Cortical Morphometry in the Psychosis Risk Period: A Comprehensive Perspective of Surface Features

Katherine S.F. Damme, Tina Gupta, Robin Nusslock, Jessica A. Bernard, Joseph M. Orr, and Vijay A. Mittal

ABSTRACT

BACKGROUND: Gyriﬁcation features reﬂect brain development in the early prenatal environment. Clarifying the nature of these features in psychosis can help shed light on the role of early developmental insult. However, the literature is currently widely discrepant, which may reﬂect confounds related to formally psychotic patient populations or overreliance on a single feature of cortical surface morphometry (CSM).

METHODS: This study compares CSM features of gyriﬁcation in clinical high-risk (n = 43) youths during the prodromal risk period to typically developing control subjects over two time points across three metrics: local gyriﬁcation index, mean curvature index, and sulcal depth (improving resolution and examination of change over 1 year).

RESULTS: Gyriﬁcation was stable over time, supporting the idea that gyriﬁcation reﬂects early insult rather than abnormal development or reorganization associated with the disease state. Each of the indices highlighted unique, aberrant features in the clinical high-risk group with respect to control subjects. Speciﬁcally, the local gyriﬁcation index reﬂected hypogyriﬁcation in the lateral orbitofrontal cortex, superior bank of the superior temporal sulcus, anterior isthmus of the cingulate gyrus, and temporal poles; the mean curvature index indicated sharper gyral and ﬂatter or wider sulcal peaks in the cingulate, postcentral, and lingual gyrus; sulcal depth identiﬁed shallow features in the parietal, superior temporal sulcus, and cingulate regions. Further, both the mean curvature index and sulcal depth converged on abnormal features in the parietal cortex.

CONCLUSIONS: Gyriﬁcation metrics suggest early developmental insult and provide support for neuro-developmental hypotheses. Observations of stable CSM features across time provide context for interpreting extant studies and speak to CSM as a promising stable marker and/or endophenotype. Collectively, ﬁndings support the importance of considering multiple CSM features.

Keywords: Cortical surface, Curvature index, Gyriﬁcation, Morphometry, Prodrome, Psychosis, Schizophrenia, Sulcal depth

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Cortical surface morphometry (CSM) may provide critical insight into the timing of developmental insults or pathogenic factors that contribute to psychotic disorders (1,2). Indeed, gyriﬁcation (a CSM feature parametrized by local gyriﬁcation index [lGI], mean curvature index [MCI], and sulcal depth) may reﬂect abnormal connectivity in utero and in early development, as cortical folding reﬂects late second– and third-trimester integrity of corticocortical and subcortical connectivity (1,2). Gyriﬁcation measured in late adolescence and early adulthood may be relatively unaltered by adolescent neumaturational processes that drive instability in other cortical features (3). This relative stability suggests that gyriﬁcation metrics may provide unique insight into the contribution of early development to risk for psychosis (2,3).

Unfortunately, little is known about the contributions of early brain development to psychosis because clinical markers of psychosis often appear in late adolescence to early adulthood, when neumaturational processes have already obscured early development (3). Indirect evidence suggests a link between early brain development and increased rates of psychosis from prenatal famine and/or mainnutrition (4,5), ﬂu exposure (6,7), and deletions of genes related to early brain development (i.e., 22q11 deletion) (8,9). Furthermore, other established markers of early prenatal development (e.g., dermatoglyphics) relate to psychosis (10,11) but do not provide a direct metric of brain development. Gyriﬁcation may provide a more direct metric of early brain development and added insight into abnormal neumaturational processes in psychosis.
With regard to schizophrenia, the CSM literature is inconsistent (12–14). These inconsistencies may be due in part to variations in methodological approaches and confounds associated with schizophrenia (e.g., substance dependence and medications) (15–17). As a result, it is unknown whether gyrification abnormalities reflect early insult alone and remain unchanged during the prodromal period. Alternatively, gyrification may be subject to later neurodegenerative or putative risk factors such as medication or substance abuse. If stable, gyrification would provide an early marker of prenatal insult that persists across pubertal neuromaturation. Additionally, gyrification metrics may confer additional sensitivity to detecting risk for psychosis, thus adding insight from prenatal development that complements structural metrics of prodromal neural reorganization (e.g., cortical thickness) (18–20).

