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Abnormal function of the brain system supporting motivated attention in medicated patients with schizophrenia: an fMRI study

PETER F. LIDDLE*†, KRISTIN R. LAURENS†, KENT A. KIEHL AND ELTON T. C. NGAN

Department of Psychiatry, University of British Columbia, Vancouver BC, Canada

ABSTRACT

Background. Patients with schizophrenia have an impaired ability to generate activity that is appropriate to current circumstances and goals.

Method. We report a study using functional magnetic resonance imaging (fMRI) to examine cerebral activity during a three-tone auditory oddball target detection task in a sample of 28 patients with schizophrenia and 28 healthy controls.

Results. The patients exhibited significantly less activation in response to target stimuli relative to baseline in an extensive set of sites in association neocortex, paralimbic cortex, limbic structures and subcortical nuclei, yet demonstrated a normal level of activation in the sensorimotor cortex. Comparison of activity elicited by rare target stimuli with that elicited by equally rare novel stimuli makes it possible to distinguish cerebral activity associated with attention to behaviourally salient stimuli from activity associated with attending to other attention-capturing stimuli. This comparison revealed that the patients with schizophrenia also exhibited a deficit in activation of basal forebrain areas that mediate motivation during the processing of behaviourally salient stimuli, including the amygdala, ventral striatum, orbital frontal cortex and rostral anterior cingulate cortex.

Conclusion. Patients with schizophrenia have a deficit in function of the brain system concerned with mediating motivation, in addition to a more general deficit in the cerebral response to attention-captivating stimuli.

INTRODUCTION

The characteristic symptoms of schizophrenia include disorganization and impoverishment of mental and motor activity (Bilder *et al.* 1985; Liddle, 1987; Arndt *et al.* 1991). These symptoms appear to reflect an impaired ability to generate activity that is appropriate to current circumstances and goals. For example, symptoms reflecting impoverishment or disorganization of mental activity are associated, respectively, with a reduction in the rate of correct responses to target stimuli and an excess of errors of commission in response to non-target stimuli during a continuous performance task in which the participant is required to respond only to specified target stimuli (Frith *et al.* 1991). These observations indicate impaired mechanisms for attending and responding to behaviourally salient stimuli.

A large body of evidence indicates that coordinated activity in an extensive network of cortical and limbic brain regions acts to direct attention towards sensory stimuli that are relevant to an individual's current goals (Mesulam, 1998). Mesulam (1998) proposes that

* Address for correspondence: Professor Peter F. Liddle, Division of Psychiatry, University of Nottingham, A Floor, South Block, Queen's Medical Centre, Nottingham NG7 2UH, UK.
(Email: peter.liddle@nottingham.ac.uk)
† These authors contributed equally to this work.

motivational influences from limbic structures (hippocampus and amygdala) are channelled via paralimbic cortex (incorporating the cingulate gyrus, parahippocampal gyrus, and cortex in the frontal operculum) to neocortical heteromodal association areas that are involved in extracting relevant features from sensory stimuli and planning of behavioural responses. The hippocampus and amygdala can also influence the function of frontal regions involved in the preparation of responses via their projections to the corpus striatum, which is a cardinal regulatory node in the cortico-striato-thalamo-cortical loops that modulate the activity of the frontal cortex (Alexander *et al*. 1986). Thus, limbic structures in the medial temporal lobe, paralimbic cortex, and the corpus striatum are all potentially important components of the mechanism for processing sensory information according to its salience for goal-orientated behaviour, rather than merely according to the intrinsic properties of the stimulus.

The three-tone auditory oddball target detection task is an informative procedure for investigating the cerebral mechanisms involved in attending to behaviourally salient stimuli. In this task, occasional target stimuli which require a response are presented against a background of repeated standard stimuli and occasional novel stimuli to which no response is required. Reduction in the amplitude of the P300 event-related electrical potential elicited by target stimuli in the auditory oddball task is one of the most frequently replicated abnormalities of brain function in schizophrenia (Jeon & Polich, 2003; Bramon *et al*. 2004).

Studies of brain activity using fMRI elicited during the oddball target detection task in healthy individuals reveal that processing of target stimuli is associated with activity in many brain sites, including heteromodal neocortical sites in parietal and frontal cortex, and also limbic, paralimbic and subcortical structures (Clark *et al*. 2000; Braver *et al*. 2001; Kiehl *et al*. 2001*a*; Ardekani *et al*. 2002). There have been few published functional imaging studies of auditory oddball target detection in schizophrenia. Using single photon emission tomography, Shajahan *et al*. (1997) found that patients with schizophrenia exhibited activity in the superior temporal gyrus, but not in the frontal cortex, during oddball target detection. In a small fMRI study of 11 patients and 11 healthy controls, Kiehl & Liddle (2001) demonstrated that patients with schizophrenia exhibit significantly less activity than healthy controls within designated areas of neocortex and paralimbic cortex in frontal, parietal and temporal lobes, and in the thalamus. In a recent study of 18 patients and 18 controls, Kiehl *et al*. (2005) confirmed the findings of Kiehl & Liddle (2001) and also demonstrated diminished activation in patients in additional areas including the amygdala.

