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ORIGINAL ARTICLE

Brain surface contraction mapped in first-episode schizophrenia: a longitudinal magnetic resonance imaging study

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Schizophrenia is associated with structural brain abnormalities, but the timing of onset and course of these changes remains unclear. Longitudinal magnetic resonance imaging (MRI) studies have demonstrated progressive brain volume decreases in patients around and after the onset of illness, although considerable discrepancies exist regarding which brain regions are affected. The anatomical pattern of these progressive changes in schizophrenia is largely unknown. In this study, MRI scans were acquired repeatedly from 16 schizophrenia patients approximately 2 years apart following their first episode of illness, and also from 14 age-matched healthy subjects. Cortical Pattern Matching, in combination with Structural Image Evaluation, using Normalisation, of Atrophy, was applied to compare the rates of cortical surface contraction between patients and controls. Surface contraction in the dorsal surfaces of the frontal lobe was significantly greater in patients with first-episode schizophrenia (FESZ) compared with healthy controls. Overall, brain surface contraction in patients and healthy controls showed similar anatomical patterns, with that of the former group exaggerated in magnitude across the entire brain surface. That the pattern of structural change in the early course of schizophrenia corresponds so closely to that associated with normal development is consistent with the hypothesis that a schizophrenia-related factor interacts with normal adolescent brain developmental processes in the pathophysiology of schizophrenia. The exaggerated progressive changes seen in patients with schizophrenia may reflect an increased rate of synaptic pruning, resulting in excessive loss of neuronal connectivity, as predicted by the late neurodevelopmental hypothesis of the illness.
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Introduction

Neuroimaging investigations have shown that schizophrenia is associated with structural brain abnormalities, with the most consistent findings being enlarged ventricles and reduced medial temporal, superior temporal and prefrontal volume.[1,2] Clarifying the timing of onset and course of these structural abnormalities will inform models of disease pathophysiology and facilitate development of novel interventions. Cross-sectional neuroimaging studies have shown brain volume reduction in patients not only in established but also in early stages of schizophrenia, suggesting that structural abnormalities exist, at least in part, before the onset of illness. Furthermore, abnormal brain asymmetry and cortical folding, signs of relatively early developmental deviations, have been found in schizophrenia patients.[3,4] These findings are in accordance with a neurodevelopmental model of schizophrenia, which posits that the brain abnormalities are caused by deviations in early pre/perinatal brain development.[5] At the same time, accumulating longitudinal neuroimaging data suggest that brain volume changes in schizophrenia

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are not restricted to early developmental stages but may be progressive around the time of onset of frank symptoms (for review, see Pantelis *et al.*[1]).

Recent longitudinal studies using high-resolution magnetic resonance imaging (MRI) and advanced image analysis techniques have demonstrated progressive volume reduction in various brain regions in schizophrenia patients. In a series of studies following up patients from their first episode, DeLisi and colleagues[6–8] identified faster-than-normal lateral ventricular expansion over a 10-year period. Exaggerated progressive ventricular expansion has also been reported by other researchers in patients at various stages of illness.[9–11] Progressive frontal volume loss was reported initially by Gur *et al.*[12] in first-episode/chronic patients and subsequently replicated in several other studies.[11,13–18] Excessive volume loss in the whole temporal lobe were reported in several studies,[11,14,15] and this seems largely attributable to changes in the superior temporal gyrus.[19,20] The most pronounced progressive changes reported to date were from a cohort of childhood-onset schizophrenia (COS) patients. Using advanced brain mapping techniques, Thompson *et al.*[16] and Vidal *et al.*[21] reported dynamic spreading of gray matter loss from the parietal lobe to the dorsolateral and medial prefrontal cortices and also to the temporal cortices in patients as compared to age-matched healthy controls.

Despite these interesting leads, considerable discrepancies exist among the findings of studies evaluating progression. Some reported rates of brain volume reduction are of dramatic magnitudes even in the chronic stage of schizophrenia. If the rates are assumed constant beyond the interscan intervals, these changes could lead to unrealistic brain volume loss that far exceeds the volume change observed in postmortem studies. In addition, the precise anatomical pattern of progressive brain changes has not been identified conclusively in that the patterns from individual studies have rarely been replicated. These discrepancies lead some authors to question the credibility of the results from longitudinal MRI studies and even the validity of using MRI volume measurement to infer neuropathological changes in schizophrenia; instead, they raise the possibility that the observed MRI volume changes were due to factors secondary to the illness or artifacts of imaging methodologies.[22]

Indeed, the lack of consistency in both magnitude and anatomical pattern of MRI brain changes in schizophrenia could be due to methodological and sampling variations. Small sample sizes, heterogeneity of patient samples and various confounding factors are among the possible reasons for variations observed across studies. Importantly, measurement error can affect the results substantially when examining potentially subtle brain changes. In some studies,[12,18] MRI images with relatively thick slices (5 mm) were used, which may be sensitive only to extremely large changes. In other studies, only whole brain changes or changes at major lobar levels were examined;[11,23] when detailed manual tracing was conducted, it was restricted to one or several regions of interest.[19] It is also important to note that scale changes between repeated scans, a potential confounding factor, have rarely been explicitly controlled for in these longitudinal MRI studies. Given all of these limitations, a variation in the results across studies is perhaps not surprising.