Evaluating clinical high-risk (CHR) populations (i.e., youths exhibiting prodromal syndromes indicating imminent risk for psychotic disorders prior to psychosis onset) can provide predictive biomarkers as well as insight into pathogenic processes. While this group does exhibit some of the same types of confounds as seen in patients with schizophrenia overall, individuals in this period tend to show fewer factors that convolute results than do populations with chronic psychosis (e.g., medication rates and doses are often lower). With respect to CSM, the few studies that focus on CHR populations do indicate surface abnormalities in these individuals (15–16,21–22). Nevertheless, there is no comprehensive understanding of CSM in CHR individuals, as these investigations rely on a single CSM metric at a single time point (see the Supplement for a review and comparison of metrics). Examining multiple time points of CSM features may establish whether gyrification reflects a preexisting early insult or pathogenic processes during the CHR period. This approach may provide insight into these features in schizophrenia and spectrum populations; specifically, this will help to determine if CSM features are sensitive to neurodegenerative processes or putative environmental factors (see Table 1; see the Supplement for review of relevant literature).

The current study evaluates three metrics of gyrification: /GI, MCI, and sulcal depth. The /GI is the ratio of an outer surface contour to buried cortical surface that employs advanced computation in three dimensions of gyrification rather than relying on a single orientation, such as gyrification index (23,24). While the /GI provides invaluable information, it references an individualized contour; taking this approach in isolation may obscure the exact nature of the specific gyral morphometry. A solution to this issue may lie in incorporating additional measures such as MCI. MCI quantifies each vertex in terms of the radius of osculating circles from the peak of each gyrus (25). This CSM metric provides further sensitivity to changes on a smaller scale and information about the shape of a given arc (i.e., higher MCI implies a sharper curve, while lower numbers represent a wider arc) (26). Finally, sulcal depth provides unique and complementary estimates of linear distance from a reference midpoint surface (i.e., the global midpoint between the gyri and sulci) (27). Thus, incorporating three metrics provides a more comprehensive and nuanced perspective, which includes an inner-to-outside surface ratio, a curve reference, and linear height and/or depth.

By incorporating data across two scan sessions and combining complementary indices (/GI, MCI, and sulcal depth) in a single population, we provide a more comprehensive account of CSM differences (see the Supplement for a review of metrics) in CHR individuals. In addition, this study benefits from incorporating data from two scan sessions, an approach that improves the likelihood of accounting for additional variance and noise (e.g., the variance in gyrification related to scan slice angle in image acquisition) (17,24) and stability of CSM variables. Further, examining CSM features over time allows for a novel perspective that clarifies if CSM features reflect a stable vulnerability trait or something that shifts as a function of pathogenic processes in the CHR period.

In the present investigation, 81 participants (43 CHR and 38 healthy control [HC] participants) completed clinical interviews, a structural scan at a baseline, and then a second scan 12 months later. We evaluated gyrification features from large-scale folding ratios (/GI), shape of the curve (MCI), and the height and/or depth of gyri and sulci (sulcal depth) in both groups (Supplement). We predicted that these CSM features develop in utero and are relatively insensitive to developmental and environmental factors. Past findings suggested both hyper- and hypogyrification in schizophrenia (12,14,28). Similarly, gyrification index, folding index, and /GI studies in CHR youths indicate widespread aberrant

