

Grey matter abnormalities in first-episode schizophrenia and affective psychosis

KEVIN D. MORGAN, PAOLA DAZZAN, KENNETH G. ORR, GERARD HUTCHINSON, XAVIER CHITNIS, JOHN SUCKLING, DAVID LYTHGOE, SARAH-JAYNE POLLOCK, SUSAN ROSSELL, JANE SHAPLESKE, PAUL FEARON, CRAIG MORGAN, ANTHONY DAVID, PHILIP K. McGUIRE, PETER B. JONES, JULIAN LEFF and ROBIN M. MURRAY

Background Grey matter and other structural brain abnormalities are consistently reported in first-onset schizophrenia, but less is known about the extent of neuroanatomical changes in first-onset affective psychosis.

Aims To determine which brain abnormalities are specific to (a) schizophrenia and (b) affective psychosis.

Method We obtained dual-echo (proton density/T2-weighted) magnetic resonance images and carried out voxel-based analysis on the images of 73 patients with first-episode psychosis (schizophrenia $n=44$, affective psychosis $n=29$) and 58 healthy controls.

Results Both patients with schizophrenia and patients with affective psychosis had enlarged lateral and third ventricle volumes. Regional cortical grey matter reductions (including bilateral anterior cingulate gyrus, left insula and left fusiform gyrus) were evident in affective psychosis but not in schizophrenia, although patients with schizophrenia displayed decreased hippocampal grey matter and increased striatal grey matter at a more liberal statistical threshold.

Conclusions Both schizophrenia and affective psychosis are associated with volumetric abnormalities at the onset of frank psychosis, with some of these evident in common brain areas.

Declaration of interests None. Funding is detailed in Acknowledgements.

Neuroimaging studies of first-episode schizophrenia have shown neuroanatomical abnormalities, including ventricular enlargement (Cahn *et al*, 2002) and subtle grey matter deficits in the whole brain (Fannon *et al*, 2000a), frontal and temporal lobes (Job *et al*, 2002). Furthermore, some abnormalities such as basal ganglia enlargement seem to appear early in the illness but only following antipsychotic exposure (Lawrie & Abukmeil, 1998). While abnormalities in the cingulate gyrus (Sassi *et al*, 2004) and temporal lobe (Kasai *et al*, 2003a) have been observed in first-onset affective psychosis, it is not clear whether they are as frequent and severe as in schizophrenia. Using high-resolution magnetic resonance imaging (MRI) and voxel-based morphometry methods of image analysis, we set out to examine the brain structure of patients participating in an epidemiological study of first-episode psychosis. We predicted that compared to healthy controls, patients with schizophrenia and affective psychosis would have frontal and temporal lobe grey matter deficits and increased ventricular and striatal volumes, and that those abnormalities would be more severe in schizophrenia.

METHOD

Sample

Patients

Participants were inner city South London residents enrolled in an epidemiological study of first-onset psychosis (ÆSOP: Aetiology and Ethnicity in Schizophrenia and Other Psychoses). Details of the ÆSOP study and the overall methodology can be found in Morgan *et al*, (2006). Inclusion criteria for the MRI study were (a) age 16–65 years; (b) resident in defined area (population 265 950); (c) presenting consecutively for the first time to local psychiatric services (in-patient and out-patient) between 1997 and 2000 with symptoms meeting functional psychosis

criteria (ICD–10: F20 Schizophrenia and F30–39 Affective disorders – psychotic codings; World Health Organization, 1992). Exclusion criteria were (a) head trauma history with >1-hour unconsciousness; (b) central nervous system disease; (c) poor English fluency; (d) transient psychotic symptoms resulting from acute intoxication (ICD–10) following consumption of psychoactive substance.

Only patients meeting criteria for a narrow definition of schizophrenia (ICD–10 F20) were included in the ‘schizophrenia’ group. Patients diagnosed with bipolar disorder or depressive psychosis were allocated to the ‘affective psychosis’ group (ICD–10 F30–39). To ensure the diagnostic homogeneity of the two groups, patients with schizoaffective disorder were excluded from either group.

