

Cerebral grey, white matter and csf in never-medicated, first-episode schizophrenia

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Received 29 June 2006; received in revised form 18 September 2006; accepted 19 September 2006

Available online 13 November 2006

Abstract

We report the first voxel-based morphometric (VBM) study to examine cerebral grey and white matter and cerebrospinal fluid (CSF) using computational morphometry in never-medicated, first-episode psychosis (FEP). Region-of-interest (ROI) analysis was also performed blind to group membership. 26 never-medicated individuals with FEP (23 with DSM-IV schizophrenia) and 38 healthy controls had MRI brain scans. Groups were balanced for age, sex, handedness, ethnicity, paternal socio-economic status, and height. Healthy controls were recruited from the local community by advertisement. Grey matter, white matter, and CSF: global brain volume ratios were significantly smaller in patients. Patients had significantly less grey matter volume in L and R caudate nuclei, cingulate gyri, parahippocampal gyri, superior temporal gyri, cerebellum and R thalamus, prefrontal cortex. They also had significantly less white matter volume in the R anterior limb of the internal capsule fronto-occipital fasciculus and L and R fornices, and significantly greater CSF volume especially in the R lateral ventricle. Excluding the 3 subjects with brief psychotic disorder did not alter our results. Our data suggest that fronto-temporal and subcortical-limbic circuits are morphologically abnormal in never-medicated, schizophrenia. ROI analysis comparing the schizophrenia group ($n=23$) with the healthy controls ($n=38$) confirmed caudate volumes were significantly smaller bilaterally by 11%, and lateral ventricular volume was significantly larger on the right by 26% in the patients. Caudate nuclei and lateral ventricular volume measurements were uncorrelated (Pearson correlation coefficient 0.30, $p=0.10$), ruling out the possibility of segmentation artefact. Ratio of lateral ventricle to caudate volume was bilaterally significantly increased ($p<0.005$, 2-tailed), which could represent an early biomarker in first-episode, never-medicated schizophrenia.

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Keywords: MRI; Psychosis; Schizophrenia; Voxel-based morphometry

1. Introduction

Schizophrenia is regarded, at least in part, as a neurodevelopmental disorder in which a range of brain morphological anomalies have been observed. Of these,

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cerebral ventricular enlargement is the most consistently replicated anomaly (Chua and McKenna, 1995; McCarley et al., 1999; Wright et al., 2000). In addition to a global reduction in brain volume (Kubicki et al., 2002; Wright et al., 2000), localised volume deficits in fronto-temporo-limbic regions (Gur et al., 2000; McCarley et al., 1999; Seidman et al., 2003; Suzuki et al., 2005), thalamus (Andreasen et al., 1994; Danos et al., 2003; Ettinger et al., 2001; Kemether et al., 2003) and basal ganglia (Corson et al., 1999; Gur et al., 1998; Dazzan et al., 2004) have been reported along with abnormalities in associated white matter tracts (Sigmondsson et al., 2001). Since brain structural volume is influenced by age of onset, duration of illness (Friedman et al., 1992) and neuroleptic medication (Chakos et al., 1994; Friedman et al., 1992), this study focuses on newly diagnosed, never-treated patients to mitigate the impact of these confounds.

Evaluation of a widely distributed but subtle brain lesion requires a tool with high spatial resolution, free from inter-operator bias. Computational morphometry permits exploratory *and* rapid analysis since it systematically examines every volume-element throughout the entire brain. It is relatively operator independent and can examine brain regions which lack readily traceable anatomical boundaries (Chua et al., 1997) with multifaceted symptoms in an illness that defies the concept of a circumscribed lesion (Brambilla et al., 2003).

