Grey Matter Abnormalities in First Episode Schizophrenia and Affective Psychosis

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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/T_2-weighted) MR images and carried out voxel-based analysis on the images of 73 first-episode psychosis patients (schizophrenia=44, affective psychosis=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.

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INTRODUCTION

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*, 2000*a*), 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 *et al*, 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 MRI and voxel-based morphometry (VBM) 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, but that those abnormalities would be more severe in schizophrenia.

METHODS

Sample

Patients

Subjects 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 AESOP study and the overall methodology can be found in Morgan *et al*, (2006). Inclusion criteria for the MRI study were: (a) age 16-65; (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 1997-2000 with symptoms meeting functional psychosis criteria (ICD10: F20 [Schizophrenia] and F30-39 [Affective disorders - psychotic codings])(WHO, 1992). Exclusion criteria were: (a) head trauma history with > one 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.

153 patients diagnosed with either schizophrenia or affective psychosis were enrolled in the ÆSOP study. 97 of those patients consented to MRI scanning. Nine of these patients did not complete the full scanning procedure and therefore were not included in the analysis. 15 further scans were excluded due to: a) subject motion=13; b) congenital hydrocephalus=1; c) sub-arachnoid cyst=1. Therefore, 73 patients were included in the analysis. 44 of these patients were diagnosed with schizophrenia; 12 with psychotic depression and 17 with bipolar disorder. These 73 patients were younger (mean age 27.1 [sd 7.6] years versus 30.1 [sd 9.1] years, t=2.8, p=0.007) and comprised proportionately more white British patients (27 [37%] versus 12[16%], χ^2=8.4, p=.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 (χ^2=1.2, p=0.27) and the number of patients with schizophrenia (χ^2=2.3, p=0.13).

Controls

58 controls were recruited from the same community as the patients. Exclusion criteria were the same as those for the patients'. Evidence of past or present psychosis, screened with the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995), was an additional exclusion criterion. We excluded eight MRI scans (subject motion=7; suspected hydrocephalus=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 sex. Thus, 44 paired controls were included the analysis of the schizophrenia patients and 29 paired controls in the analysis of the patients with affective psychosis (Table 1). In addition to the patient versus control subject analyses, an analysis directly comparing patients with schizophrenia to 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) (WHO, 1994). We made ICD-10 diagnoses in consensus meetings with senior clinicians (RM or JL), using WHO-SCAN information and clinical notes. Using the WHO-

SCAN data, we encoded (in weeks): duration of illness (DOI) as the onset date of psychotic symptoms to MRI date; and lifetime duration of antipsychotic exposure (DAE) (to MRI date). Total symptomology was scored by summing the WHO-SCAN's individual item scores using the algorithm of Wing and Sturt (1978).

Structural MR 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 4000ms and effective echo times of 20ms and 85ms were used with 8-echo train length. Matrix size was 256 x 192, collected from a rectangular field-of-view of 22cm x 16.5cm, giving an in-plane resolution of 0.859mm. Total acquisition time was 10 minutes, 12 seconds.

Structural MR Image processing

The methods used for segmentation and registration of each fast spin echo dataset are described in detail elsewhere (Bullmore *et al*, 1999, Suckling *et al*, 1996). Briefly, subject masks were generated to identify neural tissue. Extra-cerebral tissues were removed initially, 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, cerebro spinal fluid [CSF], 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) program 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 between images. 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 (SJP), blind to age, sex, ethnicity and patient/control status. Within the masked area, CSF 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 3D cluster mass (the sum of suprathreshold 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 with measures for DOI, DAE and total symptoms using Pearson correlation coefficients. Students T test calculations were used to analyse between-group differences in ventricle to brain volume ratio (VBR) and total grey matter and CSF volume.

RESULTS

TABLE 1

TABLE 2

44 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 Chi Square analyses showed there were no significant differences between the 'Schizophrenia' and 'Affective Psychosis' groups in terms of DOI, DAE, total symptom scores 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%] versus 2 [7%], $\chi^{2=}16.7$,

p<.001). More patients with affective psychosis were prescribed typical antipsychotics (48%) than patients with schizophrenia (30%). This difference did not reach statistical significance. (Table 2).

Schizophrenia versus controls

Patients with schizophrenia had, on average, 2 less years of education (mean 12.4 [sd 2.0] years versus 14.1 [sd 2.6] years, t=3.5, df=86, p=.001) and scored significantly lower on the National Adult Reading Test (NART), an estimated measure of pre-morbid IQ (Nelson and Willison, 1991) (93.3 [sd 16.0], versus 106.5 [sd 11.9], t=4.1, df=75, p<.001). T-tests and Chi Square analyses showed there were no significant differences between the schizophrenia patients and controls in terms of age, gender, handedness, parental socio-economic status (PSES) and ethnicity. (Table 1).

