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Frontal lobe volumes in schizophrenia: Effects of stage and duration of illness

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Abstract

While the changes in the volume of the temporal lobe and its sub-regions over the course of illness have been studied in patients with schizophrenia, few studies have examined changes in the frontal lobe between the first episode and the chronic stage. In this study, we focussed on the effect of illness stage and duration of illness on the volume of frontal lobe regions, though we also examined several other regions to establish the specificity of any effects, if observed, in this region. We compared the volumes of brain regions among 34 first-episode schizophrenia patients, 49 chronic schizophrenia patients, 18 healthy controls matched, on average, to the first-episode patients and 21 healthy controls matched, on average, to the chronic patients. Logarithmic regression analyses examined the relationships between the duration of illness and the brain regional volumes in the patient group. The results showed that chronic patients had smaller prefrontal cortical grey matter volumes, but larger premotor cortical and putamen volumes compared to first-episode patients and matched healthy controls. Although there were significant patient-by-control group interactions in the cerebellum and sensori–motor cortical grey matter volumes, these did not survive correction for multiple comparisons. There was a significant exponential relation between the duration of illness and the volumes of prefrontal cortex, parieto-occipital cortex grey matter, thalamus and putamen, suggesting that these regions are susceptible to change as the disorder persists. The enlargement of the premotor cortex and putamen are likely to be a result of antipsychotic medication.

Keywords: Schizophrenia; Progression; Duration of illness; Magnetic resonance imaging; Frontal lobe; Temporal lobe

1. Introduction

The idea that schizophrenia is a progressive illness associated with a neurodegenerative process has existed since the illness was first described (Kraepelin, 1899/1989, 1919/1971). However, the validity of this concept remains controversial, since there is evidence that both supports and appears inconsistent with this idea. Absence of clear neuropathologic changes consistent with a neurodegenerative process (Pakkenberg, 1993; Selemon et al., 1998; Weinberger and McClure, 2002), along with the fact that schizophrenia is characterized by abnormalities of brain structure that are present from the early stages of the illness (Copolov et al., 2000; Sharma and Kumari, 2005) are among the lines of evidence that support the hypothesis that schizophrenia is instead a neurodevelopmental process (Weinberger and McClure, 2002). It is, however, still uncertain as to whether structural abnormalities are static or progressive (Harrison, 1999; Stevens, 1991; Woods, 1998).

Longitudinal studies have demonstrated multiple influences in progressive ventricular enlargement (DeLisi et al., 1998, 2004, 1997, 1995; Leiberman et al., 2001; Mathalon et al., 2001; Nair et al., 1997; Saijo et al., 2001). DeLisi et al. (2004) observed that ventricular

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enlargement was greater during the second half of a 10-year follow-up. Whether the patients were receiving conventional, atypical antipsychotics or no antipsychotic medication at follow-up did not have a differential effect on ventricular enlargement. Leiberman et al. (2001) reported that first-episode schizophrenia or schizo-affective patients with poor clinical outcome showed ventricular enlargement over a 12-month-period, whereas the good clinical outcome patients did not show ventricular enlargement over time. Furthermore, longer duration of treatment with conventional antipsychotic medication during the inter-scan interval was associated with smaller ventricular volumes at both baseline and follow-up, though treatment duration did not seem to have any effect on the clinical outcome-ventricular change interaction. These data seem to suggest that treatment duration and clinical outcome have independent effects on ventricular volume. Nair et al. (1997) proposed a two-cluster model to describe ventricular enlargement, with one subgroup of schizophrenia individuals showing rapid enlargement and the other subgroup showing ventricular enlargement comparable with healthy controls over a 2.5-year-period, suggesting that separate pathologies may underlie schizophrenia. Furthermore, an inverse relationship between time on antipsychotic medication and rate of ventricular enlargement in the rapid enlargement subgroup indicates lower rates of ventricular progression in patients who comply with antipsychotic treatment (Nair et al., 1997). Over an 8-month-period, Puri et al. (2001) observed greater absolute change in ventricular volume in patients with first-episode schizophrenia compared to healthy controls. However, two-thirds of their patients showed ventricular enlargement, while the remaining one-third showed decrease in ventricular volume, suggesting that different pathological processes may be involved. They, however, failed to observe any association between duration of antipsychotic treatment and change in ventricular volume in the first-episode patients. These findings suggest ventricular enlargement in schizophrenia to varying degrees that may be contingent on illness stage, clinical outcome and compliance with antipsychotic treatment.

Particular changes in brain morphology may shed light on the neurodevelopmental versus neurodegenerative debate. Woods et al. (1996) found that the frontal intracranial volume was significantly smaller and the brain tissue-to-cranial volume ratio was lower in chronic schizophrenia patients than healthy controls. They inferred that while the decrease in frontal intracranial volume was due to a pathological process that occurred during brain development, the generalized reduction in brain volume to cranial volume ratio was due to a process that affected the whole cerebrum after brain growth had been completed.

Studies have also indicated a progressive change in the temporal lobe and its sub-regions. Gur et al. (1998) observed greater reduction in temporal lobe volume in first-episode patients than in previously-treated patients over a 2.5-year-period. Higher medication dose was associated with greater temporal lobe reduction in the first-episode, but not previously-treated, patients. Along the same lines, Giedd et al. (1999) reported a non-linear reduction in the hippocampus in patients with childhood-onset schizophrenia compared to controls. However, DeLisi and Hoff (2005) failed to find a decrease in temporal lobe volume in first-episode patients over a 10-year-period, whereas DeLisi et al. (1997) reported that the rate of change of the volume of the right hippocampus over a 4-year-period was lower in patients on continuous medication than in non-compliant patients. Changes in temporal lobe volume may occur early in the course of illness, but it may also be influenced by illness duration and treatment compliance later on.

