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ORIGINAL PAPER

Dissociable morphometric differences of the inferior parietal lobule in schizophrenia

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Abstract Inferior parietal lobule (IPL) forms an integral part of a critical frontoparietal network, which has been implicated in various clinical symptoms and cognitive deficits seen in schizophrenia. Despite its functional relevance, the relatively few studies that have investigated the structural changes in the IPL report inconsistent findings concerning the nature and localization of these changes. We employed a blinded, automated labelling procedure to measure cortical thickness, surface area and the degree of cortical folding of the two distinct subregions of the IPL (Angular Gyrus and Supramarginal Gyrus) in 57 patients with schizophrenia and 41 controls using high-resolution magnetic resonance imaging. Within the IPL, we observed more pronounced morphological changes in supramarginal gyrus compared to angular gyrus in schizophrenia. While supramarginal gyrus in patients showed reduced gyrification, contracted surface area and thinning, the morphometric changes in angular gyrus were largely confined to a reduction in surface area. Significant hemispheric asymmetry was observed in the gyrification of the supramarginal gyrus. Our findings suggest that in addition to abnormalities in the neurodevelopmental processes that contribute to regional surface area and cortical thickness, a specific defect in cortical folding, especially affecting the left hemisphere, is likely to occur in schizophrenia.

Keywords Gyrification · Angular gyrus · Supramarginal gyrus · Inferior parietal lobule · Disorganization · Schizophrenia

Introduction

The inferior parietal lobule (IPL) is involved in several functions that involve social cognition (action attribution, agency, theory of mind) [1], working memory and executive functions (set shifting, sustained attention, task control) [2, 3] among a myriad of other functions. A substantial portion of the IPL contributes to Wernicke's area, a key region in language processing [4]. In schizophrenia, various clinical observations such as body image disturbance, loss of insight, passivity phenomenon, disorganization and thought disorder suggest a role for parietal dysfunction [5]. In recent times, IPL has emerged as a prominent anatomical site for the therapeutic application of transcranial magnetic stimulation in schizophrenia [6, 7].

Although there is strong evidence from imaging studies indicating abnormalities in the function of the inferior parietal lobule in schizophrenia [5, 8], the evidence regarding specific abnormalities of grey matter structure from whole-brain studies is conflicting with some [9–11] but not all [12, 13] studies identifying structural changes in this region. Region-of-interest studies investigating parietal structure are more informative in understanding the IPL in schizophrenia, though there is ambiguity regarding disturbances of hemispheric asymmetry and the question of which of the two functionally distinct subdivision of the lobule (the supramarginal gyrus or angular gyrus) is affected [14–18]. These conflicts might be due to a combination of several factors: variability of the unblinded manual delineation of regional boundaries [14–16],

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developmental variation [19, 20], a failure to study the subregional [18] or hemispheric [17] differences and heterogeneity of clinical features, such as variation in symptom profile [21, 22] and duration of illness [23]. In particular, diminished grey matter volume in left inferior parietal lobe has been found to be associated with severity of formal thought disorder [24] while diminished blood flow or metabolism in the IPL has been shown to be associated with the disorganization syndrome, whose major feature is formal thought disorder [25, 26].

In a recent whole-brain study of local contractions in surface area, we observed that a significant reduction in surface area of a distributed set of regions of multimodal association cortex, including inferior parietal lobule [27]. The findings added to the evidence that parietal abnormalities are part of an extensive pattern of abnormalities embracing distributed cortical networks, consistent with the dysconnectivity hypothesis of schizophrenia [28]. However, a whole-brain analysis is not optimal for delineating abnormalities within a specific lobule and in particular, for addressing specific questions such as whether or not normal asymmetry in the lobule is disturbed and which sub-region of the lobule is most affected [29]. A region-of-interest (ROI) analysis provides a much more powerful way of addressing such questions. For this reason, in this paper, we present a focused ROI analysis of the surface anatomy of the IPL and its relationship to disorganization using the data from a previously published sample [27].

To minimize the variability introduced by manual delineation of boundaries, we have used an automated approach based on surface-based morphometry with explicit rules for parcellation. Furthermore, in the light of the evidence that features of cortical structure such as thickness, surface area and folding are determined by distinguishable developmental processes [30, 31], which might be differentially affected by the pathophysiology of schizophrenia [32], we have examined each of these three aspects of cortical structure in an attempt to comprehensively characterize the structural changes of the IPL in schizophrenia. We hypothesized that in patients, alteration in the structure of IPL will be observed along with regional differences in the three morphometric properties. Given the conflicting nature of previous literature, we did not make any explicit assumptions as to the direction of these changes in schizophrenia.

