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Letter to the Editor

Progressive post-onset reorganisation of MRI-derived cortical thickness in adolescents with schizophrenia

Dear Editor,

Progressive thinning of cortical grey matter is a normal developmental feature in healthy adolescence that coincides with cognitive maturation (Raznahan et al., 2011). Several lines of evidence suggest that cortical maturation is disrupted in patients with schizophrenia (Paus et al., 2008). Developmental maturation of cortical regions is tightly interlinked, resulting in a notable covariance pattern that recapitulates either the functional coactivation or structural connectivity of brain regions (Evans, 2013). Examining the deviant patterns of structural covariance holds the promise of providing a systems-level picture of early stage illness that is more complete than regional anatomical comparisons. In this study we test the interconnectedness (topology of structural covariance) of progressive thickness changes in adolescent-onset schizophrenia. We employ a graph theory approach in line with recent studies to examine if specific brain regions in adolescent-onset subjects display a pattern of integrated/segregated relationship with other regions, in addition to studying the system-level organisation of progressive thickness changes in adolescence. To our knowledge this study is the first longitudinal examination of structural covariance in schizophrenia (Supplement Section 1).

Structural MRI data from 18 adolescents satisfying DSM-IV criteria for schizophrenia (10 males and 8 females, age 14.2 to 18.4 years) and 19 controls (9 males and 10 females, age 13.5 to 17.8 years), from the Oxford Regional Adolescent Unit and the surrounding catchment area were studied. A follow-up scan was obtained after an average interval of 2.18 years. In line with prior work (Palaniyappan et al., 2013), for each brain region, a longitudinal annual rate of thickness change was calculated as the difference in thickness between the two scans divided by the interscan interval in years. Graphs were constructed for the 2 groups of subjects on the basis of this annualised rate of thickness change ("change graphs"). The details of the MRI data acquisition, preprocessing, graph construction are presented in the supplement (Supplement Section 2).

We compared patients and controls on all regions-of-interest (ROI) at baseline and at follow-up scan separately. Annualised rate of thickness changes was also compared, with false discovery rate correction. We compared "change graphs" of the 2 groups using a non- parametric permutation test with 1000 repetitions, based on functional data analysis (FDA) (Ramsay and Dalzell, 1991) (Supplement Section 3).

At baseline, adolescents with schizophrenia had a significant reduction in thickness affecting anterior cingulate cortex, bilateral insula, orbital, lateral frontal, superior temporal, and lateral parietal regions. There were no regions showing increased thickness in patients at baseline. At the time of follow-up, no significant differences between patients and controls (between-groups contrast of scan 2) were notable in either direction in any of the 148 brain regions examined. Annual rate of change showed significant differences between the two groups, distributed across the brain (Table 1). While healthy adolescents showed a pattern of progressive thinning in all the identified regions, patients showed either a lack of change (occipital areas) or relative post-onset thickening (posterior insula).

The topological analysis revealed a small-world organisation in both healthy adolescents and those with schizophrenia, with no notable group differences, implying an optimal balance between cohesive relationship among neighbouring regions and the integration among distributed regions in terms of progressive cortical changes. At regional level, patients with schizophrenia had a significantly elevated degree and clustering coefficient in right calcarine sulcus and high degree in right short insular gyrus (right anterior insula) (Table 1), with a high degree of covariance of these 2 nodes We did not find a confounding effect from antipsychotics in this sample. More detailed results are presented in Supplement Section 4.

Adolescent-onset patients show a distributed reduction in cortical thickness at illness onset, but these differences were nullified nearly 2 years later, during which the controls showed continued cortical thinning. In the presence of schizophrenia, several brain regions (right posterior insula, subparietal sulcus, left planum temporale) did not show the progressive thinning seen in age-matched healthy adolescents. Occipital regions showed a distinct lack of thinning, consistent with occipital sparing noted in genetically high risk adolescents (Jalbrzikowski et al., 2013) and in adults with schizophrenia (van Haren et al., 2011). However, the lack of frontal thinning in our sample is in contrast with a series of observations made in the adolescent cohorts studied by Arango et al. (2012). While the size of this frontal shrinkage is small enough to be missed in a sample of 18 subjects, it is also possible that this feature is more likely to be seen in the most severely ill subjects with higher severity of negative symptoms and several episodes of hospitalisation (Arango et al., 2012). (Supplement: Limitations).

