

Grey matter abnormalities in Brazilians

with first-episode psychosis*

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Background In low- and middle-income countries people with schizophrenia are reported to experience better outcomes than those in high-income countries.

Aims To examine structural brain differences in people with first-episode psychosis and controls in Brazil.

Method Magnetic resonance imaging using voxel-based morphometry was performed on 122 people with first-episode psychosis and 94 controls.

Results There were significant decreases in grey matter in the left superior temporal and inferior prefrontal cortices, insula bilaterally and the right hippocampal region in first-episode psychosis ($P < 0.05$, corrected for multiple comparisons). The subgroup of people with schizophrenia ($n = 62$) exhibited a similar pattern of decrease in grey matter relative to controls.

Conclusions Structural abnormalities reported in psychosis in high-income countries are also present in first-episode psychosis in Brazil.

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The outcome for people with schizophrenia is reported to be better in low- and middle-income than in high-income countries (Hopper & Wanderling, 2000). However, it is not clear whether this is because the psychoses have a different aetiology. If this is the case, then one might expect that the people with psychosis would show differences in the brain scan abnormalities associated with the illness. Such a question would be best answered by cross-national longitudinal studies comparing brain structure. However, in the absence of such studies, it is possible to compare structural brain changes identified in people with psychosis from a middle-income nation with similar studies conducted in the high-income countries.

The structural brain abnormalities characteristically associated with schizophrenia are reduced frontal and temporal lobe volumes, which are most often detected using morphometric magnetic resonance imaging (MRI) techniques (Wright *et al*, 2000; Pantelis *et al*, 2005). Recently, several morphometric MRI studies have used automated, voxel-based morphometry to investigate differences in regional grey matter volumes in samples with psychosis relative to controls. Meta-analysis of findings from voxel-based morphometry has demonstrated that the most robust regional volume deficits in schizophrenia occur in the left superior temporal gyrus and left amygdala-hippocampal complex (Honea *et al*, 2005). Grey matter reductions are next most consistently reported in the prefrontal regions (specifically involving the left inferior and medial frontal gyri), right superior temporal cortex, left parahippocampal cortex, anterior cingulate gyrus, insula and thalamus (Honea *et al*, 2005).

This paper reports the results of a population-based morphometric MRI study in which a large sample of people with first-onset schizophrenia or other functional psychoses was recruited in the city of São

Paulo, Brazil. In contrast to most previous MRI studies of psychotic disorders, we applied an epidemiological approach to the recruitment of controls, randomly selecting a large group without psychosis from the same geographical area. Voxel-based morphometry was applied to investigate whether decreases in grey matter volume would be identified in people with schizophrenia relative to controls; analyses were performed to assess the hypotheses that such grey matter decreases would be present specifically in the superior temporal, prefrontal and insular cortices, and in the hippocampal/parahippocampal region. Also, based on neuroimaging evidence that brain structural abnormalities are common across the spectrum of psychotic disorders (McDonald *et al*, 2004), we performed the same comparisons for all those presenting with first-episode psychosis, including those with affective disorders and other functional psychoses in addition to people with schizophrenia.

METHOD

Participants

The psychosis group was drawn from a sample of 200 people with first-episode psychosis identified for an epidemiological study of the incidence of psychotic disorders in São Paulo (see Menezes *et al*, 2007). People presenting with a psychotic illness were recruited from a population who had been living for a period of at least 6 months in a circumscribed geographical area of São Paulo (comprising a total of approximately 900 000 inhabitants). Participants were identified by active surveillance of all people that made contact for the first time with the mental healthcare services for that region between 2002 and 2005.

Inclusion criteria for the MRI study were: (a) current age between 18 and 50 years; and (b) diagnosis of a functional psychosis according to DSM-IV 295–298 psychotic codes (American Psychiatric Association, 1994) as assessed by the Structured Clinical Interview for DSM-IV (SCID; Spitzer *et al*, 1992). People with psychotic disorders due to a general medical condition or substance-induced psychosis were excluded. In order to obtain a population-based sample of controls, next-door neighbours were contacted and screened to exclude the presence of psychotic symptoms using the Psychosis

*Preliminary analyses of these data were presented in abstract form at the XII and XIII Biennial Winter Workshops on Schizophrenia Research, 2004 and 2006.

