Research Paper

# Psychotic symptoms are associated with lower cortical folding in youth at risk for mental illness

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**Background:** Cortical folding is essential for healthy brain development. Previous studies have found regional reductions in cortical folding in adult patients with psychotic illness. It is unknown whether these neuroanatomical markers are present in youth with subclinical psychotic symptoms. **Methods:** We collected MRIs and examined the local gyrification index in a sample of 110 youth (mean age ± standard deviation 14.0 ± 3.7 yr; range 9–25 yr) with a family history of severe mental illness: 48 with psychotic symptoms and 62 without. Images were processed using the Human Connectome Pipeline and FreeSurfer. We tested for group differences in local gyrification index using mixed-effects generalized linear models controlling for age, sex and familial clustering. Sensitivity analysis further controlled for intracranial volume, IQ, and stimulant and cannabis use. **Results:** Youth with psychotic symptoms displayed an overall trend toward lower cortical folding across all brain regions. After adjusting for multiple comparisons and confounders, regional reductions were localized to the frontal and occipital lobes. Specifically, the medial ($B = –0.42$, $p_{FDR} = 0.04$) and lateral ($B = –0.39$, $p_{FDR} = 0.04$) orbitofrontal cortices as well as the cuneus ($B = –0.47$, $p_{FDR} = 0.03$) and the pericalcarine ($B = –0.45$, $p_{FDR} = 0.03$) and lingual ($B = –0.38$, $p_{FDR} = 0.04$) gyri. **Limitations:** Inference about developmental trajectories was limited by the cross-sectional data. **Conclusion:** Psychotic symptoms in youth are associated with cortical folding deficits, even in the absence of psychotic illness. The current study helps clarify the neurodevelopmental basis of psychosis at an early stage, before medication, drug use and other confounds have had a persistent effect on the brain.

## Introduction

Psychosis is marked by hallucinations, delusions and disturbances of affect and behaviour. It manifests in major depressive disorder, bipolar disorder and most notably, schizophrenia. Although psychotic disorders are a leading cause of morbidity and disability worldwide,[1] their etiology remains unclear.[2] Multiple lines of evidence are converging to suggest that the disease stems from processes that affect neurodevelopment.[3] The neurodevelopmental hypothesis posits that genetic and environmental risk factors perturb early brain development, leading to symptoms later in life as the brain matures and copes with new stressors.[4] One process necessary for healthy brain development is cortical folding, which may be abnormal in the pathogenesis of schizophrenia.[5]

The process of cortical folding, or gyrification, results in gyri and sulci that give the cortex its wrinkly appearance. The degree of cortical folding can be quantified using the local gyrification index (LGI).[6] The LGI is a ratio of the total cortical surface to the superficially exposed outer surface tightly wrapping the cortex without entering the sulci. Cortical folding is a uniquely mammalian solution to increasing cortical grey matter without exaggerating head size. This process is also key to the optimization of axonal wiring and the functional organization of the brain.[7] The mechanisms of cortical folding are under active investigation. Recent perspectives suggest that tightly coordinated molecular genetic processes[8] and biomechanical forces[9] are involved. Radial expansion of progenitor cells might be particularly significant (see Fernández and colleagues[10] for a review). Importantly, cortical folding provides a window on early development.[11] The major folding patterns are determined largely before birth and finish undergoing the most rapid morphological changes by childhood.[12] This sensitive period of neurodevelopment overlaps with the timing of the most prominent environmental risk factors associated with psychosis.[13]

Large multisite neuroimaging studies have found reductions in cortical folding among adults with psychotic disorders.[14,15] Aberrant gyrification has also been reported in people at genetic risk for schizophrenia.[14,16] By extension, recent work

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has shown that scores indexing genetic liability to schizophrenia are associated with regional reductions in the LGI.[17] The prefrontal cortex has long been implicated in schizophrenia.[18] Early work that measured cortical folding with manual tracing of MRI slices has shown lower frontal cortical folding in patients with schizophrenia.[19] Correspondingly, recent work using automated 3D methods to quantify LGI have shown similar reductions in prefrontal cortical folding.[20]

The reported prefrontal LGI abnormalities are consistent with neuropathological findings from other imaging modalities and postmortem data.[21,22] Abnormal gyrification also predicts poor treatment response in first-episode psychosis[23] and has been used to distinguish patients with more severe illness from those with milder forms.[24] Taken together, the body of literature suggests cortical folding alterations across the psychosis spectrum. However, whether or not these alterations are present before illness onset has been more difficult to establish.

