

# Cortical Gyrfication, Psychotic-Like Experiences, and Cognitive Performance in Nonclinical Subjects

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**Background:** Psychotic-like experiences (PLE) are present in nonclinical populations, yet their association with brain structural variation, especially markers of early neurodevelopment, is poorly understood. We tested the hypothesis that cortical surface gyrfication, a putative marker of early brain development, is associated with PLE in healthy subjects. **Methods:** We analyzed gyrfication from 3 Tesla MRI scans (using CAT12 software) and PLE (positive, negative, and depressive symptom dimensions derived from the Community Assessment of Psychic Experiences, CAPE) in 103 healthy participants (49 females, mean age  $29.13 \pm 9.37$  years). A subsample of 63 individuals completed tasks from the Wechsler Adult Intelligence Scale and Controlled Oral Word Association Test. Estimated IQ and a composite neuropsychological score were used to explore mediation pathways via cognition. **Results:** Positive PLE distress was negatively associated with gyrfication of the left precuneus. PLE depression dimension showed a negative association with gyrfication in the right supramarginal and temporal region. There was no significant mediating effect of cognition on these associations. **Conclusion:** Our results support a neurobiological psychosis spectrum, for the first time linking an early developmental imaging marker (rather than volume) to dimensional subclinical psychotic symptoms. While schizophrenia risk, neurodevelopment, and cognitive function might share genetic risk factors, additional mediation analyses did not confirm a mediating effect of cognition on the gyrfication-psychopathology correlation.

**Key words:** cognitive function/endophenotype/neurodevelopment/subclinical/magnetic resonance imaging (MRI)

## Introduction

Schizophrenia is associated with core cognitive deficits predictive of risk for illness onset,<sup>1</sup> treatment response,

and recovery.<sup>2,3</sup> Hallmark dysfunctions consistently include general intellectual ability<sup>4</sup> and domains of attention, working memory, and verbal fluency.<sup>5</sup> While gradual changes in cognitive, perceptual, and negative symptoms mark the prodromal phase in the ultra-high risk (UHR) state, performances in these domains are also reduced in non-afflicted first-degree relatives<sup>6,7</sup> and healthy adults endorsing psychosis phenotypes including schizotypy and psychotic-like experiences (PLE).<sup>8,9</sup> Previously, we reported positive correlations between psychosis proneness in healthy adults and gray matter (GM) volumes in the precuneus, inferior, and parietal cortical areas.<sup>10</sup> GM, white matter, and functional abnormalities in fronto-parieto-temporal network areas,<sup>11,12</sup> parahippocampal, and cingulate gyri are frequently reported in schizophrenia.<sup>13,14</sup> Cortical and subcortical alterations in prefrontal network GM volume<sup>15,16</sup> and functional connectivity between frontal, temporal, hippocampal, and striatal regions across the psychosis continuum<sup>17–20</sup> are evident, yet somewhat inconclusive regarding directionality. Modinos et al<sup>21</sup> detected GM volume increases in the precuneus and anterior cingulate cortex in high schizotypy as well as the medial posterior cingulate areas in high positive PLE. Another study did not support regional prefrontal GM reductions associated with schizophrenia in twins and relatives of patients, suggesting that deficits in prefrontal executive function, rather than GM variation, are attributable to genetic liability for schizophrenia.<sup>22</sup>

Altogether these findings demonstrate that disease-stage and genetic risk profile account for overlap and discrepancies in functional and cortical variation, especially in prefrontal and precuneus regions. Neurobiological correlates of polygenic risk for psychotic disorders and cognitive disturbance support accumulating evidence for 2 neurodevelopmentally meaningful endophenotypes.<sup>23–26</sup>

The shared variance between polygenetic risk for schizophrenia and cognition-related pathways in a causal mediation model suggests that cognitive disturbance lies upstream to schizophrenia liability and not vice versa.<sup>27</sup> This is further supported by putative pathways involving, eg, calcium signaling associated with executive function in schizophrenia.<sup>28</sup>