Screening Questionnaire (Bebbington & Nayani, 1995). Additional exclusion criteria for both groups were: (a) history of head injury; (b) presence of neurological disorders or any organic disorders that could affect the central nervous system; and (c) contraindications for MRI. Exclusion criteria specific for the control group were personal history of psychosis or other Axis I disorders, except substance misuse or mild anxiety disorders.

From the above 200 people with psychosis, 50 did not meet the inclusion criteria because of contraindication for MRI, age above 50 years, presence of organic disorders, or subtle brain lesions identified by the MRI scans. Of the remaining 150 people, we lost contact with 15, 23 refused to participate and 5 had to be excluded owing to artefacts during image acquisition, resulting in a total of 107 from the incidence investigation who were included in the current report. There were no differences between those included in the present study ($n=107$) and those that were lost ($n=43$) in terms of their clinical and demographic profile except for a trend towards greater mean current age for those lost to the study ($P=0.063$, two-tailed t -test). The research team identified an additional 15 people with first-episode psychosis at the same mental healthcare services for the region, but these were excluded from the incidence investigation as they lived outside the catchment area. These people fulfilled criteria for MRI and were included in the present neuroimaging investigation, resulting in a total sample of 122 people with first-episode psychosis. There were no significant differences between those in the original epidemiological study ($n=107$) and those living outside the catchment area ($n=15$) in terms of their clinical and demographic profile. For the control group, a total of 114 people from the catchment area were recruited for MRI, but 11 were excluded owing to the presence of silent gross brain lesions and 9 owing to artefacts during image acquisition, resulting in a final sample of 94 controls.

Clinical measures

Current symptom severity in the psychosis group was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay *et al.*, 1987), and information about anti-psychotic drug treatment was obtained from case notes and participant or family interviews. All participants were screened

for substance use with the Alcohol Use Disorders Identification Test (AUDIT; Saunders *et al.*, 1993) and the South Westminster Questionnaire (Menezes *et al.*, 1996). Diagnostic criteria for substance abuse or dependence were assessed using the SCID (First *et al.*, 1995). Handedness was assessed with Annett's Hand Preference Questionnaire (Annett, 1970). The study was approved by local ethics committees and written informed consent was obtained from all participants.

MRI acquisition

Imaging data were acquired using two MRI scanners (at the Clinics Hospital of the University of São Paulo 1.5T GE Signa scanner, General Electric, Milwaukee Wisconsin, USA). In total 72 people with psychosis and 57 controls were investigated using scanner 1 and 50 people with psychosis and 37 controls using scanner 2. Exactly the same acquisition protocols were used (a T1-SPGR sequence providing 124 contiguous slices, voxel size $0.86 \times 0.86 \times 1.5$ mm, echo time 5.2 ms, resolution time 21.7 ms, flip angle 20, field of vision 22, matrix 256×192).

Image processing

Voxel-based morphometry was performed using the SPM2 package in Matlab (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2>). A standard template set was created specifically for the study, consisting of a mean T1-weighted image and *a priori* grey matter, white matter and cerebrospinal fluid (CSF) templates, based on the images of all people with psychosis and controls. In order to build the template, images were spatially normalised to the standard SPM T1 MRI template, based on 152 healthy controls from the Montreal Neurological Institute (MNI). This spatial normalisation was restricted to linear 12-parameter affine transformations to minimise deformations of our original images. Spatially normalised images were then segmented into grey matter, white matter and CSF compartments, using the probability maps in the SPM2 package overlaid onto the images to classify voxels in terms of their probability of belonging to a particular tissue class. The segmentation method also included an automated brain extraction procedure to remove non-brain tissue and an algorithm to correct for non-uniformity of image intensity. Finally, images were smoothed with an isotropic Gaussian kernel (8 mm

full width at half maximum), and averaged to provide the grey matter, white matter and CSF templates in Talairach and Tournoux stereotactic space.

