voxels. R, right; L, left.

regions in which electrodes were placed, including medial and antero-lateral aspects of the temporal lobe. Interestingly, studies of epilepsy patients after resection of medial and antero-lateral temporal lobes found that patients could still perform oddball tasks (Hirayasu et al 1995; Johnson 1988, 1989; Johnson and

Fedio 1987; Scheffers et al 1991). That is, removal of brain regions known to be electrical (and hemodynamic) sources associated with processing salient stimuli did not impair patients' ability to perform the task (Daffner et al 2000; Onofrij et al 1992; Polich and Squire 1993; Rugg et al 1991; Verleger et al 1994;

Yamaguchi and Knight 1991, 1993, 1995). These data led the conclusion that the presence of neural activity in a brain region does not mean that said region was required for successful task performance (Halgren and Marinkovic 1996). Rather, it seems that the brain has adopted a strategy to engage many potentially useful brain regions during salient stimulus processing, despite the low probability that these brain regions are necessary for task performance. Such a strategy might perhaps lead to superior incidental learning, memory, and performance. In addition, reflexively engaging supplemental brain regions when processing salient stimuli might be advantageous in an evolutionary sense. An organism predisposed to engage these “extra” brain regions might be in a better position to respond if the stimulus was life threatening. This mode of brain function has been termed “adaptive reflexive processing” (Kiehl et al, *in press*). One interpretation of the neuronal abnormalities observed in schizophrenia during salient stimulus processing is that they reflect disturbances in this mode of brain function. This interpretation is partially supported by the fact that disturbances in hemodynamic activity associated with salient stimulus processing were observed in schizophrenia in multiple brain regions that seem to serve a supplemental rather than an essential function with respect to oddball processing. These regions included amygdala, anterior superior temporal gyrus, and aspects of the frontal lobes. We hypothesize that the mechanism that elicits this mode of brain activity is abnormal in psychopathologic conditions. This is manifest as abnormal ERP components in electrophysiology and abnormal hemodynamics in functional brain imaging studies in psychopathologic conditions during paradigms such as target detection and novelty processing.

It is also noteworthy that patients performed the task with near-perfect accuracy, suggesting that the basic sensory and “necessary” cognitive processes underlying target detection and novelty processing are intact in schizophrenia. This argument is supported by the results from a recent ERP study that showed that the sensory and early cognitive components underlying target detection in schizophrenia are normal (van der Stelt et al 2004); however, patients were, on average, approximately 130 msec slower to respond to target stimuli than control subjects. This response slowing is a common finding in schizophrenia research. Although the response times of the schizophrenia patients were well within the normal range of reaction times (Kiehl et al, *in press*), it raises the possibility that this effect might impact group differences in hemodynamic activity. Importantly, studies have shown that second-level (i.e., contrast images in SPM) estimates of the amplitude of the hemodynamic response modeled with a canonical response function (as implemented in SPM99/2) might be biased when the latency of the hemodynamic response departs from the predicted model, as can occur when reaction times are variable. In the present study, we used a method to correct the amplitude of the hemodynamic response for this variability (Calhoun et al 2004b). An additional method to partially examine this issue is to compute a correlation between reaction time and the hemodynamics associated with target detection. We have observed no significant correlations between the amplitude of the hemodynamic response and reaction time in a large sample ($n = 100$) of healthy control subjects (Kiehl et al, *in press*). Nevertheless, it might be possible that reaction time variability might differ between patients and control subjects. Thus, although the differences in reaction time were small, it is important to recognize that this effect might have contributed, at least in part, to some of the observed group differences in hemodynamic activity. It is possible that the slower reaction

times in patients compared with control subjects are due to a number of variables, including medication effects, diminished attention and cognitive resources, or motor readiness. Future studies are needed to delineate the possible influence of these factors.

An alternative interpretation of the diffuse hemodynamic abnormalities observed in schizophrenia during oddball task performance is that these data support disconnection models of the disease. These models propose that the coordination of neural activity between diverse sites is impaired in schizophrenia and that this coordination leads to abnormalities in diffuse cortical and subcortical regions. One model proposes that the disconnection occurs primarily between frontal and temporal lobes (Friston 1999), whereas another proposes cortical–thalamic–cerebellar impairment (Andreasen et al 1999). Abnormalities during target detection and novelty processing were observed in schizophrenia patients in temporal, frontal, thalamic, and cerebellar circuits. Thus, these data might be interpreted as indirect support for both models. Avenues of future research include performing tests of functional connectivity between these latter regions, perhaps with principle components analyses or independent components analyses. These latter results might shed light on whether one or more components will show abnormality in schizophrenia during target detection and novelty processing and would provide more direct evidence supporting disconnection models.