The presence of a small-world topology in progressive thinning in healthy adolescents indicates a well-coordinated maturational process during this developmental window. In patients with schizophrenia, robust regional differences are present at baseline and a differential rate of structural change occurs in a distributed manner. Despite this, conserved small world topology indicates that these changes are not strong enough to disrupt the systems-level architecture maturation. However, the presence of significant regional differences in covariance highlights a central role for key regions in orchestrating patient-specific changes, resulting in aberrant interconnected covariance. The higher nodal degree in the anterior insula supports the insular dysfunction models of schizophrenia (Palaniyappan and Liddle, 2012) and highlights the role of cortical hub regions in targeted grey matter changes (Palaniyappan et al., 2018). The high degree and clustering of calcarine sulcus indicates higher occipital cliquishness in the presence of schizophrenia. The topological secularity of calcarine sulcus could be a compensatory structural

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Table 1
A. Regional differences in progressive change in thickness in patients compared to healthy controls. B. Topological properties of annualised change in cortical thickness.

A. Regional differences	Controls	Schizophrenia	t (p values)
R long G. of the insula	0.19 (0.36)	−0.31 (0.33)	4.40 ***
R subparietal S.	0.07 (0.12)	−0.06 (0.07)	4.00***
L planum temporale G.	0.07 (0.1)	−0.11 (0.19)	3.98***
L middle occipital S.	0.12 (0.11)	−0.03 (0.12)	3.74***
R middle frontal S.	0.10 (0.07)	−0.04 (0.15)	3.73***
L lateral occipito-temporal S.	0.08 (0.07)	−0.02 (0.11)	3.57**
L parieto-occipital S.	0.09 (0.07)	−0.02 (0.11)	3.33***
B. Topological parameters	**Controls**	**Schizophrenia**	**FDA permutation test (p values)**
Small world index	1.24 (0.056)	1.14 (0.009)	0.57
Mean local efficiency	0.81 (0.023)	0.83 (0.030)	0.23
Mean global efficiency	0.68 (0.054)	0.67 (0.06)	0.35
Regional clustering coefficient			
Right calcarine S.	0.47 (0.043)	0.71 (0.049)	0.0003[a]
Regional degree			
Right short insular G.	19 (9.3)	72.7 (9.8)	0.0005[b]
Right calcarine S.	39.1 (16.2)	88.4 (9.4)	0.0006[c]

A. Regional differences: As the contrasts are T1–T2, positive values indicate tissue reduction and negative values indicate tissue increase from baseline. All observed group differences suggest more reduction in controls than patients; G. Gyrus S. Sulcus R. Right L. Left. SD - standard deviation. Only those regions with FDR-corrected p values in each hemisphere surviving a threshold of $p < 0.05$ are reported. Uncorrected p values <0.001***; <0.005** and < 0.01* are marked. B. Topological parameters: Numbers in brackets refer to standard deviations across the different densities at which comparison were made. FDA: Functional Data Analysis.
[a] FDR corrected $p = 0.022$.
[b] FDR corrected $p = 0.0185$.
[c] FDR corrected $p = 0.0185$ in FDA permutation analysis.

change that occurs after the illness onset in patients receiving antipsychotic treatment (Supplement Discussion).

The structural covariance of post-onset thickness changes in schizophrenia reveals a non-random, small world like pattern of interconnectedness among distributed brain regions, with a cardinal role for insula and occipital cortex. This pattern of progressive change differs from normal maturation, suggestive of an active, well-coordinated post-onset structural remodelling. Further clarification of the contributory vs. compensatory role played by these regions could provide us a more complete understanding of both neuroprogression and ameliorative reorganisation seen in subgroups of patients with schizophrenia.

Conflict of interest

LP received Travel Support from Magstim Limited (2014) and speaker fees from Otsuka Canada (2017) and Canadian Psychiatric Association (2018). LP also received investigator initiated educational grants from Otsuka Canada and Janssen Canada (2017, 2018). In the last 3 years, LP has received income from the SPMM Course (UK) and held shares of Shire Inc. and Glaxo Smith Kline in his/his spousal pension funds. Other authors report no conflicts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.01.041.

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