The original images were then processed according to the SPM2 optimised protocol (Good *et al.*, 2001), comprising image segmentation and spatial normalisation of extracted grey and white matter images to the customised grey and white matter templates (12-parameter linear and non-linear ($7 \times 9 \times 7$ basis functions) transformations). The resultant parameters were reapplied to the original structural images. These fully normalised images were resliced using trilinear interpolation to a voxel size of $2 \times 2 \times 2$ mm³, and segmented into grey matter, white matter and CSF partitions. Voxel values were modulated by the Jacobian determinants derived from the spatial normalisation, thus allowing brain structures that had their volumes reduced after spatial normalisation to have their total counts decreased by an amount proportional to the degree of volume shrinkage (Good *et al.*, 2001). Statistical analyses performed on modulated images test for between-group regional differences in the absolute volume of grey matter reduction (Good *et al.*, 2001) rather than differences in grey matter concentration. Finally, images were smoothed using a 12-mm Gaussian kernel.

Statistical analysis

Regional grey matter differences between people with psychosis and controls were investigated on a voxel-by-voxel basis using the general linear model. Resulting statistics at each voxel were transformed to Z-scores and displayed as statistical parametric maps (SPMs) into standard anatomical space, at the one-tailed $P < 0.001$ level of significance (corresponding to a threshold of $Z > 3.09$). In each analysis, a measure of the total amount of grey matter was entered as a confound, given by the sum of voxels within the corresponding grey matter compartment of each participant. Only voxels with values above an absolute threshold of 0.05 entered the analyses, resulting in a total search volume of approximately 250 000 voxels. First, to investigate whether there were significant findings in areas where grey matter abnormalities had been predicted, we used the small volume correction (SVC) tool in the SPM2 package to restrict comparisons to specific voxels in the frontal cortex,

superior temporal cortex, hippocampal region and insula. These regions were circumscribed by applying spatially normalised volumes onto the SPMs, based on the anatomical volumes of interest that are available within the Automatic Anatomical Labeling (AAL) SPM toolbox. Search volumes were 1770 voxels for the right and 1858 voxels for the left insula, 946 voxels for the right and 932 voxels for the left hippocampal region, and 3141 voxels for the right and 2296 voxels for the left superior temporal cortex. For the frontal region, the predefined AAL volumes corresponding to the dorsal prefrontal region, orbitofrontal cortex and anterior cingulate gyrus were merged into one single volume of interest (resulting in a search volume of 43 808 voxels). Any clusters of voxels showing significant findings within each of those volumes of interest were reported only if surviving family-wise error (FWE) correction for multiple comparisons ($P < 0.05$) over that region. The SVC approach permits hypothesis-driven analyses to be performed with correction for the pre-specified region of interest rather than with correction for the whole brain.

Finally, the SPMs were inspected on an exploratory basis to identify significant findings in other, unpredicted regions across the entire brain. Such unpredicted findings would be reported as statistically

significant only if surviving FWE correction for multiple comparisons over the whole brain. In all analyses, we converted MNI coordinates of voxels of maximal statistical significance to the Talairach and Tournoux system.

Inter-scanner reliability

We investigated the reliability of volume measurements using the two MRI scanners, the results of which will be reported elsewhere. Briefly, six healthy volunteers were (re)scanned on the same day. Images were spatially normalised and segmented using voxel-based morphometry as described above, and grey matter images were compared between the two scanners. Intraclass correlation coefficients (ICCs) were obtained for frontal, temporal, parietal and occipital neocortical regions, medial temporal structures (hippocampus, amygdala and parahippocampal gyrus) and subcortical nuclei (caudate, putamen and thalamus). These regions were circumscribed using the spatially normalised volumes of interest within the AAL SPM toolbox; grey matter estimates were given by the mean voxel intensity values obtained within each volume of interest, calculated using the MRICro program. We obtained ICC values higher than 0.90 for all neocortical and medial temporal regions; for the subcortical

nuclei, ICC values on the left and right hemisphere were 0.79 and 0.83 for the thalamus, 0.65 and 0.78 for the caudate nucleus, and 0.23 and 0.35 for the putamen. Based on this pattern of reliability, we restricted our analyses to cortical regions and medial temporal structures.

RESULTS

Demographic and clinical characteristics

Socio-demographic and clinical data are shown in Table 1. There were no differences between people with psychosis ($n=122$) and controls ($n=94$) in age, gender or handedness. Those with psychosis had had significantly fewer years of education than controls. Substance misuse was significantly more frequent in people with first-episode psychosis compared with controls. A total of 84 people with psychosis (69%) had been on antipsychotic treatment within 3 weeks of MRI: typical antipsychotics, $n=57$; atypical antipsychotics, $n=26$; or a combination of both $n=1$. The others with psychosis ($n=38$, 31%) included a subgroup of 36 who had had pharmacological treatment but were drug-free at the time of scanning, as well as 2 drug-naïve participants. The mean period between first contact with mental health services and MRI was 18 weeks.