Longitudinal volumetric change has also been observed in the frontal cortex. Bachmann et al. (2004) reported significant decreases in left and right frontal lobe volumes in 14 first-episode patients over a 14-month-period. Gur et al. (1998) observed a greater left than right hemisphere reduction in the frontal lobe in first-episode patients than previously-treated patients over a 2.5-year-period. In addition, higher medication dose was associated with greater reduction in frontal lobe volume. Mathalon et al. (2001) observed that relative to healthy controls, the schizophrenic patients showed faster sulcal expansion and grey matter decline in the right, but not the left frontal cortex. However, Dickey et al. (2004) failed to observe a change in prefrontal volumes in 12 schizophrenia patients over a 1.5 year follow-up period. There was also no association between medication dosage at baseline and prefrontal volume change. It is possible that the propensity for prefrontal cortical volume change is greater following the first psychotic episode than at a later time point in the course of the illness (Molina et al., 2004). Molina et al. (2004) compared schizophrenia patients from two illness stages. A volumetric decrease in prefrontal cortex (PFC) grey matter, while absent in first-episode patients, was present in short-term and long-term chronic schizophrenia patients. Furthermore, there was a non-linear association between duration of illness (DoI) and PFC grey matter volume, consistent with a decrease in grey matter volume during the first years following illness onset. In addition, PFC grey matter volumes did not differ between patient receiving and not receiving risperidone.

To address further the issue of whether brain structural differences exist between chronic and first-episode schizophrenia, the present study compared frontal brain regional volume in patients with first-episode schizophrenia, chronic schizophrenia and healthy controls that were matched, on average, to patients at each illness stage. Although the focus of this study was on the frontal lobe, we also explored group differences in the volumes of the temporal, parieto-occipital, subcortical and cerebellar regions. In addition, to test whether brain volume reduction occurs early in the course of illness rather than later on, we investigated the relationship between DoI and brain regional volume in the patients using a logarithmic model. We hypothesized, based on the findings of Molina et al.

(2004), that (a) chronic patients would have smaller brain volumes compared with first-episode patients, and (b) there would be an exponential relation between DoI and brain volume across the patient groups.

2. Methods

2.1. Participants

Two studies were conducted to examine brain structural differences between individuals with schizophrenia and healthy controls. The first study comprised 34 first-episode patients with schizophrenia as determined by the Structured Clinical Interview for DSM-I (Spitzer et al., 1995) and 18 healthy controls (data from this cohort have been included in previous publications, Ettinger et al., 2002; Fannon et al., 2000; Sumich et al., 2002). Diagnosis of schizophrenia in all first-episode cases was re-confirmed after 1 year. Table 1 reports the antipsychotic medication status of each patient. None of the patients had had more than 12 weeks of antipsychotic medication or were receiving any other medication. The second study comprised 49 patients with a DSM-IV diagnosis of schizophrenia and 21 healthy controls. Patients were included if they had been receiving treatment with conventional antipsychotics for at least six weeks prior to admission to the study and were aged 18–65 years. Nine patients were also receiving anti-cholinergics. The description of the sample as having chronic schizophrenia was based on the patients having a DoI greater than 3 years (range 3–37 years). Exclusion criteria (for both studies) were a history of neurological disease, a positive urine drug screen test and a DSM-IV diagnosis of substance abuse or dependence. Exclusion criteria for controls, in addition to those applied to the patients, were the presence of a personal history of an axis I or II disorder and a family history of psychosis warranted exclusion. Diagnostic assessment using the non-patient version of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996b) were performed by experienced psychiatrists on controls.

2.2. Image acquisition

MRI scans were acquired at the Maudsley Hospital, London using a 1.5-T G.E. Signa system. This investigation was opportunistic in that data were available from two studies with slightly different imaging protocols that started independently. Although it would have been ideal to use studies with similar protocols, both studies used a region of interest (ROI) approach, making the volumetric data from the two studies comparable. A series of sagittal and axial scout views were acquired to correct for head tilt and to localize imaging coordinates. For participants from the first-episode study, a three-dimensional, inversion recovery prepared, fast spoiled gradient/recall in the steady state scan of the whole brain was performed to acquire a T1-weighted data set. These T1-weighted images were obtained in the axial plane (parallel to the z axis of the magnet) with 1.5-mm contiguous sections (TR = 11.3 ms, TI = 300 ms, TE = 2.2 ms, and the flip angle = 20° with one data average and a $256 \times 256 \times 128$ pixel matrix). The MRI protocol for participants in the chronic study was exactly the same as described for the first-episode study

Table 1
Demographic characteristics of participants

	FE patients ($n = 34$)	FE-matched controls ($n = 18$)	CH patients ($n = 49$)	CH-matched controls ($n = 21$)	Test	Statistic	df
Age, yrs – median (range)	23 (21)	25 (20)	39 (43)	37 (40)	Kruskal–Wallis	56.07*	3
Education, yrs – median (range)	11 (6)	17 (6)	12 (17)	15 (10)	Kruskal–Wallis	35.08*	3
Gender (% male)	70.60	66.70	65.30	71.40	χ^2	0.40	3
Handedness (% right-handed)	91.20	88.88	93.90	100	χ^2	2.38	3
Ethnicity					χ^2	9.56	9
Afro-caribbean	9	3	14	3			
Asian	4	0	5	1			
White	21	14	30	16			
Other	0	1	0	1			
Parental socio-economic status					χ^2	12.28	12
Professional (doctor/lawyer)	3	4	7	1			
Intermediate (manager/teacher/nurse)	8	5	5	6			
Skilled (secretary/bus driver)	17	8	17	9			
Semi-skilled manual	4	0	6	1			
Unskilled manual	0	1	3	2			
Age of onset (years)	22.75 (23.33)	–	26 (39)	–	Student's T	−1.28	84
Current antipsychotic medication type							
Typical antipsychotics	16	–	49				
Atypical antipsychotics	8	–	0				
Neuroleptic naïve	10		0				

FE, first-episode; CH, chronic.
* $p < 0.05$.

except that the images were initially acquired in the coronal view.