| Table 1. Review of Psychosis Literature on Gyrification Cortical Surface Morphometry |
|----------------------------------------|--------|----------------|----------------|----------------|
| Author et al., 2004 (15)               | 128    | GHR            | Gyrification index | Related to conversion |
| Harris et al., 2007 (30)               | 34     | FEP            | Gyrification index | Abnormal at first episode of psychosis |
| Külynych et al., 1997 (12)             | 9      | SZ             | Gyrification index | Frontal hypergyrification |
| Sasabayashi et al., 2017 (31)          | 104    | CHR            | /GI              | Related to conversion |
| Sasabayashi et al., 2017 (32)          | 62     | FEP            | /GI              | Abnormal at first episode of psychosis |
| Bakker et al., 2016 (37)               | 36     | CHR n = 18; 22q11 deletion n = 18 | /GI | Related to the 22q11 deletion |
| Mihailov et al., 2017 (57)             | 71     | 22q11 deletion | /GI              | Related to the 22q11 deletion |
| deWit et al., 2017 (54)                | 24     | CHR            | /GI              | Related to clinical severity at follow-up |
| Palaniyappan et al., 2011 (14)         | 57     | SZ             | /GI              | Frontal hypogyrification |
| Takahashi et al., 2013 (22)            | 64     | FEP            | Sulcal depth     | Related to deficits in executive function |
| Caermansky et al., 2008 (42)           | 33     | SZ             | Sulcal depth     | Asymmetric sulcal depth in temporal lobes |

CHR, clinical high-risk; FEP, first-episode psychosis; GHR, genetic high risk; /GI, local gyrification index; SZ, schizophrenia.
gyrification (15–16,21,29–32), with little convergence outside the frontal and temporal regions. From this literature, we predicted that CHR youths would show aberrant GI in frontal and temporal regions. There is no current guiding literature on curvature, and so we investigated curvature as an exploratory analyses. Based on limited evidence in the olfactory cortex indicating shallow sulcal depth in CHR youths (22), we predicted shallower peaks and depths for sulcal depth. Further, we predicted that there would be no difference in slope between time points, indicating the relative stability of gyri over time. Finally, we aimed to examine how the features relate to one another; any areas of overlap (where the CHR group shows abnormalities compared with HC group) were evaluated in both a quantitative and qualitative fashion.

**METHODS AND MATERIALS**

A total of 81 participants (CHR \( n = 43 \), HC \( n = 38 \)) were recruited through the Adolescent Development and Preventive Treatment program. CHR inclusion criteria were based on the presence of a prodromal syndrome (33) and not genetic risk. Demographic and positive symptom characteristics of the sample are described in Table 2 (see the Supplement for exclusion and recruitment criteria). The Structured Interview for Prodromal Syndromes (34) was used to diagnose CHR syndromes. Participants were also given the Word Reading subtest of the fourth edition of the Wide Range Achievement Test of the fourth edition of the Wide Range Achievement Test (35).

A 3T Siemens Tim Trio magnetic resonance imaging scanner (Siemens Corp., Munich, Germany) using a standard 12-channel head coil acquired two scans approximately 1 year apart. Structural images were collected on a T1-weighted three-dimensional magnetization prepared rapid gradient multiecho sequence (sagittal plane; repetition time [TR] 2530 ms; echo times [TE] 51.64 ms, 3.5 ms, 5.36 ms, 7.22 ms, and 9.08 ms; generalized autocalibrating partially parallel acquisitions (GRAPPA) parallel imaging factor of 2; 1-mm\(^3\) isotropic voxels, 192 interleaved slices; field of view 525 mm; flip angle 57°). The Query Design Estimate Contrast tool in the FreeSurfer 6.0 program generated the group contrasts in a general linear model, controlling for gender and medication status, and compared MCI and sulcal depth at each vertex. The GI was calculated using the general linear model tools (24). (For full data acquisition parameters and preprocessing see the Supplement).

The Query Design Estimate Contrast tool in the FreeSurfer program generated the group contrasts in a repeated-measure analysis of variance, controlling for gender and medication status, and compared MCI and sulcal depth at each vertex. To examine gyriication stability, an interclass correlation compared the CSM metrics for each time point for significant clusters to reduce the number of comparisons to the relevant vertices discussed below. These analyses treat FreeSurfer’s standardized algorithm as a single, stable rater of CSM metrics in a fixed-rater model of class correlation, which was used in the Psych package of R v.3.1.2 (36). While the Cronbach \( \alpha \) is typically reported, the Guttman \( \lambda \) has been reported here, as it better takes into account the variance of the data (36); see the Supplement for a full description.

