



Attention orienting dysfunction during salient novel stimulus processing in schizophrenia

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Abstract

Schizophrenia is characterised by marked disturbances of attention and information processing. Patients experience difficulty focusing on relevant cues and avoiding distraction by irrelevant stimuli. Event-related potential recordings indicate an amplitude reduction in the P3a component elicited by involuntary orienting to task-irrelevant, infrequent novel stimuli presented during auditory oddball detection in patients with schizophrenia. The goal of the present study was to elucidate the functional abnormality underlying the disturbed orienting to novel stimuli in schizophrenia. Twenty-eight stable, partially remitted, medicated patients with schizophrenia and 28 healthy control participants completed a novelty oddball variant during event-related fMRI. Relative to healthy participants, patients with schizophrenia were characterised by underactivity during novel stimulus processing in the right amygdala–hippocampus, within paralimbic cortex in the rostral anterior cingulate and posterior cingulate cortices and the right frontal operculum, and in association cortex at the right temporo-parietal-occipital junction, bilateral intraparietal sulcus, and bilateral dorsal frontal cortex. Subcortically, relative hypoactivation during novelty processing was apparent in the cerebellum, thalamus, and basal ganglia. These results suggest that patients less efficiently reorient

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processing resources away from the ongoing task of detecting and responding to the task-relevant target stimuli. In addition, trend results suggest that patients experienced increased distraction by novel stimuli.

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1. Introduction

Information processing and attentional dysfunctions are a cardinal feature of schizophrenia. Patients experience difficulties in focusing processing resources on relevant cues and in avoiding distraction by irrelevant stimuli (Braff, 1993). Andreasen et al. (1998) describe the critical abnormality as ‘cognitive dysmetria’, which incorporates disturbance in receiving and processing incoming information, in integrating that information with information that has been previously processed and stored, and in acting to produce a response to that information.

A principal neurophysiological index of information processing and attentional dysfunctions in schizophrenia is the relative reduction in amplitude of the P3 (or P300) event-related potential (ERP) elicited by task-relevant target tones in the auditory oddball paradigm (Ford, 1999). The P3 reduction suggests that patients allocate less (or less efficient) processing resources to performing the task than healthy participants. The P3 component elicited by oddball target processing is not a unitary brain potential arising from a discrete brain area or cognitive process (Knight and Scabini, 1998). Voluntary detection of, and response to, the task-relevant target stimulus typically elicits a P3 (the ‘P3b’) that is maximal over parietal scalp. A smaller, frontocentrally distributed ‘P3a’ component that peaks about 60–80 ms earlier than the P3b indexes involuntary orienting to the infrequent stimulus for the purposes of conscious stimulus evaluation. Both P3b and P3a amplitude reductions are reported in schizophrenia (Mathalon et al., 2000; Turetsky et al., 1998).

The P3a component is elicited strongly within an auditory oddball variant that also incorporates an infrequent distracter stimulus or non-repeating novel stimuli that require no behavioural response (Courchesne et al., 1975). These stimuli evoke a larger P3a response than do targets, and manifest the involuntary capture of attention away from the central, ongoing

task of detecting and responding to the task-relevant target stimulus (Debener et al., 2002; Friedman et al., 2001; Polich, 1998). Only three studies have made use of the novelty oddball variant to examine whether the P3b and P3a are differentially affected in schizophrenia, but each indicates a reduction in the amplitude of the P3a elicited by the novel stimuli in patients with schizophrenia relative to healthy participants, in both the auditory (Grillon et al., 1990, 1991; Merrin and Floyd, 1994) and visual modalities (van der Stelt et al., 2004). However, these reports diverge concerning whether a greater amplitude reduction in patients was observed for the P3 response elicited by the novel or target stimuli. In unmedicated and medicated samples, respectively, Merrin and Floyd (1994) and van der Stelt et al. (2004) indicated a more pronounced amplitude reduction for the P3 elicited by novel stimuli, which is suggestive of particular dysfunction occurring in patients during the involuntary orienting of attention. By comparison, two studies based on a medicated patient sample reported a significantly greater reduction in the amplitude of the P3 elicited by targets than by novel stimuli, and a greater difference between the P3a and P3b amplitudes in patients than in healthy participants (Grillon et al., 1990, 1991). This finding was interpreted as an abnormal apportioning of processing resources to the task-irrelevant versus task-relevant stimuli by patients (i.e., an increased distractibility by task-irrelevant stimuli), reflecting an inability to filter or ‘gate’ irrelevant information.