Adolescence has been described as a critical period of vulnerability for schizophrenia.[4] However, the majority of clinical high-risk studies have focused on adulthood.[25] As such, the etiology of psychosis can be clarified by examining cortical folding earlier, before the onset of a functionally impairing illness. In the current study, we addressed this gap by examining the LGI in adolescents from a cohort with enriched familial risk who had experienced psychotic symptoms but did not meet the criteria for psychotic illness. We hypothesized that psychotic symptoms would be related to lower cortical folding in symptomatic youth, particularly in the prefrontal cortex.

## Methods

### *Participants*

As part of the ongoing Families Overcoming Risks and Building Opportunities for Well-being (FORBOW) study, we collected MRI scans from 110 participants aged 9–25 years. The FORBOW study is a longitudinal study enriched for the offspring of parents with mental illness.[26] Those at familial risk for mental illness and participants from control families were invited to complete the MRI study. The study protocol was approved by the research ethics board of the Nova Scotia Health Authority. Participants provided written informed consent. For children who did not have the capacity to make a fully informed decision, a parent or guardian provided written informed consent and the child provided assent. Exclusion criteria were a personal history of psychotic illness, any serious medical or neurologic disorder, substance abuse or dependence during the previous 6 months, or MRI contraindications.

### *Participant clinical and cognitive assessment*

**Parent assessment**

We used the Schedule for Affective Disorders and Schizophrenia (SADS-IV)[27] and the Structured Clinical Interview for DSM-5 (SCID-5)[28] to establish diagnoses of mental disorders and psychosis according to DSM-IV and DSM-5. Diagnoses were confirmed in consensus meetings with a psychiatrist blind to offspring psychopathology.

**Offspring assessment**

Participating youth were interviewed using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL).[29] Offspring assessors were blinded to parent psychopathology. Full-scale intelligence quotient (FSIQ) was assessed using the Wechsler Abbreviated Scale of Intelligence, second edition.[30] Psychotic symptoms were assessed using the following instruments: the K-SADS-PL interview psychosis module and appendix, consensus-rated by child and adolescent psychiatrists blind to parent psychopathology; in participants aged 3–12 years, the Structured Interview for Prodromal Syndromes (SIPS),[31] measuring attenuated psychotic symptoms; the "Funny Feelings" interview[32–34] (we included only youth with symptoms rated as "definite psychotic symptom" by consensus between 2 independent raters); the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY)[35] for those aged 8 years and older, to assess abnormal experiences in the domains of perception, cognition, language and affect that strongly predict the development of psychosis.[36,37]

Consistent with our previous reports,[38,39] we created a dichotomous variable for the presence of psychotic symptoms captured by any one of the following: confirmed hallucinations or delusions on K-SADS-PL, positive symptoms on SIPS rated ≥ 3, definite psychotic symptoms confirmed through independent curation, and high-risk basic symptom profiles of cognitive/perceptive disturbances on the SPI-CY.

### *MRI acquisition*

Images were acquired with a 3 T General Electric Discovery MR750 scanner equipped with a 32-channel MR Instruments radiofrequency head coil. Scanning took place at the Biomedical Translational Imaging Centre (BIOTIC) in Halifax, Nova Scotia, Canada. Each participant was positioned supine in the MRI scanner, with their head supported by foam padding to reduce movement. Ear plugs were provided to minimize scanner noise. We collected a 3D $T_1$-weighted brain volume imaging (BRAVO) sequence with whole-brain coverage; 1 mm$^3$ isotropic resolution; matrix 224 × 224; field of view 224 mm; 168 sagittal slices at 1 mm thickness; repetition time 5.9 ms; echo time 2.2 ms; inversion time 450 ms; flip angle 12°; receiver bandwidth ± 62.5; number of excitations = 2; autocalibrating reconstruction for cartesian imaging (ARC) phase acceleration = 2; ARC slice acceleration = 1; no phase wrap; scan duration 5 minutes, 42 seconds.