2.3. Measurement of brain regions

Stereological measurements using the software, MEASURE (Barta et al., 1997), followed existing criteria for the following brain regions of interest (ROIs): whole brain, cortical grey matter, lateral ventricles and temporal lobe (DeLisi et al., 1995), hippocampus (Stephanis et al., 1999), thalamus (Portas et al., 1998), putamen and cerebellum (see Fig. 1). The measurement of the putamen was performed in the coronal and axial views, though the coronal view was mainly used for the rating since the ROI was present across more number of slices compared to the axial view, thereby allowing greater precision. The putamen was separated from the caudate nucleus by the internal capsule and separated from the claustrum more ventrally by the external capsule. On the coronal slices before the appearance of the globus pallidus, the most distinct appearance of the internal capsule was used as a guide to determine the last horizontal line of pixels to be counted for that slice. In the more ventral slices, the pixels in the putamen that were contiguous with the temporal pole were excluded from the measurement. The cerebellum was seen as a distinct structure consisting of four lobes that were

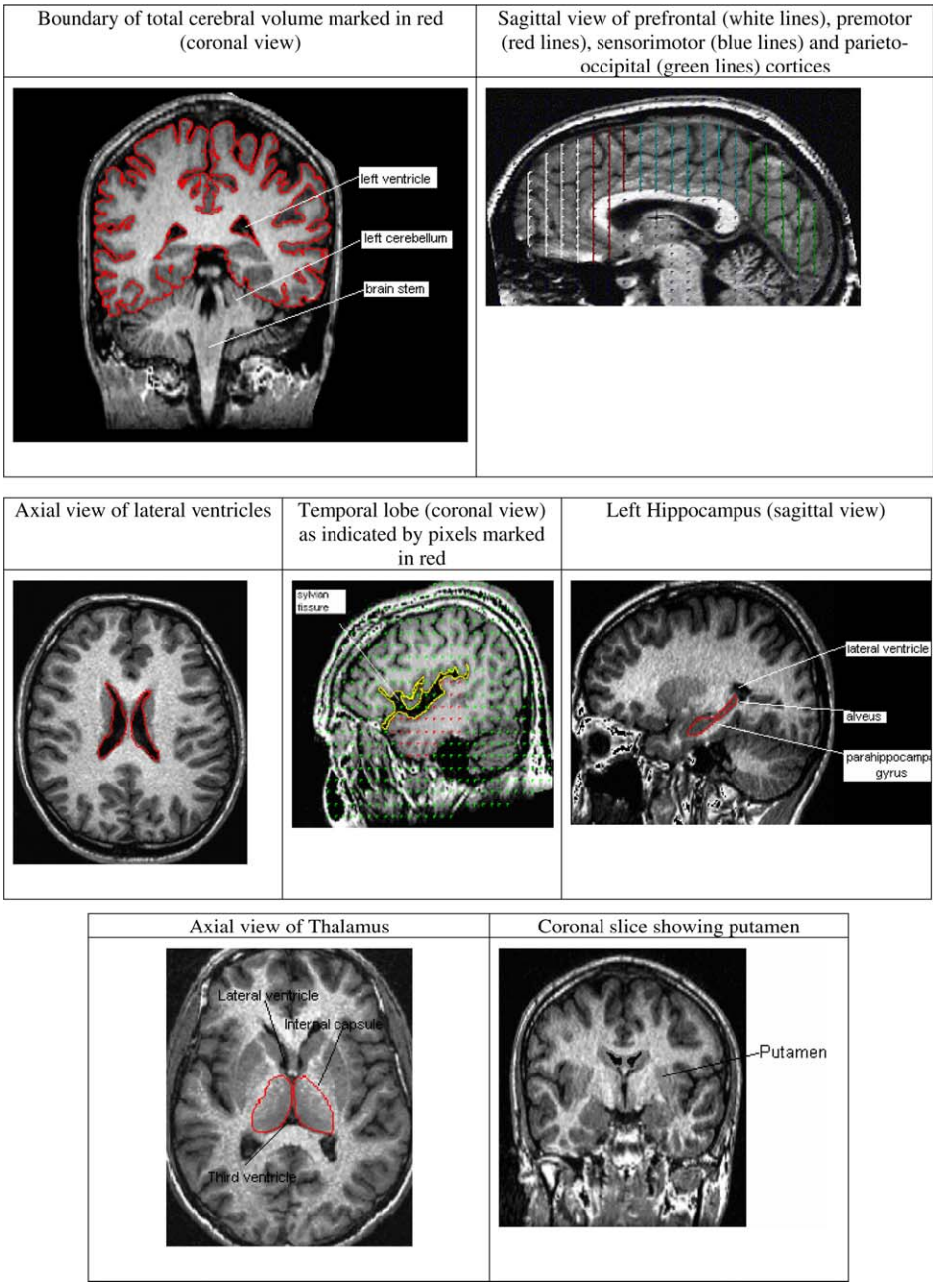

Fig. 1. Figure of the regions of interest. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

separate from the cerebral cortex and brain stem. The cortex itself was divided into four sub-regions based on cytoarchitectonic boundaries: prefrontal, premotor, sensorimotor and parieto-occipital ROIs (Bilder et al., 1994). Separate total and grey matter ROIs for cortical sub-regions led to 17 ROIs. Ratings were performed by researchers, including one of the authors (P.P.), blind to participant diagnosis. The raters were trained in rating ROIs on 10 random scans from the two studies until an inter-rater reliability $\geqslant 0.9$ was achieved.