Just 5 structural MRI (sMRI) studies to-date have used VBM to compare brain morphology in first-episode psychosis patients and healthy controls (Ananth et al., 2002; Job et al., 2002; Kubicki et al., 2002; Salgado-Pineda et al., 2003; Jayakumar et al., 2005). Of these, only 2 recruited never-medicated subjects (Jayakumar et al., 2005; Salgado-Pineda et al., 2003): both reported grey matter reduction in fronto-striato-thalamic and parahippocampal regions as well as smaller caudate volumes. However, neither performed confirmatory region-of-interest (ROI) analysis even though VBM is prone to systematic registration errors during spatial normalisation that may modify the size or shape of brain structures under study (Bookstein, 1991). Moreover, both disagreed on the presence of grey and white matter and CSF differences. Smallish sample sizes were used e.g. 13 and 18 patients in Salgado-Pineda et al. (2003) and Jayakumar et al. (2005) respectively. Therefore, we recruited 29 never-medicated FEP patients (of which 23 had schizophrenia) and 40 healthy controls and used VBM to localise regional volume differences for each principal brain tissue class. We also performed ROI analysis of caudate nuclei and lateral ventricles. We predicted fronto-temporal grey and white matter and

CSF abnormalities, together with lateral ventricular enlargement and caudate volume deficits.

2. Materials and methods

2.1. Subjects

Consecutive patients in our hospital were screened based on inclusion criteria : age 18–55 years; no previous neuroleptic exposure; first experience of psychotic symptoms (i.e. hallucinations, and/or delusions, and/or thought disorder) no significant mood/organic disorder, with decline in daily functioning) and diagnosed as DSM-IV schizophrenia, schizophreniform or brief psychotic disorder (Diagnostic and Statistical Manual of Mental Disorders, 1994) by two independent specialists in Psychiatry. We assessed duration of psychosis using the IRAOS (Interview for the Retrospective Assessment of Schizophrenia) (Hafner et al., 1992) as described in detail elsewhere (Chen et al., 2005). Healthy controls from the local community were recruited by advertisement after screening for good physical health with no history of psychiatric or neurological disorder. Exclusion criteria were: any history of neurological problems; loss of consciousness; persistent headaches; head trauma; electroconvulsive therapy; psychostimulant use; special school attendance. The study received the approval of the Ethical Committee of the hospital concerned. All subjects were Chinese. After complete description of the study to the subjects, written informed consent was obtained to participate according to the Declaration of Helsinki. MRI scanning was performed before starting neuroleptic medication.

2.2. MRI data acquisition

Subjects were scanned on a GE Signa 1.5 Tesla system (General Electric, Milwaukee, WI, USA). Scanning time was 20 min. A consultant radiologist (KST), blind to diagnosis, reviewed MRI scans for any gross anomaly. The following sequences were performed, aligned to the AC-PC line, acquired across the whole brain including the brain stem : *PD/T2 sequence* – Dual-echo fast spin echo data-sets with TR 5–6secs, antero-posterior direction 0.86 mm, right–left direction 1.15 mm, slice thickness 3 mm, matrix size 256×192, contiguous, phase inversion time 10 ms, 2 echoes with TE=20/80 ms, number of excitations=1, echo train length=8. *PD/T2* scans were used for voxel-based morphometric analysis. *T1 sequence* – Fast SPGR 3D oblique scans with 128 slices, contiguous, 1.2 mm thick, Nex=1, TR 11.4 s, TE 4.2 ms, flip angle 15°, FOV

24 × 24, Matrix 256 × 256. T1 scans were used for region-of-interest analysis.

2.3. Pre-processing and statistical analysis of brain images

Group differences in grey and white matter and CSF were mapped using BAMB software (Brain Analysis Morphological Mapping version 2.5, <http://www-bmu.psychiatry.cam.ac.uk/BAMB/index.html>) on a SPARC workstation (Sun Microsystems Europe Inc., Surrey, UK). This process has been previously described in detail (McAlonan et al., 2002; McAlonan et al., 2005; Sigmundsson et al., 2001). According to standard protocol which has been described elsewhere (Suckling et al., 1999a) PD/T2 images were processed to remove extra-cerebral tissues and then segmented into grey and white matter, as well as CSF, dura and other non-

cerebral tissues, which were subsequently ignored (Suckling et al., 1999b). We found that using PD and T2 images afforded excellent grey and white matter differentiation, especially the subcortical grey and white matter was clearly delineated following image segmentation (see Fig. 1A, middle image.). Whole brain, grey and white matter, and CSF volumes were calculated and compared across groups using independent *t* tests.