**RESULTS**

**Group Comparison of the CSM Gyrification Metrics**

In whole-brain analyses, the CHR and HC groups differed in gyriication (false discovery rate–corrected \( p < .05 \) across both hemispheres and Bonferroni corrected for three metric comparisons). The analyses revealed six significant clusters where the GI differed by group after controlling for gender and anti-psychotic status (Figure 1, Table 3). In the left hemisphere, the CHR group showed a decreased GI, or reduction in the outer surface–inner surface ratio, signifying less gyriication, in the bank of the superior temporal sulcus and the temporal pole. In the right hemisphere, the CHR group showed a reduction in GI, or less gyriication, in the lateral orbitofrontal cortex, bank of the superior temporal sulcus, parahippocampal gyrus, and fusiform gyrus. Interestingly, no cluster demonstrated increased gyriication in the CHR group, suggesting hypogyriication in the CHR group compared with that of the HC group.

Whole-brain analyses revealed nine significant clusters where MCI differed by group (Figure 2, Table 4). For many

<table>
<thead>
<tr>
<th>Table 2. Demographic Characteristics</th>
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<tr>
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<tr>
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<tr>
<td>Gender, ( n )</td>
</tr>
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<td>Education, Years, Mean (SD)</td>
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<td>Parent Education, Years, Mean (SD)</td>
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<td>Symptom Domains, Mean (SD)*</td>
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<td>Positive baseline</td>
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<tr>
<td>Positive follow-up</td>
</tr>
<tr>
<td>Wide Range Achievement Test Score, Mean (SD)</td>
</tr>
</tbody>
</table>

CHR, youths exhibiting prodromal syndromes indicating imminent risk for psychotic disorders prior to psychosis onset.

*Positive symptoms reflect total sums from domains from the Structured Interview for Prodromal Syndromes.
regions on the left hemisphere, the CHR group demonstrated a decreased MCI, or sharper gyral curves, in the lingual gyrus, inferior parietal lobule, and postcentral gyrus. A single left-hemisphere cluster demonstrated opposing results, with the fusiform gyrus showing sharper gyri in the CHR group. In the right hemisphere, the CHR group showed a decreased MCI with decreased peak angles in the superior parietal lobule, isthmus of the cingulate gyrus, and superior parietal lobule. A single right-hemisphere cluster demonstrated opposing results in a sulcus of the superior parietal lobule, which showed sharper gyri in the CHR group.

In each hemisphere, the CHR and HC groups differed in sulcal depth. The analyses revealed nine significant clusters where sulcal depth differed by group after controlling for gender and antipsychotic status (Figure 3, Table 5). In the left hemisphere, the CHR group showed decreased sulcal depth, or gyral height from the cortical midpoint, in the postcentral gyrus, posterior cingulate, rostral middle frontal gyrus, and lingual gyrus. Again, there was a single cluster of increased sulcal depth on the fusiform gyrus. In the right hemisphere, the CHR group had decreased sulcal depth in gyral areas of the superior parietal lobule and anterior cingulate with a single cluster of increased sulcal depth in the CHR group in the superior parietal lobule.

Comparison of CSM Across Metrics and Time
To evaluate whether CSM clusters converge on vertices or identify unique vertices of surface morphometry, significant clusters were overlaid pairwise, generating two unique masks: a convergence map (containing vertices where metrics overlap on CSM abnormalities) and a uniqueness map (demonstrating the unique information provided by each metric) (Table 5, Figure 1).
Spatial convergence of significant voxels occurred between only two metrics, MCI (19.5% of vertices overlap in the left hemisphere, 28.72% of vertices overlap in the right hemisphere) and abnormal sulcal depth (34.61% of vertices overlap in the left hemisphere, 26.44% of vertices overlap in the right hemisphere). Qualitatively, while the ratio metric of GI demonstrated distinct gyriﬁcation in frontal and temporal regions, the geometric distance and shape metrics, MCI, and sulcal depth clusters were primarily in parietal, occipital, and cingulate regions, respectively (Supplemental Table S1).