2.4. Statistical analysis

Due to the lack of homogeneity of variance between the four participant groups, we performed non-parametric Kruskal–Wallis H tests for age and education. χ^2 tests were performed for gender, handedness, ethnicity and parental socio-economic status. Student's *T*-test was performed on age of illness onset in the patients.

To test the hypothesis that brain volume is lower in chronic schizophrenia compared with first-episode schizophrenia and healthy controls, we performed a Roy-Bargman stepwise multivariate analysis of co-variance (MANCOVA; Wilks' F) on 15 regions, with brain regional volumes entered into the model in order of increasing univariate *F*-value. This analysis allowed us to determine the unique variance contributed by the volume of each brain region to the overall group effect. We utilized a stepwise multivariate analysis of variance (MANOVA) procedure that partials out the variance of previous variables entering the model, thus no multiple test correction was applied. We included total brain volume as a covariate because total intracranial volume is a strong predictor of regional volumes (DeLisi et al., 2004), and age as a covariate to discount any age-related effects. Since growing evidence indicates that conventional and atypical antipsychotics may have a different influence on regional cortical volumes (Chakos et al., 1994; Corson et al., 1999; Garver et al., 2005; Lang et al., 2004; Lieberman et al., 2005; Weinberger and Lipska, 1995), we replicated the analysis in patients currently receiving conventional antipsychotics (no chronic patient was on atypical antipsychotics). To test whether the slope of the difference between first-episode and chronic patients differed significantly from that of the difference between first-episode and chronic controls, we specified an interaction term: (participant type: patient versus control) by (illness stage: first-episode versus chronic). Heterogeneity of variance meant that Wilcoxon signed ranks tests were performed for hippocampus and putamen.

To determine whether medication type has a differential effect on regional volume, we repeated the MANCOVA in first-episode patients receiving conventional antipsychotics and all chronic patients and healthy controls, since all chronic patients were receiving conventional antipsychotic treatment.

The relation between DoI and brain regional volumes was tested using a logarithmic regression analysis because it was expected that brain volume change over time would not be linear (Molina et al., 2004) and because of variance heterogeneity in DoI between patient groups. Age-corrected whole brain volumes were estimated from a regression analysis run within the Statistical Package for Social Sciences (SPSS) that allows to compute the unstandardized age-predicted values for whole brain volume. For the remaining brain regions, regression analyses were repeated using both raw scores and age- and whole brain-corrected volumes, as it was felt that the latter alone would not be sensitive to regional differences in volume-DoI relations. Age- and whole-brain-corrected volumes were estimated using regression analyses as described above for age-corrected whole brain volume. Given that brain regional volumes are generally correlated with each other, Bonferroni correction was applied while assessing the significance of observed effects for the 17 brain regions (p value set at 0.003).

All statistical analyses were performed using the SPSS version 10.1.3.

3. Results

As expected and shown in Table 1, chronic patients and controls were older than first-episode patients and controls. Patients had fewer years in education than controls (Table 1).

3.1. Brain region comparisons

The overall participant type-by-illness stage interaction was significant ($F = 2.98$, df=15,106, $p = 0.001$). The Roy-Bargman stepwise *F*-score of the participant type-by-illness stage interaction was significant in the prefrontal cortical grey matter, total premotor cortex, sensori–motor cortex, cerebellum and putamen (see Table 2a). Patients and controls differed in brain volume; and in turn, first-episode patients differed from chronic patients. The effect was strongest in the grey matter of the PFC as shown in Table 2a.

Post hoc Scheffe tests revealed that the difference in PFC grey matter volume was greater between patient groups than between control groups. The chronic patients had smaller volumes than first-episode patients (mean difference = 13.76 cm^3, SE = 2.54) and chronic controls (mean difference = 10.57 cm^3, SE = 2.97).

The above pattern of effect was reversed for total premotor cortex and putamen. The premotor cortical volume was larger in chronic patients only in comparison with first-episode patients (mean difference = 18.43 cm^3, SE = 6.09). The mean volumes of the putamen also suggest that chronic patients had larger volumes than the first-episode patients (mean difference = 2.28 cm^3, SE = 0.33) and chronic controls (mean difference = 1.49 cm^3, SE = 0.38). Although there were significant patient-by-control group interactions in the cerebellum and sensori–motor cortical grey matter volumes, post hoc Scheffe tests for grey matter

Table 2a
Means (SD) for region of interest volumes (cubic cm) in first-episode patients, chronic patients and matched healthy controls