Finally, PD/T2 segmented brain images of each individual were mapped onto Talairach space (Talairach and Tournoux, 1988) by affine transformation of its proton density image to a standard template and applying the derived mappings to the tissue maps. All the transformed images were smoothed with a standard 4.4 mm FWHM kernel (Suckling et al., 1999b; McAlonan et al., 2005). Maps of the appropriate standardized coefficient were subject to an inference procedure in which the significance of 3-D cluster

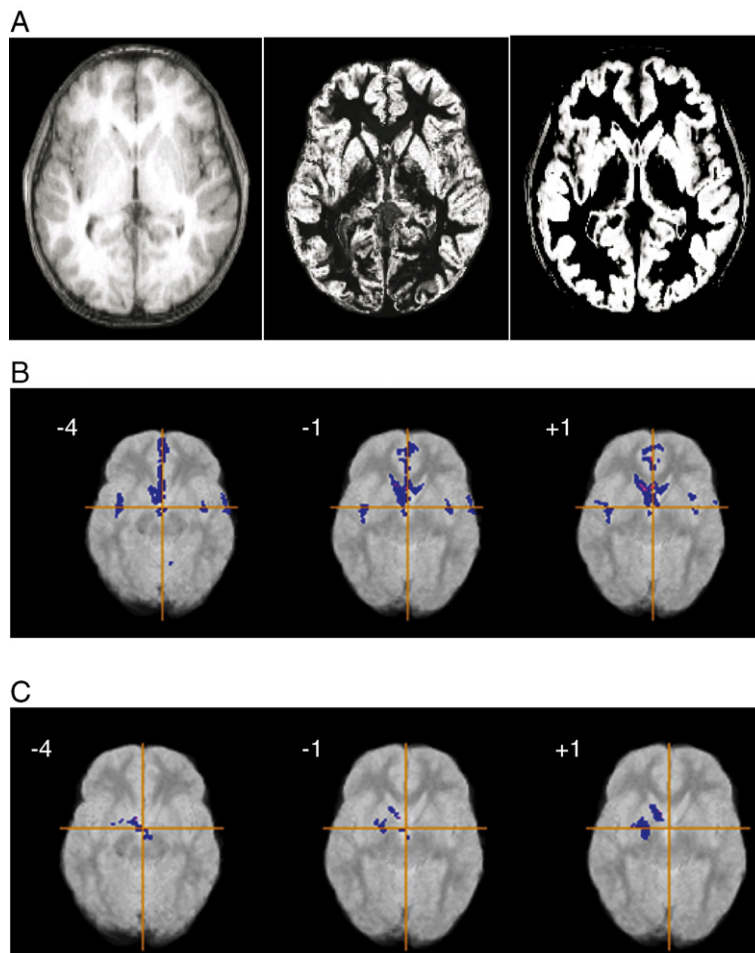


Fig. 1. A. To show SPGR T1 brain image (left), and grey matter map from T2/PD segmentation (middle) and from T1 segmentation (right). B, C. Cerebral grey and white matter deficits in FEP group.

Table 1
Subject characteristics ($n=64$)

Variable	Healthy controls ($n=38$)	FEP patients ($n=26$)	p -value
Age (years) (Mean, S.D.)	33 (8.1)	32 (10)	.875 nsd
Sex (M:F)	18:22	12:17	.936 nsd
Handedness (% right-handed)	97%	79%	.088 nsd
Ethnicity	Han Chinese	Han Chinese	–
Paternal SES (Mean, S.D.)	3.4 (1.5)	3.4 (1.6)	.181 nsd
Height (Mean, S.D.)	162 (5.0)	158(6.7)	.116 nsd
IQ (Mean, S.D.)	97 (14)	89 (26)	.095 nsd
Years of education (Mean, S.D.)	13 (3.2)	10 (3.1)	.001 sig
Duration untreated psychosis (Median in days)	n/a	120	n/a
Total PANSS score (Mean, S.D.)	n/a	72 (17)	n/a

statistics was assessed using non-parametric permutation methods (Bullmore et al., 1999).