In this study, we applied Cortical Pattern Matching in combination with Structural Image Evaluation, using Normalisation, of Atrophy (SIENA) to repeated MRI scans in first-episode schizophrenia (FESZ) patients and healthy controls, mapping local brain changes throughout the lateral cortical surface. Cortical Pattern Matching is an advanced brain registration technique that can achieve accurate anatomical correspondence between brain surfaces. It has proven successful in detecting longitudinal changes of cortical gray matter density and thickness in normal and pathological development and degeneration.[24] SIENA is a technique to detect local brain surface contraction as an index of longitudinal brain volume changes. It employs skull images to correct for scale differences between sequential images and, importantly, can detect subtle brain changes at a subvoxel resolution (for example, see Filippi *et al.*[25]) such that contraction or expansion at the cortical surface of less than 1 mm per year can be detected. By combining these two methods, we generated a detailed anatomical pattern of brain changes in schizophrenia patients. We hypothesized that greater brain volume reduction occurs in FESZ patients compared with healthy controls. Regionally, according to the relatively convergent findings from the prior longitudinal MRI, we hypothesized that there is greater frontal volume reduction in schizophrenia patients.

Materials and methods

Participants

A total of 16 patients with FESZ and 14 age-matched healthy control subjects were included in the study. All of the first-episode patients were recruited from the ORYGEN Research Centre, Melbourne, Australia. DSM-IV diagnoses were based on chart review and structured diagnostic interviews. All of the first episode patients had an Axis I diagnosis of a psychotic disorder at intake and a confirmed diagnosis of schizophrenia at follow-up. The subtype diagnoses of schizophrenia were: paranoid ($n=3$), disorganized ($n=3$), undifferentiated ($n=3$) and residual ($n=7$). The mean total PANSS score at follow-up was 86.6 ± 19.1. The healthy control subjects were recruited by approaching ancillary hospital staff and through advertisements. These subjects were from similar sociodemographic backgrounds as the patients. Demographic and clinical characteristics are summarized in Table 1. Among the 16 patients, 7 were on typical antipsychotic medicines during the follow-up period, 7 patients were on mainly atypical

Table 1 Sample characteristics

	FESZ Patients	*Controls*	P-*value*
Sex (male/female)	13/3	11/3	0.855
Age at first scan	21.75 ± 3.45 (17.34–28.10)	21.10 ± 3.69 (16.20–28.74)	0.62
Age at second scan	23.80 ± 3.96 (18.49–32.28)	23.41 ± 4.29 (18.06–32.65)	0.79
Days between scans	749 ± 301 (294–1527)	844 ± 332 (342–1428)	0.417
Age of onset	21.65 ± 3.43 (17.10–27.69)		
Days between onset and first scan	40.63 ± 42.48 (4–149)		

Abbreviation: FESZ, first-episode schizophrenia.
All measures are shown as means ± s.d., with range in parenthesis.

antipsychotic medicines (including risperidone for six cases and clozapine for three cases, with overlaps), whereas the types of medicines taken by the remaining 2 patients are unknown. The duration and accumulating dosage of antipsychotics were not available. The median of total lifetime chlorpromazine-equivalent dosage of antipsychotics for seven patients with available records was 2800 mg, with a range of 100–13384 mg, and the total chlorpromazine-equivalent dosages for the month before the follow-up were 500, 7000, 15500 and 21700 mg for four patients, respectively.

All participants were screened for comorbid medical and psychiatric conditions by clinical assessment and physical and neurological examinations. Exclusion criteria were: a history of significant head injury, seizures, neurological diseases, impaired thyroid function, steroid use or DSM-IV criteria of alcohol or substance dependence. Control subjects with a personal history of psychiatric illness or family history of psychosis were also excluded.

The study was approved by the local research and ethics committee in Melbourne, Australia, and by the Internal Review Board at the University of California, Los Angeles, USA. Participants or their legal guardians (if age <18) gave written informed consent before participating in the study.

Image processing and analysis

All participants were scanned twice on the same 1.5T General Electric Signa MRI scanner. A three-dimensional volumetric spoiled gradient recalled echo sequence generated 124 contiguous, 1.5 mm coronal slices. Imaging parameters were: time-to-echo, 3.3 msec; time-to-repetition, 14.3 msec; flip angle, 30°; matrix size, 256×256; field of view, 24×24 cm matrix; voxel dimensions, $0.938 \times 0.938 \times 1.5$ mm. A numerical code was used to ensure blind analysis of data.