### *MRI analysis*

Data were preprocessed using the open-source Human Connectome Pipeline.[40] As part of the validated pipeline, we reconstructed the $T_1$-weighted scan surface using FreeSurfer version 5.3.[41] An automated labelling system subdivided the cerebral cortex into gyral-based parcellations corresponding to the Desikan–Killiany atlas.[42]

**Local gyrification index**

We quantified the 3D LGI from FreeSurfer output, as the ratio of the total cortical surface area (including cortex buried in sulci) to the outer cortex surface area, which tightly wraps the brain but does not enter the sulci. Thus, a higher LGI represents more cortical folding in each brain parcel, and a lower LGI represents less cortical folding. Details of the automated LGI computation can be found in the validation paper[6] and on the FreeSurfer website (https://surfer.nmr.mgh.harvard.edu/fswiki/LGI).

### *Statistical analysis*

We performed statistical analyses in R Studio (version 3.5.0).[43] We compared demographic and clinical variables using *t* tests for continuous variables and $\chi^2$ tests for categorical variables. The LGI for each of the 34 cortical parcellations across both hemispheres served as the primary dependent variable. The primary independent variable was the presence or absence of psychotic symptoms.

We tested the relationship between lifetime psychotic symptoms and LGI using mixed-effect generalized linear models. We accounted for the non-independence of brain data from related individuals by including the family identifier as a random effect. We included age and sex as covariates in the model. We controlled for multiple comparisons across brain parcellations using false discovery rate (FDR).[44] We reported effect sizes using standardized regression estimates (*B*) and their 95% confidence intervals (CIs).

To ensure that the observed relationship between cortical folding and psychotic symptoms was not due to the use of psychoactive substances or other factors linked to changes in brain structure, we conducted sensitivity analyses. In the brain regions found to be significant after correcting for multiple testing, we further covaried for lifetime cannabis use, lifetime stimulant use, FSIQ and estimated total intracranial volume (eTIV).

## Results

### *Demographic variables*

Of the 110 youth scanned, 48 (43.64%) met the criteria for a definite psychotic symptom on 1 or more assessments. Table 1 summarizes demographic and clinical characteristics by symptom status. General cognitive ability did not differ between participants with or without psychotic symptoms ($t$ = 0.67, $p$ = 0.51). We found a statistically significant difference in eTIV ($t$ = −3.15, $p$ = 0.002): youth with psychotic symptoms showed smaller eTIV (mean 1427.8 ± 168.0 cm$^3$) than youth without symptoms (1522.2 ± 138.6 cm$^3$).

### *Overall differences in cortical folding across brain regions*

We examined overall differences in cortical folding averaged across all brain regions. In a model controlling for sex, age and familial clustering, average whole-brain cortical folding was lower in youth with psychotic symptoms ($B$ = −0.13, 95% CI −0.21 to −0.05, $p$ = 0.001). This effect was no longer statistically significant following covariance for eTIV ($B$ = −0.05, 95% CI −0.13 to 0.03, $p$ = 0.22). Figure 1 shows the mean differences in folding across all structures.

### *Prefrontal cortical folding*

We used the same model to explore regional differences in cortical folding. In line with our hypothesis, the exploratory analysis revealed lower prefrontal cortical folding in youth with psychotic symptoms (Fig. 2). Specifically, the mixed-effect generalized linear models controlling for sex, age and familial clustering localized the lower cortical folding to the medial ($B$ = −0.42, 95% CI −0.71 to −0.12, $p$ = 0.006, $p_{FDR}$ = 0.04) and lateral ($B$ = −0.39, 95% CI −0.66 to −0.12, $p$ = 0.005, $p_{FDR}$ = 0.04) aspects of the orbitofrontal cortex (OFC).