Total tissue and ventricular volumes

There were no between-group differences in total grey matter or CSF volume. However, patients with schizophrenia had significantly larger lateral ventricle VBR (+24.9% volume: t=2.33, df=86, p<.03) and larger third ventricle VBR (+63.2% volume: t=3.08, df=86, p<.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 .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 precentral gyrus. The deficit cluster was located at the right parahippocampal gyrus.

Symptomology, DOI and DAI

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

Affective psychosis versus controls

T-tests and Chi Square analyses showed there were no significant differences between the affective patients and controls in terms of age, gender, years of education, NART, handedness, PSES and ethnicity. (Table 1).

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 VBR than controls (+70% volume: $t=2.72$, $df=56$, $p<.01$), 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 psyhcosis compared to the controls. These were located: 1) bilaterally within the anterior cingulate gyrus (centred Brodmann's Area (BA) 24), and extending anteriorly to BA31 and BA31 and posteriorly to BA23; 2) within the left insula; 3) at the right postcentral gyrus (BA1 and BA2); 4) 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; Figure 1).

Symptomology, DOI and DAE

Longer DAE correlated with increased third ventricle volume (r=.49, p=.007) and increased lateral ventricle volume (r=.54, p=.003). Increased third ventricle volume correlated with higher total symptom scores (r=.41, p=.03). The amount of grey matter in the regional deficit and excess tissue clusters identified did not correlate with symptomology scores, DOI or DAE. (Table 4).

TABLE 4 HERE

FIGURE 1 HERE

Schizophrenia versus affective psychosis

The proportion of males in the schizophrenia group was significantly higher (n=31 [70.4%] versus n=11 [38.0%] χ^2=7.60 , df=1, p=.006). Patients with schizophrenia had on average, 1.1 less years of education (mean 12.4 [sd 2.0] years versus 13.5 [sd 2.5] years, t=1.96, df=71, p=.056) and scored significantly lower on the National Adult Reading Test (NART) (93.3 [sd 16.0], versus 102.8 [sd 14.0], t=2.5, df=63, p=.016). Patients with schizophrenia were on average 3.2 years younger than the patients with affective psychosis (25.8 [sd 7.1] years versus

29.0 [sd 7.9] years). This difference in age bordered on statistical significance (t=1.78, df=71, p=.079). T-tests and Chi Square analyses showed there were no significant differences between the two patient groups in terms of handedness, parental socio-economic status (PSES) and ethnicity. (Table 1).

Total tissue and ventricular volumes

An ANCOVA (controlling for age and sex) was used compare total tissue and ventricular volumes. There were no between-group differences in total grey matter, CSF volume or ventricular volumes. (Table 3).

Regional proportional grey tissue volume differences

In addition to age and total grey matter volume, sex was also 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 (typicals, atypicals 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*, 2000*b*, Cahn *et al*, 2002). Evidence of ventricular enlargement in first-episode patients either never treated, or minimally treated with antipsychotics (Fannon *et al*, 2000*b*) 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, DOI or DAE. 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 (Fannon *et al*, 2000a, Job *et al*, 2002, Lawrie *et al*, 1998).

Affective Psychosis

We found enlargement of third ventricle in the affective psychoses, but in contrast to the schizophrenia patients, this was correlated with higher total symptom scores and longer DAE. 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 (ACG) 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 ACG 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 ($t=2.8$, $p=.008$), but a post-hoc analysis showed no correlation between severity of affective symptoms and the amount of grey matter in the ACG cluster.

Recent findings have shown left fusiform grey matter deficits in patients with mixed psychotic disorders, scanned one 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, DOI and DAE. Similarly, no association was found between those variables and grey matter volume in the two other deficit regions identified in our affective psychotic patients: the post central gyrus and the left insula. While a recent VBM 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 VBM 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 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 (Lieberman *et al*, 2005; Garver *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% versus 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 sub-cortical 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 patients groups (controlling for between-group differences in age, sex and total grey matter volume) revealed grey matter of the anterior cingulate gyrus in the affective psychosis patients, but no other neuroanatomical differences. This was consistent with the findings of the patient-control comparisons. The affective psychosis patients 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 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 first-episode schizophrenia patients 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.

CLINICAL IMPLICATIONS

- Ventricular enlargement was associated with symptomology and duration of illness in affective psychosis but not in schizophrenia. This may indicate that this particular brain abnormality is more likely to reflect a neurodevelopmental pathology in schizophrenia compared to the affective psychoses.

- As in schizophrenia, patients with affective psychotic disorders show subtle neuroanatomical changes early in their illness,

- Differential treatment with typical and atypical antipsychotics may contribute to brain structural differences seen in patients with schizophrenia and affective psychosis.

