Archival Report

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) youth 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 neurodevelopmental 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 [GI], 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 unchanged by adolescent neuromaturational 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 neuromaturational 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 malnutrition (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 neurodevelopmental 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 preclinical 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., youth 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 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-out outer 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 youth indicate widespread aberrant gyrification.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Population</th>
<th>Metric</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris et al., 2004</td>
<td>128</td>
<td>GHR</td>
<td>Gyrification index</td>
<td>Related to conversion</td>
</tr>
<tr>
<td>Harris et al., 2007</td>
<td>34</td>
<td>FEP</td>
<td>Gyrification index</td>
<td>Abnormal at first episode of psychosis</td>
</tr>
<tr>
<td>Kulynych et al., 1997</td>
<td>9</td>
<td>SZ</td>
<td>Gyrification index</td>
<td>Frontal hypergyrification</td>
</tr>
<tr>
<td>Sasabayashi et al., 2017</td>
<td>104</td>
<td>CHR</td>
<td>GI</td>
<td>Related to conversion</td>
</tr>
<tr>
<td>Sasabayashi et al., 2017</td>
<td>62</td>
<td>FEP</td>
<td>GI</td>
<td>Abnormal at first episode of psychosis</td>
</tr>
<tr>
<td>Bakker et al., 2016</td>
<td>36</td>
<td>CHR (n = 18; 22q11 deletion n = 18)</td>
<td>GI</td>
<td>Related to the 22q11 deletion</td>
</tr>
<tr>
<td>Mihailov et al., 2017</td>
<td>71</td>
<td>22q11 deletion</td>
<td>GI</td>
<td>Related to the 22q11 deletion</td>
</tr>
<tr>
<td>deVlV et al., 2017</td>
<td>24</td>
<td>CHR</td>
<td>GI</td>
<td>Related to clinical severity at follow-up</td>
</tr>
<tr>
<td>Palaniyappan et al., 2011</td>
<td>57</td>
<td>SZ</td>
<td>GI</td>
<td>Frontal hypogyrification</td>
</tr>
<tr>
<td>Takahashi et al., 2013</td>
<td>64</td>
<td>FEP</td>
<td>Sulcal depth</td>
<td>Related to deficits in executive function</td>
</tr>
<tr>
<td>Csernansky et al., 2008</td>
<td>33</td>
<td>SZ</td>
<td>Sulcal depth</td>
<td>Asymmetric sulcal depth in temporal lobes</td>
</tr>
</tbody>
</table>

CHR, clinical high-risk; FEP, first-episode psychosis; GHR, genetic high risk; GI, local gyrification index; SZ, schizophrenia.
Cortical Morphometry in the Psychosis Risk Period

(15–16,21,29–32), with little convergence outside the frontal and temporal regions. From this literature, we predicted that CHR youth 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 youth (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 gyriﬁcation 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 as a measure of general intelligence. The Wide Range Achievement Test is a well-validated and broadly used measure of achievement and broad learning ability for adolescents and young adults (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 (sgittal 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) parallel imaging factor of 2; 1-mm³ 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 gyriﬁcation stability, an interclass correlation compared 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 α is typically reported, the Guttman λ 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 gyriﬁcation (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 antisocial status (Figure 1, Table 3). In the left hemisphere, the CHR group showed a decreased GI, or reduction in the outer surface-to–inner surface ratio, signifying less gyriﬁcation, 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 gyriﬁcation, in the lateral orbitofrontal cortex, bank of the superior temporal sulcus, parahippocampal gyrus, and fusiform gyrus. Interestingly, no cluster demonstrated increased gyriﬁcation in the CHR group, suggesting hypogyriﬁcation 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>
<td></td>
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<tr>
<td>CHR Group</td>
</tr>
<tr>
<td>Age, Years, Mean (SD)</td>
</tr>
<tr>
<td>Gender, n</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Education, Years, Mean (SD)</td>
</tr>
<tr>
<td>Parent Education, Years, Mean (SD)</td>
</tr>
<tr>
<td>Symptom Domains, Mean (SD)*</td>
</tr>
<tr>
<td>Positive baseline</td>
</tr>
<tr>
<td>Positive follow-up</td>
</tr>
<tr>
<td>Wide Range Achievement Test Score, Mean (SD)</td>
</tr>
</tbody>
</table>

CHR, youth 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-}

fication 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-}

fication 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).
Figure 4. 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 \( \mathcal{G} \)I demonstrated distinct gyri
cation in frontal and temporal re-
gions, 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, mm(^2)</th>
<th>Talairach Coordinates</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>&gt; .0001</td>
<td>3285.18</td>
<td>(-34.9) (-69.5) (45.4)</td>
<td>Bank of the superior temporal sulcus</td>
</tr>
<tr>
<td></td>
<td>&gt; .001</td>
<td>351.98</td>
<td>(-51.8) (-0.2) (-28.2)</td>
<td>Temporal pole</td>
</tr>
<tr>
<td>Right</td>
<td>&gt; .0001</td>
<td>1833.49</td>
<td>(42.3) (26.5) (-14.4)</td>
<td>Lateral orbitofrontal cortex</td>
</tr>
<tr>
<td></td>
<td>&gt; .001</td>
<td>1163.56</td>
<td>(49.5) (-57.8) (32.1)</td>
<td>Bank of the superior temporal sulcus</td>
</tr>
<tr>
<td></td>
<td>&gt; .001</td>
<td>720.58</td>
<td>(26.3) (-42.1) (-6.8)</td>
<td>Parahippocampal gyrus</td>
</tr>
<tr>
<td></td>
<td>&gt; .001</td>
<td>30.13</td>
<td>(47.9) (-66.7) (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. The images show the (A, top) right-hemisphere 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 the healthy control subjects (group average shown in gray [B3, top]). The group average images were overlaid to highlight the surface differences (B5, B6).
Psychiatry: CNNI