There were 153 patients diagnosed with either schizophrenia or affective psychosis enrolled in the ÆSOP study; 97 of those patients consented to MRI scanning; 9 of these did not complete the full scanning procedure and therefore were not included in the analysis. Fifteen further scans were excluded due to (a) subject motion $n=13$; (b) congenital hydrocephalus $n=1$; (c) subarachnoid cyst $n=1$. Therefore, 73 patients were included in the analysis, 44 of whom were diagnosed with schizophrenia, 12 with psychotic depression and 17 with bipolar disorder. These 73 patients were younger (mean age 27.1 years (s.d.=7.6) *v.* 30.1 years (s.d.=9.1), $t=2.8$, $P=0.007$) and comprised proportionately more White British patients (27 (37%) *v.* 12 (16%), $\chi^2=8.4$, $P=0.004$) than the 80 patients not included in the MRI analysis. There were no significant differences between the patients included and those not included in the analysis in terms of the proportion of male patients ($\chi^2=1.2$, $P=0.27$) and the number of patients with schizophrenia ($\chi^2=2.3$, $P=0.13$).

Controls

There were 58 controls recruited from the same community as the patients. Exclusion criteria were the same as those as for the patients. Evidence of past or present psychosis, screened with the Psychosis Screening Questionnaire (Bebbington & Nayani, 1995), was an additional exclusion criterion. We excluded 8 MRI scans (subject motion $n=7$; suspected hydrocephalus $n=1$). For the MRI analysis, controls were separately compared to the patients with (a) schizophrenia and (b) affective psychosis.

The controls were paired with the patients in the schizophrenia and affective psychosis groups on the basis of age (± 5 years) and gender. Thus, 44 paired controls were included in the analysis of the schizophrenia patients and 29 paired controls in the analysis of the patients with affective psychosis. In addition to the patient versus control subject analyses, an analysis directly comparing patients with schizophrenia with those with affective psychosis was conducted.

Ethical approval was granted by the South London and Maudsley Trust Research Ethical Committee. All participants gave written, informed consent.

Clinical assessments

Patients were interviewed using the WHO Schedules for Clinical Assessment in Neuropsychiatry (WHO-SCAN) (World Health Organization, 1994). ICD-10 diagnoses were made in consensus meetings with senior clinicians (R.M. or J.L.), using WHO-SCAN information and clinical notes. Using the WHO-SCAN data we encoded (in weeks): duration of illness as the onset date of psychotic symptoms to MRI date; and lifetime duration of antipsychotic exposure (to MRI date). Total symptomology was scored by summing the individual item scores on the WHO-SCAN using the algorithm of Wing & Sturt (1978).

Structural magnetic resonance image acquisition

Scans were acquired with a GE Signa 1.5-T system, at the Maudsley Hospital, London. Contiguous, interleaved proton-density- and T2-weighted 3mm thick coronal plane dual-echo images were acquired, providing whole brain coverage. A repetition time of 4000 ms and effective echo times of 20 ms and 85 ms were used with 8-echo train length. Matrix size was 256×192 , collected from a rectangular field-of-view of $22 \text{ cm} \times 16.5 \text{ cm}$, giving an in-plane resolution of 0.859 mm. Total acquisition time was 10 min, 12 s.

Structural magnetic resonance image processing

The methods used for segmentation and registration of each fast spin echo data-set are described in detail elsewhere (Suckling *et al*, 1996; Bullmore *et al*, 1999). Briefly, subject masks were generated to identify neural tissue. Extracerebral tissues were removed first, using an automated algorithm.

Manually editing the skull-stripped images was necessary only to remove brainstem and cerebellum from the cerebral hemispheres and diencephalon. The probability of each intracerebral voxel belonging to each of four possible tissue classes (grey matter, white matter, cerebrospinal fluid, or dura/vasculature) was estimated with a modified fuzzy clustering algorithm (Suckling *et al*, 1996). This type of segmentation assigns for each voxel a value in the range 0–1 indicating the fraction of the voxel comprised by each tissue type (e.g. a grey matter value of 0.7 means 70% of tissue represented by that voxel is grey matter; therefore the value indicates the proportion of the voxel occupied by grey matter). Total grey tissue volume was calculated at this stage of the analysis.