A growing body of research recognizes cortical gyrfication as a neurobiological marker of early genetic and environmental modulation in cortical surface morphology in schizophrenia. Signifying the degree of cortical folding that peaks during early neurodevelopment, gyrfication has been strongly implicated as an early endophenotype in psychopathology.<sup>29</sup> Increased spatial resolution is achieved by quantifying the local gyrfication of individual surface vertices.<sup>30</sup> A recent study using vertex-wise local gyrfication index (GI),<sup>31</sup> for instance, has shown an association with polygenic risk indicating an early neurodevelopmental disturbance in schizophrenia.<sup>32</sup> Compared with cortical thickness, morphometry of cortical gyrfication might be less susceptible to heterogeneous illness-related effects.<sup>33</sup> This can aid to delineate etiological phenomena across groups of varying phenotype expression without confounds of acute neuroanatomical changes in schizophrenia<sup>34</sup> and antipsychotic treatment thereof.<sup>35</sup> Thus, gyrfication provides a novel approach to map differential phenotype correlates,<sup>36,37</sup> which are continuously expressed in the general population.<sup>38</sup> Case-control studies of gyrfication in schizophrenia have pointed to prefrontal and temporal alterations, but have not always been consistent.<sup>37,39–41</sup> While psychotic phenomena such as auditory hallucinations have been linked to cortical folding abnormalities in schizophrenia patients,<sup>42</sup> studies of cortical folding in nonclinical subjects are rare.<sup>43</sup> Hence, there is a paucity in the studies linking gyrfication to subclinical phenomena, such as PLE, that form part of the psychosis spectrum. These mostly transitory PLE<sup>38</sup> feature positive (delusional, hallucinatory, and dissociative experiences) and negative (affective flattening, avolition, and social withdrawal) subclinical phenomena corresponding to the typical dimensions of schizophrenia spectrum disorders.<sup>44,45</sup> Recently, a study using local GI found a significant role of the persistence of psychotic experiences during a 2-year follow-up period on gyrfication reduction in the left temporal gyrus and brain volume in left occipital and right prefrontal brain regions,<sup>23</sup> thus replicating morphological findings in regions implicated in schizophrenia. Negative associations of cortical volume and local GI in orbitofrontal, parietal, and temporal regions were driven by the interaction of polygenic risk score and psychotic experiences. However, these symptoms were not differentiated by dimensionality or quality, such as PLE frequency or symptom-related distress accounting for cortical variation in relevant areas, including left precuneus and right inferior temporal pole.<sup>46</sup>

Despite some initial volume-based morphometric studies, it is unclear whether more specific morphometric markers related to core processes such as early development/cortical gyrfication are related to different dimensions of PLE (positive, negative, and depressive) and cognitive function. Our aims were, therefore, 2-fold: our primary objective, based on previous GM volumetric studies of PLE, was to test the hypothesis that variation in cortical surface morphology is associated with different dimensions of subclinical PLE in healthy nonclinical individuals. Guided by previous voxel-based morphometry (VBM) findings,<sup>10</sup> we expected associations between psychosis proneness (assessed by CAPE) and gyrfication in prefrontal, superior parietal, and precuneus regions. Secondly, we tested the hypothesis that PLE-associated gyrfication is mediated by cognitive function in this nonclinical cohort. This hypothesis was based on the findings in the clinical spectrum, showing close relations between cognition and clinical outcomes across high-risk, first-episode, and multi-episode patients<sup>47,48</sup> and cognition pathways mediating some genetic risk on schizophrenia in a recent study.<sup>27</sup>

## Methods

### *Subjects*

We included 103 healthy participants (49 males, 54 females; mean age = 29.13 years, SD = 9.37) recruited from the local community. We obtained written informed consent from each participant for the study protocol approved by the local Ethics Committee of the Jena University Medical School and in line with the Declaration of Helsinki. The sample is based on a previously published community sample, which was enlarged subsequently.<sup>10</sup> Mean laterality index for the overall sample was 73.78 (SD = 36.38) right-handedness.<sup>49</sup> Subjects were recruited from the local community by advertising (press releases and word of mouth) and were compensated for study participation. They first underwent telephone screening and subsequent screening in person to assess the inclusion and exclusion criteria. A semi-structured interview was used to screen subjects for the absence of current or previous psychiatric disorders, including substance abuse or dependence, psychiatric or psychological treatment, intake of psychopharmacotherapy, or first-degree family liability for psychotic disorders. Subjects were also excluded if any neurological disorders, untreated major chronic or acute organic medical conditions, history of traumatic brain injury/loss of consciousness, or intellectual disability/ learning impairment (IQ < 80) were present. Next, all subjects underwent screening about lifetime history of psychiatric and general medical health care, and illicit substance and alcohol use. These screening questions were a requirement for subsequent scanning to ensure the inclusion of healthy volunteers from the general population only.