In this study, a relatively small smoothing kernel was used to achieve a greater discriminatory power for detecting differences in smaller regions (Honea et al., 2005). Further, since the effect of diagnostic group is estimated by a non-parametric method, this is free of any assumption of smooth distribution of error (Suckling and Bullmore, 2004), and so a relatively smaller smoothing kernel is admissible. The statistical thresholds were corrected for multiple comparisons by setting the p -value such that <1 false positive cluster is expected in each map under the null-hypothesis (Suckling and Bullmore, 2004). A cluster of grey matter abnormality was defined as ‘deficit’ or ‘excess’ depending on whether volume was less or more in the first-episode schizophrenia group relative to the healthy control group. As cluster level statistics were corrected for multiple comparisons with such an approach, Moorhead et al. (2005) has proposed that adjusting the cluster extent of results corrected base on Random Field theory (RF) may not be directly applicable. We report significant 3-D regional brain volume differences between first-episode, neuroleptic-naïve patients and healthy controls. To determine whether the educational level and handedness differences between groups had an impact on our results we entered the volumes derived in a MANCOVA (SPSS 11.5.1 General linear model, multivariate analysis) with educational level and handedness as covariate.

2.4. ROI analysis

Caudate and lateral ventricular volumes were evaluated using the T1 dataset followed methods previously described (Murphy et al., 1992; Murphy et al., 1993a,b). Using MEASURE software (Barta et al., 1997) the axial scans were first uniformly aligned along the AC-PC line by one independent operator who was blind to group membership. Left and right caudate nuclei and lateral ventricles were then traced according to standard anatomical boundaries (Cahn et al., 2002). Volumes were calculated by multiplying the summed pixel cross-sectional areas by slice thickness. Since all measurements were performed ‘blind’ by a single operator, only intra-class correlation coefficient (ICC) was calculated. For total caudate and total lateral ventricle volumes on 10 scans at 1 month apart, ICC was 0.94 and 0.99 for the caudate nuclei and lateral ventricles respectively.

3. Results

3.1. Demographic and clinical comparison of groups

Our recruitment rate among patients was approximately 90%. 32 patients were screened as eligible for participation but 3 were subsequently excluded when they declined to participate or were deemed too unsettled on the date of the MRI scan. In total, 29 patients with psychosis and 40 healthy controls agreed to MRI brain scan, comprising a sample of $n=69$. However, 1 patient had an incidental 4 cm right parietal cyst; 2 patients’ and 2 controls’ brain images failed to

Table 2
Global brain volumes

Global brain volumes	Control group $n=38$ (ml)	FEP group $n=26$ (ml)	Group difference %	p -value
Whole brain (SD)	1401.0 (315.3)	1349.3 (64.4)	–3.7	nsd
Cerebral grey matter (SD)	636.2 (150.7)	586.2 (69.5)	–7.9	nsd
Cerebral white matter (SD)	546.7 (94.8)	513.8 (40.70)	–6.0	nsd
CSF (SD)	218.1 (75.9)	249.3 (89.5)	+12.5	nsd
Grey matter/ whole brain ratio	0.45 (0.01)	0.43 (0.05)	–4.2	0.027
White matter/ whole brain ratio	0.39 (0.1)	0.38 (0.2)	–2.9	0.022
CSF/whole brain ratio	0.15 (0.0)	0.18 (0.1)	+19.8	0.007

Table 3
Regional grey and white matter deficits in FEP ($p < 0.004$)^a

	x	y	z	Voxels	Controls n=38 (ml)	Patients n=26 (ml)
<i>Grey matter deficits</i>						
Fronto-subcortical						
R caudate extending to R med. frontal, R thalamus, R cingulate gyri	2.6	14	1	1187	4.40	3.46
L and R cingulate gyri	1.4	-48.2	25.0	315	1.60	1.28
R parahippocampal gyri, R uncus, R hippocampus	28.1	8.5	-19.6	139	0.67	0.52
L parahippocampal gyrus, L uncus	-17.5	0.3	-22.5	55	0.24	0.17
L caudate, extending to L insula, L putamen	-36.1	3.9	0.9	79	0.27	0.22
Temporal lobe						
R superior temporal gyrus	39.3	-0.6	3.4	267	0.96	0.77
L superior temporal gyrus	-55.7	3.9	-4.6	70	0.25	0.18
Cerebellum						
L cerebellum	-4.6	-49.7	-21.8	413	1.39	1.04
R cerebellum	28.3	-42.7	-33.2	60	0.31	0.24
Brainstem	2.1	-46.3	37.8	53	0.54	0.41
<i>White matter deficits</i>						
R anterior internal capsule, extending to R corpus callosum, bilateral fornices	17	2.7	5.9	592	1.03	0.78
R fronto-occipital fasciculus	25	-47.8	16.2	135	0.70	0.52