### Table 3. Talairach Coordinates of Regions Showing Group Differences—Comparing Control Participants With Clinical High-Risk Participants—in Local Gyriﬁcation Index

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>p Value</th>
<th>Size, mm²</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>&gt;0.0001</td>
<td>3285.18</td>
<td>−34.9</td>
<td>−69.5</td>
<td>45.4</td>
<td>Bank of the superior temporal sulcus</td>
</tr>
<tr>
<td></td>
<td>&gt;0.001</td>
<td>351.98</td>
<td>−51.8</td>
<td>−0.2</td>
<td>−28.2</td>
<td>Temporal pole</td>
</tr>
<tr>
<td>Right</td>
<td>&gt;0.001</td>
<td>1833.49</td>
<td>42.3</td>
<td>26.5</td>
<td>−14.4</td>
<td>Lateral orbitofrontal cortex</td>
</tr>
<tr>
<td></td>
<td>&gt;0.001</td>
<td>1163.56</td>
<td>49.5</td>
<td>−57.8</td>
<td>32.1</td>
<td>Bank of the superior temporal sulcus</td>
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<tr>
<td></td>
<td>&gt;0.001</td>
<td>720.58</td>
<td>26.3</td>
<td>−42.1</td>
<td>−6.8</td>
<td>Parahippocampal gyrus</td>
</tr>
<tr>
<td></td>
<td>&gt;0.001</td>
<td>30.13</td>
<td>47.9</td>
<td>−66.7</td>
<td>14.3</td>
<td>Fusiform gyrus</td>
</tr>
</tbody>
</table>

**Figure 2.** Mean curvature index of clinical high-risk subjects compared with that of healthy control subjects. (A) The images show the right-hemisphere (top) and left-hemisphere (bottom) false discovery rate-corrected p < .05. Panel (B) highlights peak clusters (group statistical images shown in B1 and B2) to demonstrate how each feature varies between the clinical high-risk subjects (group average shown in blue [B4, bottom]) and the healthy control subjects (group average shown in gray [B3, top]). The group average images were overlaid to highlight the surface differences (B5, B6).
To use both time points as a converging data point, we tested the assumption that the gyrification is stable over time. These time points also provided us with a unique opportunity to confirm the stability of gyrification and assess whether these metrics changed during the prodromal period. Across all participants, the CSM metrics were significantly and highly stable over time (Supplement). These measures were also highly reliable: GI (λ = .92), MCI (λ = .86), and sulcal depth (λ = .93). In parallel analyses, the CHR group did not significantly vary in the stability of their CSM (Supplemental Table S2). Follow-up analyses compared peak clusters with symptoms (Supplement and Supplemental Table S3).

**DISCUSSION**

This study was highly innovative in examining a number of CSM characteristics over two time points (1 year apart) during the CHR period. This approach yielded several important findings. First, CSM characteristics appeared highly stable over time, which has relevance for informing conceptual models of psychosis. Next, we observed distinct abnormalities in CSM features across cingulate, parietal, orbitofrontal, and superior temporal regions. Further, we detected clusters of aberrant CSM matrices that converged on the parietal lobule. Taken together, this novel approach was effective in providing a comprehensive perspective that yielded new discoveries about CSM features. Specifically, each index highlighted unique aberrant features in the CHR group, which would have been missed if we had employed a single-variable approach. With GI, CHR participants exhibited hypogyrification in the lateral orbitofrontal cortex, superior bank of the superior temporal sulcus, anterior isthmus of the cingulate, and temporal poles. For curvature, the CHR youths had both sharper peaks on the gyri and flatter and/or wider sulcal peaks in the posterior isthmus of the cingulate, postcentral gyrus, and lingual gyrus. For sulcal depth, we observed shallower overall gyrification in the CHR youths, with distinct local parietal, parietal operculum, inferior bank of the superior temporal sulcus, and rostral cingulate regions.

In line with predictions, there was abnormal gyrification in the CHR group in the temporal and frontal lobes. The evaluation of GI identified entirely spatially unique clusters where groups differed. The distinct spatial and conceptual information (i.e., local ratios rather than linear or arc metric) provided by this metric highlights the importance integrating multiple metrics of CSM features. The CHR group demonstrated hypogyrification compared with the HC group, and this finding is consistent with reports from other studies of CHR participants. Bakker et al. (37) found a similar hypogyrification pattern that was predictive of later symptoms. Similarly, Hirjak et al. (38) found clinical features related to aberrant gyrification along the bank of the superior temporal sulcus, a region that was also identified in the current study. Finally, these findings are consistent with single–time–point analyses of CHR (31,32), first-episode psychosis (31,32), and schizophrenia (39), in which investigators found similar patterns of gyrification in the temporal, frontal, and parahippocampal regions when compared with those of control subjects.