Little work has been done to elucidate the functional abnormality underlying voluntary and involuntary processing dysfunctions in patients with schizophrenia during auditory oddball performance. Using SPECT, Shajahan et al. (1997) observed hypofrontality in patients with schizophrenia relative to healthy participants during target processing (Ebmeier et al., 1995). Kiehl and Liddle (2001) reported reduced haemodynamic activity (both in extent and magnitude) during

target processing in patients relative to healthy participants in the caudal anterior and posterior cingulate gyri, right anterior frontal cortex, and bilateral cortex at the anterior superior temporal sulcus, intraparietal sulcus, and temporoparietal junction, as well as the thalamus. Thus, schizophrenia appears to be associated with abnormality throughout the corticolimbic network that supports target processing in healthy individuals (see Kiehl et al., 2001a,b; Laurens et al., 2005), rather than a single locus of disturbance. No neuroimaging study has yet ascertained the dysfunction underlying disturbed involuntary orienting to novel stimuli during auditory oddball detection in schizophrenia. Lesion (Knight, 1996; Knight and Scabini, 1998) and neuroimaging (Downar et al., 2002; Kiehl et al., 2001a,b) data suggest that orienting to novel stimuli presented during oddball target detection also recruits a corticolimbic network, including particularly the limbic cortex, cortex at the temporoparietal junction, and prefrontal cortex.

This study sought to ascertain the nature of functional abnormality elicited during novel stimulus processing in a large sample ($n=28$) of patients with schizophrenia using the novelty oddball task. This paradigm affords an examination of novel stimulus processing not only in relation to the nontarget baseline, but also, relative to the processing of the salient task-relevant target events. The reduced P3a component elicited by novel stimuli in patients with schizophrenia suggests that relative hypoactivity may be observed in patients within the corticolimbic network recruited by healthy participants during novelty processing, particularly in prefrontal, temporoparietal, and limbic cortex. However, evidence that patients with schizophrenia may also experience increased distraction by task-irrelevant stimuli during auditory oddball processing (Grillon et al., 1990, 1991) raises the possibility that, in at least some cerebral areas, the haemodynamic response elicited by orienting to novel stimuli may be greater in patients than in healthy participants.

2. Method

2.1. Participants

Twenty-eight healthy adults (7 female) and 29 patients with schizophrenia (9 female) participated in

the experiment. However, one patient experienced claustrophobia during scanning and could not complete the task. All but one participant in each group was right-handed (assessed using the questionnaire of Annett, 1970). All procedures complied with University and Hospital ethical requirements.

Patients were stable, partially remitted, medicated outpatients recruited from community mental health teams in Vancouver, BC and outpatient programs at the University of British Columbia Hospital. All patients met DSM-IV criteria for schizophrenia ($n=24$) or schizoaffective disorder ($n=4$), as diagnosed by an institutional or University Hospital psychiatrist, and confirmed by a research psychiatrist on the basis of a clinical interview and case note review (American Psychiatric Association [APA], 1994). Mean duration of illness (i.e., time elapsed since diagnosis) was 7 years (S.D. 7.2), with a range spanning 1 to 24 years. All patients except two received atypical antipsychotics as their primary medication over the 6-month period preceding scanning. Dosages in each patient were constant during that time. The majority of patients received olanzapine (mean dose 17.3 mg/day, range 7.5–30), seven patients received risperidone (mean dose: 3.4 mg/day, range 2–6), and one patient received clozapine (500 mg/day). Two patients received a second atypical antipsychotic as an adjunctive medication (1 mg/day of risperidone, and 50 mg/day of clozapine), while three patients received a typical antipsychotic adjunctive to the atypical medication (5 mg/day of fluphenazine, 5 mg/day of loxapine, and 2 mg/day of trifluoperazine). One patient received only a typical antipsychotic as their primary medication (10 mg/day loxapine), and one patient received no antipsychotic medication. In addition to antipsychotic medication, several patients were medicated with benzodiazepines ($n=5$), anticholinergics ($n=6$), and anti-depressants ($n=11$).

On the day of scanning, a trained psychiatrist evaluated the symptoms experienced by the patients with schizophrenia during the week preceding scanning 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. Consistent with the partially remitted status of the patients recruited, overall symptom levels reported were low, with a mean total score on the SSPI of 12.7 (S.D. 5.7;

range 1–23). Syndrome (i.e., symptom cluster) scores for Reality Distortion, Disorganisation, and Psychomotor Poverty (Liddle, 1987) were calculated from the items based on the factor loadings described for the SSPI in Liddle et al. (2002) (see Table 1(b) for mean scores).

Healthy participants were medication-free volunteers without history of neurological or Axis I psychiatric illness. Participant groups did not differ significantly on the demographic variables of age, gender, parental socioeconomic status (Hollingshead and Redlich, 1958), or on estimates of premorbid (National Adult Reading Test [NART]; Nelson, 1982; Sharpe and O'Carroll, 1991) and current (Quick Test; Ammons and Ammons, 1962) intellectual functioning (all tests $p \geq 0.16$; see Table 1(a) for mean data).