The target tones in the three-tone oddball task attract attention not only because they have salience for behaviour, but also because they are relatively rare. The novel tones are equally rare, but do not demand a behavioural response. Therefore, examination of the contrast between brain activation elicited by target tones with that elicited by novel tones is informative about the brain activity specifically associated with attending to a behaviourally salient stimulus, irrespective of rarity. The hypothesis that patients with schizophrenia suffer a specific deficit in directing attention to behaviourally relevant stimuli leads to the prediction that the deficit in limbic function will be most apparent in the contrast of target processing with novel stimulus processing.

In this paper we report an fMRI study of cerebral activity elicited by target stimuli during the three-tone auditory oddball task, in 28 patients and 28 healthy controls. The first objective of the study was to confirm that patients with schizophrenia exhibit decreased activity during target processing in the neocortical, paralimbic and thalamic sites reported by Kiehl & Liddle (2001) and by Kiehl and colleagues (2005). The second objective was to test the hypothesis that patients with schizophrenia exhibit decreased activity in limbic structures that is most apparent in the contrast of target processing with novel stimulus processing.

METHOD

Participants

Twenty-eight healthy adults (seven female) and 28 patients with schizophrenia (nine female), all of whom provided written informed consent, participated in the study. An additional patient was recruited but experienced claustrophobia

in the scanner and could not complete the experimental task. In each group, all but one participant 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 out-patients recruited from community mental health teams in Vancouver, British Columbia, and out-patient programmes at the University of British Columbia Hospital. All patients met DSM-IV criteria (APA, 1994) 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. Mean duration of illness (i.e. time elapsed since diagnosis) was 7 years (S.D. = 7·2), with a range spanning 1–24 years.

All patients except two received atypical antipsychotics as their primary medication during 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), while seven patients received risperidone (mean dose: 3·4 mg/day, range 2–6), and one patient received clozapine (500 mg/day). One patient received a typical antipsychotic as 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 antidepressants ($n=11$).

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).

Healthy participants were medication-free volunteers without history of neurological or Axis I psychiatric illness. Participant groups did not differ significantly in age [patients 31·6 years (S.D. = 10·1), controls 28·2 years (S.D. = 8·9)], parental socioeconomic status [assessed using the scale of Hollingshead & Redlich (1958) (patients 3·2 (S.D. = 1·5), controls 3·0 (S.D. = 1·3)]; or intellectual functioning [assessed using the Quick Test (Ammons & Ammons, 1962), patients 104 (S.D. = 11·8), controls 109 (S.D. = 11·2)].

Task procedure and imaging parameters

Two scanning runs of 244 auditory stimuli each were presented to participants, and behavioural responses to the stimuli recorded, as in the study by Kiehl & Liddle (2001). Auditory stimuli comprised three classes: repeating target stimuli (1500 Hz tones; probability of occurrence 0·10); novel stimuli (non-repeating synthesized digital noises; probability 0·10); and repeating standard stimuli (1000 Hz tones; probability 0·80). Three to five standard stimuli preceded each occurrence of a target or novel stimulus. Reaction times were computed for motor responses committed within 100–2100 ms post-stimulus. Errors of commission included responses to novel and standard stimuli within this time window, while errors of omission constituted a failure to respond to target stimuli during this time.

Images were acquired as described in Kiehl & Liddle (2001), using a standard GE 1.5T system fitted with a Horizon Echo-speed upgrade (GE Healthcare Technologies, Waukesha, WI, USA) [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)].

Image processing

Functional images were reconstructed offline, realigned, normalized to modified Talairach stereotaxic space, resliced into 4 mm × 4 mm × 4 mm voxels, smoothed with an 8-mm full-width at half-maximum Gaussian kernel, and high- and low-pass filtered using the procedures described by Friston and co-workers (1995) and detailed in Laurens *et al.* (2005*a*) using Statistical Parametric Mapping 99 (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Estimated movement parameters were incorporated into the analysis

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as covariates of no interest (Friston *et al.* 1996), and a Group (schizophrenic patients, healthy participants) × Movement (translation, rotation) × Displacement Axis (x, y, z) analysis of variance (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.

Statistical analysis was performed within each voxel using the general linear model approach implemented in SPM99. 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 standard events ('standard false alarms'). The standard events were treated as a baseline and not explicitly modelled. A high-pass filter was applied to remove noise associated with low frequency confounds (e.g. respiratory artefact).

For each participant, a contrast image that compared target processing relative to the baseline of processing repeated standard stimuli was entered into a series of second-level random-effects analyses. Separate one-sample *t* tests within each group [27 degrees of freedom (df)] identified voxels in which there was significant activation during target processing relative to baseline processing within that group; and a two-sample *t* test (with 54 df) identified voxels in which there were significant differences between the patient and control groups. In addition, a second-level analysis comparing the groups using analysis of covariance (ANCOVA), with each participant's mean reaction time to target stimuli as a covariate (with 52 df), was performed to allow for variation between individuals in reaction time.