**Table 1: Demographic and clinical characteristics of the study sample ($n$ = 110)***

| Characteristic | No psychotic symptoms | Psychotic symptoms | *p* value |
|---|---|---|---|
| Participants, no. | 62 | 48 | — |
| Female sex, no. (%) | 31 (50.0) | 33 (68.8) | 0.08 |
| Mean age ± SD, yr | 13.7 ± 3.4 | 14.5 ± 4.1 | 0.28 |
| Siblings, no. (%) | 11 (17.8) | 12 (25.0) | 0.49 |
| Anxiety disorder, no. (%) | 21 (33.9) | 25 (52.1) | 0.09 |
| Parent diagnosis, no. (%) | | | 0.12 |
| None | 18 (29.0) | 6 (12.5) | — |
| Depression | 23 (37.1) | 27 (56.3) | — |
| Bipolar disorder | 17 (27.4) | 13 (27.1) | — |
| Schizophrenia | 4 (6.5) | 2 (4.2) | — |
| Parent psychosis, no. (%) | 11 (17.8) | 9 (18.8) | 1.00 |
| Cannabis use, no. (%) | 7 (11.3) | 6 (12.5) | 1.00 |
| Stimulant use, no. (%) | 2 (3.2) | 6 (12.5) | 0.08 |
| Mean FSIQ score ± SD | 106.2 ± 14.3 | 107.9 ± 11.3 | 0.51 |
| Mean eTIV ± SD, cm$^3$ | 1522.2 ± 138.6 | 1427.8 ± 168.0 | 0.002 |

eTIV = estimated total intracranial volume; FSIQ = Full Scale Intelligence Quotient; SD = standard deviation.
*We compared demographic and clinical variables using *t* tests for continuous variables and $\chi^2$ tests for categorical variables.

In sensitivity analyses of this finding, youth with psychotic symptoms robustly showed lower OFC folding in models controlling for cannabis use, stimulant use, FSIQ and eTIV, both medially ($B$ = −0.34, 95% CI −0.63 to −0.04, $p$ = 0.025) and laterally ($B$ = −0.28, 95% CI −0.54 to −0.01, $p$ = 0.042).

### *Occipital lobe cortical folding*

Along with the OFC findings, the exploratory analysis revealed 3 additional regions that survived brain-wide correction for multiple comparisons in models controlling for age,