For each scan, a radio-frequency bias field correction was performed. The SIENA method[26,27] was then applied to obtain brain surface contraction between sequential scans from each individual, with several modifications to adapt for the current analyses, described briefly as follows. The cerebral images were extracted from the remainder of the head images. The supratentorial portion of the intracranial space was manually traced for each scan, with the cerebellum excluded, and an inner skull surface was derived from the supratentorial intracranial volume. The cerebral images and the inner skull surfaces were used as input for SIENA instead of the default whole brain images and the exterior skull images derived by SIENA; the reason was that (1) they were available during the above well-defined preprocessing for Cortical Pattern Matching, and (2) the inner skull image derived from manual tracing was a better representation of the intracranial space, a space that remains constant over time during early adulthood. The baseline and follow-up brain images were mutually mapped to their halfway space with a rigid body registration, and the inner skull images were utilized to correct for potential image scale changes from the calibration drift of the scanner. The scale correction was found to be necessary as it significantly reduced the variability of the supratentorial intracranial volume (Supplementary Method 1). In the halfway space, brain-cerebrospinal fluid boundary voxels for both baseline and follow-up brain images were determined by finding the edge voxels of tissue-classified brain images. The distance between two brain surfaces was then measured at subvoxel resolution on the basis of the difference of image intensity change between two sequential images along the direction perpendicular to each boundary voxel,[27] the value in millimeters was assigned to the voxel as the intensity value and an image of the brain surface contraction was obtained.

Both baseline and follow-up brain images from the same individual were then mapped from their own halfway space to a standard three-dimensional coordinate space[28] with an identical nine degrees-of-freedom linear transformation, which was determined by the registration of the baseline image to the standard space. The surface contraction images were also transformed to the standard space. To keep the intensity values (contraction values in millimeters) during the image transformation, nearest-neighbor interpolation methods were used. These images were further input into the Cortical Pattern Matching process to identify the cortical regions showing change.

Cortical Pattern Matching was performed on the brains in the standard space independent of the derivation of the brain surface contraction maps.[24] Briefly, a cortical surface model was extracted from

each scan. On each hemisphere of the surface model, 17 major anatomical landmark curves were manually traced by the following major sulci. In addition, a set of eight control curves along the longitudinal fissure that delineate the lateral surface and the medial surface were traced. The tracing protocol is available on the internet (http://www.loni.ucla.edu/~esowell/edevel/new_sulcvar.html). An image analyst (DS), who was blind to subject demographics and diagnosis, traced all sulci and control curves. The reliability of tracing was tested on six standard brain surfaces, and the average distance between the sulcal curves tracing by the current analyst and the standard sulcal curves was <2 mm in most regions.

The brain surfaces and curves were then flattened to a two-dimensional plane, and average curves were created by averaging the positions of the same curves across all subjects. The brain surfaces were elastically warped to each other on the basis of matching individual curves to their corresponding average curves in the two-dimensional plane, whereas the coordinate positions of each surface point in their three-dimensional space were preserved.

To measure local brain surface contraction, a sphere of 5 mm radius was positioned on each point of the brain surface, and the mean intensity (which represents the brain surface contraction in millimeters) of voxels in the contraction image within the sphere was calculated. The resulting values were then assigned to the corresponding voxel locations in the group average surface to create composite maps of brain surface contraction. It has been shown that the brain surface contraction detected by SIENA was highly correlated with local brain volume decreases (Supplementary Method 2).

Statistical analysis

Individual brain surface contraction was annualized by dividing the contraction value in millimeters by the between-scan interval in years, and this surface contraction rate was taken as the primary variable for the following statistical analyses. *T*-tests were performed to compare surface contraction rates between patient and control groups at each of the 65 026 brain surface points, and P-maps were generated. Set-level permutation tests were conducted to determine whether any suprathreshold ($P<0.01$ uncorrected) distribution of effects was not observed in random permutations of the sample, with >95% confidence. We conducted 100 000 randomized permutations (by randomly assigning subjects to groups) at the hemispheric level and further in major lobes and regions of interest in the frontal lobe including the superior/middle frontal gyri. While these threshold-based permutation tests allow inferences about group differences within the defined regions, they do not control for multiple inference at the level of individual surface points. To evaluate statistical maps of group differences in rates of surface contraction, a false discovery rate method[29] was used to control the rate of false positive statistical tests under multiple inference.

In addition, a comparison was conducted between the seven patients on typical antipsychotics and seven patients on atypical antipsychotics during follow-up to determine whether these antipsychotics had differential effects on brain surface contraction. Contraction maps of both groups were created and the between-group difference was tested using pointwise *t*-tests and permutation tests.