Brain region	FE patients	FE controls	CH patients	CH controls	Univariate F	Roy-Bargman F	p	95% CI	
	($n = 34$)	($n = 18$)	($n = 49$)	($n = 21$)				Lower CI	Upper CI
Whole brain	836.62 (72.18)	903.86 (92.76)	820.36 (125.87)	855.76 (115.95)					
Grey matter of PFC	70.95 (10.42)	74.66 (13.89)	57.19 (11.45)	67.76 (10.36)	8.29*	8.29*	0.01	0.63	4.20
Total premotor cortex	155.40 (17.05)	165.91 (25.24)	173.83 (32.75)	160.97 (28.27)	8.28*	4.99*	0.03	−10.60	−2.03
Cerebellum	101.26 (10.04)	107.68 (13.77)	103.14 (16.55)	100.20 (11.56)	6.09*	6.66*	0.01	−3.74	0.75
Grey matter of POC	147.12 (20.65)	165.14 (19.66)	128.90 (25.27)	152.61 (25.27)	5.86*	0.59	0.45	0.57	8.13
Total PFC	110.93 (15.36)	118.05 (18.74)	97.51 (19.63)	111.94 (21.94)	4.86*	0.09	0.77	0.34	5.54
Total temporal lobe	101.49 (16.03)	112.68 (17.65)	100.57 (21.52)	99.23 (19.34)	4.21*	3.13	0.08	−4.47	0.18
Cortical grey matter	463.64 (44.33)	502.46 (57.24)	420.06 (72.21)	460.96 (59.42)	3.19	0.17	0.68	−1.70	12.87
Grey matter of PMC	75.23 (14.32)	82.68 (14.64)	81.25 (18.51)	80.26 (16.49)	2.15	0.19	0.66	−5.85	0.20
Total lateral ventricle	9.83 (5.28)	8.38 (3.28)	13.46 (5.51)	9.43 (4.61)	1.49	0.001	0.98	−1.99	0.07
Grey matter of T. lobe	72.16 (10.67)	82.06 (12.18)	66.62 (12.94)	66.09 (13.97)	0.39	0.37	0.55	−2.59	1.19
Thalamus	11.91 (1.35)	12.57 (1.25)	10.90 (1.52)	11.07 (1.22)	0.28	0.08	0.78	−0.319	0.13
Grey matter of SMC	104.75 (23.44)	100.51 (16.08)	95.07 (20.90)	93.31 (20.81)	0.28	4.05*	0.05	−3.75	3.88
Total SMC	221.37 (30.31)	225.54 (39.87)	216.98 (37.38)	223.21 (30.12)	0.08	0.16	0.69	−4.20	7.47
Total POC	231.65 (28.64)	269.79 (33.67)	223.83 (36.63)	248.28 (44.24)	0.02	1.84	0.18	−4.32	5.49
Putamen[a]	5.13 (0.90)	4.44 (0.68)	7.41 (1.86)	5.92 (1.16)	−5.80*				
Hippocampus[a]	4.39 (0.50)	5.04 (0.45)	3.97 (0.92)	4.63 (0.57)	−1.29				

[a] Wilcoxon signed ranks test performed due to heterogeneity of variance.
* $p < 0.05$.

Table 2b
Results of MANCOVA repeated using a subgroup of first-episode patients receiving conventional antipsychotics only (all chronic patients were receiving conventional antipsychotics)

Brain region	FE patients	FE controls	CH patients	CH controls	Univariate F	Roy-Bargman F	p	95% CI	
	($n = 16$)	($n = 18$)	($n = 49$)	($n = 21$)				Lower CI	Upper CI
Total premotor cortex	155.26 (16.46)	165.91 (25.24)	173.83 (32.75)	160.97 (28.27)	7.30*	7.30*	0.01	−10.45	−1.60
Grey matter of PFC	70.10 (7.76)	82.68 (14.64)	81.25 (18.51)	80.26 (16.49)	6.11*	3.16	0.08	0.46	4.17
Grey matter of POC	146.44 (21.87)	165.14 (19.66)	128.90 (25.27)	152.61 (25.27)	5.16*	1.08	0.30	0.56	8.23
Total temporal lobe	101.30 (15.69)	112.68 (17.65)	100.57 (21.52)	99.23 (19.34)	4.55*	4.54*	0.04	−4.94	−0.22
Total PFC	111.01 (13.26)	118.05 (18.74)	97.51 (19.63)	111.94 (21.94)	4.55*	0.03	0.86	0.20	5.61
Grey matter of PMC	71.43 (14.31)	82.68 (14.64)	81.25 (18.51)	80.26 (16.49)	2.93	0.28	0.60	−5.63	0.42
Cerebellum	104.77 (10.60)	107.68 (13.77)	103.14 (16.55)	100.20 (11.56)	2.81	2.14	0.15	−4.19	0.35
Total lateral ventricle	9.70 (4.70)	8.38 (3.28)	13.46 (5.51)	9.43 (4.61)	2.49	0.13	0.72	−1.82	0.21
Cortical grey matter	461.69 (41.75)	502.46 (57.24)	420.06 (72.21)	460.96 (59.42)	1.87	0.17	0.68	−2.29	12.44
Thalamus	11.94 (1.57)	12.57 (1.25)	10.90 (1.52)	11.07 (1.22)	0.74	0.67	0.42	−.33	0.13
Grey matter of T. lobe	72.40 (7.87)	82.06 (12.18)	66.62 (12.94)	66.09 (13.97)	0.70	0.80	0.37	−2.74	1.12
Total POC	230.05 (31.83)	269.79 (33.67)	223.83 (36.63)	248.28 (44.24)	0.12	2.68	0.11	−4.18	5.94
Total SMC	223.11 (30.66)	225.54 (39.87)	216.98 (37.38)	223.21 (30.12)	0.09	0 .02	0.90	−5.13	6.90
Grey matter of SMC	105.14 (24.92)	100.51 (16.08)	95.07 (20.90)	93.31 (20.81)	0.001	0.015	0.90	−3.93	4.03
Putamen[a]	5.15 (0.85)	4.44 (0.68)	7.41 (1.86)	5.92 (1.16)	−5.83*,[b]				
Hippocampus[a]	4.39 (0.51)	5.04 (0.45)	3.97 (0.92)	4.63 (0.57)	−1.29[b]				

[a] Wilcoxon signed ranks test performed due to heterogeneity of variance; PFC, prefrontal cortex; PMC, premotor cortex; POC, parieto-occipital cortex; SMC, supplementary-motor cortex; T. lobe, temporal lobe.
[b] Z score.
* $p < 0.05$.

of sensori–motor cortex and cerebellum suggested no significant difference in brain volume between any groups.