Patients with schizophrenia demonstrated normal to excessive hemodynamic activity in left motor cortex (precentral gyrus) and medial frontal cortex (see Figure 1, Table 1). These latter motor regions were 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). It is important to note, however, that previously we reported no group differences in the amplitude of the hemodynamic response between patients with schizophrenia and control subjects in the left postcentral gyrus of the motor system. In the present study, however, a significant group difference emerged at this site (see Table 1). There are a number of possible explanations for the differences observed in the left postcentral gyrus between the two samples. Possible explanations include that the two studies differed in power (the present study had more power [$n = 18$ participants per group compared with $n = 11$ in Kiehl and Liddle 2001]) and image-processing techniques (e.g., estimates of the amplitude of the hemodynamic response, different spatial smoothing kernels). Nevertheless, it is important to recall that the purpose of the “internal physiological standard” (see Callicott et al 1998) is to assess whether there are some brain regions in which patients show normal hemodynamic activity compared with control subjects. This latter control region helps to ensure that group differences observed in other brain areas are not due to problems with image quality, increased variability in patients, or other potential image-processing issues. In this study there were several regions, including the left precentral gyrus and supplementary motor area (medial frontal gyrus) that showed normal hemodynamic activity in patients with schizophrenia. This evidence of normal hemodynamic activity in these latter brain regions suggests that the regional differences in other sites are not due to problems with image quality.

In addition, when examining the entire brain, evidence was found for excessive activity in bilateral motor regions in schizophrenia relative to control subjects during target detection (see Figure 1, far left panel). We note that this latter effect did not reach conventional levels of significance after correcting for

searching the entire brain and thus must be considered preliminary. There is mixed evidence of motor cortex abnormalities in schizophrenia, with some studies showing normal activity and some studies showing abnormal activity (Barch et al 2003; Muller et al 2002; Stephan et al 2001); however, there is clear evidence of abnormal hemispheric laterality of cognitive and motor functions in schizophrenia (Crow 1997). The preliminary finding of excessive hemodynamic activity in bilateral motor cortices suggests that the coordination of motor behavior is abnormal at some level in schizophrenia.

Recall that abnormalities in the scalp-recorded ERPs associated with salient stimulus processing are some of the most replicated findings in the schizophrenia literature (Mathalon et al 2000; McCarley et al 1991a, 1991b). These abnormalities seem to be most prominent during the 200–600-msec poststimulus time window (i.e., the P3 ERP). It is tempting to conclude that some of the observed abnormalities in hemodynamics in schizophrenia during salient stimulus processing might be related to specific ERP components (i.e., P3); however, at present the relationships between hemodynamic activity and specific ERP components are unclear, and thus it is not possible to make any strong conclusions in this regard.

The present study used a medicated patient population, raising the possibility that some of the observed group differences might be due to the effects of medication. Previous ERP studies have shown that abnormal neuronal activity associated with processing oddball stimuli in schizophrenia is at least partially independent of medication (Eikmeier et al 1992; Faux et al 1993; Ford et al 1994; Rao et al 1995). This suggests that at least some of the abnormalities in regional cerebral activity during oddball detection, observed in this study, are independent of medication status. To more fully examine this issue, fMRI studies of mediation naïve patients, or patients who are unmedicated are needed.

In summary, this study sought to replicate and extend our understanding of the hemodynamics underlying auditory target detection and response to novelty in health and in schizophrenia. The results of the healthy participants replicated prior research. The schizophrenia data replicated and extended prior research and support the argument that schizophrenia is a disorder characterized by diffuse neuronal abnormalities that affect many cerebral areas, including association cortex and subcortical sites. The abnormalities in schizophrenia might be related to difficulties with attention and memory and possibly to processes related to adaptive reflexive processing.