### CAPE Assessment

Clinically meaningful levels of psychosis risk can be detected in healthy individuals using self-report measures, such as the 42-item Community Assessment of Psychic Experiences (CAPE).<sup>50</sup> The CAPE is widely used to assess lifetime prevalence of PLE in the general population whilst available in multiple languages. These strengths were recently demonstrated in a meta-analysis<sup>45</sup> and a cross-cultural study,<sup>51</sup> and it may be cost-effectively employed in non-specialized settings to examine traits associated with psychosis proneness.<sup>52,53</sup> Including positive (CAPE-*pos*, 20 items) and negative (CAPE-*neg*, 14 items) subscales, the CAPE provides a comprehensive and reliable<sup>45</sup> self-report measure of the dichotomous symptom dimensions reflecting both frequency and distress related to psychosis-prone traits. Additionally, we also explored the depressive symptom (CAPE-*dep*) subdimension, which consists of an 8-item scale from the 3-factor model.<sup>44</sup>

### Neuropsychological Assessment

In a subsample of 63 healthy subjects (28 females; mean age 30.32 years, SD = 10.47), we assessed cognitive performance using multiple subtests of the German Wechsler Intelligenztest für Erwachsene (WIE),<sup>54</sup> the German adaptation of Wechsler Adult Intelligence Scale (WAIS-III)<sup>55</sup> neuropsychological testing battery, and the Controlled Oral Word Association Test (COWAT).<sup>56</sup> A general estimate of intelligence (IQ) was obtained from a German-language multiple-choice vocabulary test (Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B).<sup>57</sup> The MWT-B provides a resourceful approximation of crystallized intelligence.<sup>58</sup> The combination of cognitive tasks typically utilized in clinical schizophrenia<sup>25,59</sup> and UHR samples<sup>60</sup> from the 2 extensive test batteries included Letter-Number Sequencing task (LNS), Digit Symbol Coding task (DSCT) of the WAIS-III, Letters FAS, and Animals of the COWAT (table 1).

### MRI Acquisition and Surface-Based Morphometric Analysis

We obtained high-resolution T1-weighted scans using a 3 Tesla Siemens Tim Trio scanner (Siemens) with standard quadrature head coil and MPRAGE sequence for all subjects. Images were visually inspected followed by automated data quality check with homogeneity bias correction and tissue segmentation of images, followed by surface-based morphometry (SBM) analysis conducted using the CAT12 toolbox, v12.5 r1363 (Christian Gaser, Structural Brain Mapping Group, Jena University Hospital; <http://www.neuro.uni-jena.de/cat12/>) within SPM12 v7219 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) for Matlab R2017a (The

MathWorks, Inc.). This novel pipeline allows for the computation of surface-based parameters based on, eg, the mean curvature. Images were smoothed using a Gaussian kernel with 20-mm full width at half maximum, as recommended for vertex-wise gyrification in the CAT12 user manual (<http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>). All subjects passed both the visual quality inspection and the CAT12 data quality checks. Together, all scans from 103 participants reached a weighted average (IQR) of 86.01% (range 82.32%–86.55%) corresponding to a quality grade B.

### Statistical Analysis

For statistical analysis of CAPE-gyrification associations ( $N = 103$ ), we applied general linear models (GLM) implemented in SPM12 and the CAT12 toolbox using CAPE subscale scores as predictors for local gyrification, while covarying for age and sex nuisance in the vertex-wise analysis (i.e. multiple linear regression models). We applied familywise error (FWE) cluster-level correction at  $P < .05$  (with initial  $P < .001$  uncorrected peak-level thresholding) for significance testing.<sup>61</sup> Secondly, in the subsample of  $n = 63$  subjects, we examined the relationship between neuropsychological predictors and CAPE outcome variables. Due to previously reported negative relationships between cognitive measures and psychosis proneness,<sup>8</sup> we carried out 1-tailed partial correlations using Statistical Package for the Social Sciences (SPSS, Version 25, IBM Corp.). Finally, in this subsample, we explored mediating effect IQ and cognition on mean extracted predicted values in anatomical regions-of-interest (ROI) from the primary GLM analysis (ie, CAPE-gyrification association) as predictors and CAPE as outcome variables using the ordinary least squares (OLS) regression analysis implemented in PROCESS Version 3.3<sup>62</sup> for SPSS. Model coefficients  $P$ -values were adjusted with the false discovery rate (FDR)<sup>63</sup> correction for multiple comparisons using R.<sup>64</sup> For mediation model predictors, we used mean gyrification estimates across Desikan-Killiany atlas regions.<sup>65</sup>

## Results

### PLE Measures

In our whole sample, subjects scored on CAPE-*pos* dimension with mean frequency 1.24 (SD = 0.18, range 1.00–2.15, kurtosis = 5.80, skewness = 1.87) and mean distress 1.64 (SD = 0.50, range 1.00–3.13, kurtosis = -0.10, skewness = 0.45), CAPE-*neg* dimension with mean frequency 1.72 (SD = 0.43, range 1.07–3.14, kurtosis = 1.10, skewness = 0.97) and distress mean 1.88 (SD = 0.65, range 1.00–3.50, kurtosis = -0.61, skewness = 0.49), and CAPE-*dep* scale with mean frequency 1.69 (SD = 0.40, range 1.13–3.88, kurtosis = 7.99, skewness = 2.05) and distress mean 2.02 (SD = 0.67, range 1.00–3.83, kurtosis = 0.10, skewness = 0.52).