Group comparisons of MCI, an understudied metric of gyrification, revealed distinct parietal geometry of gyrification related to the CHR group. This metric indicated many clusters in the parietal lobe, demonstrating steeper, sharper curves on the edge of gyri and wider curves within the sulci. While no previous studies of CHR individuals have investigated MCI, studies of schizophrenia do demonstrate a pattern of parietal sulcal curvature distinct from that of control subjects (40). Drawing instead from related work in connectivity (41) and other metrics of gyrification (31–32,39), investigators have found ample evidence relating superior temporal, orbitofrontal, cingulate, and parietal regions in psychosis in adolescence, but none of these findings have been taken directly from MCI. Here, we provided further support for the notion that MCI may be a useful metric of pathological early development, identifying distinct CHR cingulate curvature features not previously identified in the literature. Importantly, MCI was sensitive to the CSM features that would not have been identified by examining GI alone. While several MCI features converged with sulcal depth to identify surface features that distinguished CHR from HC groups, 76.4% of voxels identified by MCI were unique. This MCI-specific pattern highlighted again the importance of a comprehensive approach to analyzing CSM features. Furthermore, while common CSM-feature sites were identified, each metric provided unique conceptual information about these voxel sites. Specifically, MCI identified distinct shape features of curvature but provided no insight into the gray matter to white matter ratio or height or depth of gyri and sulci.
The sulcal depth group analysis indicated aberrant structure in the CHR group, largely in parietal, opercular, and cingulate regions. While the only CHR study of sulcal depth focused on a region of interest in the olfactory sulcus (22), the current parietal pattern of sulcal-depth abnormalities is consistent with findings that identified postcentral and parietal opercular regions of aberrant sulcal depth in schizophrenia (42). While many CSM features overlapped with the features identified by MCI, several of the clusters of sulcal-depth metrics were distinct in their identification of critical clusters. Additionally, sulcal depth provided unique information about these clusters. MCI indicated that parietal clusters fall away more steeply into wider sulcal curves, and sulcal-depth findings suggested that these curves were also shallower in sulcal depth. Taken together, the HC group had both higher gyri and lower sulci compared with those of the CHR group in these clusters.

The neural diathesis-stress conceptualization of psychosis suggests that genetic factors and early developmental insults confer early vulnerability for psychosis. Then later, in adolescence, this preexisting aberrant CSM-feature vulnerability interacts with neuromaturational factors. This interaction of early and neuromaturational factors—both normative and pathological brain development—eventually forms psychotic symptoms (20,43,44). Examining the adolescent period immediately preceding onset yielded many important findings. However, our understanding of both the early insult period and how early insult later interacts with pubertal factors is limited.

The present findings provide two important advancements in this regard. First, youths who met criteria for a prodromal syndrome did, in fact, show marked brain characteristics that may speak to an early insult, as CSM features developed and hardened in response to connectivity. Second, the present results provide a new perspective on the stability of CSM

Figure 3. Sulcal depth of clinical high-risk subjects compared with that of healthy control subjects. The images show the right-hemisphere (A, top) and (A, bottom) left-hemisphere false discovery rate–corrected $p < .05$. Panel (B) highlights peak clusters (group statistical images shown in B1 and B2) to demonstrate how each feature varies between the clinical high-risk subjects (group average shown in blue [B4, bottom]) and healthy control subjects (group average in shown in gray [B3, top]). The group average images were overlaid to highlight the surface differences (B5, B6).
features across adolescent neuromaturational processes in both CHR individuals and control subjects. While gyri
cation developed in tandem with brain connectivity in utero (45), most
studies emphasized neural development in the adolescent
prodromal period (29,46). The vast adolescent neuromatura-
tional changes led researchers to question whether CSM fea-
tures undergo further changes in the prodrome or after onset
(15,16). Additionally, present findings suggest that gyri
cation was remarkably static, which has implications for the way we
view stable versus changing vulnerability factors in a period of
active normative and pathological development. Additionally,
these findings may affect the way we interpret findings in the
context of leading neurodevelopmental (20,44) and dis-
connectivity conceptualizations of psychosis (18). Finally,
IGI is a potential early biomarker of risk, distinguishing CHR, psy-
chosis converters, and first-episode psychosis subjects from
HC subjects (15,16,30–32). In this regard, CSM gyri
cation metrics may have added value when combined with gray
matter and white matter changes over adolescence in identi-
fying risk and predicting conversion with techniques like
machine-learning classification. Additionally, connectomics
across metrics of gyri
cation may refine prediction and indi-
vidualization of treatment (39).