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- Aguirre GK, Zarahn E, D'Esposito M (1998): The inferential impact of global signal covariates in functional neuroimaging analyses. *Neuroimage* 8:302–306.
- Ammons RB, Ammons CH (1962): The Quick Test (Qt): Provisional manual. *Psychol Rep* 11:111–161.
- Ammons RB, Ammons CH (1979): Use and evaluation of the Quick Test (Qt): Partial summary through October, 1979: I. Published papers. *Psychol Rep* 45:943–946.
- Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M (1999): Defining the phenotype of schizophrenia: Cognitive dysmetria and its neural mechanisms. *Biol Psychiatry* 46:908–920.
- Annett M (1970): A classification of hand preference by association analysis. *Br J Psychol* 61:303–321.
- Ardekani BA, Choi SJ, Hossein-Zadeh GA, Porjesz B, Tanabe JL, Lim KO, et al (2002): Functional magnetic resonance imaging of brain activity in the visual oddball task. *Brain Res Cogn Brain Res* 14:347–356.
- Barch DM, Mathews JR, Buckner RL, Maccotta L, Csernansky JG, Snyder AZ (2003): Hemodynamic responses in visual, motor, and somatosensory cortices in schizophrenia. *Neuroimage* 20:1884–1893.
- Baudena P, Halgren E, Heit G, Clarke JM (1995): Intracerebral potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. *Electroencephalogr Clin Neurophysiol* 94:251–264.
- Calhoun VD, Kiehl KA, Liddle PF, Pearlson GD (2004a): Aberrant localization of synchronous hemodynamic activity in auditory cortex reliably characterizes schizophrenia. *Biol Psychiatry* 55:842–849.
- Calhoun VD, Stevens MS, Pearlson GD, Kiehl KA (2004b): fMRI analysis with the general linear model: Removal of latency-induced amplitude bias by incorporation of hemodynamic derivative terms. *Neuroimage* 22:252–257.
- Callicott JH, Ramsey NF, Tallent K, Bertolino A, Knable MB, Coppola R, et al (1998): Functional magnetic resonance imaging brain mapping in psychiatry: Methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* 18:186–196.
- Casey BJ, Forman SD, Franzen P, Berkowitz A, Braver TS, Nystrom LE, et al (2001): Sensitivity of prefrontal cortex to changes in target probability: A functional MRI study. *Hum Brain Mapp* 13:26–33.
- Clark VP, Fannon S, Lai S, Benson R, Bauer LO (2000): Responses to rare visual target and distractor stimuli using event-related fMRI. *J Neurophysiol* 83:3133–3139.
- Clarke JM, Halgren E, Chauvel P (1999a): Intracranial ERPs in humans during a lateralized visual oddball task: I. Occipital and peri-Rolandic recordings. *Clin Neurophysiol* 110:1210–1225.
- Clarke JM, Halgren E, Chauvel P (1999b): Intracranial ERPs in humans during a lateralized visual oddball task: II. Temporal, parietal, and frontal recordings. *Clin Neurophysiol* 110:1226–1244.
- Courchesne E, Hillyard SA, Galambos R (1975): Stimulus novelty, task relevance and the visual evoked potential in man. *Electroencephalogr Clin Neurophysiol* 39:131–43.
- Crow TJ (1997): Schizophrenia as failure of hemispheric dominance for language. *Trends Neurosci* 20:339–343.
- Daffner KR, Mesulam MM, Scinto LF, Acar D, Calvo V, Faust R, et al (2000): The central role of the prefrontal cortex in directing attention to novel events. *Brain* 123(Pt 5):927–939.
- Desjardins AE, Kiehl KA, Liddle PF (2001): Removal of confounding effects of global signal in functional magnetic resonance imaging analyses. *Neuroimage* 13:751–758.
- Dickinson D, Iannone VN, Wilk CM, Gold JM (2004): General and specific cognitive deficits in schizophrenia. *Biol Psychiatry* 55:826–833.
- Donchin E, Coles MGH (1988): Is the P300 component a manifestation of context updating? *Behav Brain Sci* 11:357–374.
- Eikmeier G, Lodermann E, Zerbini D, Gastpar M (1992): P300, clinical symptoms, and neurophysiological parameters in acute and remitted schizophrenia: A preliminary report. *Biol Psychiatry* 31:1065–1069.
- Faux SF, McCarley RW, Nestor PG, Shenton ME, Pollak SD, Penhune V, et al (1993): P300 topographic asymmetries are present in unmedicated schizophrenics. *Electroencephalogr Clin Neurophysiol* 88:32–41.
- First MB, Spitzer M, Miriam G, Williams JBW (2002): *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP)*. New York: Biometrics Research, New York State Psychiatric Institute.
- Ford JM, Mathalon DH, Marsh L, Faustman WO, Harris D, Hoff AL, et al (1999): P300 amplitude is related to clinical state in severely and moderately ill patients with schizophrenia. *Biol Psychiatry* 46:94–101.
- Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A (1994): ERPs in schizophrenia: Effects of antipsychotic medication. *Biol Psychiatry* 36:153–170.
- Freire L, Mangin JF (2001): Motion correction algorithms may create spurious brain activations in the absence of subject motion. *Neuroimage* 14:709–722.
- Freire L, Roche A, Mangin JF (2002): What is the best similarity measure for motion correction in fMRI time series? *IEEE Trans Med Imaging* 21:470–484.