### Cortical Gyrfication and PLE

For the CAPE-*pos* scale, we found cluster-level significant ( $P = .015$ , FWE-corr.) effects in a cluster comprised of 178 vertices in the precuneus/cuneus region of the left hemisphere. We also found a trend-level effect for this scale in a cluster comprising 112 vertices in the left pars triangularis extending from the inferior prefrontal lobe to the pars opercularis region in the left middle frontal region ( $P = .080$ , FWE-corr.) (figure 1). CAPE-*neg* was associated with gyrfication in the right posterior and isthmus cingulate area; however, these correlations were not significant at the chosen  $P < .05$  FWE-correction level. GLM with CAPE-*dep* yielded negative associations with gyrfication spanning supramarginal to superior temporal gyrus (STG) regions ( $P = .001$ , FWE-corr.) (figure 2; supplementary table 2). All results significant at the  $P < .05$  FWE-threshold concerned CAPE PLE-associated distress levels.

### Neuropsychological Findings

Nonparametric and where appropriate parametric correlational analyses between individual raw scores of each neuropsychological subtest and CAPE frequency and distress scores were conducted to explore the relationship between cognitive and PLE phenotype variables. Correlation coefficients from partial 1-tailed correlation analyses controlled for age and sex are shown in table 2.

### Mediation of ROI-Associated PLE via IQ and Cognition

Using the extracted mean predicted gyrfication values of the 3 ROI identified in the primary analysis of

gyrfication (left precuneus, right STG, and the FWE-trend-level sig. left inferior prefrontal cluster), we conducted mediation analyses to predict PLE distress levels. A global neuropsychological performance measure was computed from  $z$ -transformed raw scores added together to obtain a single composite score per participant. In separate models, global cognitive measure and MWT-B IQ estimate were entered as mediators. Global cognitive performance significantly predicted MWT-B estimated IQ [ $F(1,61) = 31.16$ ,  $P < .001$ ,  $R^2 = 0.34$ ]. There was no significant mediating effect of either estimated IQ or global cognitive performance in the prediction of dimensional PLE distress in the subsample. This is seen in the inclusion of null values in 10 000 bootstrap-sampled confidence intervals of indirect effect coefficients in supplementary table S1.

### Discussion

This study tested 2 hypotheses in healthy individuals with varying levels of PLE. First, we tested the effect of PLE on gyrfication. Subsequently, we tested the individual explanatory contribution of cognitive performance in brain regions significantly associated with PLE. Both neural and cognitive variables were considered as endophenotypes with some shared genetic variance. In this study, we provide a first evidence of subtle neurodevelopmental variations in cortical areas linked to subclinical psychotic symptoms in nonclinical healthy subjects.

Unlike previous studies on PLE, which used volume-based imaging markers (VBM or cortical thickness), our gyrfication approach relates PLE more specifically to the variation of a neurodevelopmental marker. Previous

**Table 1.** Demographic and Cognitive Sample Characteristics of 103 Healthy Adults

Variable	<i>N</i>	Mean	SD	Skewness	Kurtosis
Age	103	29.13	9.37	1.80	2.68
Female (%)	49 (47.60%)				
IQ (MWT-B estimate)	103	105.28	12.08	1.30	1.20
Neuropsychological assessment					
Age	63	30.32	10.47	1.52	1.48
Female (%)	28 (44.40%)				
IQ (MWT-B estimate)	63	108.70	13.42	0.94	-0.10
MWT-B Score	63	29.22	3.48	-0.03	-0.53
WAIS-III					
Arithmetic	63	16.41	3.78	-0.48	-0.78
Digit symbol coding task	63	83.63	14.93	-0.04	-0.48
Matrix reasoning	63	20.89	3.45	-0.72	-0.21
Digit span	63	19.03	3.69	0.05	-0.73
Information	63	19.92	5.53	-0.77	-0.43
Letter-number sequencing	63	13.17	2.55	-0.44	-0.51
COWAT					
Letters FAS	63	39.84	12.08	0.27	-0.71
Animals	63	25.83	6.32	0.20	-0.15

*Note:* Of 103 healthy adults, 63 participants also completed neuropsychological tasks from the Wechsler Adult Intelligence Scale (WAIS-III) and Controlled Oral Word Association Test (COWAT). MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; SD, standard deviation.