The construction of the sample's template image is described elsewhere (Dazzan *et al*, 2004). In summary, a template image was constructed using the AFNI (Analysis of Functional Neuroimages) programme from 6 proton-density images acquired from 6 healthy controls and then averaging these images. Tissue distribution maps were registered onto the template by first registering each subject's proton density image using a 9-parameter affine registration, minimising between image grey-level difference. This registration aligns all the images together, and scales them to the same gross dimensions. The derived mapping was then applied to the corresponding tissue maps.

Ventricular volume

Additional masks were generated per subject by tracing around the lateral and third ventricles in native space, in every slice in which they were visible. Ventricles were traced by one rater (S.-J.P.), masked to age, gender, ethnicity and patient/control status. Within the masked area, cerebrospinal fluid volume was calculated using the data generated from the previously described modified fuzzy clustering algorithm.

Statistical analysis

Between-group regional differences in grey matter volume were estimated by fitting an analysis of covariance (ANCOVA) model at each intracerebral voxel in standard space covarying for age and total grey matter volume. Permutation testing was used to assess statistical significance, and regional relationships were tested at voxel cluster level (Bullmore *et al*, 1999, Sigmundsson *et al*, 2001). 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 informed only by single voxel data. We set the statistical threshold for cluster significance in all analyses so that the expected number of false-positive clusters (P -value times number of tests) was < 1 false-positive. We examined the association between grey matter cluster size and measures for duration of illness, duration of antipsychotic exposure and total symptoms using Pearson correlation coefficients. Student's t -test calculations were used to analyse between-group differences in ventricle to brain volume ratio and total grey matter and cerebrospinal fluid volume.

RESULTS

Forty-four patients received an ICD-10 schizophrenia diagnosis and 29 patients a diagnosis of bipolar disorder ($n=17$) or psychotic depression ($n=12$). T -tests and χ^2 analyses showed there were no significant differences between the schizophrenia and affective psychosis groups in terms of duration of illness, duration of antipsychotic exposure, total symptom scores (Table 1) and number of compulsory admissions. The percentage of patients who were prescribed atypical antipsychotics was higher among patients with schizophrenia than in those with affective psychosis (22 (50%) *v.* 2 (7%), $\chi^2=16.7$, $P<0.001$). More patients with affective psychosis were prescribed typical antipsychotics ($n=14$, 48%) than patients with schizophrenia ($n=13$, 30%). This difference did not reach statistical significance.

Schizophrenia *v.* controls

Patients with schizophrenia had, on average, 2 fewer years of education (mean 12.4 years (s.d. 2.0) *v.* 14.1 years (s.d. 2.6), $t=3.5$, $d.f.=86$, $P=0.001$) and scored significantly lower on the National Adult Reading Test (NART), an estimated measure of premorbid IQ (Nelson & Willison, 1991) than the control group (93.3 (s.d. 16.0) *v.* 106.5 (s.d. 11.9), $t=4.1$, $d.f.=75$, $P<0.001$). Analyses using t -tests and χ^2 showed there were no significant differences between the schizophrenia patients and controls in terms of age, gender, handedness, parental socio-economic status and ethnicity (Table 2).

Table 1 Clinical characteristics of the patient sample

	Schizophrenia (n=44) mean (s.d.)	Affective psychosis (n=29) mean (s.d.)	Analysis t (d.f.=71)
Duration of illness in weeks	67.1 (124.9)	48.7 (109.9)	0.52 ¹
Total symptom rating	30.1 (20.5)	32.5 (13.3)	0.43
Affective symptoms	6.8 (8.6)	12.7 (8.4)	2.75
Duration of antipsychotic treatment in weeks	8.5 (8.2)	6.5 (9.4)	0.98

1. Analysis based on logarithmic transformation of duration of illness data.

Total tissue and ventricular volumes

There were no between-group differences in total grey matter or cerebrospinal fluid volume. However, patients with schizophrenia had significantly larger lateral ventricle to brain ratio (+17.7% volume: $t=2.33$, $d.f.=86$, $P<0.03$) and larger third ventricle to brain ratio (+63.2% volume: $t=3.08$, $d.f.=86$, $P<0.01$) than healthy controls (Table 3).