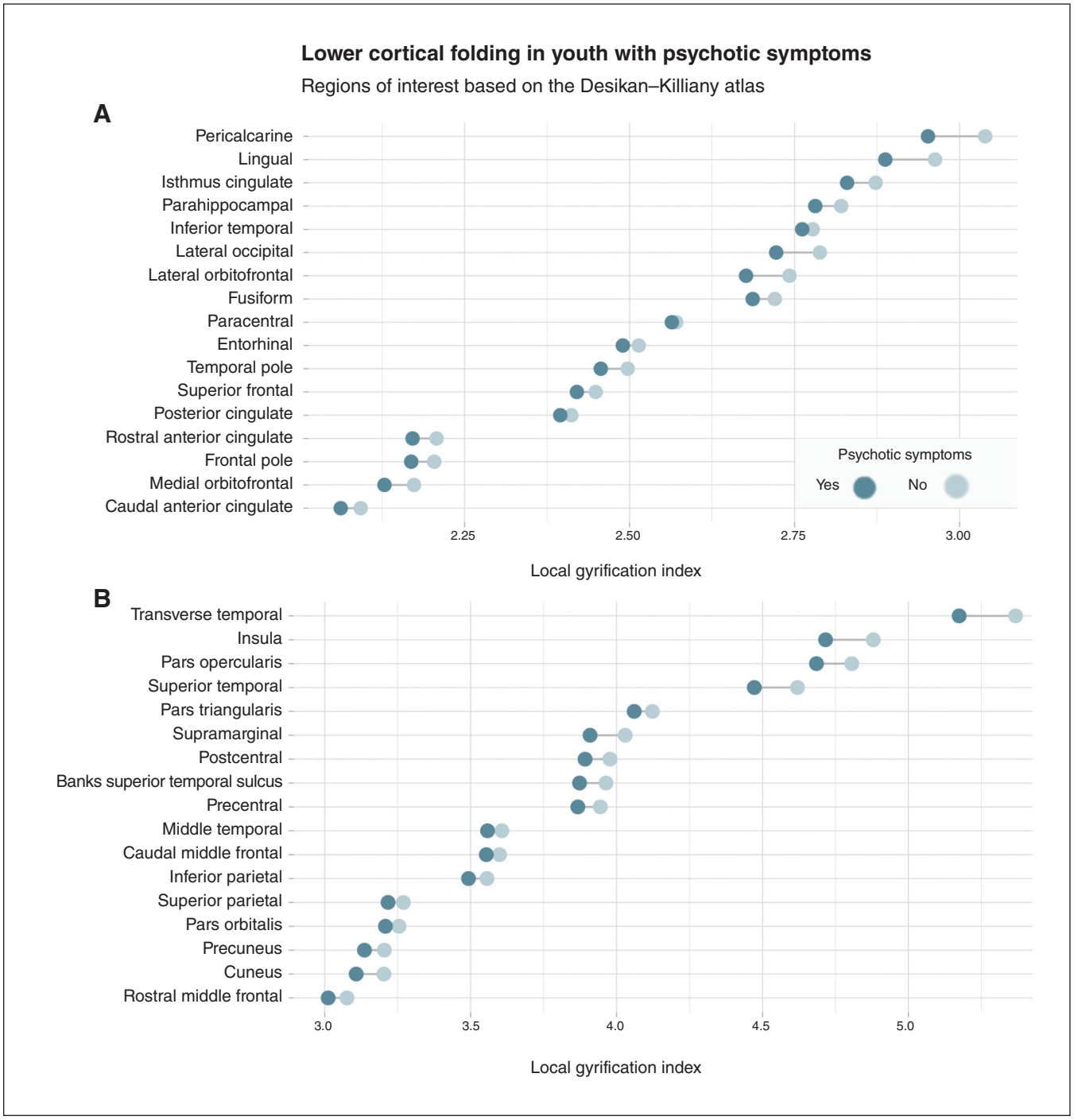


**Fig. 1:** Differences in mean cortical folding across the anatomical boundaries of the Desikan–Killiany atlas. Dark blue dots represent youth with psychotic symptoms ($n$ = 48), light blue dots represent those without ($n$ = 62). We found an overall trend toward lower cortical folding in youth with psychotic symptoms. (A) Regions of interest with mean local gyrification index < 3.0. (B) Regions of interest with mean local gyrification index > 3.0.

sex and familial clustering (Fig. 3). Psychotic symptoms were associated with lower regional gyrification in the occipital lobe—specifically the cuneus ($B$ = −0.47, 95% CI −0.75 to −0.19, $p$ = 0.001, $p_{FDR}$ = 0.03), the pericalcarine gyrus ($B$ = −0.45, 95% CI −0.73 to −0.17, $p$ = 0.002, $p_{FDR}$ = 0.03) and the lingual gyrus ($B$ = −0.38, 95% CI −0.66 to −0.11, $p$ = 0.006, $p_{FDR}$ = 0.04). We saw the same pattern of results when examining symptoms from a dimensional perspective (Appendix 1, available at jpn.ca/180144-a1).

We conducted sensitivity analyses to determine if the differences in cuneus, pericalcarine and lingual cortical folding might be attributable to extraneous variables rather than to symptom status. Again, we implemented models identical to the exploratory analysis while simultaneously covarying for cannabis use, stimulant use, FSIQ and eTIV. As with the prefrontal results, the link between psychotic symptoms and occipital folding remained significant for the cuneus ($B$ = −0.46, 95% CI −0.74 to −0.18, $p$ = 0.001) and the pericalcarine ($B$ = −0.40, 95% CI −0.69 to −0.11, $p$ = 0.007) and lingual ($B$ = −0.35, 95% CI −0.63 to −0.07, $p$ = 0.015) gyri.

## Discussion

We sought to determine whether youth with psychotic symptoms displayed cortical aberrations before the onset of impairing psychotic illness. To answer that question, we examined 3D reconstructions of cortical folding, an early neurodevelopmental marker of cortical expansion. We found a pattern of lower cortical folding in adolescents who had psychotic symptoms but who did not meet the criteria for a psychotic disorder.

### *Lower cortical folding*

In our study, psychotic symptoms were related to lower cortical folding across all brain regions, with statistically significant regional effects. This unidirectional pattern is supported by the literature on brain structure among adult patients with schizophrenia-spectrum disorders. Nesvåg and colleagues[15] examined cortical folding among 207 patients with schizophrenia and 206 controls. They found that patients had a lower LGI in large clusters of the cerebral cortex, leading them to conclude that reduced gyrification is a feature of the brain pathology in schizophrenia. Similar to our work, no regions had significantly higher LGI among patients. Nanda and colleagues[14] examined the LGI in 388 patients with psychotic disorders and 243 controls. Their multicentre study found that patients with psychotic disorders had a significantly lower LGI than controls. Importantly, the directionality of the finding was consistent with our findings, in that no regions were less folded among controls.