Table 5. Talairach Coordinates of Regions Showing Group Differences—Comparing Control Participants With Clinical High-Risk Participants—in Sulcal Depth

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>p Value</th>
<th>Size, mm²</th>
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<th>y</th>
<th>z</th>
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<td>32.54</td>
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<td>238.92</td>
<td>28.4</td>
<td>−54.1</td>
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<td>Superior parietal lobule</td>
</tr>
<tr>
<td></td>
<td>&gt;.0001</td>
<td>212.01</td>
<td>31.7</td>
<td>−43.4</td>
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<td></td>
<td>&gt;.01</td>
<td>94.53</td>
<td>11</td>
<td>13.5</td>
<td>34.5</td>
<td>Caudal anterior cingulate gyrus</td>
</tr>
</tbody>
</table>

Altogether, it is particularly interesting that areas that
develop earlier (i.e., visual and parietal regions) showed aber-
rant curvature and sulcal depth, while IGI clusters tended to-
ward later developing regions (i.e., frontal lobe and temporal
areas). This distinction may be driven by the content of the
metrics, as both sulcal depth and MCI exclusively measure gray
matter surface features, while IGI is also sensitive to the
white matter surface features. Therefore, it is possible that our
findings in the parietal lobule are reflective of abnormal brain
development and connectivity in utero, while the broader re-
gions implicated by IGI may also be picking up on aberrant
white matter surface features that occurred later in develop-
ment (myelination). However, it will be important for future
larger longitudinal studies with more developmental time
points to confirm this possibility. Further, it will be important for
future studies to consider how these features contribute
uniquely to behavioral and cognitive aspects of psychosis.
Additionally, future research should examine whether mea-
sures of the prenatal environment such as substance use,

![Image](image.png)

Figure 4. Regional clusters with overlap of sig-
ificance for local gyri
cation index (blue), mean
curvature index (yellow), and sulcal depth (red).
measures of stress, parental education, parental socioeconomic status, urbanicity (47), obstetric complications, or neurological soft signs such as motor impairment may relate to CSM features (48). It is also important to examine the relationship between gyration and potentially related metrics such as connectivity and cortical gray matter and white matter volumetrics. Collectively, the findings, indicating substantive novel contributions from each index, support a recommendation that all future studies of CSM features include multiple indices. Furthermore, it will be necessary to investigate convergence longitudinally in separate investigations, as this could be an informative empirical question to apply to psychosis and cortical morphology broadly.

This study shows great promise, but there are still important limitations to consider. While this study sample is comparable to, or larger than, those of other longitudinal studies (17–37 individuals) (15,16,30,49–52), future work could benefit from increased sample sizes. Notably, this represents one of the largest studies in a CHR population to include two scan time points (15,16,30). Additionally, moving forward, it will be important to understand the relationship between CSM features and antipsychotic medication use. While some CSM features (e.g., gray matter volume) are sensitive to antipsychotic medication (53–58), it remains unclear whether gyration is stable across treatment. This study included only a small number of the CHR participants treated with antipsychotic medications (n = 8) and did not find a significant effect of medication. Nonetheless, the influence of neuroleptic treatment on cortical and subcortical structure remains an important empirical question, and future work, with better-powered studies, should continue to evaluate medication effects on CSM features. Further, this study included an uneven sex distribution between groups (in part reflecting the nature of psychosis), and while we did not detect any effects for sex, future work should carefully evaluate possible sex differences.

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