**Table 2.** One-Tailed Partial (Covariates Age and Sex) Spearman's ( $r_s$ ) and Pearson's ( $r$ ; in Italics) Correlation Coefficients for Neuropsychological Subtest Raw Scores and IQ Estimated by MWT-B and Global Neuropsychological Composite Scores Correlated With Dimensional Community Assessment of Psychic Experiences (CAPE) Scales With Uncorrected ( $P$ ) and False Discovery Rate Adjusted ( $P_{adj}$ ) Significance Levels

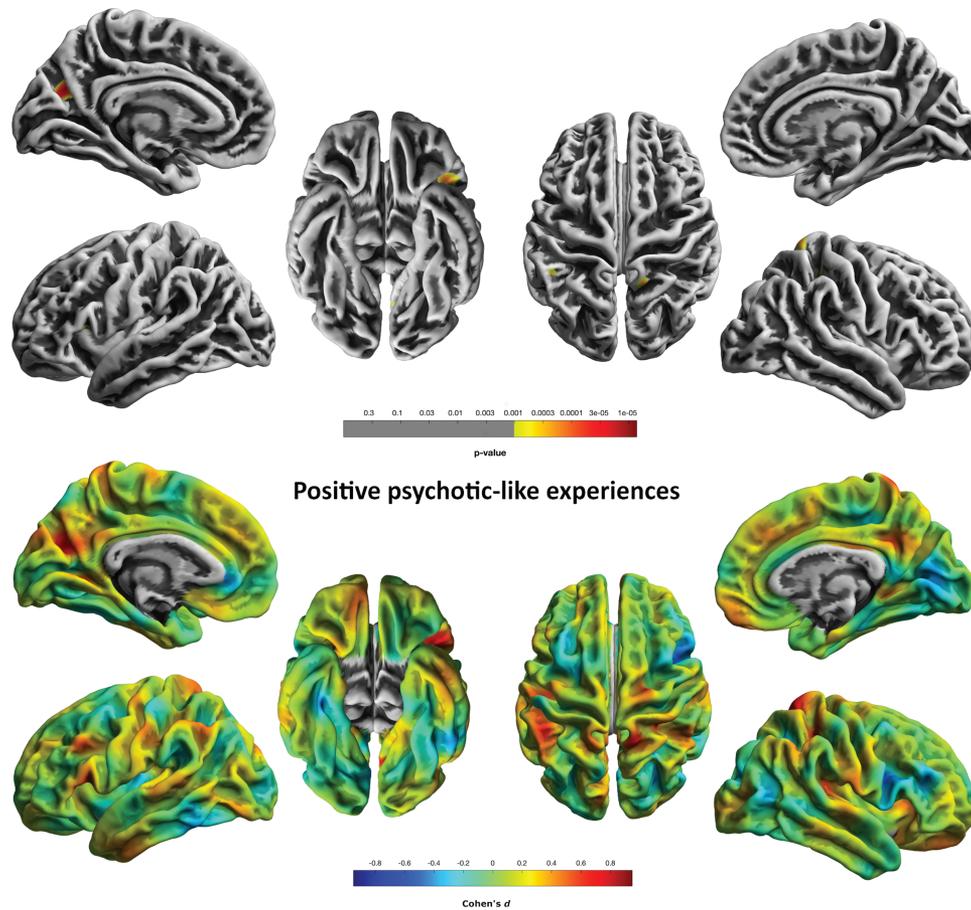
		Positive Dimension		Negative Dimension		Depressive Dimension	
		Frequency	Distress	Frequency	Distress	Frequency	Distress
DSCT	$r/r_s$	-.132	-.113	.027	-.013	-.207	-.118
	$P$	.156	.194	.418	.461	.055	.182
	$(P_{adj})$	(.478)	(.478)	(.478)	(.493)	(.374)	(.478)
Arithmetic	$r_s$	<b>-.399</b>	-.055	-.193	.060	-.036	-.058
	$P$	<b>.001</b>	.337	.068	.322	.391	.327
	$(P_{adj})$	(.066)	(.478)	(.374)	(.478)	(.478)	(.478)
Matrix reasoning	$r_s$	-.039	.052	.027	-.007	.023	-.159
	$P$	.383	.344	.420	.480	.430	.110
	$(P_{adj})$	(.478)	(.478)	(.478)	(.493)	(.481)	(.433)
Digit span	$r/r_s$	-.063	.034	<b>-.267</b>	.084	-.031	.048
	$P$	.314	.398	<b>.019</b>	.260	.407	.358
	$(P_{adj})$	(.478)	(.478)	(.314)	(.478)	(.478)	(.478)
Information	$r_s$	<b>-.217</b>	.156	-.211	<b>.228</b>	.042	.008
	$P$	<b>.047</b>	.114	.052	<b>.039</b>	.375	.475
	$(P_{adj})$	(.374)	(.433)	(.374)	(.374)	(.478)	(.493)
LNS	$r_s$	-.001	.124	-.058	.056	.057	-.100
	$P$	.496	.171	.329	.335	.332	.221
	$(P_{adj})$	(.496)	(.478)	(.478)	(.478)	(.478)	(.478)
Animals	$r/r_s$	-.183	-.005	-.154	.070	.030	-.060
	$P$	.079	.486	.118	.295	.409	.323
	$(P_{adj})$	(.374)	(.493)	(.433)	(.478)	(.478)	(.478)
Letters FAS	$r/r_s$	-.139	.037	-.186	-.007	-.074	-.090
	$P$	.143	.390	.076	.478	.285	.245
	$(P_{adj})$	(.478)	(.478)	(.374)	(.493)	(.478)	(.478)
MWT-B	$r_s$	<b>-.279</b>	.057	-.044	.181	.083	-.050
	$P$	<b>.015</b>	.331	.369	.082	.262	.352
	$(P_{adj})$	(.314)	(.478)	(.478)	(.374)	(.478)	(.478)
Global cognitive performance	$r_s$	<b>-.225</b>	.038	-.178	.136	.010	-.083
	$P$	<b>.041</b>	.385	.085	.148	.469	.261
	$(P_{adj})$	(.374)	(.478)	(.374)	(.478)	(.493)	(.478)
IQ	$r_s$	<b>-.279</b>	.057	-.044	.181	.083	-.050
	$P$	<b>.015</b>	.331	.369	.082	.262	.352
	$(P_{adj})$	(.314)	(.478)	(.478)	(.374)	(.478)	(.478)