- Friston KJ (1999): Schizophrenia and the disconnection hypothesis. *Acta Psychiatr Scand Suppl* 395:68–79.
- Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ (1995): Spatial registration and normalization of images. *Hum Brain Mapp* 2:165–189.
- Grillon C, Courchesne E, Ameli R, Geyer MA, Braff DL (1990): Increased distractibility in schizophrenic patients. Electrophysiologic and behavioral evidence. *Arch Gen Psychiatry* 47:171–179.
- Halgren E (1980): Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science* 210:803–805.
- Halgren E, Baudena P, Clarke JM, Heit G, Liégeois C, Chauvel P, Musolino A (1995a): Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. *Electroencephalogr Clin Neurophysiol* 94:191–220.
- Halgren E, Baudena P, Clarke JM, Heit G, Marinkovic K, Devaux B, et al (1995b): Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. *Electroencephalogr Clin Neurophysiol* 94:229–250.
- Halgren E, Marinkovic K (1996): General principles for the physiology of cognition as suggested by intracranial ERPs. In: Ogura C, Koga Y, Shimokochi M, editors. *Recent Advances in Event-Related Brain Potential Research*. Amsterdam: Elsevier, 1072–1084.
- Halgren E, Marinkovic K, Chauvel P (1998): Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalogr Clin Neurophysiol* 106:156–164.
- Hirayasu Y, Ohta H, Fukao K, Ogura C, Mukawa J (1995): Transient P300 abnormality of event-related potentials following unilateral temporal lobectomy. *Psychiatry Clin Neurosci* 49:223–226.
- Horowitz SG, Skudlarski P, Gore JC (2002): Correlations and dissociations between BOLD signal and P300 amplitude in an auditory oddball task: A parametric approach to combining fMRI and ERP. *Magn Reson Imaging* 20:319–325.
- Huetzel SA, McCarthy G (2004): What is odd in the oddball task? Prefrontal cortex is activated by dynamic changes in response strategy. *Neuropsychologia* 42:379–386.
- Johnson RJ (1988): Scalp-recorded P300 activity in patients following unilateral temporal lobectomy. *Brain* 111:1517–1529.
- Johnson RJ (1989): Auditory and visual P300s in temporal lobectomy patients: Evidence for modality-dependent generators. *Psychophysiology* 26:633–650.
- Johnson RJ, Fedio P (1987): Task-related changes in P300 scalp distribution in temporal lobectomy patients. *Electroencephalogr Clin Neurophysiol Suppl* 40:699–704.
- Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF (2001a): An event-related fMRI study of visual and auditory oddball tasks. *J Psychophysiol* 21:221–240.
- Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF (2001b): Neural sources involved in auditory target detection and novelty processing: An event-related fMRI study. *Psychophysiology* 38:133–142.
- Kiehl KA, Liddle PF (2001): An event-related fMRI study of an auditory oddball task in schizophrenia. *Schizophr Res* 2:159–171.
- Kiehl KA, Liddle PF (2003): Reproducibility of the hemodynamic response to auditory oddball stimuli: A six-week test-retest study. *Hum Brain Mapp* 18:42–52.
- Kiehl KA, Stevens MS, Laurens KR, Pearson GD, Calhoun VD, Liddle PF (in press): An adaptive reflexive processing model of neurocognitive function: Supporting evidence from a large scale (n = 100) fMRI study of an auditory oddball task. *Neuroimage*.
- Levit A, Sutton S, Zubin J (1973): Evoked potential correlates of information processing in psychiatric patients. *Psychological Medicine* 3:487–494.
- Liddle PF (2001): *Disordered Mind and Brain: The Neural Basis of Mental Symptoms*. London: Gaskell.
- Liddle PF, Duffield G, Kho K, Warren AJ (2002): Signs and Symptoms of Psychotic Illness (SSPI): a rating scale. *Br J Psychiatry* 180:45–50.
- Linden DE, Prvulovic D, Formisano E, Voellinger M, Zanella FE, Goebel R, Dierks T (1999): The functional neuroanatomy of target detection: An fMRI study of visual and auditory oddball tasks. *Cereb Cortex* 9:815–823.
- Madden DJ, Whiting WL, Provenzale JM, Huetzel SA (2004): Age-related changes in neural activity during visual target detection measured by fMRI. *Cereb Cortex* 14:143–155.
- Mathalon DH, Ford JM, Pfefferbaum A (2000): Trait and state aspects of P300 amplitude reduction in schizophrenia: A retrospective longitudinal study. *Biol Psychiatry* 47:434–449.