2.2. Task procedure and imaging parameters

Two scanning runs of 244 auditory stimuli each were presented to participants, and behavioural responses to the stimuli recorded, using the methods described in Kiehl and Liddle (2001). Auditory stimuli comprised three classes: Repeating target stimuli (1500 Hz tones; probability of occurrence 0.10), novel stimuli (non-repeating digital noises; probability 0.10), and repeating nontarget stimuli (1000 Hz tones; probability 0.80). Three-to-five nontarget stimuli preceded each occurrence of a target or novel stimulus. Reaction times (RTs) were

computed for motor responses committed within 100–2100 ms post-stimulus. Errors of commission included responses to novel and nontarget stimuli within this time window, while errors of omission constituted a failure to respond to target stimuli during this time.

Image acquisition proceeded as in Kiehl and Liddle (2001), using a standard GE 1.5T system fitted with a Horizon Echo-speed upgrade (gradient-echo sequence, TR/TE 3000/40 ms, flip angle 90°, 24×24 cm field of view, 64×64 matrix, 62.5 kHz bandwidth, 3.75 mm×3.75 mm in plane resolution, 5 mm thickness, 29 slices; effectively covering the entire brain [145 mm axial extent]).

2.3. Image processing

Functional images were reconstructed offline, realigned, normalised to modified Talairach stereotaxic space (Talairach and Tournoux, 1988), smoothed with an 8-mm full width at half-maximum Gaussian kernel, and high- and low-pass filtered using the procedures described by Friston et al. (1995) and detailed in Laurens et al. (2005) using Statistical Parametric Mapping 99 (SPM99, Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>). To remove the influence of motion from the data, estimated movement parameters (i.e., three translation and three rotation parameters) were incorporated into

Table 1

(a) Demographic data for patients with schizophrenia and matched healthy control participants, and (b) syndrome scores for patients with schizophrenia

(a) Demographic variables	Healthy participants		Patients with schizophrenia	
	Mean	S.D.	Mean	S.D.
Age	28.2	8.9	31.6	10.1
Parental socioeconomic status (Hollingshead)	3.0	1.3	3.2	1.5
Premorbid intellectual functioning (NART)	116	4.6	115	4.8
Current intellectual functioning (quick test)	109	11.2	104	11.8
(b) Syndrome	Mean	S.D.	Range	
Reality distortion: (sum of 2 items: delusions and hallucinations)	2.8	2.2	0–7	
Disorganisation: (sum of 3 items: inappropriate affect, thought form disorder, and impaired attention)	1.6	1.5	0–5	
Psychomotor poverty: (sum of 4 items: underactivity, flat affect, poverty of speech, and anhedonia)	4.0	3.2	0–12	

the analysis as covariates of no interest (Friston et al., 1996). Moreover, a Group (schizophrenic patients, healthy participants)×Movement (translation, rotation)×Displacement Axis (x , y , z) ANOVA was conducted on the maximal and mean absolute estimated movement parameters to confirm that the participant groups did not differ significantly in extent of head motion.

2.4. Image analysis

Statistical analysis was performed within each voxel using the general linear model approach implemented in SPM99 (Josephs et al., 1997; Friston et al., 1998), and described previously in Kiehl and Liddle (2001). Event-related responses were modelled separately for five event-types: correct hits to target events ('targets'), correctly rejected novel events ('novels'), errors of omission on target events ('misses'), errors of commission on novel events ('novel false alarms'), and errors of commission on nontarget events ('nontarget false alarms'). The nontarget events were treated as a baseline and not explicitly modelled. Only the novel processing analyses (relative to the nontarget baseline and to target stimuli) are reported in this manuscript. Target processing analyses (relative to nontargets and to novels) are reported in a separate manuscript (Liddle et al., in preparation).

For all analyses, the significance of the activation elicited was assessed across the entire brain volume at the cluster level ($p \leq 0.05$ corrected for multiple comparisons, with the height threshold for inclusion in the cluster set at $p \leq 0.005$ uncorrected) according to the method of Friston et al. (1994) implemented in SPM99.

2.4.1. Novel stimulus processing (relative to the nontarget baseline)

2.4.1.1. Within-group analyses of novel stimulus processing. For each participant, a contrast image summarising the amplitude of the fitted response in each voxel for novels relative to the nontarget baseline was created. These contrast images were entered into separate second-level, one-sample t -tests (27 degrees of freedom) for each participant group in order to test the null hypotheses that the mean of the

observations for novel events did not differ significantly from zero in either the healthy participant group or the patient group.

2.4.1.2. Between-group comparisons of novel stimulus processing. The contrast images for novels were subsequently entered into an independent samples t -test at the second-level (54 degrees of freedom) to test the null hypothesis that there was no difference between patients and healthy participants in the mean amplitude of the fitted haemodynamic response elicited by novel events.