^aA sample Talairach co-ordinate (x, y, z) is given for the approximate centre of each 3-D cluster but the 3-D cluster is not confined to this area alone. The volume of grey or white matter within each cluster is shown for the groups in ml.

segment due to motion artefact. The final MRI dataset analysed consisted of 26 FEP, never-medicated patients (23 with paranoid schizophrenia, 3 with brief psychotic disorder) and 38 healthy controls. All patients have since been followed up for 1–2 years by a dedicated team lead by an early psychosis specialist (EYH) and the diagnosis of schizophrenia confirmed. Groups were balanced for age, sex, handedness, ethnicity, paternal socio-economic class, height, and verbal IQ. As expected, healthy controls had about 3 years more education (see Table 1).

3.2. Brain volumetric findings

Average whole brain volume in the FEP group was 3.7% smaller than controls. This difference was non-significant. Grey matter and white matter volume was also smaller in the patient group, whereas CSF volume was larger. After correcting for whole brain volume,

patients had significantly smaller grey matter to whole brain ratio by 4.2% (Independent samples *t* test, $p = 0.027$, 2-tailed), significantly smaller white matter to whole brain ratio by 2.9% ($p = 0.022$, 2-tailed), and significantly larger CSF to whole brain ratio by 19.8% ($p = 0.007$, 2-tailed). These results were unchanged after excluding the 3 patients with brief psychotic disorder, and covarying for group differences in educational level and handedness (see Table 2).

3.2.1. Grey and white matter volume differences

The FEP group had significantly smaller grey matter in L and R caudate nuclei, cingulate gyri, parahippocampal gyri, superior temporal gyri and R prefrontal cortex, cluster-wise p -value < 0.004 . The FEP group also had significantly less white matter in the R anterior limb of the internal capsule, R fronto-occipital fasciculus and L and R fornices; cluster-wise p -value $p < 0.02$ (see Fig. 1B, C and Table 3). Repeating the analysis with only schizophrenia

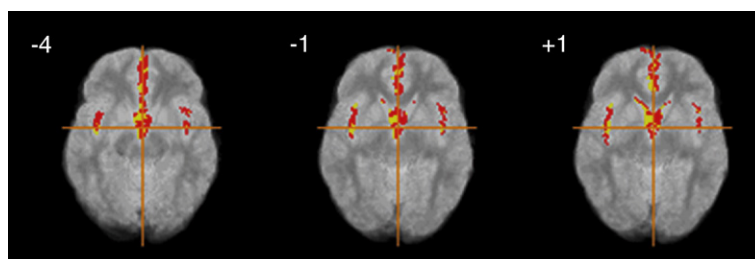


Fig. 2. CSF excess in FEP group.

Table 4
CSF excess in FEP ($p < 0.01$)^a

	<i>x</i>	<i>y</i>	<i>z</i>	Voxels	Controls <i>n</i> = 38 (ml)	Patients <i>n</i> = 26 (ml)
<i>Intracerebral space</i>						
R lateral ventricle	0.8	26.7	2.6	1405	3.59	4.69
<i>Extracerebral space</i>						
R lateral sulcus	38.9	3.6	1.0	218	0.40	0.55
L lateral sulcus	-37	7.3	-1.1	98	0.14	0.19
R Sylvian cistern	22.2	5.0	-19.3	73	0.15	0.21
L Sylvian cistern	-17.6	1.0	-20.5	17	0.04	0.07
Inter-hemispheric sulcus, at R cingulate area	0.4	-14.6	31.5	33	0.04	0.06
Inter-hemispheric sulcus, at L cingulate area	-0.6	36.5	37.1	28	0.11	0.15

^aA sample Talairach co-ordinate (*x*, *y*, *z*) is given for the approximate centre of each 3-D cluster but the 3-D cluster is not confined to this area alone. The volume of grey or white matter within each cluster is shown for the groups in ml.

patients ($n = 23$) and healthy controls ($n = 38$) did not make any essential difference to the findings. Covarying for age, handedness, whole brain volume and education level also did not alter these findings.