The analysis was repeated using only patients receiving conventional antipsychotics and the healthy control groups (see Table 1). The overall MANCOVA was statistically significant ($F = 1.79$, df = 14,87, $p = 0.05$). The Roy-Bargman stepwise analysis revealed that the interaction was strongest in the premotor cortex (see Table 2b).

3.2. Relationship between DoI and brain volumes in patients

Logarithmic regression analyses tended to explain a greater proportion of the variance in the brain volumes than linear regressions (e.g., PFC grey matter: linear $R^2 = 0.16$, $\log R^2 = 0.22$; total PMC: linear $R^2 = 0.02$, $\log R^2 = 0.07$; POC grey matter, linear $R^2 = 0.06$, $\log R^2 = 0.11$). It was therefore felt that a logarithmic regression was a better model of the association between brain volume and DoI. There was a significant logarithmic association between DoI and age-corrected whole brain volume ($R^2 = 0.24$, $F = 25.88$, df = 81, $p < 0.001$) (Fig. 2a), such that the whole brain volume decreased more rapidly during the initial years of illness and slowed down in later years (Fig. 2a). In a similar manner, we found a significant association between DoI and raw volumes of PFC grey matter ($R^2 = 0.22$, $F = 22.86$, df = 81, $P < 0.001$) (Fig. 2b), grey matter of parieto-occipital cortex ($R^2 = 0.11$, $F = 9.49$, df = 81, $P = 0.003$), total PFC ($R^2 = 0.11$, $F = 9.48$, $p = 0.003$) and thalamus ($R^2 = 0.10$, $F = 9.33$, df = 81, $p = 0.003$). The direction of this association was reversed between DoI and putamen so that longer DOI was associated with larger putamen ($R^2 = 0.32$, $F = 38.13$, df = 81, $p < 0.001$).

The DoI–volume association failed to reach significance at the chosen level ($p = 0.003$ with Bonferrani correction) for the raw volumes of cortical grey matter ($R^2 = 0.08$, $F = 7.27$, df = 81, $p = 0.009$), total sensori–motor cortex ($R^2 = 0.004$, $F = 0.28$, df = 81, $p = 0.6$), the grey matter of sensori–motor cortex ($R^2 = 0.03$, $F = 2.69$, df = 81, $p = 0.11$) (Fig. 2c), total parieto-occipital cortex ($R^2 = 0.01$, $F = 0.87$, df = 81, $p = 0.86$), total premotor cortex