Regional proportional grey tissue volume differences

There were no regional differences in grey matter volume between patients and controls (Table 4).

However, a secondary analysis of the grey matter map using a lowered statistical threshold for cluster significance (P -value set at 0.01), detected 3 excess grey matter areas and 1 grey matter deficit area in the patients. The excess clusters were located in the left and right lenticular nucleus and the right pre-central gyrus. The deficit cluster was located at the right parahippocampal gyrus.

Symptomology, duration of illness and duration of antipsychotic exposure

These clinical factors were not associated with lateral or third ventricle volume (Table 4).

Affective psychosis v. controls

Analyses using t -tests and χ^2 showed there were no significant differences between the patients with affective psychosis and controls in terms of age, gender, years of education, NART, handedness, parental socio-economic status and ethnicity (Table 2).

Total tissue and ventricular volumes

There were no between-group differences in total grey matter or CSF volume. Patients with affective psychosis had larger third ventricle to brain ratio than controls (+70% volume: $t=2.72$, $d.f.=56$, $P<0.01$), but there was no significant between-group difference in lateral ventricle volume (Table 3).

Regional proportional tissue volume differences

Four regional clusters of grey matter deficit were identified in patients with affective psychosis compared to the controls. These were located: (a) bilaterally within the anterior cingulate gyrus (centred Brodmann's Area (BA) 24), and extending anteriorly to BA31 and posteriorly to BA23; (b) within the left insula; (c) at the right postcentral gyrus (BA1 and BA2); (d) at the left fusiform gyrus (BA37) and extending laterally into the lingual gyrus. The patients had a

single grey matter excess cluster located in the left lenticular nucleus (Table 4; see Fig. DS1 in data supplement of online version of this paper).

Symptomology, duration of illness and duration of antipsychotic exposure

Longer duration of antipsychotic exposure correlated with increased third ventricle volume ($r=0.49$, $P=0.007$) and increased lateral ventricle volume ($r=0.54$, $P=0.003$). Increased third ventricle volume correlated with higher total symptom scores ($r=0.41$, $P=0.03$). The amount of grey matter in the regional deficit and excess tissue clusters identified did not correlate with symptomology scores, duration of illness or duration of antipsychotic exposure (Table 4).

Schizophrenia v. affective psychosis

The proportion of males in the schizophrenia group was significantly higher ($n=31$ (70.4%) *v.* $n=11$ (38.0%) $\chi^2=7.60$, $d.f.=1$, $P=0.006$). Patients with schizophrenia had on average 1.1 less years of education (mean 12.4 years (s.d. 2.0) *v.* 13.5 years (s.d.=2.5), $t=1.96$, $d.f.=71$, $P=0.056$) and scored significantly lower on NART (93.3 (s.d.=16.0), *v.* 102.8 (s.d.=14.0), $t=2.5$, $d.f.=63$, $P=0.016$). Patients with schizophrenia were on average 3.2 years younger than patients with affective psychosis (25.8 years (s.d.= 7.1) *v.* 29.0 years (s.d.=7.9)). This difference in age bordered on statistical significance ($t=1.78$, $d.f.=71$, $P=0.079$). Analyses using t -tests and χ^2 showed there were no significant differences between the two patient groups in terms of handedness, parental socio-economic status and ethnicity (Table 2).