To quantify the similarity of anatomical patterns of brain changes across the lateral cortical surface between the FESZ and control groups, we conducted a correlational analysis on the maps of group-mean contraction rates by correlating the rates at each corresponding surface point of the two groups. If the anatomical patterns were similar, strong positive correlations would be expected. Plots were made for the whole cortex and the left and right hemispheres, respectively. Plots for the frontal lobes were superimposed to examine whether they followed different patterns of surface contraction between patients and control subjects. The large number of data points (surface contractions at all cortical surface points) made scatter plots ineffective to show the distribution of surface contraction, and therefore contour maps were created instead to display differential density of the gathering of surface points across the ranges of surface contraction rates for both groups (Figure 4). Lines of the first principal components were plotted for the whole cortex, hemispheres, and frontal lobes to show the differences in contraction rates, which minimized the sums of squared perpendicular distances from data points to the fitted lines. Standard regression was not appropriate because there was no natural distinction between predictor and response variables, and both variables (contractions for patients and controls) incorporated random error components.[30]

To address whether brain surface contraction was associated with gray matter change, we conducted correlation analyses between brain surface contraction and both whole cerebral gray and white matter reductions and local gray matter density decrease among all the subjects. Cerebral gray and white matter reductions were calculated on the basis of tissue segmentation results on the whole cerebral images from both time points, and these were correlated to mean surface contraction across the cortical surface. Furthermore, we conducted gray matter density measurement following the cortical pattern matching procedure[24] and correlated longitudinal gray matter density decrease to brain surface contraction, and correlational R- and P-maps were created across the cerebral cortex.

To assess whether the brain surface contraction was asymmetric between the left and right hemispheres, we conducted the following tests: each hemispheric surface was parcellated into 11 regions along major sulci and landmarks, which included the orbitofrontal, inferior frontal, middle frontal, superior frontal,

motor, sensory, superior parietal, inferior parietal, occipital, superior temporal, and middle and inferior temporal regions. The mean surface contraction for each region was calculated, and repeated measures analysis of variance was conducted to assess surface contraction, with sides and regions as within-subject variables and patient and control groups as between-subject variables; interactions by group and side were examined.

Results

In the comparison of brain surface contraction rates between the FESZ patients and the age-matched healthy controls, three-dimensional maps of local surface contraction rates for the patient and the control group and the difference maps between the two groups were constructed (Figure 1). In the healthy control group, brain surface contraction occurred mainly along the dorsal prefrontal surface. The majority of other surface regions showed either considerably less surface contraction or surface expansion of a very small magnitude (<0.05 mm per year; Figure 1, column 1). In the FESZ group, surface contraction also occurred in the dorsal prefrontal regions, but at a much greater magnitude. The pre- and postcentral gyri and parietal regions also showed surface contraction in the patient group, in contrast to the mixed pattern of more subtle contraction and expansion in the healthy controls (Figure 1, column 2). The absolute differences in mean surface contraction between the two groups were isolated to the dorsal surfaces of the frontal and parietal lobes (Figure 1, column 3). As a whole, the FESZ patients and the healthy controls showed very similar spatial patterns of brain surface contraction, with those of the former exaggerated in magnitude.

The patterns of brain surface contraction in the FESZ and control groups were confirmed in within-group *t*-tests, as shown in the three-dimensional maps of significance in Figure 2 (columns 1 and 2). In the between-group comparisons, the FESZ group showed significantly greater brain surface contraction in the anterior parts of the superior and middle frontal gyri bilaterally, and in the right pre-/postcentral gyri and the adjacent parietal regions (P-maps in Figure 2, column 3).

Permutation analysis (100 000 randomized replicates) on the whole cerebral surface and regional surfaces confirmed the between-group differences summarized above. The adequacy of the number of permutations was confirmed by the consistent results from 10 separate permutations of 10 000 randomized replicates. The permutation analyses revealed a significant between-group difference for the right hemisphere ($P=0.032$; left hemisphere: $P=0.142$). Regionally, surface contraction was significant for the right frontal lobe ($P=0.017$), whereas the left frontal lobe showed a trend toward significance ($P=0.084$). The results were further confirmed in more specifically delineated regions, including the prefrontal regions as a whole (right $P=0.014$; left $P=0.072$) and the right superior frontal gyri

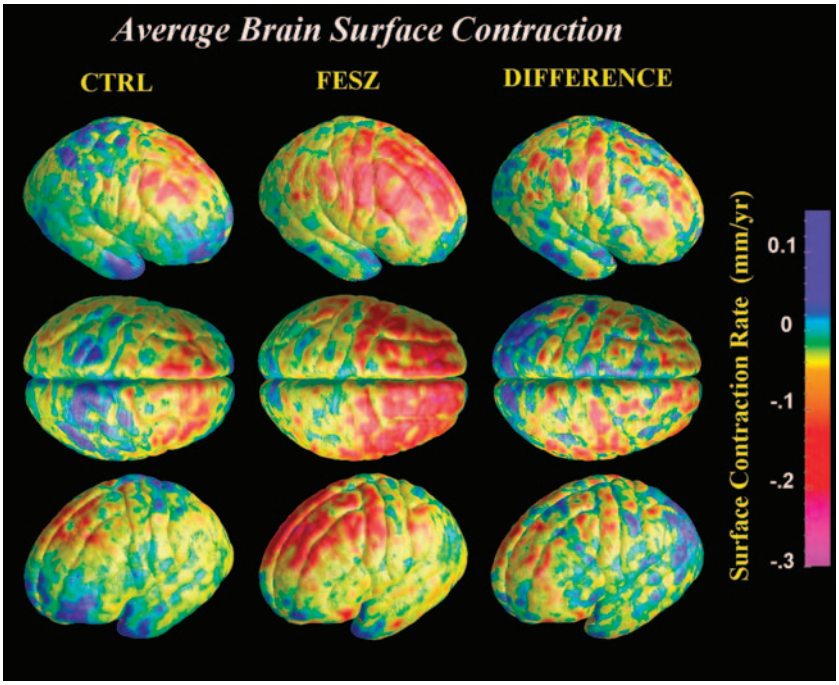

Figure 1 Average brain surface contraction rates (mm per year) in control subjects (CTRL, left column), first-episode schizophrenic patients (FESZ, middle column) and the absolute difference between two groups (right column). Negative values (purple, red and yellow colors) denote surface contractions.

