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Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis

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Background Neuroanatomical abnormalities are a well-established feature of schizophrenia. However, the timing of their emergence and the extent to which they are related to vulnerability to the disorder as opposed to psychotic illness itself is unclear.

Aims To assess regional grey matter volume in the at-risk individuals who subsequently developed psychosis.

Method Magnetic resonance imaging data from at-risk individuals who developed psychosis (n=12) within the following 25 months were compared with data from healthy volunteers (n=22) and people with first-episode psychosis (n=25).

Results Compared with healthy volunteers, individuals who subsequently developed psychosis had smaller grey matter volume in the posterior cingulate gyrus, precuneus, and paracentral lobule bilaterally and in the left superior parietal lobule, and greater grey matter volume in a left parietal/posterior temporal region. Compared with first-episode patients, they had relatively greater grey matter volume in the temporal gyrus bilaterally and smaller grey matter volume in the right lentiform nucleus.

Conclusions Some of the structural brain abnormalities in individuals with an at-risk mental state may be related to an increased vulnerability to psychosis, while others are associated with the development of a psychotic illness.

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Structural imaging studies clearly indicate that schizophrenia is associated with neuroanatomical abnormalities, with the most replicated findings being ventricular enlargement and reductions in frontal and medial temporal lobe grey matter volume (Wright *et al*, 2000; Shenton *et al*, 2001). However, the timing of these brain changes in relation to the onset of the disorder is unclear (Keshavan *et al*, 2005). A recent meta-analysis suggested that some of these abnormalities were present at first onset, while others emerge later during the illness (Vita *et al*, 2006). Qualitatively similar volumetric abnormalities are also present in at-risk populations such as first-degree relatives and the healthy co-twins of patients with schizophrenia (Lawrie *et al*, 1999; Seidman *et al*, 1999; Staal *et al*, 2000; Baare *et al*, 2001; Job *et al*, 2003; Hulshoff Pol *et al*, 2004), which would be in accordance with the neurodevelopmental hypothesis of schizophrenia (Murray & Lewis, 1987; Weinberger, 1987). However, the only longitudinal studies of people with an at-risk mental state (ARMS) (Pantelis *et al*, 2003) conducted so far suggest that further brain changes occur close to or during transition to psychosis.

We have previously studied the group with an at-risk mental state as a whole (Borgwardt *et al*, 2006, 2007) but this group is very heterogeneous, with many of the patients not yet having developed psychosis. In the present study, regional grey matter volume in individuals with an at-risk mental state who later developed psychosis was compared with healthy controls and patients with first-episode psychosis using a voxel-based morphometric approach. We aimed to identify those brain abnormalities in subjects who later developed psychosis that were already present before the psychosis emerged as opposed to merely being secondary consequences of psychosis. Based on what is known about the timing of different magnetic resonance imaging (MRI) abnormalities in psychosis, we hypothesised that the participants with at-risk mental state who later developed psychosis would show brain abnormalities in insula and temporal and cingulate cortex relative to controls. We further hypothesised that these abnormalities would be qualitatively, but not yet quantitatively similar to those seen in patients with first-episode psychosis.

METHOD

Participants

Patients were recruited between 1 March 2000 and 28 February 2004 from a service area covering 200 000 habitants in and around Basel, Switzerland, and were part of a larger early psychosis project, the FEPSY study (Früherkennung von Psychosen; early detection of psychosis).

The FEPSY study (Riecher-Rössler *et al*, 2006, 2007) is an open, prospective study aimed at identifying and investigating individuals at risk of psychosis, and patients experiencing a first psychotic episode. Each individual identified as being at risk for psychosis by a screening procedure was thoroughly examined using a multi-level approach including structural neuroimaging and electrophysiological and cognitive investigations covering potential predictors of schizophrenia. All individuals with at-risk mental state have been followed up over 5 years. The study seeks a validation of the postulated risk factors and indicators for beginning psychosis by comparing those subjects who in fact developed manifest psychosis during follow-up with those who did not. All aspects (including the neuroimaging part presented here) of the study were approved by the local ethics committee of the University of Basel and written informed consent was obtained from each participant.

Here, we included 12 participants with an at-risk mental state who had developed psychosis in the follow-up period, and compared them with 22 healthy matched volunteers and 25 patients with first-episode psychosis. Participants were included in the current analysis if they agreed to an MRI scan and if the MRI sequences were of adequate quality.