LIMITATIONS

- The finding of grey matter abnormalities in the schizophrenia patients at a lower statistical threshold suggests that more grey matter changes in this group may have been identified in a larger sample.

- 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.

- Our appraisal of the relationship between antipsychotic medication, grey matter change and diagnosis was limited by the fact that patients could not be selected into the study of their basis of drug prescription (or drug free) status.

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Table 1: Characteristics of sample: patients and controls

	Schizophrenia *n=44*	Matched controls *n=44*	Analysis		Affective psychosis *n=29*	Matched controls *n=29*	Analysis		Analysis: schizophrenia vs affective psychosis	
	mean (sd)	mean (sd)	t	p	mean (sd)	mean (sd)	t	p	t	p
Age	25.8 (7.1)	25.8 (7.1)	.01	.99	29.0 (7.9)	28.8 (7.3)	.09	.93	1.78	.079
Years of education	12.4 (2.0)	14.1 (2.6)	3.5	.001	13.5 (2.5)	14.0 (2.5)	.74	.46	1.96	.056
Pre-morbid IQ (NART) [a]	93.3 (16.0)	106.5 (11.9)	4.1,	<.001	102.8 (14.0)	106.7 (10.8)	1.16	.25	2.50	.016
	n	n	χ^2	p	n	n	χ^2	p	χ^2	p
Sex: male/female	31/13	31/13	0	1.0	11/18	11/18	0	1.0	7.61	.006
Parental SES: managerial/ intermediate/working	14/12/18	13/18/13	2.0	.38	11/5/13	9/13/7	5.6	.06	1.0	.60
Ethnicity: White British/ Not white British	16/28	18/26	.66	.83	10/19	13/16	.65	.42	.03	.87
Handedness [b] Right /Left	6/38	4/38	.45	.50	1/28	4/28	2.1	.15	2.3	.32

[a] NART scores not available for 6 patients with schizophrenia, 2 patients with 'affective psychosis' and 7 controls.

[b] Handedness data not available for 2 patients with schizophrenia and 2 controls.

Table 2 : Clinical characteristics of the patient sample

	Schizophrenia *(n=44)*	Affective psychosis *(n=29)*	Analysis	
	mean (sd) [median]	mean (sd) [median]	t (df=71)	p
Duration of illness (weeks)	67.1 (124.9) [22.4]	48.7 (109.9) [26.7]	.52*	.60
Total symptom rating	30.1 (20.5)	32.5 (13.3)	.43	.67
Affective symptoms	6.8 (8.6)	12.7 (8.4)	2.75	.008
Duration of antipsychotic treatment (wks)	8.5 (8.2)	6.5 (9.4)	.98	.33
	n (%)	n (%)	χ^2	
Type of antipsychotic				
Typical only	13 (30)	14 (48)	.04	.85
Atypical only	22 (50)	2 (7)	16.7	<.001
Mixed	2 (5)	3 (10)	0.20	.66
None	7 (16)	10 (35)	0.53	.47
Compulsory admission	26 (60)	15 (52)	.54	.46

* Analysis based on logarithmic transformation of DOI data

Table 3: Mean total tissue, total CSF and ventricular volumes (ml) in patients and normal controls

	Grey matter	**Total CSF**	**Lat. ventricle***	**Third ventricle** [a]
Schizophrenia (n=44)	581.2 (64.4)	156.9 (32.4)	18.6 (10.2)	.31 (.21)
Matched controls (n=44)	595.8 (57.0)	160.2 (28.8)	15.3 (6.7)	.19 (.15)
% vol. difference	-2.5	-2.1	+17.7	+63.2
Analysis:	t=1.24, p=.26	t=.51, p=.61	t=2.33, p<.03	t=3.08, p<.01
Affect. Psychosis (n=29)	561.3 (52.3)	147.8 (30.6)	15.7 (6.7)	.34 (.26)
Matched controls (n=29)	573.5 (52.9)	148.5 (27.2)	13.31 (6.3)	.20 (.14)
% vol. difference	-2.1	-.5	+18.0	+70.0
Analysis	t=.88, p=.38	t=.09, p=.93	t=1.70, p=.09	t=2.72, p<.01
Schizophrenia vs Affect. Psychosis				
% vol. difference:	+3.5	+6.2	+18.5	-9.7
Analysis	f=.01, p=.09	f=.13, p=.72	f=1.46, p=.23	f=.84, p=.36