Methods

Participants

A sample of 57 patients satisfying DSM-IV criteria [33] for schizophrenia and 42 healthy controls was recruited. Clinicians attached to community mental health teams and rehabilitation services initially referred the patients to the research team. The diagnosis of schizophrenia was made in a clinical consensus meeting among a team of research psychiatrists in accordance with the procedure of Leckman et al. [34], using all available information including a review of case files and a standardized clinical interview (Symptoms and Signs in Psychotic Illness—SSPI [35]). Most patients had paranoid [DSM-IV 295.30] ($n = 47$) subtype of the illness, with some qualifying for undifferentiated [DSM-IV 295.90] ($n = 7$) and disorganized [DSM-IV 295.10] ($n = 3$) subtypes. All patients were in a stable phase of schizophrenia (defined as a change of no more than 10 points in their global assessment of function (GAF) score [33], assessed 6 weeks prior and immediately prior to study participation) and the mean duration of illness was 4.3 years (SD: 3.09). Subjects with neurological disorders, current substance dependence and IQ <70 using Quick Test [36] were excluded. All patients were receiving treatment with antipsychotic medications and had no change in their prescriptions for the 6 weeks preceding the scan. The average dose in chlorpromazine equivalents was 288.7 mg (range: 100–1,200 mg). Three were on clozapine (mean chlorpromazine equivalents: 683.33 mg), while 54 were on non-clozapine atypical antipsychotics [quetiapine, olanzapine, risperidone, amisulpride] (mean chlorpromazine equivalents: 266.77 mg).

Chlorpromazine equivalent doses were computed for oral antipsychotic medication using data presented by Woods [37]. In the case of Risperidone Consta injection, 25 mg Consta injection every 14 days was taken to equate to 4 mg oral risperidone per day, in accordance with the recommendation of the British National Formulary [38]. Patients with schizophrenia were interviewed on the same day of the scans by a research psychiatrist and symptom scores assigned according to the SSPI. SSPI provides scores for the three characteristic syndromes (reality distortion, disorganization and psychomotor poverty) identified in schizophrenia.

Healthy controls were recruited from the local community via advertisements and originally included 42 subjects free of any psychiatric or neurological disorder matched in age (±3 years) and parental socio-economic status (measured using NSSEC: National Statistics—Socio Economic Classification [39]) to the patient group. Controls had similar exclusion criteria to patients; in addition, subjects with history of psychotic illness in first-degree relatives were excluded. One control subject was excluded in the final analysis due to a movement artefact in the MRI image that precluded volumetric computations. Handedness was assessed using Annett's questionnaire [40] and quantified using continuous scores varying between −12 and +12 in line with White et al. [41]. The study was

approved by the Regional Ethics Committees (Nottinghamshire and Derbyshire).

Image acquisition

Magnetic resonance scans were collected using Philips 3-T imaging system equipped with 8-channel phased-array head coil. The scanning protocol included a single high-resolution three-dimensional T1-weighted MPRAGE volume with 160 slices of isotropic voxel size $1 \times 1 \times 1$ mm^3, flip angle 8°, field of view $256 \times 256 \times 160$ mm^3.

Surface extraction

Surface extraction and cortical parcellation were carried out using FreeSurfer version 4.5.0 [42]. The pre-processing was carried out according to the description available at (http://surfer.nmr.mgh.harvard.edu/). Briefly, following skull-stripping and intensity correction, the grey–white matter boundary for each cortical hemisphere was determined using tissue intensity and neighbourhood constraints. The resulting surface boundary was tessellated to generate multiple vertices across the whole brain before inflating. Using a deformable surface algorithm guided by the grey-CSF intensity gradient, the resulting grey-white interface was expanded to create the pial surface. The inflated surface was then morphed into a sphere followed by registration to an average spherical surface for optimal sulcogyral alignment.