Screening procedure

For screening purposes, we developed the Basel Screening Instrument for Psychosis (BSIP), a 46-item checklist based on variables which have been shown to be

Table 1 Domains of the Basel Screening Instrument for Psychosis (BSIP)

Domain	Criteria
Psychopathology	• 'Prodromal' symptoms according to DSM–III–R (first occurrence within the past 5 years and persisting up to now) • Other prodromal signs as derived from the literature (first occurrence within the past 2 years and persisting up to now) • (Pre-)psychotic symptoms (previous or current)
Social decline	• Marked deterioration of psychosocial functioning with serious consequences for work, education, relationships (occurence during the past 5 years and persisting up to now)
Drug abuse	• Regularly within the past 2 years
Psychiatric history	• Previous psychiatric disorders and treatments
Genetic risk	• Schizophrenia/psychoses in first- or second-degree relatives
At-risk age	• Age <30 years in women, <25 in men

Source Riecher-Rössler *et al*, 2007.

predictors of psychosis (Riecher *et al*, 1990; Häfner *et al*, 1991; Riecher-Rössler *et al*, 2006, 2007) such as DSM–III–R 'prodromal' symptoms, social decline, drug abuse, previous psychiatric disorders or genetic liability for psychosis (see Table 1). It is used in combination with the Brief Psychiatric Rating Scale (BPRS) to assess the severity of (pre-)psychotic phenomena. The BSIP was constructed as a screening checklist to identify those at risk and is followed by a more extensive early detection interview (details available from author on request) in a next assessment step. All assessments were conducted by experienced psychiatrists who undergo regular training.

Inclusion criteria for individuals with an at-risk mental state, patients with a first-episode and healthy volunteers

At-risk mental state transition group. The at-risk mental state group was defined using criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria (Yung *et al*, 1998) employed in previous MRI studies of patients with an at-risk mental state (Phillips *et al*, 2002; Pantelis *et al*, 2003). Inclusion thus required one or more of the following: (a) 'attenuated' psychotic-like symptoms, (b) brief limited intermittent psychotic symptoms (BLIPS), or (c) a first- or second-degree relative with a psychotic disorder plus at least two further risk factors according to the screening instrument such as a marked decline in social or occupational functioning. Inclusion because of attenuated psychotic symptoms required scores of 2 or 3 on the hallucination item, or 3 or 4 on the unusual thought content or suspiciousness items of the BPRS at least several times a week and persisting for more than 1 week. Inclusion because of BLIPS required scores of 4 or above on the hallucination item, or 5 or above on the unusual thought content, suspiciousness or conceptual disorganisation items of the BPRS, with each symptom lasting less than 1 week before resolving spontaneously.

First-episode group. The first-episode group was defined as participants who met the operational criteria for first episode psychosis described by Yung *et al* (Yung *et al*, 1998), again as used to define first episode psychosis in the previous MRI studies of the ARMS (Phillips *et al*, 2002; Pantelis *et al*, 2003). Inclusion required scores of 4 or above on the hallucination item, or 5 or above on the unusual thought content, suspiciousness or conceptual disorganisation items of the BPRS. The symptoms must have occurred at least several times a week and persisted for more than 1 week.

Control group. Healthy volunteers were recruited from the same geographical area as the other groups through local advertisements. These individuals had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, substance dependency, and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical interview.

Exclusion criteria

Age <18 years, insufficient knowledge of German, IQ <70, previous episode of schizophrenic psychosis (treated with major tranquillisers for more than 3 weeks), psychosis clearly due to organic factors or substance dependency, or psychotic symptoms within a clearly diagnosed affective psychosis or borderline personality disorder.

Clinical follow-up and transition to psychosis

All subjects were offered supportive counselling and clinical management. Transition to psychosis was monitored by means of the transition criteria of Yung *et al* (1998). During the first year of follow-up, individuals with an at-risk mental state were assessed monthly. During the second and third years, all individuals were assessed 3-monthly and thereafter once a year. The diagnosis was determined by a diagnostic interview using ICD–10 research criteria (World Health Organization, 1992) at the time of transition, then corroborated by a subsequent assessment at least 1 year post-transition using the Operational Criteria (OPCRIT) checklist for psychotic and affective illness.