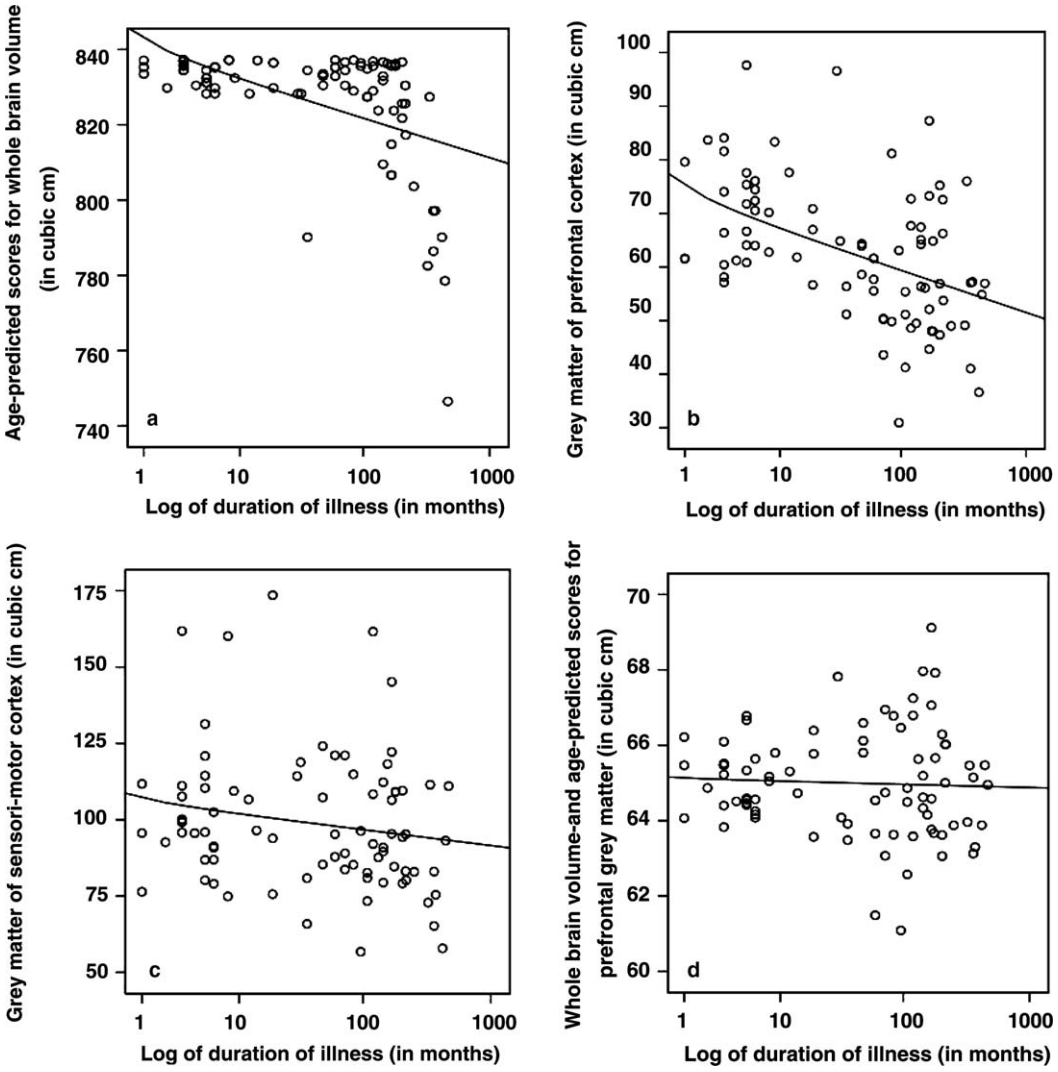

Fig. 2. Plot of logarithm of DoI (in months) and volume of brain regions of interest (in cubic cm).

($R^2 = 0.07$, $F = 6.14$, df = 81, $p = 0.02$), grey matter of premotor cortex ($R^2 = 0.03$, $F = 2.75$, df = 81, $p = 0.1$), grey matter of sensori–motor cortex ($R^2 = 0.03$, $F = 2.69$, df = 81, $p = 0.11$), total temporal lobe ($R^2 < 0.001$, $F = 0.02$, df = 81, $p = 0.88$), grey matter of temporal lobe ($R^2 = 0.02$, $F = 1.84$, df = 81, $p = 0.18$), hippocampus ($R^2 = 0.03$, $F = 2.21$, df = 81, $p = 0.14$) and cerebellum ($R^2 = 0.001$, $F = 0.12$, df = 81, $p = 0.73$).

The four brain regions that showed patient-by-control group interactions on the MANCOVA, were not significantly associated with DoI after correcting for age and whole brain volume: prefrontal cortical grey matter ($R^2 = 0.002$, $F = 0.17$, df = 81, $p = 0.68$) (Fig. 2d), premotor cortex ($R^2 = 0.002$, $F = 0.17$, df = 81, $p = 0.68$), sensori–motor cortical grey matter ($R^2 = 0.002$, $F = 0.17$, df = 81, $p = 0.68$) and cerebellum ($R^2 = 0.002$, $F = 0.17$, df = 81, $p = 0.68$).

4. Discussion

This investigation found that differences in brain volume between chronic and first-episode patients are greater than the difference in brain volume between old and young healthy controls. Specifically, the chronic patients had smaller prefrontal cortical grey matter, but larger premotor cortical and putamen volumes than the first-episode patients. The grey matter of parieto-occipital cortex also showed a significant interaction among groups only when considered independently, but not when considered relative to other brain regions. There were also associations between specific brain volume and DoI, such that smaller volumes of the PFC, parieto-occipital cortex grey matter, thalamus and total cortical grey matter, and larger volumes of the premotor cortex and putamen, were associated with a longer DoI. The volumes of the sensori–motor cortex and cerebellum were not associated with DoI. The fact that not all regions showed an association with DoI suggests that the observed associations were not a general effect of age and total brain volume. Including age and total brain volume in the exponential regression equation may have had the effect of over-correcting for any between-group differences.

Our findings on PFC grey matter are consistent with the findings of Molina et al. (2004). PFC grey matter was smaller in chronic patients compared with first-episode patients, whereas PFC grey matter was not smaller in first-episode patients compared with healthy controls. Furthermore, the association between DoI and PFC grey matter volume was exponential. Gur et al. (1998) reported a greater rate of frontal lobe reduction over a 2.5 year duration in first-episode patients compared with previously-treated patients. It is possible that much of the change in the PFC takes place following the first psychotic episode than at a later stage in the illness. However, a recent study in 13–18 year olds with childhood-onset schizophrenia (Vidal et al., 2006) revealed severe medial frontal grey matter loss over a 5-year-period as determined by an image analysis technique known as cortical pattern matching, suggesting that early developmental changes in the PFC are possible. A sharp boundary in the pattern of grey matter loss separating the frontal regions and cingulate limbic areas suggested that the two regions may not be equally vulnerable to grey matter attrition.

A second finding was that the premotor cortex and putamen were larger in the chronic patients compared to the first-episode patients and that larger volumes were seen with a longer DoI. It can be speculated that the premotor cortex was enlarged secondary to neuroleptic medication. Analysis of the subgroup of patients receiving only conventional antipsychotics seemed to strengthen the effect of premotor cortical and putamen enlargement. Brain enlargement in schizophrenia has been typically reported in the basal ganglia as a result of neuroleptic medication (Bridle et al., 2002; Chakos et al., 1994, 1998; Corson et al., 1999; Gur et al., 1998). The supplementary motor area (SMA) sends projections to the basal ganglia and also receives projections from the basal ganglia via the thalamus (Frackowiak et al., 1997). It is therefore possible that the premotor cortex enlargement was secondary to that of the putamen. Alternately, the volumetric increase in the premotor cortex may reflect an attempt to cope with a volumetric reduction in the PFC as the disease develops in an effort to take over some of the functions of the PFC.