2.4.2. Novel relative to target stimulus processing

Additional contrasts were specified to estimate and test for differences in the amplitude of the fitted haemodynamic response elicited by the novels and targets at each voxel. For each participant, a contrast image was created to indicate voxels in which novels elicited relatively greater activity than targets. Separate one-sample t -tests were conducted within each group to determine whether there were any brain regions in which the mean difference between the stimulus types departed significantly from zero. A two sample t -test was conducted to compare the participant groups directly on the mean difference in amplitude of the fitted response between novel and target stimuli (i.e., to assess whether there was a Group×Stimulus Type interaction).

3. Results

3.1. Behavioural data

Although both groups performed the task well, healthy participants were faster and more accurate than patients in processing the targets. Mean reaction times for healthy participants (398 ms; S.D. 78) and patients with schizophrenia (569 ms; S.D. 184) differed significantly [$t_{(54)} = -4.517$, $p < 0.0001$]. Healthy participants and patients correctly responded to 99.3% and 95.2% of targets, respectively. Both groups committed few errors of commission: Healthy participants and patients committed novel false alarms on 3.0% and 4.3% of novel trials, respectively, and nontarget false alarms on 0.03% and 0.13% of nontarget trials, respectively. A Group

Table 2

Selected local maxima contained within the significant clusters of activation observed during novel stimulus processing relative to the nontarget stimulus baseline for (a) healthy participants and (b) patients with schizophrenia. Column (c) indicates selected local maxima from within the significant clusters in which healthy participants demonstrated greater activation than patients with schizophrenia for novel relative to nontarget stimuli

Functional anatomic area (Brodmann area)	(a) Healthy participants				(b) Patients with schizophrenia				(c) Healthy participants > patients with schizophrenia			
	Talairach co-ordinates			<i>t</i> score	Talairach co-ordinates			<i>t</i> score	Talairach co-ordinates			<i>t</i> score
	<i>x</i>	<i>y</i>	<i>z</i>		<i>x</i>	<i>y</i>	<i>z</i>		<i>x</i>	<i>y</i>	<i>z</i>	
<i>Limbic-paralimbic cortex</i>												
L. amygdala	−24	−4	−24	4.79 ^b								
R. amygdala	20	−8	−16	5.12 ^a					24	0	−24	4.32 ⁿ
L. hippocampus	−28	−20	−12	3.81 ^b								
R. hippocampus	32	−20	−12	3.08 ^a					20	−12	−16	4.98 ⁿ
L. anterior superior temporal sulcus (38/21/22)	−52	12	−16	7.86 ^b ***	−52	8	−20	4.07 ^g				
R. anterior superior temporal sulcus (38/21/22)	56	8	−12	10.17 ^a ***	52	12	−12	7.62 ^f ***	44	16	−20	4.75 ⁿ
L. orbitofrontal cortex (47)	−36	20	−12	6.83 ^b **	−36	24	0	6.28 ^h *				
R. orbitofrontal cortex (47)	36	16	−4	6.19 ^a *	48	20	−8	7.48 ^f ***	36	28	−16	4.35 ⁿ
L. anterior insula (13)	−36	16	−12	4.93 ^b	−36	20	4	3.61 ^h				
R. anterior insula (13)	40	8	−12	5.52 ^a	36	20	0	5.72 ^f *	44	0	0	3.19 ⁿ
Rostral anterior cingulate cortex (24/32)	0	32	28	4.35 ^b					8	48	8	4.13 ^l
Caudal anterior cingulate cortex (24/32)	4	28	36	4.61 ^b	8	28	32	5.77 ⁱ *				
Mid-cingulate cortex (24)	−4	4	36	5.26 ^b	−8	−4	48	6.09 ⁱ *				
Posterior cingulate cortex (31/23/29/30)	0	−36	28	6.88 ^b **					0	−36	24	4.30 ^q

Temporoparietal junction

L. superior temporal gyrus (22)	-64	-36	20	7.80 ^b ***	-56	-40	16	10.33 ^g ***				
R. superior temporal gyrus (22)	56	-40	4	11.97 ^a ***	60	-44	4	12.09 ^f ***				
L. inferior parietal lobule (40/39)	-60	-48	24	3.48 ^b	-60	-44	24	4.48 ^g				
R. inferior parietal lobule (40/39)	64	-28	32	4.58 ^a	64	-32	32	3.26 ^f				
R. middle-inferior temporal/ occipital gyrus (21/39/37/19)	64	-48	-8	6.55 ^a *					44	-64	12	4.88 ^o