Similarly, contrast images representing target processing minus novel stimulus processing for each participant were entered into second-level random-effects analyses, including separate *t* tests (27 df) within each group and a two-sample *t* test (with 54 df) to identify significant differences between the patient and control group in the contrast of target stimuli with novel stimuli. Only the target processing analyses (relative to the non-target baseline and to novel stimuli) are reported in this paper. Novel processing analyses are reported in a separate study (Laurens *et al.* 2005*a*). To optimize power to detect group effects extending over a spatial extent at least as large as the inter-individual variability in location of cognitive activation (of order 10 mm), we employed the significance criterion based on spatial extent of suprathreshold voxel clusters proposed by Friston and colleagues (1994). The criterion for inclusion of a voxel in a cluster was set at $p = 0{\cdot}005$ and a cluster was regarded as significant if the cluster extent was significant at level $p < 0{\cdot}05$ after correcting for multiple comparisons across the entire brain. With this criterion, clusters of 60 voxels (having radius 10 mm in the case of a globular cluster) or more, would be significant.

RESULTS

Behavioural data

Both groups exhibited few errors, but healthy participants exhibited somewhat fewer errors and were substantially faster in processing the target stimuli. Mean reaction times to target stimuli for healthy participants (398 ms, S.D. = 78) and patients with schizophrenia (569 ms, S.D. = 184) differed significantly [$t(54) = -4{\cdot}517$, $p < 0{\cdot}0001$]. Healthy participants and patients correctly responded to 99·3% and 95·2% of targets respectively. Healthy participants made errors of commission on 3·0% of novel trials and 0·03% of standard stimulus trials, while patients made errors of commission on 4·3% of novel trials and 0·13% of standard trials respectively. A Group (healthy participants, patients with schizophrenia) × Inaccuracy (misses, novel false alarms, standard false alarms) ANOVA revealed a significant main effect of Group [$F(1, 54) = 5{\cdot}573$, $p = 0{\cdot}022$], indicating that patients with schizophrenia performed the task less accurately than healthy participants. The Group × Inaccuracy interaction was not significant.

Imaging data

Target processing relative to baseline

For healthy participants, the second-level random-effects analysis revealed that target stimuli elicited significant activation in an extensive cluster of 11 595 voxels ($p < 0{\cdot}001$ corrected for multiple comparisons) embracing

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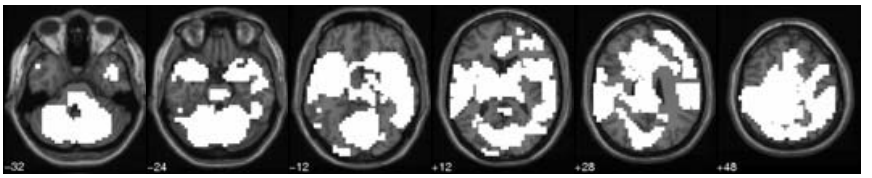
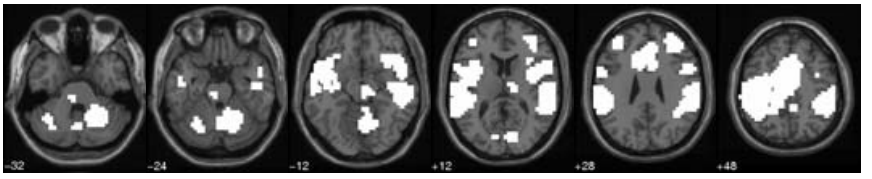
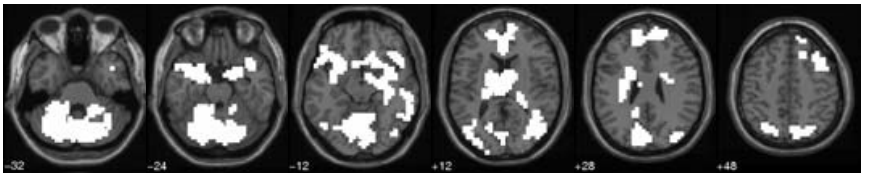


(*a*) Healthy participants



(*b*) Patients with schizophrenia



(*c*) Healthy participants > patients with schizophrenia

FIG. 1. Significant clusters of activation elicited during target stimulus processing relative to the standard stimulus baseline. (*a*) Healthy subjects; (*b*) patients with schizophrenia; (*c*) activation in healthy subjects greater than in patients with schizophrenia. Statistical maps 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). Slices are labelled with the z coordinate, measured in millimetres relative to the anterior commissure-posterior commissure (AC-PC) plane. Voxel threshold for inclusion in a cluster: $p < 0{\cdot}005$; clusters of voxels are significant at $p < 0{\cdot}05$ after correction for multiple comparisons.

neocortex bilaterally in superior and inferior parietal lobes, temporo-parietal junction, superior temporal gyrus, and lateral frontal cortex (most strongly on the right), as well as paralimbic cortex bilaterally in temporal pole and insula, and rostral and caudal anterior cortex and posterior cingulate cortex; limbic structures including amygdala and anterior hippocampus bilaterally, and other subcortical structures including the ventral striatum, thalamus and cerebellum bilaterally. For many voxels within the cluster, *t* statistic values were in excess of 5·72, corresponding to a probability level of 0·05 corrected for multiple comparisons throughout the brain (see Fig. 1*a* and Table 1).