### *Differences in prefrontal cortex folding*

Lower prefrontal cortical folding was localized to the medial and lateral OFC. Our finding was in line with previous work implicating abnormalities in the OFC cortical folding pattern in psychosis,[23,45] first-episode schizophrenia[46] and chronic

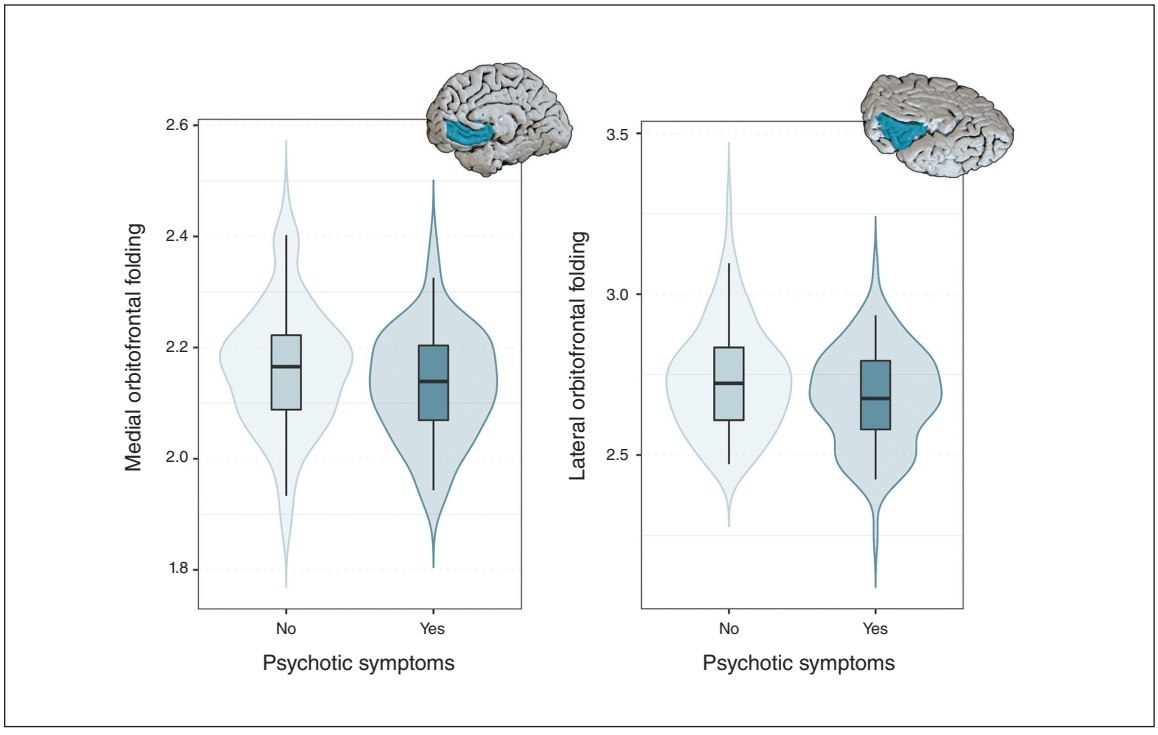


**Fig. 2:** Lower prefrontal cortical folding in youth with psychotic symptoms ($n$ = 48) versus those without ($n$ = 62). Symptomatic youth in darker blue. Violin plots present cortical folding distributions by symptom status. Box plots nested within display median differences.