Total tissue and ventricular volumes

An ANCOVA (controlling for age and gender) was used compare total tissue and

Table 2 Characteristics of sample: patients and controls

	Schizophrenia (n=44) n	Matched controls (n=44) n	Analysis χ^2	Affective psychosis (n=29) n	Matched controls (n=29) n	Analysis χ^2	Analysis: schizophrenia v. affective psychosis χ^2
Gender, male/female	31/13	31/13	0 1.0	11/18	11/18	0 1.0	7.61 0.06
Parental socioeconomic status: managerial/ intermediate/working	14/12/18	13/18/13	2.0 0.38	11/5/13	9/13/7	5.6 0.06	1.0 0.60
Ethnicity: White British/Other	16/28	18/26	0.66 0.83	10/19	13/16	0.65 0.42	0.03 0.87
Handedness ¹ Right /Left	6/38	4/38	0.45 0.50	1/28	4/28	2.1 0.15	2.3 0.32

1. Handedness data not available for 2 patients with schizophrenia and 2 controls.

Table 3 Mean total tissue, total cerebrospinal fluid and ventricular volumes (ml) in patients and normal controls¹

	Grey matter	Total cerebrospinal fluid	Lateral ventricle	Third ventricle
	ml (%), % volume difference, t			
Schizophrenia (n=44)	581.2 (64.4) –2.5, 1.24	156.9 (32.4), –2.1, 0.51	18.6 (10.2), +17.7, 2.33	0.31 (0.21), +63.2, 3.08
Matched controls (n=44)	595.8 (57.0)	160.2 (28.8)	15.3 (6.7)	0.19 (0.15)
Affective psychosis (n=29)	561.3 (52.3), –2.1, 0.88	147.8 (30.6), –0.05, 0.09	15.7 (6.7), +18.0, 1.70	0.34 (0.26), +70.0, 2.72
Matched controls (n=29)	573.5 (52.9)	148.5 (27.2)	13.31 (6.3)	0.20 (0.14)

1. Analysis calculated according to ratio of ventricle to total grey matter volume.
 $P < 0.05$, ** $P < 0.001$.

ventricular volumes. There were no between-group differences in total grey matter, cerebrospinal fluid volume or ventricular volumes.

Regional proportional grey tissue volume differences

In addition to age and total grey matter volume, gender was added as a covariate in the analysis of regional grey matter differences. One regional cluster of grey matter deficit was identified in the affective psychosis group. This was located bilaterally within the anterior cingulate gyrus, centred on Brodmann's Area (BA) 24, and extending anteriorly to BA31 and BA32 and posteriorly to BA23 (Table 4). As there were significant differences in the type of antipsychotic taken, an additional analysis adding type of antipsychotic as a covariate (typical, atypical or none) was performed. When type of antipsychotic was added as a covariate, there were no differences between groups in regional grey matter.

DISCUSSION

In contrast with other first-onset MRI investigations, we found relatively few structural abnormalities in schizophrenia but identified several regional grey matter deficits in the affective psychoses. Furthermore, in patients with affective disorders, but not with schizophrenia, we found increased ventricular volumes to be associated with higher total symptom ratings and longer lifetime use of antipsychotics.

Schizophrenia

Our finding of increased ventricular volume is consistent with other first-episode schizophrenia studies (Fannon *et al*, 2000b; Cahn *et al*, 2002). Evidence of ventricular enlargement in patients with first-episodes either never treated or minimally treated with antipsychotics (Fannon *et al*, 2000b) suggests that this abnormality either predates

or closely follows psychosis onset and it is perhaps of note that in our sample, ventricular abnormalities in schizophrenia were not associated with symptomology, duration of illness or duration of antipsychotic exposure. Contrary to our prediction that patients with schizophrenia would show frontal and temporal grey matter reductions and increased striatal grey matter, no grey matter abnormalities were found. To explore the possibility that this could have been due to a lack of statistical power, we re-ran the grey matter comparison using a lower statistical threshold. This analysis identified grey matter differences in two of the predicted locations: lenticular nuclei increases (left and right) and reductions in the right parahippocampal gyrus (part of the temporal lobe). Although in this post-hoc analysis the possibility of false-positive type 1 errors is increased, the findings may nevertheless indicate the presence of a pattern of structural abnormalities similar but less pronounced than that reported elsewhere (Lawrie & Abukmeil, 1998; Fannon *et al*, 2000a; Job *et al*, 2002).