Structural magnetic resonance imaging

Acquisition of magnetic resonance imaging data

Participants were scanned using a Siemens (Erlangen, Germany) Magnetom Vision 1.5 T scanner at the University Hospital Basel. Head movement was minimised by foam padding and velcro straps across the forehead and chin. A 3-D volumetric spoiled gradient recalled echo sequence generated 176 contiguous, 1 mm thick sagittal slices. Imaging parameters were: time-to-echo, 4 ms; time-to-repetition, 9.7 ms; flip angle, 12; matrix size, 200×256; field of view, 25.6×25.6 cm matrix; voxel dimensions, $1.28 \times 1 \times 1$ mm.

Analysis of grey matter volume

Image pre-processing. Optimised voxel-based morphometry pre-processing was performed with Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neurosciences, University College London). The image processing steps have been described in detail elsewhere (Ashburner & Friston, 2000; Good *et al*, 2001). The segmentation

algorithm implemented in SPM incorporates an *a priori* knowledge of the likely spatial distribution of tissue types in the brain with prior probability tissue maps derived from a large number of individuals. To ensure the most accurate segmentation possible, we created study-specific customised prior probability maps used in a previous study (Borgwardt *et al*, 2007). The pre-processing stages were as follows: (a) scans were segmented into probabilistic maps of grey and white matter and cerebrospinal fluid with a modified mixture model clustering algorithm; (b) the segmented grey matter map was mapped to a grey matter template, and the derived warping parameters were applied to the original T1-weighted image to map it into standard space (this procedure prevents skull and other non-brain voxels from contributing to the registration, while avoiding the need for explicit skull-stripping); (c) the registered image was then re-segmented, which is necessary because the *a priori* knowledge incorporated into the SPM2 segmentation algorithm means that it works optimally on images in standard space. The segmented maps were then modulated through multiplying voxel values by the Jacobian determinants from the spatial normalisation to correct for volume changes. Finally, all normalised, segmented, modulated grey matter tissue maps were smoothed with a Gaussian filter of 5 mm full width at half maximum (FWHM).

Statistical analysis of magnetic resonance imaging data

Using x-BAMM (Brain Activation and Morphological Mapping, version 2.5, http://www-bmu.psychiatry.cam.ac.uk/software/), between-group differences in grey matter volume were estimated by fitting an analysis of covariance (ANCOVA) model at each intracerebral voxel in standard space, covarying for total grey matter volume and age at scan. Given that structural brain changes are likely to extend over a number of contiguous voxels, test statistics incorporating spatial information, such as 3-D cluster mass (the sum of supra-threshold voxel statistics), are generally more powerful than other possible test statistics, which are informed only by data at a single voxel. Therefore, our approach was to initially set a relatively lenient P value ($P \leqslant 0.05$) to detect voxels putatively demonstrating differences between groups. We then searched for spatial clusters of such voxels and tested the cluster mass of each cluster. Permutation testing was used to assess statistical significance at both the voxel and cluster levels. At the cluster level, we set the statistical threshold for cluster significance for each analysis such that the expected number of false positive clusters was $\geqslant 1$, and quote the P value at which this occurred. The principal advantages of cluster-level testing are that it confers greater sensitivity by incorporating information from more than one voxel in the test statistic and also substantially reduces the search volume or number of tests required for a whole brain analysis, thereby mitigating the multiple comparisons problem. We did a three-group comparison (at-risk mental state-T *v.* first-episode *v.* control) to look for overall effects between the groups and two-group comparisons for specific between-group differences.

Significant clusters were anatomically localised using the atlas of Talairach & Tournoux (1988), except for foci in and close to the cerebellum, which were localised using the atlas of Schmahmann *et al* (1999).

Statistical analysis of demographic data

Clinical and socio-demographic differences between groups were examined using one-way analysis of variance (ANOVA), *t*-test, or χ^2 test. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS version 12.0 for Windows).