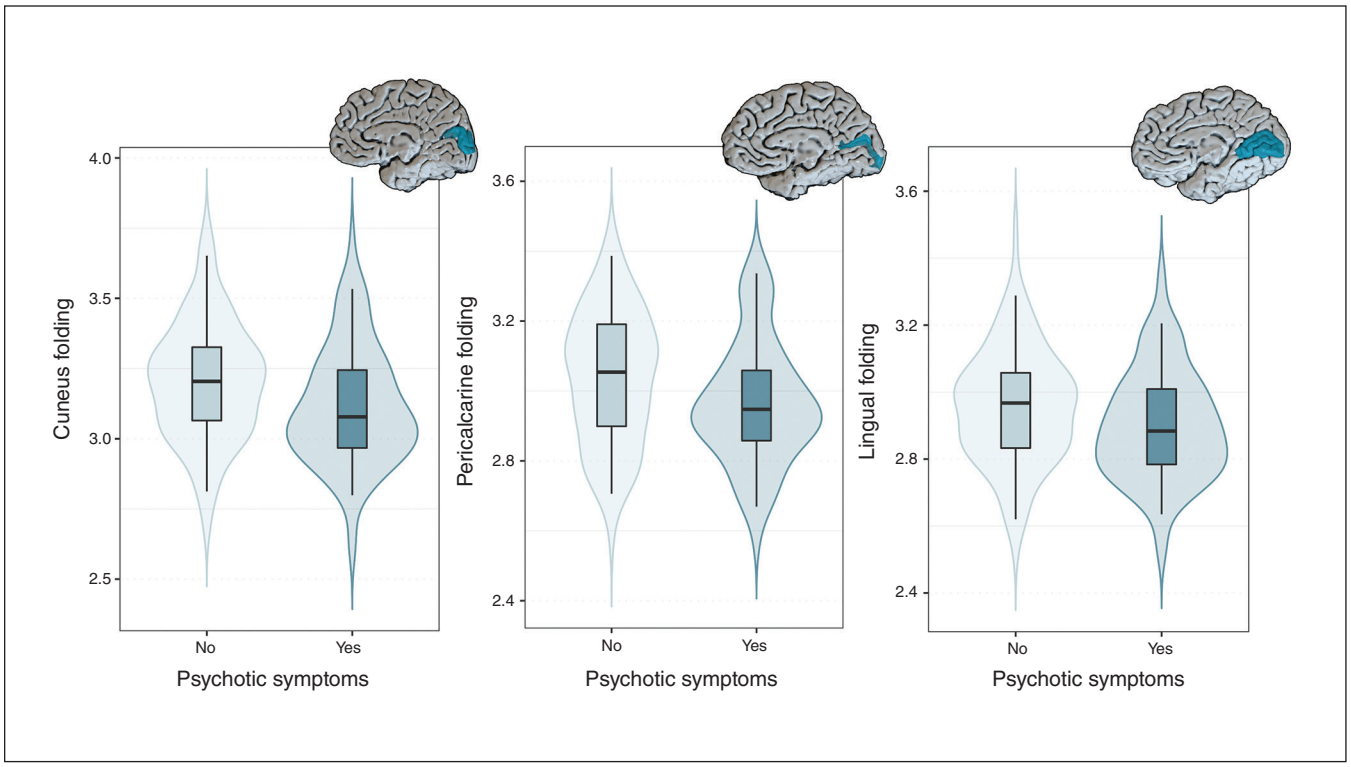


**Fig. 3:** Lower occipital cortical folding in youth with psychotic symptoms ($n$ = 48) versus those without ($n$ = 62). Symptomatic youth in darker blue. Violin plots present cortical folding distributions by symptom status. Box plots nested within display median differences.

schizophrenia.[47] In our adolescent sample, this difference was unlikely to be attributable to common confounders in psychosis research, such as illness burden or the effects of medication. The localization to the OFC in our study was consistent with prospective studies in patients at clinical high risk and in animal models. Patients at clinical high risk who convert to psychosis show steeper rates of cortical thickness decline and grey matter reduction in the OFC than non-converters at clinical high risk and controls.[48,49] Furthermore, OFC neurons have been shown to be common targets for both typical and atypical antipsychotic drugs.[50]

Characteristics of schizophrenia include aberrant perception and cognitive deficits. The OFC is involved in a number of disorder-related functions, such as sensory integration, learning, and social and emotional decision-making.[51,52] Our previous work examining cognition showed that youth with psychotic symptoms exhibited deficits in executive functioning.[39] We specifically found impaired emotional decision-making, even after controlling for general cognitive ability. The combination of a reduction in OFC folding and impaired decision-making may be a neurocognitive marker of a propensity for psychotic symptoms.

### *Differences in occipital cortex folding*

We found lower cortical folding in the cuneus and the pericalcarine and lingual gyri. The cuneus is located between the calcarine and parieto-occipital sulci. The pericalcarine gyrus can be visualized between the cuneus and lingual gyrus on a midline view of the brain. The lingual gyrus sits within the tentorial surface of the occipital lobe, inferior to the calcarine sulcus.