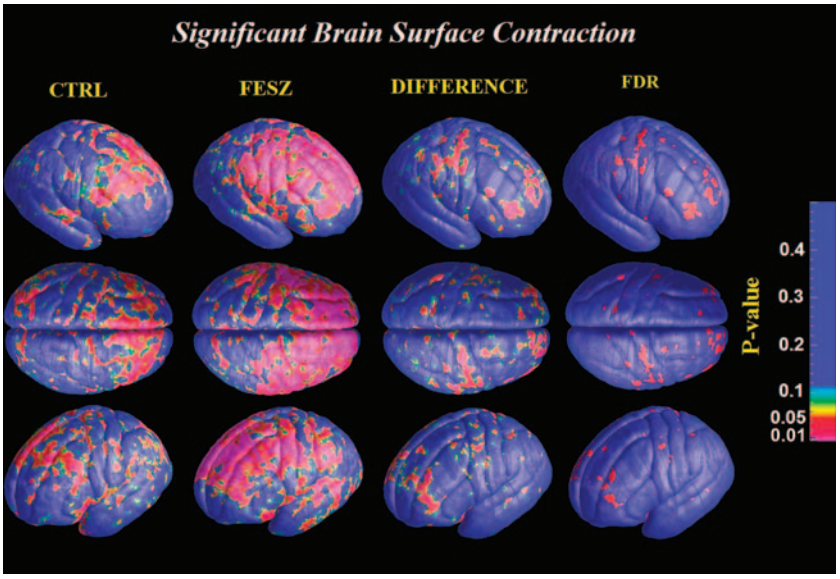

Figure 2 P-maps (two-tailed, uncorrected) of brain surface contraction rates and false discovery rate (FDR) maps: column 1, P-maps for control subjects (CTRL); column 2, P-maps for first-episode schizophrenic patients (FESZ); column 3, P-maps of the between-group comparison; and column 4, FDR corrected P-maps of the between-group comparison. The suprathreshold pattern of differences shown in column 3 was confirmed using permutation tests at $P<0.05$ in both hemispheres, in the frontal lobe and in the superior/middle frontal gyri. As an additional test controlling for multiple comparisons, FDR (column 4) confirmed that 75% of the suprathreshold voxels on the overall cortical surface were expected to be reliable as true positives ($q=0.25$, $P=0.02$) and that 85% of the suprathreshold voxels in the superior/middle frontal gyri were expected to be true positives ($q=0.15$, $P=0.007$).

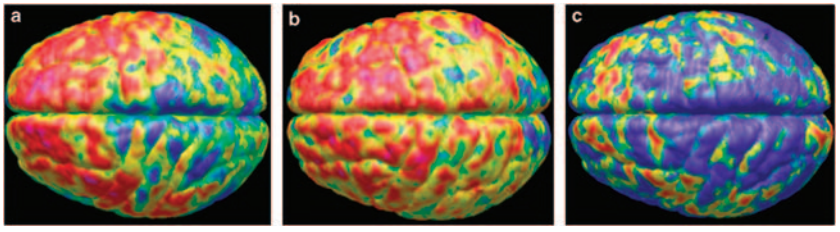

Figure 3 Brain surface contraction rates in patients who were treated with typical antipsychotics and atypical antipsychotics: (**a**) typical; (**b**) atypical; (**c**) absolute difference (nonsignificant in all regions).

($P=0.008$) and middle frontal gyri (right $P=0.020$; left $P=0.047$), respectively. In the right parietal lobe, there was a nonsignificant trend for a steeper rate of contraction in the patients ($P=0.087$).

These permutation analyses demonstrate that the suprathreshold distributions of effects seen in the case–control comparisons in all of the above regions were not observed in random permutations of the sample, with >95% confidence. False-discovery-rate corrected P-maps (Figure 2, column 4),[29] which do not assume interchangeability of the case and control distributions, further confirmed the significance of all of the major findings reported above, although with slightly smaller number of supratheshold voxels in each cluster.

In the comparison of typical versus atypical antipsychotics, although patients taking typical antipsychotics exhibited greater magnitude of contraction in the right prefrontal region, this difference was not significant either in the voxelwise *t*-tests or in the permutation tests (Figure 3).