In the one-sample *t* test conducted on data from the 28 patients with schizophrenia, eight significant clusters of activation ($p \leqslant 0{\cdot}05$ corrected for multiple comparisons) were observed for target processing relative to the non-target baseline. The total number of voxels included in these clusters was 5131. These clusters are illustrated on transaxial slices in Fig. 1*b*, and voxel-level statistics from selected local maxima within the clusters are provided in Table 1. Significant activation was apparent in many brain regions, particularly in caudal anterior cingulate cortex and the sensorimotor brain areas typically activated during right-handed responding (e.g. the left postcentral gyrus and anterior SMA). Indeed, the maximal *t* score reported for patients in the left postcentral gyrus [i.e. $t(27) = 18{\cdot}08$, $p < 0{\cdot}001$ corrected, at coordinate x, y, z = −40, −32, 56] was greater than that observed in the left postcentral gyrus for the healthy participant group [i.e. $t(27) = 12{\cdot}90$, $p < 0{\cdot}001$ corrected, at coordinate x, y, z = −36, −44, 60], demonstrating that the experimental procedure and analysis strategy were capable of identifying reliable activation during target processing in both groups of participants. The significant clusters of activation in patients also incorporated paralimbic cortex at the frontal operculum and caudal anterior cingulate cortex,

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Table 1. *Selected local maxima contained within significant clusters of activation observed during target stimulus processing relative to the standard stimulus baseline for (a) healthy participants and (b) patients with schizophrenia. Column (c) provides selected local maxima from within significant clusters in which healthy participants were characterized by greater activation than patients with schizophrenia (we quote voxel level statistics for information, but we employed a cluster criterion to identify significant differences between groups. All reported voxels are within significant clusters)*

	(*a*) Healthy participants				(*b*) Patients with schizophrenia				(*c*) Healthy > schizophrenia			
	Talairach coordinates				Talairach coordinates				Talairach coordinates			
Functional anatomic area (Brodmann Area)	x	y	z	*t* score (27 df)	x	y	z	*t* score (27 df)	x	y	z	*t* score (54 df)
Limbic–paralimbic cortex												
L amygdala	−24	−4	−20	4·15**					−20	−4	−24	4·16**
R amygdala	24	0	−24	5·08***					24	−12	−16	4·14**
L hippocampus	−32	−24	−12	3·59*								
R hippocampus	28	−32	−8	4·64***					32	−28	−12	3·42*
L anterior superior temporal sulcus	−56	8	−12	7·98***	−56	8	−8	5·71***	−36	12	−20	4·14**
R anterior superior temporal sulcus	52	12	−12	11·22***	52	12	−12	9·09***	40	16	−20	5·16***
L orbitofrontal cortex (47)	−32	20	−12	7·27***	−32	24	−4	6·83***	−32	24	−12	3·97**
R orbitofrontal cortex (47)	36	24	−16	9·56***	28	24	−4	8·13***	28	24	−20	2·95*
L anterior insula (13)	−44	0	8	10·11***	−44	−4	8	8·91***	−24	16	−8	4·82***
R anterior insula (13)	32	16	0	10·15***	36	16	0	9·82***	40	0	−12	2·96*
Subcallosal gyrus (25)	12	24	−12	7·03***					12	24	−12	4·81***
Rostral anterior cingulate cortex (24/32)	0	36	24	6·81***	8	36	20	3·00*	0	36	12	4·92***
Posterior cingulate cortex (23/31)	4	−40	24	7·49***					4	−40	24	3·13*
Temporoparietal junction												
L superior temporal gyrus (22)	−64	−36	8	8·89***	−60	−36	12	5·11***				
R superior temporal gyrus (22)	52	−40	4	8·53***	60	−44	8	7·82***				
L inferior parietal lobule (40/39)	−60	−48	24	6·27***	−64	−24	28	7·96***				
R inferior parietal lobule (40/39)	64	−36	24	5·96***	56	−36	32	5·45***				
Intraparietal sulcus												
L superior parietal lobule (7)	−24	−56	60	8·06***	−28	−48	64	8·53***	−28	−68	52	4·4***
R superior parietal lobule (7)	28	−52	60	6·18***					28	−68	48	3·1*
L inferior parietal lobule (40)	−60	−32	40	11·96***	−44	−40	48	9·29***	−32	−60	44	2·94*
R inferior parietal lobule (40)	48	−40	56	10·36***	48	−44	48	5·48***	36	−56	44	3·3*
Frontal cortex												
L middle-inferior frontal gyri	−16	44	12	6·11***	−36	44	24	5·33***	−48	32	−8	3·02*
L superior-middle frontal gyri	−36	−16	64	8·49***					−40	16	52	2·74*
R middle-inferior frontal gyri	56	12	24	8·27***	52	12	20	5·13***	40	12	40	3·38*
R superior-middle frontal gyri	32	−12	52	6·56***	32	0	56	3·47*	40	12	48	3·55**
Subcortical structures												
L thalamus	−12	−20	4	8·43***	−12	−20	4	4·36**	−12	−8	12	4·35**
R thalamus	4	−16	8	7·61***	12	−20	8	4·27**	8	−4	12	5·27**
L ventral striatum	−8	12	−8	7·67***					−8	12	−8	5·0**
R ventral striatum	8	8	−8	5·57**					8	12	−8	3·57*
L cerebellum	−28	−68	−36	9·45***	−32	−56	−36	4·44**	−28	−68	−36	5·77**
R cerebellum	16	−52	−28	11·17***	16	−60	−20	7·28***	20	−72	−28	4·68**