Affective psychosis

We found enlargement of third ventricle in the affective psychoses, but in contrast to the schizophrenia group, this was correlated with higher total symptom scores and longer duration of antipsychotic exposure. The latter may indicate that this brain abnormality is less likely to reflect neurodevelopmental pathology than in schizophrenia

The grey matter deficits we found are in line with other studies of affective disorders. Anterior cingulate gyrus deficits have been found in bipolar disorder (Sassi *et al*, 2004) and major depression (Bremner *et al*, 2002) and in people with a genetic risk for bipolar disorder, but not for schizophrenia (McDonald *et al*, 2004). Findings such as these suggest a role for the anterior cingulate gyrus in the regulation of

emotions. Combined ratings for affective symptoms (depression and mania) in the affective psychosis group were as one might expect higher than in the schizophrenia group ($t=2.8$, $P=0.008$), but a post-hoc analysis showed no correlation between severity of affective symptoms and the amount of grey matter in the anterior cingulate gyrus cluster.

Recent findings have shown left fusiform grey matter deficits in patients with mixed psychotic disorders, scanned 1 year after psychosis onset (Pantelis *et al*, 2003). The possible role of the fusiform gyrus in the psychopathology of psychosis remains unclear but it has been suggested that it is implicated in the appraisal and encoding of faces in disorders such as schizophrenia (Onitsuka *et al*, 2003). In our sample we found no correlation between fusiform grey matter volume and symptoms scores, duration of illness and duration of antipsychotic exposure. Similarly, no association was found between those variables and grey matter volume in the two other deficit regions identified in our patients with affective psychosis: the post central gyrus and the left insula. Although a recent ventricle to brain ratio study (Job *et al*, 2002) observed reduced postcentral gyrus grey matter in schizophrenia, there have been few reports elsewhere in the psychosis literature of structural abnormalities in this region. On the other hand, left insula grey matter deficits have previously been reported in ventricle to brain ratio studies of affective psychosis (Kubicki *et al*, 2002), as well as in first-onset schizophrenia (Kasai *et al*, 2003b) and schizophrenia of mixed chronicity (Kubicki *et al*, 2002).

The finding of more grey matter deficits in affective psychosis than in schizophrenia was contrary to our predictions and is at variance with other studies of psychosis. It is unlikely the findings can be accounted for by anomalies in image acquisition or processing as such effects would not occur

Table 4 Regional differences in grey matter: patients v. normal controls and schizophrenia v. affective psychosis, and correlation of clinical factors with grey matter volume and ventricle to whole brain ratios

Anatomical area	Number of voxels in cluster	Location of cluster centre, x, y, z	Correlations, R		
			Duration of illness	Total symptoms scores	Duration of antipsychotic exposure
Schizophrenic patients (n=44) v. matched controls (n=44)					
Lateral ventricle to whole brain ratio	–	–	0.12	0.02	0.01
Third ventricle to whole brain ratio	–	–	0.16	0.28	0.11
Affective psychosis (n=29) v. matched controls (n=29)					
Grey matter deficits:					
Anterior cingulate gyrus BA 24, extending bilaterally to BA 32, 31, 23	728	1, –10, 30	0.10	–0.05	–0.10
Insula cortex (left)	269	–41, 0, –2	0.20	0.10	0.24
Post central gyrus (right) BA 1, 2	230	47, –21, 37	0.38	–0.10	–0.35
Fusiform gyrus BA 37, 19 (left), extending laterally to lingual gyrus	158	–25, –52, –11	–0.10	–0.01	–0.20
Other areas					
Lenticular nucleus (left): grey matter excess	474	–28, –6, 6	–0.26	0.29	–0.15
Lateral ventricle to whole brain ratio	–	–	0.02	0.26	0.54**
Third ventricle to whole brain ratio	–	–	–0.21	0.41*	0.49**
Schizophrenic patients (n=44) v. affective psychosis (n=29)					
Grey matter deficit (in affective psychosis):					
Anterior cingulate gyrus BA 24, extending bilaterally to BA 32, 31, 23	720	1, –2, 36	0.17	–0.06	0.02

BA, Brodmann's area.
* $P < 0.05$, ** $P < 0.01$.