Note: Significant ( $P < 0.05$ ) correlations are bold. DSCT, Digit Symbol Coding Task; LNS, Letter-Number-Sequencing task; MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest.

animal and human studies have shown cortical gyrfication to result primarily from complex neurodevelopmental processes, beginning at week 16 of gestation and extending into early childhood.<sup>66</sup> Between ages 2 and 6, the cortical folding organization reaches a peak<sup>29</sup> terminating into a considerably stable marker after adolescence with little variation across the lifespan.<sup>67</sup> A recent study of gyrfication in manifest schizophrenia compared with healthy controls found convergence between regions of structural GM alterations and cortical thickness; however, threshold-significant gyrfication results were more distinctive.<sup>37</sup> In line with these findings, we report PLE gyrfication effects in the prefrontal and temporal regions. Past studies focused on gyrfication patterns in clinical psychotic disorders<sup>39,68</sup> but investigations within the sub-clinical spectrum of psychotic symptoms found across general population cohorts are lacking. A few studies that

focused on dimensional PLE were almost exclusively limited to VBM<sup>10</sup> and cortical thickness,<sup>69</sup> leading to a lack of findings to infer on neurodevelopmental alterations within the wider psychosis continuum. In the present sample, a subclinical positive psychosis phenotype correlated negatively with gyrfication, a marker linked to perinatal and early neurodevelopment.

Higher PLE distress in the CAPE-*pos* dimension was associated with reduced gyrfication in the inferior frontal gyrus of the prefrontal lobe at the subthreshold FWE-corrected significance level. Similar to psychotic samples, positive subclinical psychotic signs are associated with prefrontal cortical organization, underlining their relevance in a dimensional psychosis spectrum. Discriminating gyrfication correlates between bipolar disorder I and schizophrenia showed some specificity of alterations in anterior medial prefrontal and orbitofrontal