L, left; R, right.
Probability of achieving the *t* score (with no correction for multiple comparisons): *** $p < 0{\cdot}00005$, ** $p < 0{\cdot}0005$, * $p \leqslant 0{\cdot}005$.

as well as heteromodal association cortex in the temporoparietal junction and ventral and dorsal frontal areas. Activation in the intraparietal sulcus was largely restricted to the inferior bank (i.e. the inferior parietal lobule), with little activation apparent in the superior parietal lobule and precuneus, especially in the right hemisphere. Several limbic and paralimbic regions that were active in healthy participants at the equivalent significance threshold did not form part of the clusters activated in patients during target processing, including the amygdala-hippocampal complex.

The two-sample *t* test comparing activation elicited by targets relative to baseline in healthy individuals with that in patients with schizophrenia revealed three significant clusters ($p \leqslant 0{\cdot}05$ corrected for multiple comparisons) containing 3008, 234 and 93 voxels respectively, in which activation elicited in healthy participants was significantly greater than that elicited in patients. (see Fig. 1*c* and Table 1). These clusters encompassed cortex in the amygdala-hippocampal complex, paralimbic cortex in the frontal operculum, rostral and caudal anterior cingulate cortex, and posterior cingulate cortex, heteromodal association areas including bilateral frontal cortex and the intraparietal sulcus, and subcortical structures including thalamus, ventral striatum and cerebellum. The contrast that tested for regions more strongly activated during target processing in patients with schizophrenia than in healthy participants revealed no clusters of activation that were significant after correcting for multiple comparisons.

The analysis employing ANCOVA to assess the differences between the groups with reaction time as a covariate yielded very similar results to the two-sample *t* test. The contrast testing for voxels in which the activation was greater in healthy control subjects than in patients revealed two significant clusters of 3349 and 101 voxels, embracing very similar brain areas to those included in the significant clusters identified using the two-sample *t* test.

Target relative to novel stimulus processing

In healthy participants, the second-level, one-sample *t* test that tested for brain areas in which the amplitude of the fitted haemodynamic response for target events was significantly greater than that for novel events revealed a single large cluster of 6306 voxels that was significant after correction for multiple comparisons. This cluster is illustrated on transaxial brain slices in Fig. 2*a*, and selected local maxima from within the cluster are reported in Table 2. Incorporated within the cluster are bilateral heteromodal association areas in the intraparietal sulcus, in parietal cortex at the temporoparietal junction; as well as in dorsal frontal/premotor areas and posterior ventral frontal cortex, areas of limbic and paralimbic cortex, basal ganglia, thalamus and cerebellum, all of which showed significant activation in healthy participants during both target and novel stimulus processing. Thus, although this network of areas was active in healthy participants during orienting to novelty, the areas were activated more strongly by target processing.

In patients with schizophrenia, the one-sample *t* test examining the difference in response amplitude for target relative to novelty processing revealed five significant clusters of activation. These clusters encompassed a subset of the areas that were preferentially active in healthy participants for target relative to novel events (see Fig. 2*b* and Table 2). As in the healthy participants, the paralimbic areas that were active in patients during both target and novel stimulus processing were more strongly activated by the target stimuli relative to novel stimuli. Bilateral intraparietal sulcus and parietal cortex in the temporoparietal junction, as well as dorsal frontal/premotor and posterior ventral frontal areas were also more strongly activated by target stimuli than novel stimuli in patients with schizophrenia.