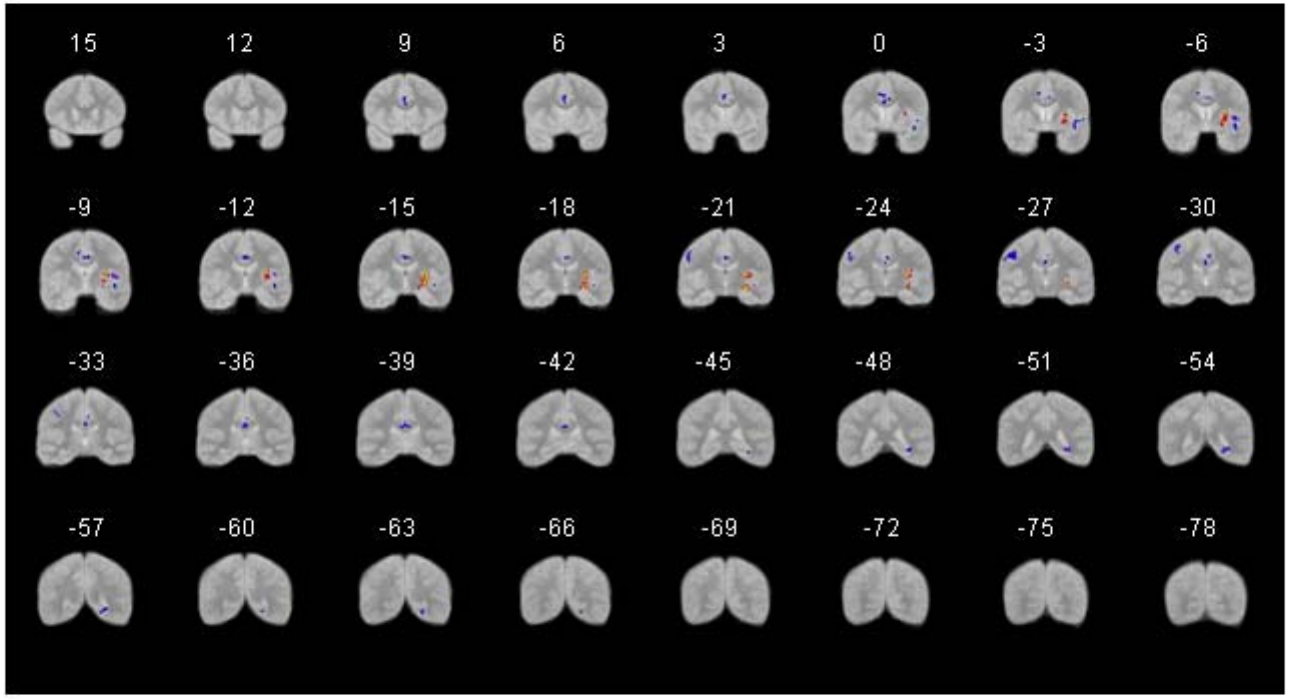
[a] Volume (ml) shown, analysis calculated according to ratio of ventricle to total grey matter volume
[b] ANCOVA (controlling for age and sex) performed in schizophrenia vs affective psychosis analysis

Table 4: a) Regional differences in grey matter: patients versus normal controls and schizophrenia versus affective psychosis
b) Correlation of clinical factors (DOI, total symptoms scores [TSS] and duration of antipsychotic exposure [DAE] 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*		
Schizophrenic patients (n=44) versus matched controls (n=44)			DOI	TSS	DAE
Lateral ventricle to whole brain ratio	-	-	.12	.02	.01
Third ventricle to whole brain ratio	-	-	.16	.28	.11
Affective psychosis (n=29) versus matched controls (n=29)					
Grey matter deficits:					
Anterior cingulate gyrus BA 24, extending bilaterally to BA 32, 31, 23	728	1, -10, 30	.10	-.05	-.10
Insula cortex (left)	269	-41, 0, -2	.20	.10	.24
Post central gyrus (right) BA 1,2	230	47, -21, 37	.38	-.10	-.35
Fusiform gyrus BA 37, 19 (left), extending laterally to lingual gyrus	158	-25, -52, -11	-.10	-.01	-.20
Other areas:					
Lenticular nucleus (left): *grey matter excess*	474	-28, -6, 6	-.26	.29	-.15
Lateral ventricle to whole brain ratio	-	-	.02	.26	**.54**[b]
Third ventricle to whole brain ratio	-	-	-.21	**.41**[a]	**.49**[b]
Schizophrenic patients (n=44) versus 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	.17	-.06	.02

[a] $p<.05$, [b] $p<.01$, BA = Brodmann area

Figure 1: Regional differences in grey matter in patients with affective psychosis versus controls.



Red/yellow regions denote areas of grey matter excess in the patients relative to the control subjects. Blue regions denote areas grey and white matter deficit in the patients. The results are displayed on averaged grey matter maps. The left side of the image corresponds to the right side of the brain. Numbers refer to the approximate y coordinates in the standard space of Talairach and Tournoux.