Anatomical parcellation

The two subregions of the inferior parietal lobule were defined using the anatomical conventions followed by Duvernoy and described in detail by Destrieux et al. [43]. The parcellations were obtained using the automated segmentation procedure that generates probabilistic anatomical labels based on sulcogyral morphology [43]. The IPL was identified as the cortical region posterior to the postcentral sulcus and inferior to the intraparietal sulcus. The sulcus intermedius primus (of Jensen) divides the inferior parietal lobule into supramarginal (anterior) and angular (posterior) gyri. Jensen's sulcus runs, approximately perpendicular to the interparietal sulcus, towards the temporal lobe inferiorly. In subjects where Jensen's sulcus is poorly defined, the scheme uses a dividing line halfway between superior temporal sulcus and the lateral sulcus. The supramarginal gyrus follows the posterior angle of the lateral sulcus. The angular gyrus is posterior to the supramarginal gyrus and extends up to the intraparietal sulcus. Duvernoy's conventions are widely used in defining IPL subregions [14, 15]. The rule-based automatic parcellation used by Freesurfer helps to overcome some of the imprecision seen in manual tracing, related to the variability of the sulcal boundaries reported in classical texts such as Duvernoy [44] and Ono atlases [45]. Freesurfer-based automated labelling has been previously employed to delineate supramarginal gyrus and angular gyrus [46, 47]. Figure 1 (Web Supplement) displays the extracted IPL regions.

Surface-based morphometry

Cortical thickness and surface area were calculated for supramarginal gyrus and angular gyrus on both hemispheres using the methods developed by Fischl and Dale [48]. Gyrification was measured with Schaer's Local Gyrification Index (LGI) using images reconstructed through the Freesurfer pipeline [49]. Schaer's method is an extension of Zilles' gyrification index applicable to 3-dimensional reconstructions that gives a ratio of the inner folded contour to the outer perimeter of the cortex [50]. Schaer's local gyrification index for each vertex on pial surface reflects the amount of cortex buried in its locality [49]. A spherical region-of-interest of 25 mm radius is constructed around each vertex to determine the amount of buried cortex; the final LGI value is a weighted average of multiple loci within the sphere, with the weight being inversely proportional to the distance from the vertex of interest. Hence, the estimated LGI for each vertex is strongly influenced by the immediately proximal folding pattern. The mean LGI calculated using all vertices present within a predefined sulcogyral region of the atlas is used as the LGI of that anatomical sub-region in line with Janssen et al. [51]. Further details of the procedure used in the present sample can be found elsewhere [27, 52]. We obtained the LGI, surface area and cortical thickness for supramarginal gyrus and angular gyrus for each hemisphere.

Statistical analysis

All statistical analyses were carried out using the Statistical Package form Social Sciences (SPSS 16.0: Chicago, Illinois). As we were primarily interested in the group differences in the surface anatomy across the two subregions of the IPL, three separate General Linear Model (repeated measures analysis of covariance) were used for LGI, thickness and area. To control for global brain differences in each of the models, appropriate anatomical covariates were used as follows: mean global thickness for thickness measures, total cortical area (the total surface area of the grey-white boundary) for surface area measures and mean global gyrification index for the LGI measures. In addition, age, gender and parental NSSEC scores were also used as nuisance covariates. Hemisphere (right and left) and regions (supramarginal and angular) were entered as within-subject factors, while diagnosis was treated as

between-subjects factors. Follow-up tests comparing adjusted means of individual morphometric measures between the two groups were carried out using independent *t* tests with Bonferroni–Holm correction for multiple testing [53]. In addition, planned analysis for the two hemispheres was carried out to test for the previously reported hemispheric differences in the IPL. Asymmetry Index (left − right)/(0.5*(left + right)) was calculated for the all three anatomical measures and compared between the two groups. The relationship between anatomical measures and antipsychotic dose was analysed using Spearman's correlation at a lenient threshold of $p = 0.1$. We also analysed the association between the anatomical measures and (1) symptom scores for the disorganization syndrome and (2) illness duration from the time of onset of positive psychotic symptoms using Spearman's correlation. The latter analyses were strongly influenced by the previous literature, and the threshold was set at $p = 0.05$.

Results

There were no significant group differences in demographic features such as age (t (1,96) = −1.32, $p = 0.17$) or parental socio-economic status (Mann–Whitney U test, $Z = -1.46$, $p = 0.16$; mean 2.54 in patients, 2.02 in controls) or handedness scores (t (1,96) = −1.53, $p = 0.13$) between the two groups. Gender distribution was not significantly different between the two groups (Fisher's exact test; $df = 1$, $p = 0.19$), though both groups were composed of male subjects predominantly. The mean total symptom score on the SSPI was 10.28 out of a maximum of 80 (range: 0–29), indicating a low symptom burden and consistent with recruitment of patients living in the community in a stable phase of illness. The mean score on Reality Distortion (delusions and hallucinations) among the patient group was three out of a maximum of eight (range: 0–7), indicating that despite clinical stability, the current sample included patients with delusions and/or hallucinations at the time of the study. The mean score on psychomotor poverty dimension was 2.9 (range: 0–9) and on disorganization dimension was 0.74 (range: 0–4). The demographic features of the sample are shown in Table 1.