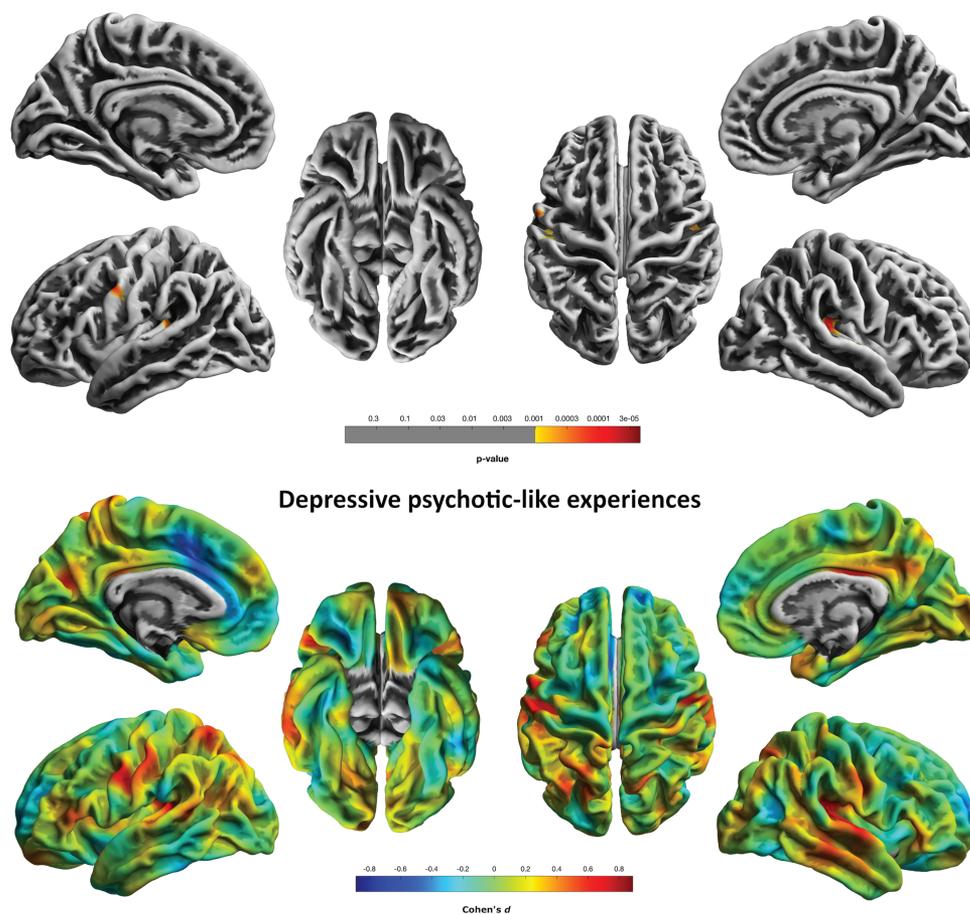


**Fig. 1.** Logarithmic  $P$ -value maps of significant negative correlations of cortical gyrfication and CAPE-*pos* scale in 103 healthy individuals ( $P < 0.001$ , uncorrected, for display purposes) (top). Cohen's  $d$  maps of effect sizes for uncorrected correlations of gyrfication with the CAPE-*pos* scale in 103 healthy individuals (bottom).

cortices for schizophrenia compared with controls. While hypergyrfication in regions of affective processing was unique in bipolar disorder, regions associated with cognition were pronounced in both diagnostic phenotypes with some anatomical divergence.<sup>40</sup> This raises the question of whether prefrontal correlates of positive psychotic symptoms are a widespread trend at both non-clinical and transdiagnostic levels. Regulatory changes of the dopaminergic and glutamatergic systems linked to typical neurocognitive symptoms of schizophrenia<sup>70,71</sup> and specifically prefrontal variation<sup>72-74</sup> perhaps also translate to prefrontal morphological and functional signatures in individuals with increased positive PLE. In contrast to positive prefrontal effects (gyrfication increase) reported in schizophrenia,<sup>37</sup> gyrfication patterns in the left inferior frontal gyrus showed a trend for a negative association in our finding. This discrepancy may be reflective of the fluctuations in endophenotype effects across the psychosis spectrum spanning from minor subclinical symptoms in the general population, over increased symptom frequency in high-risk subjects, to those individuals developing schizophrenia spectrum disorders. In order to further support this interpretation,

larger nonclinical and clinical samples would have to be combined to test linear vs. nonlinear relationships across such a spectrum.

Prefrontal structural variation within the psychosis spectrum,<sup>75</sup> extending to psychosis proneness signified by PLE, is robust and associated with neurodevelopmental processes,<sup>76</sup> such as synaptic pruning aberrances.<sup>77</sup> A previous study reported impairments on selective domains such as verbal knowledge and working memory but not processing speed to be associated with PLE.<sup>7</sup> While none of our results survived FDR-corrections, the trends might suggest heterogeneity dependent on scales, dimensions, and cognitive domain. Both estimated IQ and the global cognition scale comprising all individual tasks showed low to medium (uncorrected) negative correlations with the frequency of positive PLE. Together with previous findings of cognition mediating the genetic risk of schizophrenia, ie, cognitive dysfunction preceding schizophrenia-liability,<sup>27,78</sup> this may suggest that increased cognitive performance achieves neuroprotective effects in the presence of PLE. This notion is supported by the positive effects of increased cognitive reserve in first-episode psychosis patients on global function and