In the correlation analysis of the anatomical patterns of brain changes, the correlations between the control and FESZ groups were moderate to strong for both the left and right hemispheres (left: $r=0.46$, right: $r=0.59$). Figure 4 (left panel) shows the correlation between mean surface contraction in the FESZ and control groups using all surface points as the basis for analysis. The slope of the line representing the first principal component was 1.68, meaning that globally the surface contraction rate of the FESZ group was more than two-thirds greater than that of the control group. This relationship held almost exactly for both cerebral hemispheres, and also within the frontal lobes, where the maximum surface contraction was observed in both groups (Figure 4 middle and right panels).

Brain surface contraction was shown to be correlated with gray matter volume reduction among all subjects (Figure 5). There was a significant correlation between cerebral gray matter volume reduction and

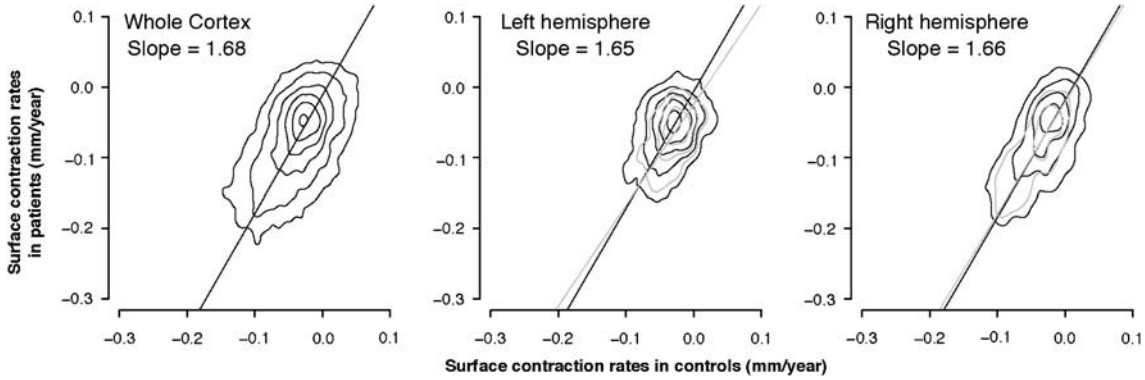

Figure 4 Whole cortical and hemispheric bivariate distribution patterns of group-mean surface contraction for control subjects (CTRL) and first-episode schizophrenic patients (FESZ). The contours represent data point gathering across brain surface voxels at iso-density levels of smoothed distributions; the straight lines represent the first principal component through all data points. The left panel shows the bivariate distribution of the whole cortical surface, and the middle and right panels show that of the left and right hemispheres. On the hemispheric plots, the contours and first principal component lines for the frontal lobes are superimposed as gray lines on the whole hemispheric data. As the slopes of first principal component lines for all plots are close to each other, the figure shows that similar patterns of surface contractions between CTRL and FESZ were present at both global and regional levels.

mean surface contraction (Figure 5a); further, the decrease of local gray matter density from baseline to follow-up significantly correlated with local brain surface contraction in a large portion of the cortical surface, including bilateral prefrontal regions (Figure 5c). There was no significant correlation between cerebral white matter change and mean surface contraction (Figure 5b). In addition, it is worth noting that gray matter density decreases did not show a significant difference between patients and controls.

Repeated measures analysis of variance to assess the left-right asymmetry of surface contraction showed no significant effects for side ($F = 0.01$, df = 28, $P = 0.925$) and no significant side by group interaction ($F = 1.62$, df = 28, $P = 0.213$), which was consistent with the symmetric pattern suggested by visualization of the brain surface maps (Figure 1).

Discussion

With a combination of state-of-the-art image analysis techniques, we were able to compare progressive brain changes in small samples of FESZ patients and age-matched healthy subjects across relatively short-time periods. The techniques allowed us to measure very subtle structural brain changes, even in the healthy controls, and to perform inter-individual anatomical correspondence, thereby providing detailed maps of local brain changes in the cortex. We found significantly greater prefrontal surface contraction that was localized to the right superior frontal gyrus and the right and left middle frontal gyri in patients, and the overall anatomical pattern of these changes resembled an exaggeration of the pattern observed in the normal control subjects.

Further, because the current method measuring cortical surface contraction was not able to provide the exact anatomical sources of brain volume reduction, that is, whether the surface contraction was from gray matter, white matter or other subcortical structures, we assessed the relationship to gray matter density changes using previously published methods.[24] We found significant positive correlations between surface contraction and gray matter density decrease in a large portion of the cortical surface, including the prefrontal lobes, suggesting that our findings of differential surface contraction rates between patients and controls resulted from greater reductions in gray matter in patients compared with control subjects.

This study revealed a detailed anatomical distribution of brain changes throughout the lateral cortical surface related to schizophrenia. The findings of regional changes for the first-episode patients are consistent with prior studies in which progressive frontal volume reduction has been reported.[11–14,17] The magnitude of surface contraction was in the order of 0.3 mm per year for the first-episode patients, which is about 0–0.2 mm per year faster than normal changes. Thus, the rate of contraction in patients is not contrary to the observation of significant but subtle brain volume reduction in schizophrenia patients postmortem. It should be noted that such subtle changes could not be detected by metrics dependent on a voxel level analysis, for example, gray matter density, as the intrinsic voxel size ($0.938 \times 0.938 \times 1.5\,mm^3$) is larger than the degree of interscan surface contraction in the patient group.