The two-sample *t* test that tested for areas exhibiting a Group × Task Interaction (i.e. areas in which the participant groups showed a differential pattern of activation for target relative to novelty processing and/or for novelty relative to target processing), revealed a single significant cluster of activation comprising 91 voxels (see Table 2 and Fig. 2*c*). The cluster incorporated activation in the left amygdala and in paralimbic cortex within the left frontal operculum and rostral anterior cingulate cortex, as well as subcortical activation in the basal ganglia. Examination of the data revealed that healthy participants exhibited greater activation in this area during target relative to novel stimulus processing than did patients with

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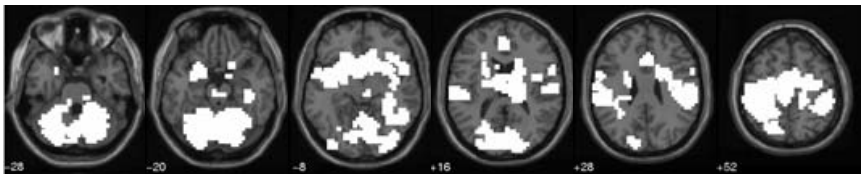
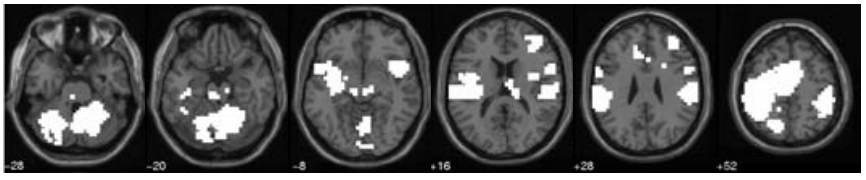
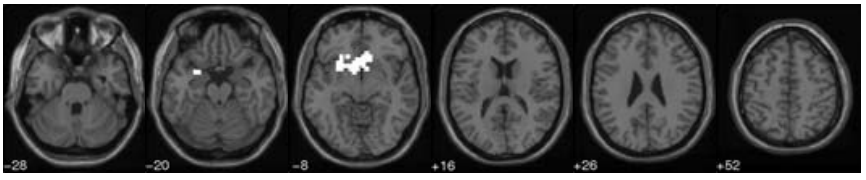


(*a*) Healthy participants



(*b*) Patients with schizophrenia



(*c*) Healthy participants > patients with schizophrenia

FIG. 2. Significant clusters of activation elicited during target stimulus processing relative to processing of novel stimuli. (*a*) Healthy subjects; (*b*) patients with schizophrenia; (*c*) activation in healthy subjects greater than in patients with schizophrenia. Statistical maps 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). Slices are labelled with the z coordinate, measured in millimetres relative to the AC-PC plane. Voxel threshold for inclusion in a cluster: $p < 0{\cdot}005$; clusters of voxels are significant at $p < 0{\cdot}05$ after correction for multiple comparisons.

schizophrenia. This effect is presented graphically in Fig. 3, which illustrates the mean magnitude of the difference in amplitude of the fitted response for target relative to novel stimuli in the healthy participant and patient groups within selected limbic and paralimbic voxels listed in Table 2. There were no significant clusters of voxels in which the patients exhibited a greater excess of activation by target stimuli relative to that for novel stimuli compared with healthy subjects.

DISCUSSION

The analysis of the activation elicited by target stimuli relative to baseline, and also relative to that elicited by novel stimuli in healthy participants closely replicates the pattern of activation reported in previous studies of healthy participants during auditory oddball target processing (Clark *et al*. 2000; Braver *et al*. 2001; Kiehl *et al*. 2001*a*; Ardekani *et al*. 2002). Furthermore, it is consistent with data from intracerebral electrical recordings by Halgren and colleagues (Baudena *et al*. 1995; Halgren *et al*. 1995*a*, *b*) who recorded stimulus-locked electrical activity from a wide range of cerebral sites, including the dorsal and ventral frontal cortex, dorsal and ventral parietal cortex, medial paralimbic cortex, and limbic regions of the medial temporal lobe, approximately 300 ms after stimulus presentation during the three-tone auditory oddball task. These observations add to the growing evidence from fMRI studies employing various simple target detection tasks that an attentional network, embracing neocortex in both upper and lower banks of the intraparietal sulcus, the temporoparietal junction and lateral frontal cortex; paralimbic cortex in the insula and cingulate gyrus; the amygdala and hippocampus; and subcortical nuclei including the ventral striatum, thalamus and cerebellum, mediates attention to behaviorally salient stimuli (Laurens *et al*. 2005*b*).