systematically in one group only. One possible confounder is between-patient group differences in prescribed antipsychotics; this could provide some explanation for these findings as recent research suggests different effects of typical and atypical antipsychotics on brain structure (Garver *et al*, 2005; Lieberman *et al*, 2005). Indeed, in an earlier analysis of our sample (Dazzan *et al*, 2005) we found that, in comparison to drug-free patients, patients taking typicals, but not those taking atypicals, had smaller volumes in the lobulus paracentralis; anterior cingulate gyrus; superior and medial frontal gyri; superior and middle temporal gyri; insula; and precuneus. It is conceivable that such an effect might explain the greater deficits in the affective psychosis group rather than the schizophrenia group as more patients with affective psychosis were taking typical antipsychotics (48%) than patients with schizophrenia (30%) and significantly more patients with schizophrenia were taking atypicals (50% v. 7%). A role for differences in pharmacological treatment was confirmed by our additional analysis showing that when these differences are taken into account, there are no regional differences in brain structure between patient groups.

Treatment with typical antipsychotics may also be relevant to the increased left lenticular nucleus grey matter as these drugs have a strong affinity to subcortical D2 dopamine receptors and receptor blockade may induce cellular growth and increase blood flow (Corson *et al*, 2002). Striatal enlargement appears less likely in patients treated only with atypical antipsychotics (Corson *et al*, 1999), which have weaker D2 receptor affinity. Indeed, in a previous analysis on this first-onset sample, we showed that patients treated with atypicals have similar striatal volumes to drug-free patients, while subjects taking typicals had significantly larger basal ganglia volumes than drug-free patients (Dazzan *et al*, 2005).

Schizophrenia and affective psychosis

A direct comparison of the two patient groups (controlling for between-group differences in age, gender and total grey matter volume) revealed grey matter of the anterior cingulate gyrus in the patients with affective psychosis, but no other neuroanatomical differences. This was consistent

with the findings of the patient-control comparisons. The patients with affective psychosis were prescribed more typical antipsychotics and significantly less atypical antipsychotics than the patients with schizophrenia. When the analysis was repeated, controlling for type of antipsychotic, no between-group differences were found. This suggests that grey matter changes may be associated with variations in the type of antipsychotic taken and is consistent with our previous finding of typicals being associated with grey matter reductions in the anterior cingulate gyrus (Dazzan *et al*, 2005).

The finding of regional deficits in the patients with affective psychosis was of interest and indicates that some morphological changes take place in those patients close to illness onset or at prodromal or even premorbid stage. We found significant, but fewer neuroanatomical abnormalities in schizophrenia. The absence of more widespread differences in these patients might be accounted for by the epidemiological basis of our study, in which both patients and controls were recruited from the same catchment area. Using an epidemiologically based sample avoids the potential bias of recruiting subjects

according to factors such as illness severity and family history. Many reports on patients with first-episode schizophrenia come from university clinics, referral centres and in-patient samples, which attract subjects not necessarily representative of first-episode schizophrenia in general (Job *et al*, 2002, Pantelis *et al*, 2003) and it is possible that our findings do not reflect the findings reported in patients with more severe illnesses. The use of an epidemiological sample may also explain in part the findings in the affective psychosis sample. The recruitment of those patients was not based on referrals from bipolar and other affective clinics and may have resulted in a more psychotic affective sample than that seen in earlier MRI studies of affective disorders.

Limitations

This study is not without limitations. First, the finding of grey matter abnormalities in the schizophrenia patients at a lower statistical threshold suggests that more grey matter changes in this group might have been identified in a larger sample. Second, because there may be longitudinal MRI changes following the first episode, a different pattern of group differences may be evident when patients are studied later in the illness. And third, our appraisal of the relationship between antipsychotic medication, grey matter change and diagnosis was limited by the fact that patients were not selected into the study on the basis of drug prescription status. This would have allowed for a more systematic analysis of the potential effects of exposure to different types of antipsychotic and that of drug-free status.

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Correspondence: Kevin Morgan, Department of Psychology, University of Westminster, 309 Regent Street, London W1B 2UW, UK. Email: k.d.morgan@wmin.ac.uk