The brain surface contraction in healthy controls is consistent with several studies that have shown gray matter volume decline in the prefrontal lobe during adolescence and early adulthood as a function of normal development,[32–34] which could reflect underlying pruning of synapses.[31,35] The current result

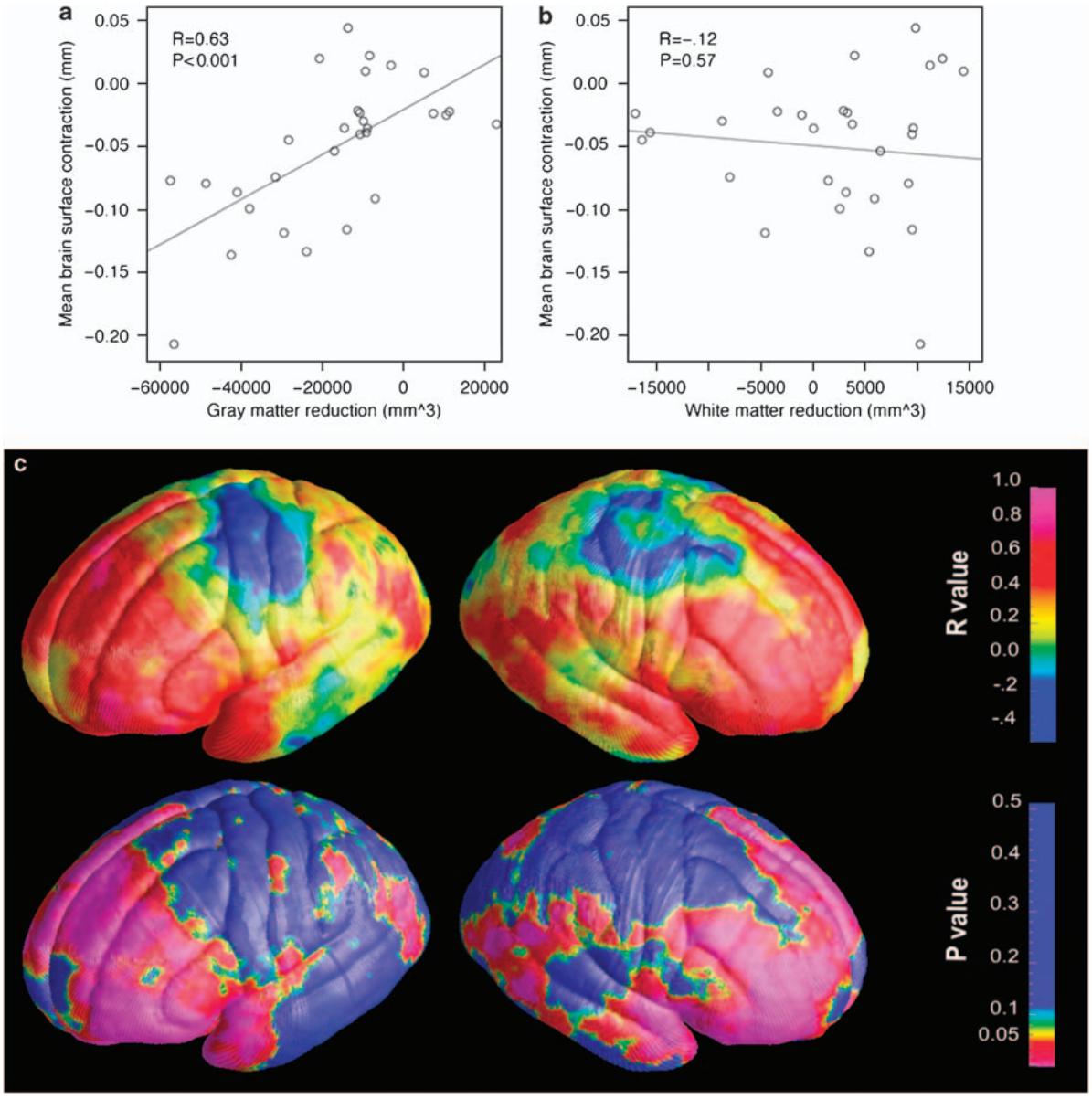

Figure 5 Correlations between brain surface contraction and brain gray matter density changes: (**a**) correlation between cerebral gray matter volume reduction and mean brain surface contraction ($R=0.63$, $P<0.001$); (**b**) correlation between cerebral white matter volume reduction and mean brain surface contraction ($R=-0.12$, $P=0.57$); (**c**) R- and P-maps showing correlation between local gray matter density reduction and surface contraction: most cerebral regions show positive correlations (that is, the greater the gray matter density reduction, the greater the surface contraction), with bilateral prefrontal, temporal pole regions and temporal–occipital conjunctions showing significant correlations.

demonstrates significant brain contraction in the same region that correlated with decreases of gray matter density, consistent with the notion that synaptic elimination is a dominant cellular event at this stage of development. In this context, our finding of brain surface contraction is in contrast to a cross-sectional MRI study in which correlations between gray matter reduction and brain growth were found in the dorsal frontal and parietal regions from childhood to adolescence.[36] Together with the present results based on young adult subjects, these findings suggest that the range of age has a critical influence on brain changes, probably through complex interactions between pruning and myelination.