Table 1 Socio-demographic and clinical characteristics of the sample

Variables	Total psychosis group ($n=122$)	Schizophrenia subgroup ¹ ($n=62$)	Controls ($n=94$)	Statistical significance total psychosis group v. controls, P	Statistical significance schizophrenia subgroup v. controls, P
Gender, n					
Male	66	44	53	0.73	0.066
Female	56	18	41		
Age, years: mean (s.d.)	28.5 (8.4)	27.6 (8)	30.2 (8.4)	0.15	0.063
Education, years: mean (s.d.)	8.4 (4.1)	8.6 (3.8)	10 (4.1)	0.005	0.03
Handedness, n					
Right	111	55	91	0.22	0.12
Left	8	5	2		
Mixed	3	2	1		
Substance misuse, n (%)	37 (30)	22 (35.5)	5 (5.3)	<0.0001	<0.0001
Duration of illness, weeks: median (s.d.)	24.5 (51)	25 (65)			
Age at psychosis onset, years: mean (s.d.)	27.8 (8.5)	26.7 (8.1)			
PANSS score: mean (s.d.)					
Positive	10.5 (5.3)	10.8 (5)			
Negative	12.2 (6)	13.6 (6)			
Total	45.8 (12)	47.8 (12)			

PANSS, Positive and Negative Syndrome Scale.

1. Subgroup of participants with diagnosis of schizophrenia or schizophreniform disorder.

There were 62 participants who fulfilled DSM-IV criteria for schizophrenia or schizophreniform disorder (50.8%), 24 with bipolar affective disorder (19.7%), 25 with major depressive disorder (20.5%) and 11 (9%) with other psychosis (schizoaffective disorder, brief psychosis and psychotic disorder not otherwise specified). Clinical details for the subgroup with schizophrenia ($n=62$) are given in Table 1. Their demographic profile was similar to that of the overall group with psychosis relative to controls.

Grey matter volumes

There were no significant differences in global grey matter values between participants with first-episode psychosis and controls ($t=0.74$, $P=0.46$). However, there were significant regional grey matter reductions in the group with psychosis in three voxel clusters involving brain structures where abnormalities had been predicted, located in the left prefrontal cortex, with maximal statistical significance in the left inferior frontal gyrus (Brodmann’s area, BA, 9/45/46) and also encompassing the left middle frontal gyrus (BA=9/46); the left superior temporal cortex (BA=41/22); the right hippocampus/anterior parahippocampal region (BA=28/35); and the insula bilaterally (BA=13) (Table 2, Fig. DS1a in data supplement to online version). There were no areas of grey matter excess in participants with psychosis. Inspection of the SPMs revealed no other findings of decreased or increased grey matter in participants with psychosis relative to controls.

Grey matter volumes in the schizophrenia subgroup

There were no significant differences in global grey matter volumes between participants with schizophrenia and controls ($t=0.50$, $P=0.62$). However, SVC-based analyses demonstrated significant grey matter reductions in participants with schizophrenia relative to controls in the left inferior prefrontal cortex (BA=45/47), left superior temporal cortex (BA=22/41), right hippocampus/anterior parahippocampal cortex (BA=28/35) and insula (BA=13) bilaterally (Table 2, Fig. DS1b in data supplement to online version). There was an additional site of grey matter reduction in the right prefrontal cortex (BA=9/46) (Table 2, Fig. DS1b). There were no areas of grey matter excess in the participants with schizophrenia relative to controls in

Table 2 Grey matter reductions in first-episode psychosis patients relative to controls