Intraparietal sulcus

L. superior parietal lobule (7)	-36	-64	52	5.61 ^b					-32	-68	52	4.70 ^p
R. superior parietal lobule (7)	36	-60	48	6.28 ^b *					40	-60	48	4.58 ^q
L. precuneus (7)	-4	-60	48	4.52 ^b					-4	-64	48	4.21 ^q
R. precuneus (7)	8	-76	36	6.25 ^b *					16	-76	52	4.59 ^q
L. inferior parietal lobule (40)	-36	-56	40	6.31 ^b *					-56	-48	48	4.52 ^p
R. inferior parietal lobule (40)	36	-60	44	5.38 ^b					42	-56	48	4.49 ^o

Dorsal and ventral frontal cortex

L. inferior-middle frontal/ precentral gyrus (9/45/6)	-48	4	36	4.91 ^c	-56	16	20	6.14 ^h *				
R. inferior-middle frontal gyrus (9/46/45)	52	16	28	5.80 ^a *	44	12	24	4.54 ^j				
R. middle frontal/precentral gyrus (6/8)	48	4	48	5.62 ^a	40	4	40	4.32 ^j	44	16	44	4.51 ^l
L. superior-middle frontal gyrus (10/9)									-12	44	32	5.42 ^l *
R. superior-middle frontal gyrus (10/9)	16	52	28	6.58 ^a **					16	56	28	6.65 ^l ***

L.=Left, R.=Right. The clusters from which the voxels derive are indicated with a superscript label (a–q). Cluster information (number of voxels in cluster, and cluster p value after correcting for multiple comparisons) for healthy participant data: a=1628, $p<0.0005$; b=2145, $p<0.0005$; c=636, $p<0.0005$; d=113, $p=0.003$; e=79; $p=0.021$. Clusters for patient data: f=754, $p<0.0005$; g=557, $p<0.0005$; h=145, $p<0.0005$; i=252, $p<0.0005$; j=120; $p<0.0005$. Clusters for healthy participants > patients: k=888, $p<0.0005$ (cerebellum, not shown); l=549, $p<0.0005$; m=145, $p<0.0005$ (thalamus and basal ganglia; not shown); n=144, $p=0.001$; o=91, $p=0.009$; p=102, $p=0.005$; q=494, $p<0.0005$. Probability of achieving the t score in the voxel after correcting for multiple comparisons: *** $p<0.0005$, ** $p\leq 0.005$, * $p\leq 0.05$.

(healthy participants, patients with schizophrenia) \times Inaccuracy (misses, novel false alarms, nontarget false alarms) ANOVA revealed a significant main effect of Group [$F_{(1, 54)}=5.573, p=0.022$], indicating that patients performed the task less accurately than healthy participants. Thus, error trials were modelled separately in the imaging analysis, and the results reported include only those trials on which participants performed correctly.

3.2. Imaging data

The absence of significant main effects and interactions for the Group factor in the ANOVAs examining maximal and mean head motion during scanning suggests that movement did not contribute differentially to the haemodynamic results obtained for healthy participants and patients with schizophrenia. Nevertheless, all results reported in this experiment reflect analyses in which the estimated movement parameters were entered as covariates of no interest so as to remove movement-related artefacts from the fMRI time series (Friston et al., 1996).

3.2.1. Novel stimulus processing (relative to the nontarget baseline)

3.2.1.1. Healthy participants. The second-level one sample *t*-test conducted on healthy participant data revealed five significant clusters of activation elicited during the processing of infrequent, novel auditory events relative to a baseline of nontarget processing. Novelty processing elicited activation in a widespread network of bilateral limbic–paralimbic cortex, association cortex, and subcortical areas. Cluster statistics, and voxel-level statistics from selected local maxima within the significant clusters, are reported in Table 2(a), and the clusters of activation are illustrated on transaxial brain slices in Fig. 1(a).

3.2.1.2. Patients with schizophrenia. Five significant clusters of activation elicited by novelty processing relative to the nontarget baseline were also revealed in the one-sample *t*-test for patients. These clusters are illustrated in Fig. 1(b) and cluster statistics, and voxel-level statistics from selected local maxima within the significant clusters, are reported in Table 2(b).

Generally, these clusters encompassed a subset of the regions activated in healthy participants at the equivalent threshold. However, the voxel-level statistics reported for patients in the region of the temporoparietal junction incorporated slightly greater *t*-score values than were observed for healthy participants, indicating strong activation in patients in parts of the network of areas activated in healthy participants during novelty processing.

3.2.1.3. Between-group comparisons. The two-sample *t*-test directly comparing the pattern of activation elicited by novels in the healthy participant and patient groups revealed seven significant clusters as relatively more active in healthy participants than in patients (see Table 2(c) and Fig. 1(c)). Patients with schizophrenia were characterised by significant relative underactivity compared with healthy participants in limbic, paralimbic, and association cortex, and subcortically in the bilateral cerebellum, thalamus, and basal ganglia. Patients also showed less activation than healthy participants in a cluster of 36 voxels centred in left posterior hippocampal gyrus; however, this activation was significant only at a cluster significance of $p<0.05$ uncorrected for multiple comparisons. Nevertheless, the difference is noteworthy given lesion data that suggests a critical role for the posterior hippocampus in novelty detection (Knight, 1996).