- McCarley RW, Faux SF, Shenton ME, LeMay M, Cane M, Ballinger R, Duffy FH (1989): CT abnormalities in schizophrenia: A preliminary study of their correlations with P300/P200 electrophysiological features and positive/negative symptoms. *Arch Gen Psychiatry* 46:698–708.
- McCarley RW, Faux SF, Shenton ME, Nestor PG (1991a): Event-related potentials in schizophrenia: Their biological and clinical correlates and a new model of schizophrenic pathophysiology. *Schizophr Res* 4:209–231.
- McCarley RW, Faux SF, Shenton ME, Nestor PG, Holinger DP (1991b): Is there P300 asymmetry in schizophrenia? *Arch Gen Psychiatry* 48:380–381.
- Mesulam MM (2000): *Principles of Behavioral and Cognitive Neurology*, 2nd ed. New York: Oxford University Press.
- Muller JL, Roder CH, Schuierer G, Klein H (2002): Motor-induced brain activation in cortical, subcortical and cerebellar regions in schizophrenic inpatients. A whole brain fMRI fingertapping study. *Prog Neuropsychopharmacol Biol Psychiatry* 26:421–426.
- Nelson HE, O'Connell A (1978): Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex* 14:234–244.
- Onofrj M, Fulgente T, Nobilio D, Malatesta G (1992): P3 recordings in patients with bilateral temporal lobe lesions. *Neurology* 42:1762–1767.
- Polich J, Squire LR (1993): P300 from amnesic patients with bilateral hippocampal lesions. *Electroencephalogr Clin Neurophysiol* 86:408–417.
- Rugg MD, Pickles CD, Potter DD, Roberts RC (1991): Normal P300 following extensive damage to the left medial temporal lobe. *J Neurol Neurosurg Psychiatry* 54:217–222.
- Schall U, Catts SV, Karayanidis F, Ward PB (1999): Auditory event-related potential indices of fronto-temporal information processing in schizophrenia syndromes: valid outcome prediction of clozapine therapy in a three-year follow-up. *Int J Neuropsychopharmacol* 2:83–93.
- Scheffers MK, Johnson R, Ruchkin DS (1991): P300 in patients with unilateral temporal lobectomies: The effects of reduced stimulus quality. *Psychophysiology* 28:274–284.
- Sharpe K, O'Carroll R (1991): Estimating premorbid intellectual level in dementia using the National Adult Reading Test: A Canadian study. *Br J Clin Psychol* 30:381–384.
- Sokolov EN (1963): Higher nervous functions: The orienting reflex. *Ann Rev Physiol* 25:545–580.
- Stephan KE, Magnotta VA, White T, Arndt S, Flaum M, O'Leary DS, Andreasen NC (2001): Effects of olanzapine on cerebellar functional connectivity in schizophrenia measured by fMRI during a simple motor task. *Psychol Med* 31:1065–1078.
- Stevens AA, Skudlarski P, Gatenby JC, Gore JC (2000): Event-related fMRI of auditory and visual oddball tasks. *Magn Reson Imaging* V18:495–502.
- Strange BA, Dolan RJ (2001): Adaptive anterior hippocampal responses to oddball stimuli. *Hippocampus* 11:690–698.
- Strange BA, Henson RN, Friston KJ, Dolan RJ (2000): Brain mechanisms for detecting perceptual, semantic, and emotional deviance. *Neuroimage* 12:425–433.
- Sutton S, Braren M, Zubin J, John ER (1965): Evoked-potential correlates of stimulus uncertainty. *Science* 150:1187–1188.
- Sutton S, Tueting P, Zubin J, John ER (1967): Information delivery and the sensory evoked potential. *Science* 155:1436–1439.
- van der Stelt O, Frye J, Lieberman JA, Belger A (2004): Impaired P3 generation reflects high-level and progressive neurocognitive dysfunction in schizophrenia. *Arch Gen Psychiatry* 61:237–48.
- Verleger R, Heide W, Butt C, Koempf D (1994): Reduction of P3-sub(b) in patients with temporo-parietal lesions. *Brain Res Cogn Brain Res* 2:103–116.
- Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996): A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 4:58–73.
- Yamaguchi S, Knight RT (1991): Anterior and posterior association cortex contributions to the somatosensory P300. *J Neurosci* 11:2039–2054.
- Yamaguchi S, Knight RT (1993): Association cortex contributions to the human P3. In: Haschke W, Roitbak AI, Speckmann E-J, editors. *Slow Potential Changes in the Brain*. Boston: Birkhauser, 71–84.
- Yamaguchi S, Knight RT (1995): Contributions of anterior and posterior association cortex to the human somatosensory P3. *Electroencephalogr Clin Neurophysiol Suppl* 44:130–139.