As schizophrenia is correlated with antipsychotic treatments, hospitalization, psychological stress and life style changes, it is possible that factors secondary to schizophrenia contributed to the steeper rate of frontal lobe surface contraction in the patients compared with controls. Antipsychotic medications are a particularly important potential confounding factor for studies of longitudinal brain changes in schizophrenia. The effects of these factors cannot be fully addressed in the current analyses and need

to be examined with strictly controlled human and animal studies. Although patients taking typical antipsychotics showed greater prefrontal contraction than patients who took atypical antipsychotics, consistent with previous reports,[14] this effect was not significant.

The intriguing similarity in anatomical patterns of brain changes between patients and healthy people seems not readily explained by the above factors secondary to schizophrenia; rather, this correspondence in anatomical patterns suggests that normal developmental processes are involved in the neuropathology of schizophrenia, which is consistent with the late neurodevelopmental hypothesis of the illness originally proposed by Feinberg.[37] This hypothesis cannot be addressed by direct evidence because of the impracticability of examination of synaptic connections on human brain tissue at the early stage of illness. Postmortem neuropathological findings, cross-sectional in nature, largely reflect a terminal stage of pathological changes in schizophrenia, and thus the timing of onset of the brain changes is obscure. Progressive brain MRI volume loss in schizophrenia has been referred to as supporting evidence for the above hypothesis, but its strength is hindered by the lack of consistency and specificity in anatomical patterns. The current observation of an exaggerated normal anatomical pattern of cortical surface contraction in schizophrenia patients is novel in that it fits the prediction of the 'late development/synaptic pruning' hypothesis. It is interesting that a recent study reported differential trajectories of global brain changes between schizophrenia patients and healthy subjects across adulthood by showing excessive volume decreases in patients within the first two decades of illness but not afterward.[38] This was explained as evidence of maturational abnormalities, though only the whole brain and global components were examined in this study.

The high anatomical correlation but differential rates of surface contraction in homologous brain regions between schizophrenia and normal groups suggests that more pronounced synaptic pruning occurs in regions that experience greater normal developmental changes in the late adolescent/early adult period, and this finding may provide an explanation of the apparent differential involvement of prefrontal cortical changes in schizophrenia. The prefrontal region experiences most pronounced developmental changes during late adolescence and early adulthood, and it is the region where anatomical and physiological changes have been most consistently observed in schizophrenia. This is in accordance with the central role of this brain region in working memory, executive function and other higher-order cognitive functions, all of which are impaired in schizophrenia. It is also this region that shows signs of reduced neuronal connectivity in postmortem studies.[39–41] Cortical mapping in twins discordant for schizophrenia shows both genetic and disease-specific influences on gray matter deficits in the prefrontal region,[42] and several susceptibility genes for schizophrenia have been associated with prefrontal structural and functional abnormalities.[43,44] The above evidence is compatible with an exaggerated deviation of prefrontal development in schizophrenia patients.[1]

This study has shown the anatomical pattern of exaggerated normal changes in patients with FES, and the pattern is consistent with findings from a series of MRI studies on patients with COS. COS patients demonstrated a dynamic wave of gray matter loss beginning from the parietal lobe and spreading anteriorly to the dorsolateral and medial prefrontal cortices.[16,21] This dynamic pattern of cortical changes resembled a back-to-front pattern revealed in studies on normal cortical development, which was confirmed by subsequent studies on larger COS samples encompassing an extended age range.[45,46] The COS patients also showed progressive gray matter loss in the superior temporal region,[15,16,46] which was not found in this study. The differences could be due to differences in patient cohorts (childhood-onset versus adulthood-onset), stages of illness (chronic versus first-episode), ages, and the parameters of brain changes (gray matter loss versus brain surface contraction). In addition, the superior surface of the temporal lobe was not detectable with the current method because it is buried in the Sylvian fissure.

In summary, by using an advanced brain surface matching method and a surface contraction detection method sensitive to subtle changes, we have shown that brain changes occurring during the early stages of schizophrenia resemble an exaggerated normal anatomical pattern, suggesting the involvement of deviated normal neurodevelopmental processes in the pathophysiology of the disease. The findings call for further examinations of the anatomical patterns of brain changes in schizophrenia with detailed brain mapping techniques in that they can provide information beyond regional volumetric differences. The results also encourage further studies of neurobiological underpinnings of schizophrenia, especially in relation to the model of late neurodevelopmental disruption in the onset of psychosis. It is conceivable that with deepened understanding of the mechanisms underlying brain volume loss, novel therapeutic and preventive strategies targeting these mechanisms can be developed to arrest the progression of the illness immediately following or even before the onset of psychosis.

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