No significant clusters were observed in which patients showed greater activation than healthy participants after the criterion for cluster significance of $p<0.05$ corrected for multiple comparisons was applied. The largest non-significant cluster of 32 voxels ($p=0.019$ uncorrected) was located in the medial frontal gyrus (i.e., supplementary motor area).

3.2.2. Novel and target stimulus processing comparisons

3.2.2.1. Novel relative to target stimulus processing: healthy participants. After applying a correction for multiple comparisons conducted across the entire brain, the second-level, one-sample *t*-test conducted on data from healthy participants revealed no brain areas to be significantly more active during novelty processing than during target processing. A small

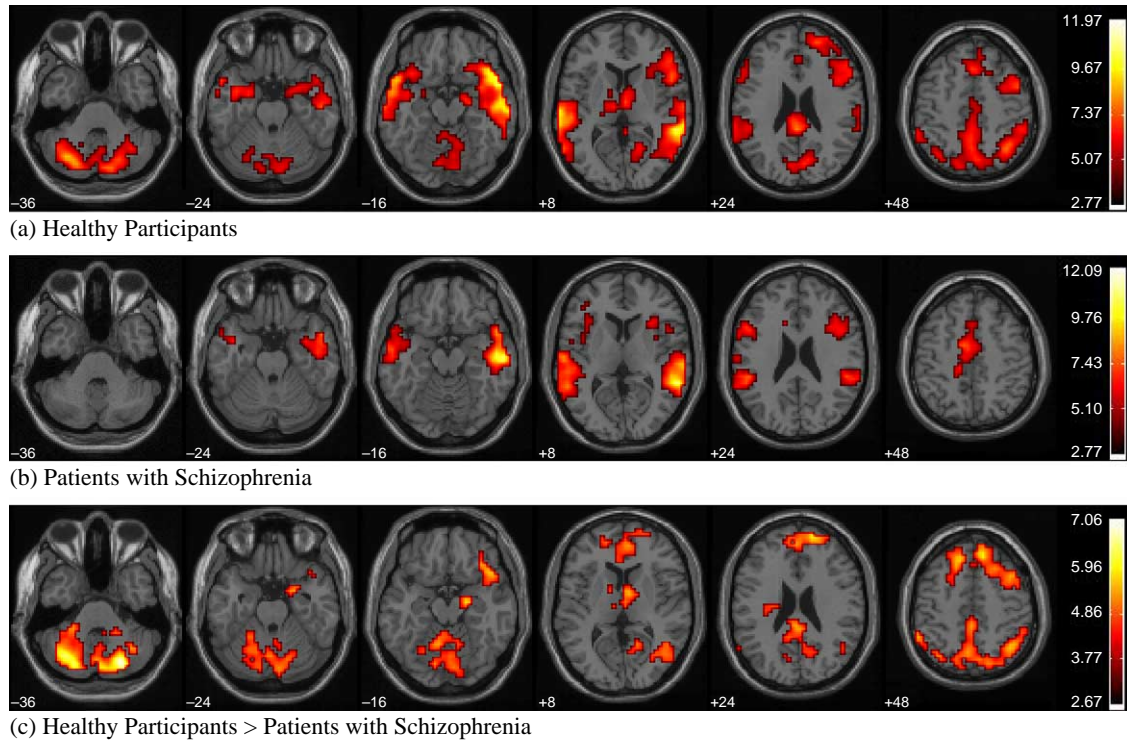


Fig. 1. Illustration of the significant clusters of activation observed during novel stimulus processing relative to the nontarget stimulus baseline in (a) healthy participants and (b) patients with schizophrenia. Part (c) illustrates the significant clusters in which healthy participants demonstrated a greater haemodynamic response than patients with schizophrenia during novel stimulus processing relative to the nontarget baseline. Data are presented in the modified Talairach space used in SPM99, and rendered onto transaxial slices of a standard reference brain according to neurological convention (i.e., the left hemisphere is illustrated on the left). From left to right, the transaxial slices are located at $z = -36, -24,$ and -16 mm below, and $8, 24,$ and 28 mm above, the AC-PC plane. The images are thresholded at a height threshold corresponding to a significance level of $p \leq 0.005$ uncorrected for multiple comparisons conducted throughout the whole brain. The clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

cluster of 42 voxels ($p = 0.014$, uncorrected) in the left posterior intraparietal sulcus, and another cluster of 32 voxels ($p = 0.028$, uncorrected) in the left inferior-middle frontal gyri, exceeded threshold, but neither of these clusters were significant after correcting for multiple comparisons.