Table 1 Demographic features of the sample

	Patients with schizophrenia	Healthy controls
Number	57	41
Gender (male/female)	50/7	39/2
Mean handedness score (with SD)	9.37 (5.26)	7.17 (8.89)
Age range (in years with mean and SD)	19–47 (26.10; 7.49)	18–44 (28.04; 6.63)
Mean parental NS-SEC (with SD)	2.54 (1.57)	2.02 (1.44)

NS-SEC national statistics-socio economic status, *SD* standard deviation

Gyrification

The repeated measures ANCOVA model showed a significant effect of diagnosis ($F = 43.45$, $df = 1$, 92; $p < 0.001$, partial eta 0.32) in explaining the differences in IPL gyrification. There was a significant region X diagnosis effect ($p < 0.001$) in addition to hemisphere X diagnosis interaction ($p = 0.010$). Follow-up t tests (Table 2) revealed significantly reduced gyrification in both left and right supramarginal gyrus, with a trend towards reduction in the left angular gyrus in patients with schizophrenia. The normal left > right asymmetry of supramarginal gyrification was not seen in patients (Table 3). There was a trend towards right lateralization of angular gyrus gyrification in patients.

Surface area

The repeated measures ANCOVA model showed a significant effect of diagnosis ($F = 14.80$, $df = 1$, 92; $p < 0.0001$, partial eta 0.14) in explaining the differences in IPL area. There was a significant region X diagnosis effect ($p = 0.03$) but no hemisphere X diagnosis interaction ($p = 0.30$). Follow-up t tests (Table 2) revealed significantly reduced area in both left and right supramarginal gyrus, and in left angular gyrus in patients with schizophrenia. There was a significant trend towards right lateralization of angular gyrus surface area in patients (Table 3).

Cortical thickness

The repeated measures ANCOVA model showed a significant effect of diagnosis ($F = 162.9$, $df = 1$, 92; $p < 0.0001$, partial eta 0.64) in explaining the differences in IPL thickness. There was a significant region X diagnosis effect ($p < 0.001$) but no hemisphere X diagnosis interaction ($p = 0.897$). Follow-up t tests (Table 2) revealed significantly reduced thickness in both left and right supramarginal gyrus, but not in the angular gyrus in patients with schizophrenia. There was no change in the left > right lateralization of cortical thickness in both the subregions of the IPL in schizophrenia (Table 3).

Table 2 Mean thickness (in mm), area (in mm^2) and gyrification (Local Gyrification Index: no units) adjusted for global covariate in patients with schizophrenia and controls

	Left hemisphere			Right hemisphere		
	Controls	Patients	*t* test	Controls	Patients	*t* test
Angular gyrus						
Gyrification	3.356 (0.026)	3.270 (0.022)	$t = 2.53$ $p < 0.1$	3.369 (0.026)	3.329 (0.022)	$t = 1.17$ $p > 0.5$
Thickness	2.756 (0.026)	2.722 (0.022)	$t = 1.00$ $p > 0.5$	2.717 (0.026)	2.685 (0.022)	$t = 0.94$ $p > 0.5$
Area	1,744.3 (55.51)	1,543.1 (46.38)	$t = 2.79$ $p < 0.05$	2,176.1 (57.42)	2,042.2 (48.02)	$t = 1.79$ $p > 0.1$
Supramarginal gyrus						
Gyrification	3.755 (0.060)	3.155 (0.050)	$t = 7.70$ $p < 0.005$	3.733 (0.047)	3.284 (0.039)	$t = 7.38$ $p < 0.005$
Thickness	2.694 (0.030)	1.963 (0.025)	$t = 18.78$ $p < 0.005$	2.680 (0.032)	1.937 (0.027)	$t = 17.76$ $p < 0.005$
Area	2,150.0 (66.61)	1,773.3 (55.66)	$t = 4.35$ $p < 0.005$	2,065.6 (58.16)	1,740.0 (48.59)	$t = 4.31$ $p < 0.005$

p values are corrected for multiple comparisons. Figures in brackets denote standard error of the mean