Brain region	Cluster size ¹	Peak z-score ²	P ³	Coordinates ⁴		
				x	y	z
Total psychosis group (n=122)						
Left prefrontal cortex (BA=9/45/46)	292	4.77	0.004	-48	19	25
Left superior temporal cortex (BA=41/22)	148	4.04	0.005	-44	-12	1
Left insula (BA=13)	158	3.94	0.006	-43	-10	0
Right insula (BA=13)	87	3.87	0.008	41	10	1
Right hippocampus/parahippocampal gyrus (BA=28/35)	85	4.30	0.001	24	-20	-9
Schizophrenia subgroup⁵						
Left prefrontal cortex (BA=47/45)	156	4.39	0.021	-38	23	-1
Right prefrontal cortex (BA=9/46)	250	4.20	0.044	46	34	19
Left superior temporal cortex (BA=41/22)	215	3.89	0.009	-59	-23	12
Left insula (BA=13)	382	4.53	0.001	-36	23	1
Right insula (BA=13)	222	4.17	0.003	40	12	3
Right hippocampus/parahippocampal gyrus (BA=28/35)	34	3.68	0.009	22	-20	-11

1. Total number of contiguous voxels in each region above the initial cut-off of $Z > 3.09$.
2. Z-scores for the voxel of maximal statistical significance in each region.
3. Statistical significance v. controls after correction for multiple comparisons (voxel level).
4. Talairach and Tournoux coordinates of the voxel of maximal statistical significance within each region.
5. Subgroup of participants with diagnosis of schizophrenia or schizophreniform disorder.

the *a priori* hypothesised regions. Also, there were no foci of grey matter reduction in participants with schizophrenia relative to the controls in other brain regions.

Effects of antipsychotics on regional brain volumes

Exploratory analysis across the entire brain revealed no areas of grey matter reduction in those currently treated with antipsychotics ($n=84$) relative to those 38 who were untreated ($P < 0.05$, corrected). Small volume-corrected analyses demonstrated significant grey matter reductions in participants treated with antipsychotics relative to the untreated subgroup in the right insular cortex (BA=13, cluster size 12, $P=0.033$, coordinates x, y, z=49, 10, -2) and in the right superior temporal gyrus (BA=22/38, cluster size 140, $P=0.005$, coordinates x, y, z=63, 0, -2). There were no areas of grey matter excess in those treated with antipsychotics relative to untreated participants with first-episode psychosis.

Grey matter volumes in those without substance misuse

Because the group with psychosis had significantly higher rates of substance misuse, subsequent analyses were performed with substance misuse as an additional exclusion criterion for both participants with psychosis and controls. The SVC-based

comparison showed a significant grey matter reduction in patients relative to controls in the left inferior and middle frontal cortex (BA=9/45/46, cluster size 285, $P=0.009$, coordinates x, y, z=-48, 19, 25), left superior temporal gyrus (BA=22, cluster size 18, $P=0.03$, coordinates x, y, z=-53, 6, -4) and bilaterally in the hippocampal region (left hippocampus, BA=28/35, cluster size 116, $P=0.01$, coordinates x, y, z=-28, -22, -11; right hippocampus, BA=28/35, cluster size 141, $P < 0.0001$, coordinates x, y, z=24, -20, -9) and insula (left insula, BA=13, cluster size=186, $P=0.012$, coordinates x, y, z=-36, 21, 1; right insula, BA=13, cluster size=93, $P=0.008$, coordinates x, y, z=42, 10, 1). There were no additional areas of grey matter reduction or excess in the group with psychosis and no substance misuse relative to controls.

DISCUSSION

Main findings

To the best of our knowledge, this is the first study with an epidemiological design and a population-based sample in a middle-income country to report brain changes in people with first-episode psychosis. Our results demonstrate significant reductions in grey matter in Brazilian people with first-episode psychosis which are similar to those observed in high-income

nations (Job *et al.*, 2002; Pantelis *et al.*, 2005; Steen *et al.*, 2006). A similar pattern emerged when our analyses were restricted to the subgroup with schizophrenia. These findings were not significantly influenced by the presence of substance misuse. These results suggest that the supposed better outcome of psychosis in low- and middle-income compared with high-income countries (Hopper & Wanderling, 2000) is not related to differences in the brain mechanisms underlying the symptoms.

We identified areas of reduced grey matter in the left inferior and middle frontal, left superior temporal and bilateral insular cortices, and in the right hippocampus/anterior parahippocampal cortex. Similar clusters of grey matter reduction were identified in the smaller number of participants with schizophrenia. The finding of grey matter reduction in the left superior temporal cortex is in agreement with meta-analysis (Honea *et al.*, 2005). Another meta-analysis of structural brain changes in people with first-episode psychosis has reported bilateral hippocampal volume reduction (Vita *et al.*, 2006). Our study replicated this finding in the right hippocampus in both the overall group with first-episode psychosis and the schizophrenia subgroup.