Furthermore, in accord with the findings reported by Kiehl & Liddle (2001) and by Kiehl

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Table 2. *Selected local maxima contained within significant clusters of activation observed during target stimulus processing relative to novel stimulus processing for (a) healthy participants and (b) patients with schizophrenia. Column (c) provides selected local maxima from within significant clusters in which healthy participants were characterized by greater activation than patients with schizophrenia*

	(*a*) Healthy participants				(*b*) Patients with schizophrenia				(*c*) Healthy > schizophrenia			
	Talairach coordinates				Talairach coordinates				Talairach coordinates			
Functional anatomic area (Brodmann Area)	x	y	z	*t* score (27 df)	x	y	z	*t* score (27 df)	x	y	z	*t* score (54 df)
Limbic–paralimbic cortex												
L amygdala	−24	4	−20	5·29***					−24	4	−20	2·89*
R amygdala	16	0	−16	3·24*								
L hippocampus	−28	−8	−24	2·78*	−32	−20	−12	2·97*				
R hippocampus	28	−40	0	8·30***								
L anterior superior temporal sulcus	−60	4	−4	4·81***	−56	4	4	5·20***				
R anterior superior temporal sulcus	56	8	−8	4·98***	60	8	4	5·16***				
L orbitofrontal cortex (47)	−24	16	−12	5·99***					−24	24	−12	2·97*
R orbitofrontal cortex (47)	36	24	−12	4·46**								
L anterior insula (13)	−32	0	−12	6·08***	−44	4	0	5·82***	−28	12	−8	3·89**
R anterior insula (13)	28	12	−12	5·90***	44	0	−4	5·91***				
Rostral anterior cingulate cortex (24/32)	0	40	16	4·64***	−12	36	28	3·84**	4	20	−8	3·40*
Posterior cingulate cortex (23/31)	−20	−68	8	4·50**								
Temporoparietal junction												
L inferior parietal lobule (40/39)	−56	−28	24	3·84**	−60	−44	28	3·72**				
R inferior parietal lobule (40/39)	56	−36	28	4·82**	60	−32	24	3·83**				
Intraparietal sulcus												
L superior parietal lobule (7)	−24	−56	64	7·69***	−28	−48	64	7·23***				
R superior parietal lobule (7)	28	−52	60	3·40*	28	−48	64	4·40**				
L inferior parietal lobule (40)	−36	−44	56	7·99***	−40	−52	48	4·00**				
R inferior parietal lobule (40)	48	−36	56	4·55**	36	−36	44	6·30***				
Frontal cortex												
L middle-inferior frontal gyri	−56	0	24	4·26**	−60	4	32	4·93***				
R middle-inferior frontal gyri	60	12	16	3·47*	56	8	28	4·48**				
L superior-middle frontal gyri	−36	−16	60	9·58***	−28	−20	68	9·88***				
R superior-middle frontal gyri	32	−12	52	4·96***								
Subcortical structures												
L thalamus	−12	−24	4	7·69***	−20	−20	4	4·61***				
R thalamus	8	−24	0	4·95***	8	−20	8	4·18**				
L ventral striatum	−8	8	−8	5·30***					−8	12	−8	3·84**
R ventral striatum	12	12	−8	5·98***								
L cerebellum	−20	−80	−24	7·64***	−24	−60	−24	7·44***				
R cerebellum	16	−56	−24	11·72***	12	−56	−20	9·61***				

L, left; R, right.
Probability of achieving the *t* score (with no correction for multiple comparisons): *** $p < 0{\cdot}00005$, ** $p < 0{\cdot}0005$, * $p \leqslant 0{\cdot}005$.

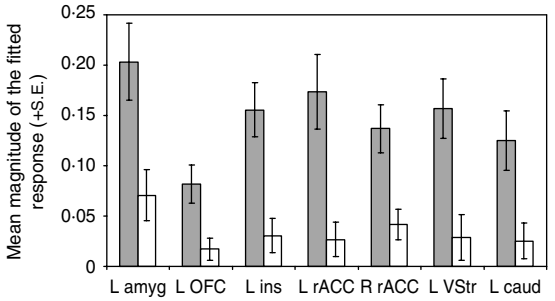

FIG. 3. Bar chart illustrating the magnitude of the increase in BOLD response elicited during target processing relative to novel stimulus processing, in healthy controls (▩) and in patients with schizophrenia (□) at selected limbic and paralimbic voxels. (L amyg, left amygdala; L OFC, left orbitofrontal cortex; L ins, left insula; L rACC, left rostral anterior cingulate cortex; R rACC, right rostral anterior cingulate cortex; L VStr, left ventral striatum; L caud: left caudate nucleus.

et al. (2005), the activity elicited by target stimuli is significantly less in patients with schizophrenia at many sites throughout this network. Not only is the activation less at neocortical and paralimbic sites and thalamus, but also in limbic structures such as the amygdala, as observed by Kiehl *et al*. (2005), and also in the hippocampus, and in the ventral striatum. The reduction in activation at multiple sites does not reflect a failure to perform the task, as the reported analyses include only those trials in which the participants responded correctly. Nor is the reduction due to a global reduction in brain activity, as the patients exhibited a normal level of activation in the left primary sensorimotor cortex. Although the patients reacted to targets significantly more slowly than the healthy controls, similar differences in activation between the patients and control groups were observed after allowing for individual variation in reaction time.