RESULTS

Sample characteristics

The mean duration of follow-up of the subject with an at-risk mental state who subsequently developed psychosis (at-risk mental state–transition group, n=12) was 306 days (range 25–1137 days). Ten of the transitions to psychosis occurred during the first year of follow-up, with one in the second year and one in the fourth. The healthy volunteers (control group) did not differ significantly from the at-risk mental state–transition group with respect to ethnicity, age, gender, educational level or total intracranial brain volume. The first-episode psychosis and the at-risk mental state–transition group did not differ significantly in ethnicity, age, gender, handedness and total intracranial brain volume. The first-episode group achieved a lower educational level than any of the groups (Table 2). The groups were matched for premorbid IQ: at-risk mental state–transition: 113 (s.d.=12), first episode: 103 (s.d.=15), control: 108 (s.d.=5) and did not differ in terms of current and previous alcohol intake.

Grey matter abnormalities

Three-group comparison

Over all groups, there were significant between-group differences in grey matter volume including two main regions: (a) the left superior and middle temporal gyrus, the adjacent part of the left insula as well as the inferior parietal lobule, the postcentral and fusiform gyrus, and (b) the right middle and inferior temporal gyrus (Table 3, see Fig. DS1 in the online data supplement to this paper, P=0.002). Post-hoc testing revealed that in both these regions, the volume in the at-risk mental state–transition group was significantly larger than that in the first-episode group but was not significantly different from that in the control group.

At a less stringent statistical threshold (P=0.01) there were additional differences in region spanning the right insula and superior temporal gyrus coordinates of cluster centroids x=34.5, y=8.8, z=12.0), in the posterior cingulate gyrus (−0.1, −66.6, 10.6) and in the cerebellum (−7.9, −48.9, −35.9 and 7.8, −46.0, −36.0) bilaterally.

When repeating the same analysis without the subjects on antipsychotic medication, the results did not change.

At-risk mental state–transition v. control

To further clarify the nature of the abnormalities in the at-risk mental state–transition group we then compared them with controls directly. There was an area of smaller grey matter volume in a midline region that included the posterior cingulate gyrus, precuneus, and paracentral lobule bilaterally and extended into the left superior parietal lobule (Table 4, see Fig. DS2, P=0.002).

At the same time the at-risk mental state–transition group had a relatively greater grey matter volume compared with the healthy controls in a left parietal/posterior temporal region that included the left supramarginal and angular gyri and inferior parietal lobule, plus the posterior portions of the superior and middle temporal gyri (Table 4, P=0.002).

At a less stringent statistical threshold (P=0.01) there were additional areas of

Table 2 Sample characteristics of the individuals with at-risk mental state who developed a psychosis, patients with first-episode psychosis and controls

Characteristic	At-risk mental state–transition group (*n*=12)	First-episode group (*n*=25)	Control group (*n*=22)	*P*
Age at baseline, mean years (s.d.)	24.6 (5.3)	27.1 (6.3)	23.0 (4.3)	NS
Gender (male), *n* (%)	9 (75)	18 (72)	13 (59)	NS
Handedness (mixed or left)[1], *n* (%)	3 (25)	5 (20)	6 (29)	NS
Educational level, *n* (%)				<0.05
<9 years	3 (25)	12 (48)	2 (9)	
9–11 years	4 (33)	9 (36)	7 (32)	
12–13 years	5 (42)	1 (4)	10 (45)	
>13 years	0	3 (12)	3 (14)	
Brief Psychiatric Rating Scale, score (s.d.) at intake	40.8 (11.5)	52.4 (13.2)	–	<0.05
Scale for Assessment of Negative Symptoms, score (s.d.) at intake	9.8 (5.8)	9.9 (5.1)	–	NS
Patients with antipsychotics at MRI scan, *n* (%)	1 (8)	10 (40)	–	<0.05
Days between MRI and onset of psychosis, days	306 (mean) 263 (median)			

1. One value each is missing in the at-risk mental state–transition and control groups.

Table 3 Regions where grey matter volume differed between subjects with an at-risk mental state who developed psychosis, patients with first-episode psychosis and controls[1]

Area	Hemisphere	Talairach coordinates of cluster (x, y, z)[2]	Size of cluster[3]
Insula	Left	−40.4, −25.9, 20.0[5]	215
Superior temporal gyrus	Left	−54.6, −34.5, 12.0[5]	127
Middle temporal gyrus	Left	−48.1, −35.4, 4.0[5]	12
	Right	51.1, −55.8, −8.0[5]	153
Inferior temporal gyrus	Right	52.2, −56.2, −9.5[4]	1198
Inferior parietal lobule	Left	−47.1, −28.9, 24.0[5]	92
Postcentral gyrus	Left	−51.0, −27.1, 16.0[5]	45
Fusiform gyrus	Left	−46.1, −24.8, 14.5[4]	1082