Table 3 Asymmetry Index ([Left − Right]/[0.5*(Left + Right)]) in patients with schizophrenia and controls

Asymmetry	Patients mean (SE)	Controls mean (SE)	*p* value
Angular gyrus			
Gyrification	−0.019 (0.007)	−0.003 (0.005)	$t = 1.69$ $p < 0.5$
Thickness	0.012 (0.009)	0.016 (0.008)	$t = -0.34$ $p > 0.5$
Area	−0.307 (0.032)	−0.202 (0.030)	$t = 2.30$ $p < 0.1$
Supramarginal gyrus			
Gyrification	−0.044 (0.010)	0.006 (0.006)	$t = 3.84$ $p < 0.01$
Thickness	0.009 (0.013)	0.010 (0.007)	$t = 0.04$ $p > 0.5$
Area	0.000 (0.024)	0.047 (0.025)	$t = 1.32$ $p > 0.5$

p values are corrected for multiple comparisons. *Positive* values indicate left > right asymmetry, *Negative* values indicate right > left asymmetry. *SE* standard error of the mean

Correlational analyses

None of the morphometric measures correlated with chlorpromazine equivalents of antipsychotic dose in patients. Significant negative correlations were found between the scores of disorganization syndrome in SSPI and supramarginal LGI asymmetry ($\rho = -0.304$, $p = 0.02$), left supramarginal LGI ($\rho = -0.289$, $p = 0.03$) and left supramarginal area ($\rho = -0.303$, $p = 0.02$) in patients. None of the other morphometric measures showed significant correlations with the disorganization scores. To test whether the observed relationship with the symptom scores was specific to disorganization syndrome, we also related the structural measures from supramarginal and angular gyrus with the total SSPI score, and the psychomotor poverty and reality distortion scores, but did not find any significant relationships. With respect to the duration of illness, significant negative correlation was found between the duration of illness and right supramarginal thickness ($\rho = -0.494$, $p < 0.001$). No other metric was related to the illness duration.

Discussion

Our observations confirm the hypothesis that regional differences in gyrification, surface area and cortical thickness exist within the IPL in schizophrenia. Within the IPL, we observed more pronounced morphological changes in supramarginal gyrus compared to angular gyrus in schizophrenia. While supramarginal gyrus in patients show reduced gyrification, contracted surface area and thinning,

the morphometric changes in angular gyrus are largely confined to a reduction in surface area. The prominent structural changes observed in supramarginal gyrus are consistent with some [15, 54] but not all of the previous studies [14, 17]. Previous studies exploring the regional differences in IPL morphology in schizophrenia were based on manually delineated measurements of volume [14–18]. Our current findings help to clarify the reported inconsistencies by applying a blinded automatic parcellation procedure and separating the three morphometric properties of cortical grey matter.

We observed a significant reduction in IPL gyrification in schizophrenia with a reversal of normal left > right asymmetry in the supramarginal gyrus. Left > right asymmetry in the degree of cortical folding along the posterior perisylvian cortex (corresponding to supramarginal gyrus) appears to be established by the time of birth in full-term infants [55]. Investigating the sulcal patterns across the whole brain in schizophrenia, Csernansky et al. [56] found that the most significant alteration in the sulcal morphology in schizophrenia was localized to the parietal operculum. Consistent with this finding, our results suggest a significant alteration in the morphology of cortical folding along the posterior perisylvian cortex. Multiple sources of evidence suggest that cortical gyrification is closely associated with structural connectivity patterns [57, 58]. A reduction in IPL gyrification along with loss of asymmetry is strikingly similar to our previous observation of reduced gyrification and loss of asymmetry in most of the prefrontal region in schizophrenia [52]. This observation supports the notion that schizophrenia is associated with a significant dysconnectivity among various cortical areas in general [59] and altered fronto-parietal connectivity in particular. At a functional level, this altered frontoparietal interaction may be associated with the symptoms of disorganization [60], in line with the observed correlation between reduced supramarginal asymmetry and higher disorganization scores in the present study. As supramarginal gyrus forms an integral portion of Wernicke's area, the loss of left > right asymmetry in this region suggests a disturbance in language networks in schizophrenia and adds support to Crow's hypothesis of language area asymmetry being a core feature of schizophrenia [61].