3.2.2.2. Novel relative to target stimulus processing: patients with schizophrenia. Unlike the healthy participant data, the second-level, one-sample t -test conducted on patient data revealed three significant clusters of activation remaining after whole-brain correction. These were located bilaterally in the temporal lobes (including the temporoparietal junction) and in the left middle-inferior frontal cortex (see Table 3).

3.2.2.3. Group by task interaction. The direct comparison of the patient and healthy data for the contrast of novel relative to target stimulus processing did not reveal any voxels in which patients demonstrated significantly greater activity than healthy participants, although there was a trend for relative hyperactivity in patients bilaterally in the temporal lobes during novel relative to target stimulus processing (i.e., in the left temporoparietal junction, the peak voxel of activity was at xyz co-ordinate = $-64 -36 0$, $t = 2.80$, $p = 0.004$ uncorrected; in the right hemisphere, the peak voxel of activation lay more anteriorly in the middle temporal gyrus at xyz co-ordinate = $60 -12 -8$, $t = 3.40$, $p = 0.001$ uncorrected). The comparison between groups also revealed a single significant cluster of activation comprising 91 voxels in the basal

Table 3

Selected local maxima contained within the three significant clusters of activation in which novel stimulus processing elicited a greater haemodynamic response than target stimulus processing in patients with schizophrenia

Functional anatomic area (Brodmann area)	Talairach co-ordinates			<i>t</i> score
	<i>x</i>	<i>y</i>	<i>z</i>	
<i>Dorsal and ventral frontal cortex</i>				
L. middle frontal gyrus (9/46)	−56	16	36	4.50 ^c
L. middle frontal gyrus (8/6)	−44	20	48	4.12 ^c
L. inferior frontal gyrus (9/45)	−52	20	24	4.29 ^c
<i>Other neocortex</i>				
L. superior temporal gyrus (22)	−64	−44	12	4.10 ^b
L. middle temporal gyrus (21)	−68	−36	0	6.92 ^b **
R. superior temporal gyrus (22)	56	−36	4	3.65 ^a
R. middle temporal gyrus (21)	56	−12	−8	7.29 ^a **

Clusters from which the voxels derive are indicated with a superscript label (a–c) and described in the note to the table.

L.=Left, R.=Right. Cluster information (number of voxels in cluster, and cluster *p* value after correcting for multiple comparisons): for healthy participating data: a=116 voxels, *p*=0.001; b=65 voxels, *p*=0.019; c=64 voxels, *p*=0.021. Probability of achieving the *t* score in the voxel after correcting for multiple comparisons: ***p*<0.005.

forebrain in which healthy participants exhibited greater activation than patients during target relative to novel stimulus processing. The cluster incorporated limbic–paralimbic cortex and the ventral striatum; however, this result is not directly relevant to the question addressed in this paper.

4. Discussion

This study sought to localise functional abnormalities associated with disturbed involuntary orienting to salient novel stimuli in schizophrenia. Marked functional differences apparent between the groups suggest that the reorienting of processing resources to salient novel stimuli is disturbed in schizophrenia. Given that the abnormalities were observed within a sample of partially remitted patients characterised by low levels of symptomology, such dysfunction may constitute a core/trait abnormality in schizophrenia. In the following sections, we discuss first the abnormalities that are suggestive of a difficulty in reorienting processing resources away from the central task of detecting and responding to the task-relevant target stimuli, and subsequently, those abnormalities that provide tentative support for previous reports of increased distractibility by task-irrelevant novel stimuli in patients with schizophrenia.

4.1. Disturbed reorienting to novel stimuli

In healthy individuals, results converged with existing neuroimaging (Downar et al., 2002; Kiehl et al., 2001a,b), intracranial recording (Halgren et al., 1998), and lesion (Daffner et al., 2000; Knight, 1984, 1996; Knight et al., 1989) data in demonstrating the recruitment of a distributed corticolimbic network of brain sites when attentional resources are involuntarily reoriented away from an ongoing target detection task to incidentally process infrequent novel events. This network is similar to that activated in healthy participants during the processing of task-relevant target events (Kiehl et al., 2001a,b; Laurens et al., 2005), implying that a corticolimbic network may support the processing of salient exogenous stimuli in general. Many of these brain areas were active during novelty processing in patients with schizophrenia, indicating that relative hypoactivity in patients is not generalised throughout the network supporting novelty processing. However, multiple loci of dysfunction appear to contribute to the attentional orienting abnormalities observed in schizophrenia, including heteromodal association cortex at the intraparietal sulcus-precuneus and dorsal frontal cortex, and in paralimbic cortex in the rostral anterior cingulate cortex (extending into medial frontal cortex) and in the posterior cingulate cortex. Other regions of relative underactivity in patients were observed in

the right hemisphere only, including paralimbic cortex in the frontal operculum, the amygdala–hippocampus–parahippocampal gyrus, and cortex at the temporo-parietal-occipital junction. Subcortically, bilateral areas in the thalamus, the basal ganglia, and the cerebellum were underactive in patients relative to healthy participants.