Biological formation (i.e., local ratios rather than linear or arc metric) where groups differed. The distinct spatial and conceptual in-

evaluation of in the CHR group in the temporal and frontal lobes. The eval-

uation 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 hypogyri-

cation pattern that was predictive of later symptoms. Similarly, Hirjak et al. (38) found clinical features related to aberrant hypogyri-

ation 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 gyri-

nation in the temporal, frontal, and parahippocampal regions when compared with those of control subjects.

Group comparisons of MCI, an understudied metric of gyri-

nation, revealed distinct parietal geometry of gyri-

nation 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 investi-

ated 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 gyri-

nation (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 IGI 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.

To use both time points as a converging data point, we tested the assumption that the gyri-

nation is stable over time. These time points also provided us with a unique opportunity to confirm the stability of gyri-

nation 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: IGI (λ = .92), MCI (λ = .86), and sulcal depth (λ = .93). In parallel analyses, the CHR group did not signifi-

antly 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 IGI, CHR participants exhibited hypogyri-

nation in the lateral orbitofrontal cortex, superior bank of the superior tem-

poral sulcus, anterior isthmus of the cingulate, and temporal poles. For curvature, the CHR youth 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 gyri-

nation in the CHR youth, with distinct local parietal, parietal operculum, inferior bank of the superior temporal sulcus, and rostral cingulate regions.

In line with predictions, there was abnormal gyri-

nation in the CHR group in the temporal and frontal lobes. The eval-

uation of IGI identified entirely spatially unique clusters where groups differed. The distinct spatial and conceptual in-

formation (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 demon-

strated hypogyri-

nation 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 hypogyri-

ration pattern that was predictive of later symptoms. Similarly, Hirjak et al. (38) found clinical features related to aberrant gyri-

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nation in the temporal, frontal, and parahippocampal regions when compared with those of control subjects.

Table 4. Talairach Coordinates of Regions Showing Group Differences—Comparing Control Participants With Clinical High-Risk Participants—in Mean Curvature Index

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>p Value</th>
<th>Size, mm²</th>
<th>Talairach Coordinates</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>&gt; .00001</td>
<td>356.18</td>
<td>−21.8 −67.9 0.8</td>
<td>Lingual gyrus</td>
</tr>
<tr>
<td>Left</td>
<td>&gt; .0001</td>
<td>148.75</td>
<td>−36.7 −13.2 −28.3</td>
<td>Fusiform gyrus</td>
</tr>
<tr>
<td>Left</td>
<td>&gt; .0001</td>
<td>136.46</td>
<td>−40.2 −71.3 20.5</td>
<td>Inferior parietal lobule</td>
</tr>
<tr>
<td>Left</td>
<td>&gt; .0001</td>
<td>69.97</td>
<td>−60.3 −7 11.8</td>
<td>Postcentral gyrus</td>
</tr>
<tr>
<td>Left</td>
<td>&gt; .001</td>
<td>50.01</td>
<td>−57 −17.6 37.4</td>
<td>Postcentral gyrus</td>
</tr>
<tr>
<td>Right</td>
<td>&gt; .000001</td>
<td>318.16</td>
<td>21.7 −65.5 37.5</td>
<td>Superior parietal lobule</td>
</tr>
<tr>
<td>Right</td>
<td>&gt; .0001</td>
<td>182.77</td>
<td>26.7 −54.2 53.8</td>
<td>Superior parietal lobule</td>
</tr>
<tr>
<td>Right</td>
<td>&gt; .0001</td>
<td>116.57</td>
<td>13.5 −42.3 −0.3</td>
<td>Isthmus of the cingulate gyrus</td>
</tr>
<tr>
<td>Right</td>
<td>&gt; .0001</td>
<td>67.43</td>
<td>32.4 −44 44.5</td>
<td>Superior parietal lobule</td>
</tr>
</tbody>
</table>

...
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, youth 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
features across adolescent neuromaturational processes in both CHR individuals and control subjects. While gyrification developed in tandem with brain connectivity in utero (45), most studies emphasized neural development in the adolescent prodromal period (29,46). The vast adolescent neuromaturational changes led researchers to question whether CSM features undergo further changes in the prodrome or after onset (15,16). Additionally, present findings suggest that gyrification 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 disconnection conceptualizations of psychosis (18). Finally, IGI is a potential early biomarker of risk, distinguishing CHR, psychosis converters, and first-episode psychosis subjects from HC subjects (15,16,30–32). In this regard, CSM gyrification metrics have added value when combined with gray matter and white matter changes over adolescence in identifying risk and predicting conversion with techniques like machine-learning classification. Additionally, connectomics across metrics of gyrification may refine prediction and individualization of treatment (39).

Altogether, it is particularly interesting that areas that develop earlier (i.e., visual and parietal regions) showed aberrant curvature and sulcal depth, while IGI clusters tended toward 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 regions implicated by IGI may also be picking up on aberrant white matter surface features that occurred later in development (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 measures of the prenatal environment such as substance use,
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 gyriﬁcation 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 conversion 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 gryriﬁcation 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 un-even sex distribution between groups (in part re-ﬂecting 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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