The observed correlation with severity of disorganization symptoms is consistent with previous structural [24] and functional studies [25, 26]. It is noteworthy that in this sample of patients scanned during a stable phase of illness, the symptoms are likely to have been predominantly persistent symptoms. Nonetheless, the association between the disorganization scores and the gyrification and area measures of left supramarginal gyrus suggests that even in this group of patients with relatively preserved functioning, the IPL structure does account for some degree of variance in persistent disorganization scores. In the light of the evidence indicating both similarities and differences between the cognitive correlates of persistent and transient symptoms [60], future studies should assess symptoms longitudinally to determine whether reduced left supramarginal gyrus area and gyrification are related to persistence of disorganization.

Reduction in right supramarginal thickness was associated with longer illness duration in the present sample, which predominantly consisted of subjects in an early phase of illness (mean illness duration = 4.3 years, SD 3.09). This finding is consistent with several previous observations that suggest that a progressive reduction in parietal grey matter volume is seen during the early phase of schizophrenia [23, 61]. This result must be interpreted cautiously as it is likely to be confounded by cumulative antipsychotic usage. But a longitudinal study has recently shown that both illness duration and cumulative antipsychotic dosage can have independent effects on the parietal grey matter volume [62], suggesting that at least in part, the right supramarginal structure is affected by the pathophysiological processes related to the duration of schizophrenia.

Our result emphasizes the importance of dissociating area and thickness when studying asymmetry of brain regions. Significant reduction in cortical surface area was seen in both hemispheres for supramarginal gyrus, while predominantly left sided for angular gyrus resulting in more pronounced right > left asymmetry in angular gyrus area in patients. In addition, we observed right > left pattern for angular gyrus surface area in healthy controls. However, volumetric studies that do not differentiate surface area and thickness have reported inconsistent patterns in angular gyrus asymmetry in healthy individuals (both right > left [46, 63] and left > right[14] are reported). Consistent with Nesvag et al. [64] in our patient group, cortical thickness was unaffected in angular gyrus, suggesting that the previous observations of volume reduction in left angular gyrus [14, 17] are likely to be predominantly due to a reduction in surface area. Angular gyrus is often regarded as a part of a default-mode network [65]. Reduced surface area in angular gyrus could potentially explain some of the disturbances in functional connectivity seen across the default-mode network in schizophrenia [66].

Our sample was predominantly comprised of male patients. While this reduced the heterogeneity introduced by gender differences, it has limited the generalizability of current findings. Previous studies in smaller samples have reported an effect of gender while investigating the IPL [18, 54] (but see Buchanan et al. [15]), though the unintended skew in gender distribution (only nine females among 98 subjects) precluded meaningful analysis of gender differences in our sample. All of our patients were

taking antipsychotic medications during the study. Antipsychotics could adversely affect certain structural findings in MRI [62]. The differential effect of the typical and atypical antipsychotics on parietal volume is controversial. While Thompson et al. [67] showed a significant parietal-to-frontal grey matter loss associated with haloperidol but not olanzapine, Ho et al. [62] observed parietal grey matter to be significantly affected by both clozapine and non-clozapine atypicals, with a similar but trend-level association for typical antipsychotics. Though we did not find an association between IPL structure and the current antipsychotic dose, in the absence of lifetime antipsychotic usage data, the present results must be interpreted with caution. Nevertheless, in line with Zhou et al. [16], we did not find any correlation between current antipsychotic dose and structural measures of the IPL. We did not collect neuropsychological data specific for parietal functions; as a result, the cognitive consequences of the anatomical changes in the IPL cannot be inferred for the present structural study.

Conclusion

In summary, we have observed significant alterations across the three distinct morphometric properties of the grey matter within the two subregions of the IPL in schizophrenia. The dissociable nature of these changes suggests that regional structural differences seen in schizophrenia may have different mechanisms of origin. While the observed changes in both the subregions of the IPL may be related to a defective tangential expansion of cortex during development, an additional defect in gyrification affecting both the perisylvian structures and prefrontal cortex may contribute to the prominent structural changes observed in the supramarginal gyrus. These structural alterations may contribute to the generation of some of the core symptoms of schizophrenia.

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Conflict of interest P F Liddle has received honoraria for academic presentations from Glaxo SmithKline, AstraZeneca, Janssen-Cilag, Bristol Myers Squibb and Eli Lilly and has taken part in advisory panels for Eli Lilly, Pfizer and Glaxo SmithKline. L Palaniyappan has received a Young Investigator Fellowship sponsored by Eli Lilly.

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