ERP research examining novelty oddball processing in brain-lesioned patients has emphasised the importance of intact limbic cortex for attentional orienting to novel events (Knight, 1996). Mesulam (1998) described how influences from the limbic cortex are channelled via paralimbic cortex to the heteromodal frontoparietal association areas that are involved in perceptual elaboration and behavioural planning, so that incoming information may be processed according to its significance (saliency) rather than merely according to the surface properties of the stimulus. Dysfunction within the right amygdala–hippocampal complex and widespread paralimbic cortex suggests that patients may be less engaged by the novel stimuli, and therefore, less able to effectively assess their potential significance for ongoing behaviour. Limbic–paralimbic cortex dysfunction likely also impacts directly on frontoparietal association areas. Corbetta and Shulman (2002) posit that, within a ventral frontoparietal network that is predominantly right-lateralised, ventral frontal areas function to evaluate the novelty of a stimulus, whereas cortex at the temporoparietal junction is involved in determining the stimulus' behavioural significance. Whilst activation of the ventral frontal cortex was largely preserved in patients with schizophrenia, activity at the right temporo-parietal-occipital junction was reduced relative to healthy participants. Thus, patients may retain the ability to evaluate novelty per se, yet experience difficulty in extracting the relevance (or rather, irrelevance) of the novel stimuli for subsequent behaviour. Marked abnormality in patients during novelty processing was also apparent within a dorsal frontoparietal system (embracing the intraparietal sulcus and the superior frontal cortex) that is involved in identifying the characteristics of salient events and in specifying cognitive plans/intentions that target these events for behaviour (Corbetta and Shulman, 2002). Detection of salient events by the ventral frontoparietal system interrupts activity in the dorsal network so that attention is reoriented as to

reorient attention from ongoing cognition to process the salient events. Dorsal frontoparietal hypoactivity suggests that patients experience particular difficulty in reorienting processing resources when a salient novel stimulus interrupts the current task set (i.e., they experience a breakdown in the co-ordinated function of the dorsal and ventral frontoparietal systems that is necessary for orienting to salient stimuli). Cerebellar and subcortical (thalamus and basal ganglia) function were also prominently disturbed in patients during orienting to novel stimuli, in spite of there being no requirement to respond overtly to these stimuli. Andreasen et al. (1998, 1999) place particular emphasis on disordered function of the cerebellum and thalamus in the 'cognitive dysmetria' model of schizophrenia, in which disruption in prefrontal–thalamic–cerebellar connectivity produces difficulties in prioritising, processing, co-ordinating, and responding to information, all of which are relevant to successful performance of the novelty oddball paradigm. The results from the current analysis, however, suggest that dysfunction during the processing of salient novel stimuli is more widespread, and in particular, encompasses critical disturbance in higher processing centres located within limbic and paralimbic cortex.

4.2. Increased distractibility by novel stimuli

Patients with schizophrenia may experience an increased vulnerability to distraction by task-irrelevant stimuli (Braff, 1993; Grillon et al., 1991). In this study, patients showed significant overactivity bilaterally in the anterior temporoparietal junction during novel relative to target stimulus processing, although this effect was not significantly greater than in healthy participants after correction for multiple comparisons across the entire brain. In contrast, in the right posterior temporoparietal junction, patients exhibited significantly less activation than healthy subjects. As the temporoparietal junction is concerned particularly with determining the behavioural significance of a salient event (Corbetta and Shulman, 2002), the altered pattern of differential activation for novel and target stimuli suggests that patients engage an aberrant mechanism for determining behavioural relevance, possibly predisposing to greater distractibility. Nevertheless, we emphasise that the relative

overactivity in patients was significant prior to applying a conservative correction for multiple comparisons only.

All but one of the patients recruited into the current experiment were medicated with antipsychotics. Thus, it is possible that medication status may contribute to the results obtained in this study. However, ERP research has shown that the amplitude reduction in the P3a elicited by novel stimuli in patients with schizophrenia is not dependent on medication status (cf. Grillon et al., 1991; Merrin and Floyd, 1994; van der Stelt et al., 2004). Further research using previously unmedicated first-episode patients with schizophrenia will provide an opportunity to assess whether a similar pattern of functional abnormality during salient stimulus processing is present prior to the commencement of neuroleptic treatment. Regardless of whether the observed effect is secondary to medication status or represents a residual primary deficit that is only partially responsive to medication, in the absence of a reasonable alternative to neuroleptic treatment, the finding of decreased efficiency during information processing in patients with schizophrenia is pertinent to understanding the challenges patients encounter daily.

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