Blue represents significant deficits in grey matter in Fig. 1B, white matter in Fig. 1C identified. The right side of the brain corresponds to the left side of the figure. The *z* co-ordinate for each axial slice in standard Talairach and Tournoux space is given in millimeters. Statistical threshold is $p < 0.004$ corrected.

Red represents significant excess in CSF as shown in Fig. 2. The right side of the brain corresponds to the left side of the figure. The *z* co-ordinate for each axial slice in standard Talairach and Tournoux space is given in millimeters. Statistical threshold is $p < 0.01$ corrected.

Table 5
Region-of-interest (ROI) analysis of caudate and lateral ventricle (see also Fig. 3)

Volumes	Mean (S.D.) in ml	Healthy controls ($n = 38$)	Patients with schizophrenia ($n = 23$)	Group diff (%)	95% C.I. of difference	<i>p</i> -value
Left						
LV	6.50 (2.14)	7.78 (2.60)	19.6	-0.1, +2.58	.054	
CN	4.34(0.54)	3.78(0.62)	13.0	-.89, -.29	.001**	
Ratio LV: CN	1.52 (0.54)	2.14 (0.88)	40.8	+0.21, +1.02	.004**	
Right						
LV	5.77 (2.04)	7.30 (2.43)	1.53 (26%)	+0.28, +2.72	.017*	
CN	4.12 (0.59)	3.73(0.56)	0.39 (11%)	-.77, -.15	.004**	
Ratio LV: CN	1.41 (0.51)	2.01 (0.84)	42.6	+0.23, +0.98	.002**	
WBV	1350(88)	1349 (66)	nsd	-34.3, +30.8	.914	

LV=lateral ventricle, CN=caudate nucleus, WBV=whole brain volume. Independent samples *t* test, 2-tailed significance, $p \leq 0.05$ *, $p \leq 0.005$ **.

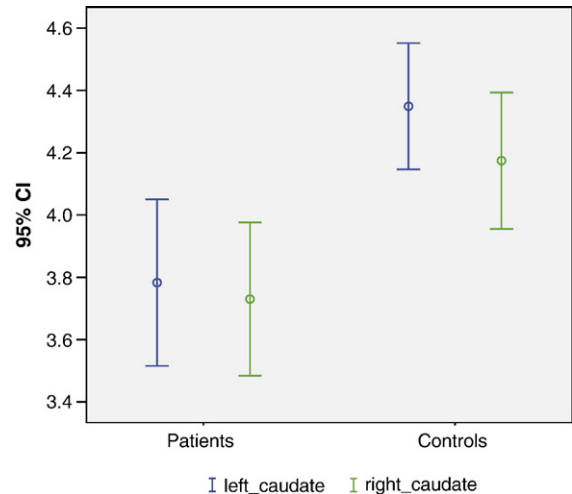


Fig. 3. Ratio of lateral ventricular volume to caudate volume.

3.2.2. CSF volume differences

Compared to controls, patients had significant volume excess in the R lateral ventricle and L and R lateral sulci extending to L and R Sylvian cisterns. Patients also had larger sulcal volume at the inter-cingulate sulcus i.e. interhemispheric sulcus medial to the cingulate gyri, cluster-wise p -value < 0.01 . There were no deficits in CSF in patients compared to controls (see Fig. 2 above, and Table 4). Again, restricting the patient group to schizophrenia only ($n = 23$) made no essential difference to these results. Covarying for whole brain volume, education level and handedness did not alter findings.