The widespread deficit in cerebral activation in patients compared with healthy controls for the contrast of target processing with the baseline condition (processing standard, non-target stimuli) demonstrates a deficient cerebral response in the brain regions activated by attention-captivating stimuli. The degree to which this deficit is specifically associated with attention to task-relevant stimuli is best determined by comparing activity elicited by target stimuli with that elicited by task-irrelevant novel stimuli. The comparison between the patient and healthy groups for the contrast of target processing compared with the processing of novel stimuli did not reveal significant differences in neocortical regions, implying that the deficit in activation of neocortical areas in patients is similar for both target and novel stimuli, and therefore might best be interpreted as a deficit in cerebral response to attention-captivating stimuli, irrespective of their task relevance. However, in a cluster of voxels embracing amygdala, ventral striatum, orbital frontal cortex and sub-genual rostral anterior cingulate cortex, the patients exhibited not only significantly less activation by target stimuli compared with baseline, but also significantly less activation by target stimuli compared with novel stimuli. This group of basal forebrain areas plays a crucial role in mediating motivational influences. In particular, the ventral striatum is a cardinal regulatory site in the limbic/paralimbic cortico-striato-thalamo-cortical loop that modulates the recruitment of frontal cortex in accord with goals (Alexander *et al*. 1986). This regulatory role of the ventral striatum is mediated via input from amygdala/hippocampus, and also by dopaminergic input from ventral tegmental area (Brown & Pluck, 2000). Because motivation was not directly manipulated, this study does not provide explicit evidence that the differences between groups were due to differences in motivation. However, the observation that the patients exhibited decreased activity in basal forebrain areas that mediate motivational influences is consistent with the hypothesis that schizophrenia is associated with a specific deficit in function of the brain system that mediates motivation.

In a recent study employing a visual oddball task, Morey *et al*. (2005) observed decreased contrast between the anterior cingulate cortex activity elicited by target stimuli and that elicited by novel stimuli in patients with schizophrenia, but they employed a region of interest analysis in which the anterior cingulate region embraced mainly dorsal rather than ventral regions, thereby making it difficult to draw conclusions regarding the ventral regions.

Because dopaminergic projections from the ventral tegmental area modulate the cortico-striato-thalamo-cortical loops (Brown & Pluck, 2000), it might be expected that dopamine-blocking antipsychotic medication would affect the observed activation in the basal-forebrain

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regions that mediate motivation. On the one hand, dopamine blockade might be expected to impede the regulatory role of the ventral tegmental area on the ventral striatum and hence to impair function of the motivated attention system. In a study of medication-naïve, first-episode cases of schizophrenia, Liddle *et al.* (2000) demonstrated that treatment with the atypical antipsychotic risperidone was associated with reduction in metabolism in the ventral striatum. This observation raises the possibility that the fact that the patients in this study were receiving antipsychotic medication might account, at least in part, for the observed underactivity in the ventral striatum and associated forebrain regions. On the other hand, the bulk of relevant evidence suggests that antipsychotic medication does not exacerbate the P300 deficit in schizophrenia. Two recent meta-analyses (Jeon & Polich, 2003; Bramon *et al.* 2004) conclude that the P300 deficit is of similar magnitude in medicated and unmedicated cases. There have been few longitudinal studies, but the available evidence indicates that treatment with atypical antipsychotics reduces the P300 deficit. For example, in the context of a double-blind treatment trial, Umbricht *et al.* (1998) found that treatment with the atypical antipsychotic clozapine, but not the typical antipsychotic haloperidol, was associated with an increase in P300 amplitude. In an open-label study, Umbricht *et al.* (1999) found that treatment with risperidone led to a reduction in prolonged P300 latency, but did not affect the reduced P300 amplitude. It is probable that the amplitude of the P300 detected at the scalp is determined mainly by cerebral activity in superficial cortical areas, and is at best only an indirect reflection of activity in deep structures such as the ventral striatum, amygdala, and hippocampus.

Nonetheless, in a small pilot study using fMRI in first-episode schizophrenia (Kiehl *et al.* 2001*b*) we observed that activation of the amydgdala and hippocampus associated with target detection in the three-tone auditory oddball paradigm employed in this study increased during 6 weeks' treatment with risperidone. On balance, it is unlikely that the deficit in activation of the basal forebrain regions that mediate motivational influences observed in the current study, in which the majority of patients were receiving atypical antipsychotic medication, was due to the effects of treatment; it is in fact possible that the treatment partially alleviated a pre-existing deficit. The apparent paradox of atypical antipsychotic medication causing a reduction in steady-state metabolism in the ventral striatum (Liddle *et al.* 2000) yet producing a partial alleviation of the P300 deficit in schizophrenia (Umbricht *et al.* 1998, 1999) might be explained if atypical antipsychotics act to reduce behaviourally irrelevant activation in ventral striatum, thereby facilitating recruitment of this system for processing behaviourally relevant stimuli.

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DECLARATION OF INTEREST

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