In both the larger group with psychosis and the schizophrenia subgroup, a large cluster of grey matter reduction was identified in the frontal lobe, involving the left inferior and middle frontal gyri. Reduced frontal volumes have consistently been reported in neuroimaging studies of schizophrenia including participants with first-episode psychosis (Job *et al.*, 2002) and to a lesser extent bipolar disorder (McDonald *et al.*, 2004). We detected less significant left-sided prefrontal volume differences between participants with schizophrenia and controls, perhaps reflecting diminished power to detect an effect owing to the smaller number in the schizophrenia subgroup (62 *v.* 122 in the overall group). Since previous studies have identified grey matter volume reductions in various parts of the frontal cortex (Honea *et al.*, 2005), we chose to consider the entire prefrontal region (including the anterior cingulate gyri) as one volume of interest. However, we acknowledge that using such a large volume of interest has the disadvantage that there is a reduced ability to detect subtle volume changes in prefrontal/anterior cingulate subregions where changes have been reported previously.

Other studies

We found reduced grey matter volumes in the insula bilaterally in both the overall group with psychosis and the schizophrenia subgroup relative to controls. Previous imaging studies have identified insular abnormalities in people with schizophrenia (Crespo-Facorro *et al.*, 2000; Pressler *et al.*, 2005). Interestingly, secondary analyses in our study identified a cluster of grey matter deficit in the right-sided insular cortex in people treated with antipsychotics relative to untreated participants. This raises the possibility that the insular grey matter reduction observed in participants with psychosis compared with controls might reflect antipsychotic treatment as opposed to illness. Exposure to antipsychotic treatment has been previously reported to affect insular morphology, such that increasing drug exposure (measured in dose-years) is associated with larger insular volume (Pressler *et al.*, 2005).

Another area of reduced grey matter in treated relative to untreated patients with psychosis is the right superior temporal cortex. Most of our participants were treated with typical antipsychotics, which have been shown to decrease right superior temporal grey matter in people with first-episode psychosis in a recent study (Dazzan *et al.*, 2005). Evidence from MRI studies suggests that both types of antipsychotics are associated with brain changes, even after short-term treatment (Dazzan *et al.*, 2005).

Methodological issues

A major strength of our study is that our sample was derived from an epidemiological, population-based case-control study of first-episode psychosis, with almost all participants from a defined geographic area, thus minimising the chance of selection bias. Although 15 people who did not live in the catchment area were included, they were identified in exactly the same way and therefore are not likely to have introduced selection bias. The voxel-based morphometric approach is automated and therefore free of problems with intra-interoperator reliability that may occur with manual tracing methods. Although there has been some debate concerning voxel-based methodology, it has produced relatively consistent results in studies of people with psychosis (Job *et al.*, 2002).

A limitation of our study is that several brain areas, including the thalamus and

basal ganglia, had to be excluded from the analysis because of less than optimal ICCs between the two MRI scanners used.

One could argue that the reported better outcomes in schizophrenia are more evident in the less urbanised centres of middle- and low-income countries and that São Paulo would be more similar to large urban centres where a better outcome for psychosis may not apply (Hopper & Wanderling, 2000). However, although São Paulo is a large Westernised urban centre, it still has the profile of a middle-income nation, with low average income, and poor socio-economic indexes and health assistance. Hence we consider São Paulo city for the investigation of clinical and neurobiological aspects of schizophrenia in a middle-income nation.

Implications

Previous studies investigating whether brain abnormalities reported as characteristic of schizophrenia in high-income countries are also present in low- and middle-income countries have been small and non-epidemiological in design. Jayakumar *et al.* (2005) used voxel-based morphometry to examine grey matter volume in a sample of 18 Indians with first-episode schizophrenia who were untreated with antipsychotics and found significantly smaller global grey matter and smaller regional grey matter volume in frontal, temporal, insular and parahippocampal cortices relative to controls. Our findings implicate the same network of brain regions, using a sample with first-episode psychosis of a size that is comparable to those of the largest MRI studies of psychotic disorders conducted in high-income countries to date (Steen *et al.* 2006).

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