3.3. ROI measurements of lateral ventricles and caudate nuclei

ICC was 0.94 each for L and R caudate volume, 0.99 for L and R lateral ventricle volume. We examined patients with schizophrenia ($n = 23$) and found L and R

caudate nuclei significantly smaller and R lateral ventricular volume significantly enlarged (see Table 5). Ratio of LV: CN (lateral ventricular: caudate nuclei) volume was significantly increased on L and R (see also Fig. 3). However, LV and CN volumes were uncorrelated (Pearson correlation coefficient 0.30, $p=0.10$). Covarying for global brain volume, handedness and educational level did not alter these results.

4. Discussion

This is the first VBM study to evaluate the principal brain tissue classes of cerebral grey matter, white matter, and CSF in a relatively large sample of never-medicated patients with first-episode psychosis. ROI analysis independently confirmed the principal findings of lateral ventricular enlargement and smaller caudate nuclei in patients with schizophrenia ($n=23$). Individuals with psychosis had smaller brain volume by 3.7%, a non-significant difference from controls. However, grey and white matter were reduced by 7.9% and 6.0% respectively, CSF larger by 12.5% and after correcting for whole brain volume, these group differences were highly statistically significant. They remained despite covarying for handedness and educational level. ROI analysis showed that L and R caudate nuclei were significantly smaller by 11–13%, R lateral ventricle significantly larger by 26% in patients with schizophrenia who also showed significantly increased ratio of lateral ventricle: caudate volume on the L and R. Importantly, caudate volume did not correlate with lateral ventricular volume (i.e. lacked inter-dependence) so segmentation artefact is an unlikely explanation.

Grey matter deficits were identified in L and R caudate nuclei, cingulate gyri, superior temporal gyri, R medial frontal cortex; white matter deficits in the R internal capsule and corpus callosum, and greater CSF volume in the R lateral ventricle (Figs. 1A, B and 2). In other words, the abnormalities in the psychosis group were periventricular and encompassed all principal tissue classes of brain tissue. Surprisingly, our VBM and ROI results did not reveal predominantly L-sided abnormality but were instead bilateral; however, this is in keeping with the 2 recent grey matter VBM studies of unmedicated, first-episode psychotic samples showing bilateral grey matter decrease in caudate nuclei (Salgado-Pineda et al., 2003; Jayakumar et al., 2005). Laterality issues are ideally addressed by confirmatory ROI work, and underscore the usefulness of evaluating non-grey matter tissue too. Our data accord with previous studies which had reported smaller whole brain volume, (Ho et al., 2003; Sigmundsson et al., 2001) frontal (Ananth et al., 2002; Job et al., 2002;

Kubicki et al., 2002; Salgado-Pineda et al., 2003; Sigmundsson et al., 2001; Suzuki et al., 2005) temporo-limbic grey matter (Job et al., 2002; Kubicki et al., 2002; Sigmundsson et al., 2001) and basal ganglia (Corson et al., 1999, Dazzan et al., 2004) in schizophrenia. Such morphological changes, present early in the course of the illness (Sowell et al., 2000), are therefore unlikely to be a consequence of chronicity or neuroleptic exposure. White matter volume deficits in the internal capsule and corpus callosum is also consistent with evidence that white matter abnormalities appear early (Sigmundsson et al., 2001; Suzuki et al., 2002). We speculate this could reflect widespread dysmyelination, failure of neuronal arborization or excessive dendritic pruning during neurodevelopment (Van et al., 2001).