1. *P*=0.002.
2. Coordinates (x, y and z) refer to the centre-of-mass in each cluster in stereotactic space as defined in the atlas of Talairach & Tournoux (1988).
3. The size refers to the volume (or area in 2-D) of the cluster in voxels.
4. Centroid of 3-D cluster.
5. Subsidiary focus (of 2-D cluster).

smaller grey matter volume in a region spanning the right insula (39.6, 7.5, −0.6), the superior (46.6, 2.9, −12.0) and middle temporal gyrus (41.9, 0.9, −20.0) and the inferior frontal gyrus (35.9, 22.5, 4.0), and in a region spanning the anterior cingulate (−0.3, 37.4, 24.0) and the medial frontal gyrus (−0.5, 36.3, 31.3). Furthermore, there were additional areas of relatively greater grey matter volume as compared to controls in the right parahippocampal gyrus (22.2, −29.7, −8.6) and in a region that included the right supramarginal (55.4, −52.5, 24.0) and inferior temporal gyrus (59.0, −53.3, −4.2).

At-risk mental state–transition v. first-episode

To test our second hypothesis, the at-risk mental state–transition subgroup was also compared with the first-episode group. In fact, no significant differences in regional grey matter volume were found at a very stringent statistical threshold (*P*=0.002). At a less stringent statistical threshold (*P*=0.01), relative to patients with first-episode, participants with an at-risk mental state who developed psychosis had areas of relatively more grey matter volume in a region spanning the superior, middle and inferior temporal gyrus bilaterally. There was also a region of smaller grey matter volume in the right lentiform nucleus (Table 5, see Fig. DS3).

When the analysis was repeated after excluding the participants on antipsychotic medication, the same regions showed significant differences.

DISCUSSION

Using voxel-based morphometry, we found that individuals with an at-risk mental state who developed psychosis (–transition) had smaller cortical volumes before the onset of psychosis in the midline region that included the posterior cingulate gyrus, precuneus, and paracentral lobule bilaterally and extended into the left superior parietal lobule, that were not different to the first-episode cohort. At a less stringent statistical threshold (*P*=0.01) there were additional areas of less grey matter volume in the right insula, superior and middle temporal gyrus, inferior frontal gyrus, anterior cingulate and medial frontal gyrus. Overall, the findings confirm our first hypothesis and are suggestive that at least some of the cortical grey matter abnormalities associated with psychosis are already present up to 2 years before the first episode of psychosis. These abnormalities may reflect abnormal developmental processes and may be related to an increased vulnerability to psychosis.

Our second hypothesis was that the subjects who went on to psychosis would

Table 4 Regions where grey matter volume differed between subjects who developed psychosis and controls[1]

Area	Hemisphere	Talairach coordinates of cluster centroid x, y, z[2]	Size of cluster[3]
At-risk mental state–transition < controls			
Precuneus	Left	−1.6, −47.7, 51.0[4]	849
Cingulate gyrus	Left	−13.7, −26.9, 40.0[5]	35
	Right	3.1, −44.6, 40.0[5]	45
Paracentral lobule	Left	−2.0, −30.5, 45.0[5]	39
	Right	1.1, −39.0, 65.0[5]	27
Precuneus	Left	−0.6, −50.2, 50.0[5]	203
	Right	2.4, −48.0, 55.0[5]	85
Superior parietal lobe	Left	−8.6, −68.5, 55.0[5]	17
At-risk mental state–transition > controls			
Supramarginal gyrus	Left	−55.0, −44.5, 25.1[4]	1081

1. P=0.002.
2. Coordinates (x, y and z) refer to the centre-of-mass in each cluster in stereotactic space as defined in the atlas of Talairach & Tournoux (1988).
3. The size refers to the volume (or area in 2-D) of the cluster in voxels.
4. Centroid of 3-D cluster.
5. Subsidiary focus (of 2-D cluster).