While the current and some previous studies (e.g. Molina et al., 2004) have suggested progressive brain changes during the course of schizophrenia, this finding has not been observed in all studies. Whitworth et al. (2005) conducted a longitudinal study comparing first- and multiple-episode male schizophrenia patients with healthy controls. Although they observed ventricular enlargement and hippocampal volume deficits in the patients relative to controls at both baseline and follow-up over a 2- to 4-year-period, they were not able to demonstrate any significant differences in the rate of annual volume changes that distinguished the patients from controls. They considered the relatively short follow-up period as accounting for a failure to observe any pathogenetic brain volume changes, but they also examined only a small number of brain regions to study longitudinal changes and did not include the frontal lobe regions which may be more susceptible to volumetric changes following the first onset. Also, it is not known if there were any differences in the regional volumes between the first-episode and multiple-episode patients in their study that, as according to our study, would suggest differential effects of illness stage on brain volume.

One of the pathogenetic models of schizophrenia to explain MRI findings of progressive abnormality but the apparent absence of neurodegenerative changes from pathological studies is that of excessive neuronal apoptosis rather than necrosis. Pathophysiological studies of schizophrenia have reported the absence of gliosis (Pakkenberg, 1993; Selemon et al., 1998), whereas apoptosis, which is not associated with gliosis, can occur as a result of exoge-

nous insult to the brain (Akbarian et al., 1996; Woods, 1998). Cortical disconnection hypotheses (Andreasen et al., 1999, 1996, 1998; Callicott, 2003; Semkovska et al., 2001) may also be relevant to our findings. Woodruff et al. (1997) observed that patients with schizophrenia had significantly reduced correlations between prefrontal, anterior cingulate and temporal lobe regions compared to healthy controls. Such regional disconnectivity may lead to a preferential volumetric loss in some regions compared to others as the illness persists, in particular the frontal regions, as our findings suggest. The absence of differences in temporal lobe volumes between chronic and first-episode schizophrenia patients in our study is in keeping with a fronto-temporal dissociation hypothesis of schizophrenia (Woodruff et al., 1997). Mitelman et al. (2005) reported that frontal gray matter volumes were correlated with temporal lobe volumes in patients with schizophrenia, but not in normal subjects. Some frontal–parietal and frontal–occipital correlations showed a similar pattern. Furthermore, poor outcome (Kraepelinian subtype) among patients with schizophrenia was associated with weaker correlations between left frontal area 9 and both medial and lateral temporal cortices, as compared to normal subjects or good-outcome patients. It is possible that our first-episode sample contained a higher percentage of good outcome patients (some of whom may not have further acute episodes) than our chronic multi-episode sample and if so this would be a factor in our findings.

Altered blood flow to brain regions may also lead to structural atrophy as suggested by perfusion studies (Andreasen et al., 1997). Prefrontal grey matter deficits and reduced cerebral perfusion in the frontal lobe were observed in patients with simple schizophrenia (Suzuki et al., 2005). Functional magnetic resonance imaging and electro-encephalography studies have consistently reported decreased metabolism and blood flow within the PFC (Andreasen et al., 1997; Buchsbaum and Hazlett, 1998; Spence et al., 2000; Wuebben and Winterer, 2001). It is possible that with continued inactivation of the frontal regions, coupled with a disconnection of the cortico-cerebellar-thalamo-cortical circuit, a structural atrophy may ensue. Morey et al. (2005) demonstrated that frontal–striatal function deteriorates with chronicity of illness, such that chronic patients showed lower activation than early schizophrenia patients of the frontal and striatal regions in response to executive function and selective attention, who in turn showed lower activation than ultra-high risk individuals and than healthy controls. These studies suggest that persisting schizophrenia may exacerbate prefrontal changes.

The observed patient-by-healthy control group interaction in the parieto-occipital cortex, albeit as an independent variable rather than relative to other brain regions, may explain frequently reported deficits in visual processing in schizophrenia (Butler and Javitt, 2005). Reduced P1 amplitudes as determined by evoked-response potential recordings of processing of successively less fragmented line drawings were observed in patients with schizophrenia to a greater extent in the parieto-occipital than occipito-temporal electrode sites (Foxe et al., 2001).

This study has certain limitations. A key limitation of the study is that of design. Only limited conclusions concerning the outcome of anatomical volumes in schizophrenia can be drawn from a cross-sectional comparison of patients from different stages of schizophrenia. The fact that chronic patients have less volume than first-episode cases does not necessarily mean that a progressive reduction of grey matter has taken place. Cross-sectional methods assume that different populations are comparable in terms of the factors that influence the outcome of the main measure. However, the chronic and first-episode groups differed in that chronic patients were receiving conventional antipsychotics, while the first-episode group comprised a mixture of patients receiving conventional or atypical antipsychotics or were neuroleptic naïve. The analysis using only patients receiving conventional antipsychotics suggested that medication did have some confounding influence on group differences in strengthening the effects for the premotor cortex and putamen and weakening the effects for the prefrontal grey matter, cerebellum and sensori–motor cortical grey matter. The different durations of treatment arising from the different durations of illness in the two patient groups may have had a further confounding influence.

In conclusion, the present study provides evidence for a difference in brain volume between patients at two different stages of schizophrenia over and above that in healthy controls. It shows that this difference is not specific to certain regions, but spans across the frontal, sensori–motor, cerebellar and limbic regions. Furthermore, the volumes of the brain regions are related exponentially to the DoI. The finding of larger premotor cortical and putamen volumes at a later stage of illness draws our attention to the potentiating effect of neuroleptic drugs.

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