Studies of cortical folding and functional connectivity in psychosis have found reduced cortical folding in the lingual cortex of patients with psychosis compared with healthy controls.[23,53] They also showed that the aberrant functional connectivity of the visual processing regions was a better predictor of symptom persistence and burden than diagnostic information. Our current work and aforementioned findings also correspond to studies examining volumetric data. Compared to healthy controls, patients with first-episode schizophrenia demonstrated significantly reduced grey matter volumes in the lingual gyrus.[54] Significant cortical thinning has also been noted in this region in patients diagnosed with schizophrenia compared to matched controls.[55,56] Finally, 22q11 deletion syndrome and genetic risk for schizophrenia based on common genetic variation have been associated with volumetric grey matter differences in the lingual gyrus and cuneus, as well as cortical thinning in the cuneus and pericalcarine and lingual gyri.[57,58]

A recent paper examined LGI in medicated young adults who met the criteria for an at-risk mental state.[59] In contrast to our findings of decreased LGI, those in an at-risk mental state showed widespread increases in LGI. Interestingly, increased gyrification in the cuneus, pericalcarine

and lingual regions was related to risk for transition to a psychotic disorder. This work underscores the relevance of occipital cortical folding in the risk for psychosis, but the discrepancy in the directionality of findings indicates the need for further longitudinal study of the developmental transition period from adolescence to young adulthood in high-risk populations.

*Limitations*

This study had several limitations. The onset of schizophrenia and other psychotic disorders typically occurs in late adolescence or early adulthood. In our developmental sample, the age range overlapped with this period. In other words, our sample included participants younger than the age with the highest risk of onset, and participants passing through this stage. Future studies can reduce this heterogeneity, particularly in cohorts examining brain development at fixed age ranges. Furthermore, the cross-sectional nature of this work limited our ability to track prospective developmental changes in regions with reduced folding. To address some of these challenges, we propose the collection of longitudinal imaging follow-up data.

We were able to minimize confounds of illness burden, comorbidities and medication use by studying youth. Nevertheless, a proportion of the sample had been exposed to marijuana and psychoactive medication, both of which could have an effect on the developing brain.[60,61] Sensitivity analyses suggested that these substances did not affect the association between reduced cortical folding and psychotic symptoms. Cannabis use remains an important covariate to control for, because adolescent initiation of cannabis use has been linked to early-onset psychosis,[62] and legalization of the substance may affect initiation or usage.

We found a significant difference in total intracranial volume in our sample. Youth with psychotic symptoms had lower eTIV. Although this finding was not part of our hypothesis, there is meta-analytic evidence for reduced intracranial and total brain volume in schizophrenia.[63] Because certain structures scale with intracranial volume,[64] we controlled for eTIV as a covariate. This correction eliminated the overall average difference in cortical folding across the brain, but the regional differences in frontal and occipital cortical folding remained robust to this correction. Future work is needed to contextualize the clinical relevance of eTIV differences in samples of risk-enriched youth.

Finally, we examined a single neurodevelopmental marker, but we know that cortical folding is related to optimization of axonal wiring and functional organization in the brain.[7] Future research should integrate additional imaging data, such as probabilistic tractography, intracortical myelination and resting-state functional connectivity. For example, one multi-analysis study showed that decreased frontal gyrification in adolescent schizophrenia may be associated with widening of the frontal sulci and reductions in cortical surface area.[65] Multimodal extension and synthesis with molecular genetic and neurocognitive data will bring new insights into the significance of our findings.

## Conclusion

This study found regional reductions in cortical folding of adolescents who had experienced psychotic symptoms. The young age of the cohort helped to clarify the neurodevelopmental basis of psychosis at an early stage, before medication, drug use and illness burden could take a persistent toll on the brain. Our findings also suggest that measurement of cortical folding may play a role in the early detection of people at risk for psychotic illness.

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**Competing interests:** None declared.

**Contributors:** V. Drobinin, M. Schmidt, M. Alda, C. Bowen and R. Uher designed the study. V. Drobinin, H. van Gestel, A. Zwicker, L. MacKenzie, J. Cumby, V. Patterson, E. Howes Vallis, N. Campbell, T. Hajek, C. Helmick and R. Uher acquired the data, which V. Drobinin and R. Uher analyzed. V. Drobinin wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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