Table 5 Regions where grey matter volume differed between subjects who developed psychosis and first-episode patients (P=0.01)

Area	Hemisphere	Talairach coordinates of cluster centroid x, y, z[1]	Size of cluster[2]
At-risk mental state–transition > first-episode			
Superior temporal gyrus	Left	−55.1, −40.5, 13.5[3]	178
	Right	55.5, −59.2, 16.0[4]	6
Inferior temporal gyrus	Right	55.7, −56.3, −6.0[3]	968
	Left	−54.2, −60.4, −8.0[4]	91
Middle occipital gyrus	Left	−52.6, −62.0, −6.1[3]	338
Middle temporal gyrus	Left	−54.5, −35.5, 4.0[4]	9
	Right	58.5, −56.3, −1.0[4]	100
Fusiform gyrus	Left	−43.7, −69.1, −16.0[4]	14
	Right	53.2, −54.4, −16.0[4]	100
At-risk mental state–transition < first-episode			
Lentiform nucleus	Right	14.8, 9.7, −10.4[3]	438

1. Coordinates (x, y and z) refer to the centre-of-mass in each cluster in stereotactic space as defined in the atlas of Talairach & Tournoux (1988).
2. The size refers to the volume (or area in 2D) of the cluster in voxels.
3. Centroid of 3-D cluster.
4. Subsidiary focus (of 2-D cluster).

show neuroanatomical differences qualitatively but not yet quantitatively similar to patients with first-episode psychosis. However, we found that individuals with an at-risk mental state who developed psychosis showed larger grey matter volumes in the temporal lobe bilaterally relative to patients with first-episode psychosis. This finding is suggestive that temporal lobe grey matter abnormalities seem to occur later in the time course of the illness and may be associated with the subsequent transition to psychosis.

Despite a large body of neuroimaging studies in schizophrenia showing multiple subtle brain abnormalities, we do not know the exact time course of their occurrence. Meta-analytic reviews have largely been conducted on samples of patients with chronic schizophrenia, and these indicate that these patients compared with healthy controls show reduced brain size, enlarged lateral and third ventricles, reduced frontal lobe volume, reduced volumes of temporolimbic structures and of corpus callosum, and increased volume of basal ganglia (for a review see Vita *et al*, 2006). The review by Vita *et al* (2006) showed that some of these abnormalities, such as those in the lateral and third ventricle, hippocampus and for whole brain volume are already present in patients with first-episode psychosis. Longitudinal MRI studies in first-episode psychosis suggest that brain changes are progressive, in particular in the initial couple of years of the illness and are associated with functional outcome (Keshavan *et al*, 2005).

Neuroimaging studies of individuals without psychosis who are at risk of psychosis could demonstrate that neuroanatomical abnormalities are also evident in first-degree relatives and healthy co-twins of patients with schizophrenia (Lawrie *et al*, 1999; Seidman *et al*, 1999; Staal *et al*, 2000; Baare *et al*, 2001; Hulshoff Pol *et al*, 2004) and are suggestive that brain changes exist prior to the onset of psychosis. In addition, a prospective study suggests that the onset of schizophrenia in the relatives of patients is associated with a reduction in the volume of the left parahippocampal gyrus (Job *et al*, 2005).

Relatively little is known about the nature of MRI abnormalities in subjects with an at-risk mental state. Using a region of interest approach, Phillips *et al* (2002) reported that hippocampal volume in these individuals was smaller than that in healthy controls but not than in patients with first-episode psychosis. Within the at-risk mental state group, those who later developed psychosis had a larger left hippocampal volume than those who did not. More recently, using a voxel-based approach in subjects from the same centre in Melbourne, Pantelis *et al* (2003) found that subjects with 'prodromal' symptoms who later became psychotic had smaller inferior frontal and cingulate gyrus volumes than those who did not. However, in a cross-sectional study, using a region of interest approach, Velakoulis *et al* (2006) reported that patients with an at-risk mental state had normal baseline hippocampal and amygdala grey matter volumes whether or not they subsequently developed psychosis. These results suggests that

some structural brain changes occur closer to the transition to psychosis than suggested by the traditional neurodevelopmental hypothesis of schizophrenia (Murray & Lewis, 1987; Weinberger, 1987). However, the numbers of subjects in these studies have been modest as their recruitment depends on the provision of specialised clinical services (Broome *et al*, 2005).