Evidence in the literature on never-medicated, FEP subjects indicates 5.5% (Corson et al., 1999) to 14% (Keshavan et al., 1998) smaller caudate volume but not unanimously so (Gur et al., 1998; Gunduz et al., 2002; Cahn et al., 2002). In the first case-control study of first-episode schizophrenia in the neuroleptic-naïve phase to use voxel-based morphometry, Salgado-Pineda et al. (2003) had examined cerebral grey matter and reported significantly decreased clusters of grey matter density in bilateral caudate and thalami, anterior cingulate, left inferior frontal, right claustrum, left pulvinar and dorsomedial thalamic nuclei. However, only a small number of male right-handed subjects were examined and superior temporal deficits reported previously in psychosis were not found (McCarley et al., 1999; Wright et al., 2000). Our findings partly overlap with their study in that we also found smaller frontal, anterior cingulate, caudate/basal ganglia and thalamic grey matter volumes. In our larger group of mixed sexes we found more extensive prefrontal, bilateral superior temporal, cerebellum and brainstem deficits. Our findings therefore agree more closely with a recent study of 18 patients and healthy controls which exclusively examined grey matter in neuroleptic-naïve schizophrenia and also identified grey matter reduction (Jayakumar et al., 2005). Can the ratio of lateral ventricular: caudate volume represent a possible biomarker for schizophrenia? Asymptomatic individuals at high-risk of developing Schizophrenia (Job et al., 2002) were reported to have fronto-temporal grey matter changes but no caudate changes. In this way these high-risk individuals brain images resembled their *medicated* first-episode psychotic relatives (Job et al., 2002). Since antipsychotic medication is believed to increase caudate size (Chakos et al., 1994; Shenton et al., 2001), we tentatively speculate that antipsychotics might even have the effect of *reversing* caudate volume pathology. However, in this cross-sectional study we limit ourselves

to the suggestion that, if independently replicated, it might provide a useful biomarker for psychosis. Antipsychotic drugs might cause hypertrophy in the caudate (Chakos et al., 1994; Shenton et al., 2001) putamen and thalamus (Gur et al., 1998) since post-synaptic contact may change gene expression and protein synthesis in the striatum or prefrontal cortex (Weinberger and Lipska, 1995), putative sites of antipsychotic action of antipsychotic drugs (Pilowsky, 2001). The coincidence of structural abnormality and neuroleptic target in psychosis adds to the evidence that effective medication modifies prefrontal-temporolimbic cortical networks most vulnerable to progressive tissue loss in the first 5 years after illness onset (Thompson et al., 2001). Follow-up of our drug-naïve subjects will chart how these compromised regions respond during treatment. The rationale for identifying susceptible brain regions in first episode neuroleptic-naïve psychosis is that future pharmacotherapy might exert a neuroprotective effect on the areas involved.

4.1. Strengths and weaknesses of the study

The principal strength of the study is that it is a relatively sizeable sample of never-medicated, first-episode psychotic (mainly schizophrenia) patients. We suggest that the fronto-temporal and subcortico-limbic widespread tissue volume deficits are likely to be related to the disorder. This sample of patients was somewhat older which might be explained by the local culture of consulting herbalists (Chua et al., 2003) and that younger subjects below the age of 18 years or having a history of substance abuse were excluded from recruited. Although the average duration of psychosis was 4 months, follow-up by a dedicated team led by an early psychosis specialist (EYH) confirm longitudinal stability of the diagnosis of schizophrenia for 23 subjects. This means that they each had at least 6 months of disturbance including negative symptoms or behavioural disorganisation, in the absence of significant mood change or a significant medical condition. The volumes we report are related to the “mass” of the 3-D voxel cluster so we did a confirmatory ROI analysis of caudate and ventricular volumes. We found raised L and R lateral ventricular: caudate volume ratio, which persisted despite covarying for age, education level, handedness and minor global brain volume differences. ROI analysis confirmed it was unlikely to be a false-positive result of pre-processing error in brain regions where grey/white/CSF differentiation is less than optimal (Good et al., 2001). It is also important to note that volume changes can occur during *nonlinear* normalisation and that many groups routinely perform modulation with the

Jacobian determinant of the deformation matrix (Good et al., 2001). However in our study, linear normalisation was used and therefore this kind of transformation does not necessarily apply. Finally, this study is only cross-sectional and can provide no information on outcome.

In summary, morphological differences are detectable in first episode of psychosis and adds to the evidence of brain dysmaturation in the disorder (Bullmore et al., 1997; DeLisi et al., 1997). In our study, localised caudate volume deficits, lateral ventricular enlargement and more generalised cerebral grey and white matter abnormalities suggest neurodevelopmental insult, unattributable to medication. Future work will focus on collecting longitudinal MRI and clinical assessments to ascertain whether baseline indicators including brain morphology can usefully predict clinical outcome.

Acknowledgement

CRCG grant to Dr SE Chua and RGC grant (No: 10202402.20376.21500) to Dr E Chen.

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