In a previous study, we compared the at-risk mental state sample as a whole (independent of subsequent clinical outcome) with the controls and the patients with first-episode psychosis (Borgwardt *et al*, 2007). We found significant between-group differences in grey matter volume in the posterior part of the left superior temporal gyrus and the adjacent part of the left insula, and in a second region involving the posterior cingulate gyrus and precuneus. Direct comparison of the at-risk mental state group and controls revealed additional areas of smaller grey matter volume in the left medial temporal cortex. However, the at-risk mental state group was heterogeneous, including both patients who later developed psychosis (–transition) and those who did not. Within the at-risk mental state group, those subjects who developed psychosis (–transition) had less grey matter than subjects who did not in the right insula, inferior frontal and superior frontal gyrus (Borgwardt *et al*, 2007).

In the present study, we found that the at-risk mental state group who subsequently became psychotic showed regional grey matter volume reductions relative to healthy controls in the posterior cingulate gyrus, precuneus, and paracentral lobule bilaterally, and they extended into the left superior parietal lobule. Reductions in the cingulate gyrus are well-established findings in patients with schizophrenia, and these areas have also been implicated in functional imaging studies, although findings have been more frequent in its anterior than its posterior part. Abnormalities in the precuneus have been less frequently described in schizophrenia, but reduced volume and differential activation have been reported (Falkai *et al*, 1988; Antonova *et al*, 2005). Our findings of normal hippocampal and amygdala volume size in patients with an at-risk mental state at the very early phase of a first-episode psychosis are consistent with a previous report assessing this patient group (Velakoulis *et al*, 2006).

We also identified areas where the at-risk mental state group who later became psychotic had relatively more grey matter volume than healthy controls. These differences were evident in the left parietal/posterior temporal region that included the left supramarginal and angular gyri and inferior parietal lobule, plus the posterior portions of the superior and middle temporal gyri. These differences might be related to an active pathological process that underlies the transition towards psychosis and is associated with greater grey matter volume. However, longitudinal MRI studies of high-risk individuals who developed psychosis have mainly found reductions, rather than increases in regional volumes over time. It is also possible that the volumetric differences of the at-risk mental state participants who did later develop psychosis are long-standing differences that predate the onset of prodromal symptoms and reflect a differential vulnerability to psychosis within the at-risk mental state group. This issue could be addressed by repeated scanning of subjects with an at-risk mental state during the at-risk period.

The subgroup of at-risk mental state subjects who developed psychosis could also be regarded as having very early first-episodes. Even if this was so, it is still true that the MRI findings predate what is conventionally regarded as the onset of psychosis. Furthermore, we also found differences between the at-risk mental state–transition and first-episode groups that suggest that there are true differences between these individuals. Our data are suggestive that neuroanatomical abnormalities emerge during the process of transition from an at-risk mental state to acute psychotic illness and support a recent longitudinal imaging study from the PACE clinic (Pantelis *et al*, 2003).

Limitations

We used a cross-sectional design, whereas a longitudinal design with repeated scans would enable intra-individual comparison. The group sizes were relatively small, however not smaller then in other neuroimaging studies of participants with an at-risk mental state. The differences in grey matter volume that we observed are very unlikely to be related to treatment with mood stabilisers or antipsychotic drugs, as the majority of the at-risk mental state–transition (92%) and the first-episode (60%) groups were naive to these medications at the time of scanning. However, when repeating the analyses including relatively many treated subjects (at-risk mental state–transition *v.* first-episode group; three-group comparison) without the subjects on medication the results did not change. It should also be acknowledged that the grey matter abnormalities are only seen at group level, so the contribution to individual diagnosis or clinical assessment of risk is modest. However, these findings provide evidence that active brain changes occur in patients developing psychosis and indicate that these brain changes may be prevented by early antipsychotic treatment within early detection clinics.

Conclusions

Overall, the results of this and earlier studies indicate that some brain abnormalities are already present before the transition to psychosis, whereas others manifest with the first psychotic episode. The early abnormalities may reflect developmental or later maturational processes in adolescence and early adulthood and are associated with an increased vulnerability to psychosis. Additional volumetric brain abnormalities within the at-risk mental state group are then particularly associated with the subsequent development of psychosis. These brain areas may be particularly informative to a better understanding of the underlying neurobiology of the progression to psychosis.

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