**Fig. 2.** Logarithmic  $P$ -value maps of significant negative correlations of cortical gyrification and CAPE-*dep* scale in 103 healthy individuals ( $P < 0.001$ , uncorrected, for display purposes) (top). Cohen's  $d$  maps of effect sizes for uncorrected correlations of gyrification with the CAPE-*dep* scale in 103 healthy individuals (bottom).

negative symptoms in a 2-year follow up.<sup>79</sup> The positive association of general intelligence<sup>80</sup> and working memory with regional cortical gyrification<sup>81</sup> further corroborates the functional findings of a parieto-frontal-integration model underlying intelligence variation.<sup>82</sup> Altered pre-frontal development might impact on the functional integrity of such networks, thus leading to changes in cognitive function. This neural-behavioral framework established in nonclinical populations may be extended for cognitive reserve and compensatory capabilities in at-risk mental health states. Volumetric integrity of these network nodes, ie, frontal, temporal, and parietal regions, is also featured in UHR subjects resilient against the transition to psychosis over a 6-year period.<sup>83</sup>

We found evidence for the negative effects of depressive symptoms on gyrification in the right STG and supramarginal regions. Left-sided STG also showed GM increase associated with low-level depressive symptoms in another healthy sample.<sup>84</sup> Convergence of decreased functional activity between psychotic disorders and major depressive disorder (MDD) highlights the critical role of the STG within the salience network in major psychiatric diagnoses. Another study also investigated

cortical folding in MDD patients based on the whole-cortex mean curvature presented here.<sup>85</sup> Within the patient group, clinical outcomes such as symptom severity were negatively associated with gyrification in parietal, occipitotemporal, and prefrontal cortices. However, the group comparison showed that MDD is associated with right STG hypergyrification pointing toward heightened vulnerability. Here, the endorsement of subclinical depressive states was associated with reduced gyrification of the right STG, which together with hypergyrification in diagnosed MDD proposes plastic alterations associated with the dopaminergic salience system and its role in cognitive interpretative processes ensuing over the course of illness.<sup>86,87</sup> These and our observations in the depressive spectrum, as well as STG-associations in schizotypy and schizophrenia,<sup>88</sup> may also indicate the absence of psychopathological and/or trait specificity, which in turn may be a result of symptom overlap.

There was a notable specificity for the PLE distress scale among the present results. The utility of CAPE as a screening tool for prodromal phenomena in clinical and non-specialized early treatment settings is particularly owed to its distinction of frequency and distress

experienced due to PLE.<sup>89,90</sup> High positive PLE levels, if perceived distressful, may, therefore, tap into higher psychopathological risk burden, supported by the covariance of positive and depressive symptoms.<sup>91</sup> Another study differentiating risk variants demonstrated that the relationship between PLE and subjective distress experienced due to PLE is moderated by the levels of trait schizotypy.<sup>92</sup> Dimensionality and psychosis specificity of the chosen scales may explain discrepancies in the directionality of precuneus GM volume in schizotypy,<sup>10,93</sup> which is further factored into positive and negative psychosis-prone traits with differential cognitive outcomes.<sup>94</sup> Moving along the spectrum, negative clinical outcomes such as imminent transition to psychosis are accompanied by intensified tissue loss and cortical thinning,<sup>95-97</sup> notably in the precuneus, parietal, and temporal regions.<sup>98</sup> In agreement with notions of dynamic neurobiology,<sup>99</sup> our findings map long-term cortical effects associated with subjective negatively perceived PLE, which are not attributed to disease progression but instead to vulnerability. Contrary to significant GM volume findings,<sup>10</sup> the absence of cortical gyrfication alterations for the CAPE-*neg* dimension suggests that the surrogate neurodevelopmental surface parameter is not sensitive to the effects of clinical avolition, affective flattening, and social anhedonia reflecting transdiagnostic features of psychosis spectrum disorders.

While we did not find a mediating effect of either estimated IQ or global neuropsychological performance, they showed low to medium (uncorrected) correlations with the frequency of positive PLE. We confined our analysis to ROI correlated with PLE distress levels but propose that PLE frequency may be of greater importance in these models. This conservative approach, together with variation in sample sizes, may cause underestimation of true mediator effects, constituting one of the main limitations of the present study. Siddi et al<sup>8</sup> showed that differences in neuropsychological performance between high and low schizotypy individuals were predominantly small (attention, visuospatial working memory, learning, short-term visual, and long-term memory) to medium (verbal working memory) sized. A post hoc sensitivity analysis with an 85% power criterion showed that the size of the subsample included in the present mediation analysis was only sufficient to detect medium effects ( $f^2 = 0.18$ ) of additional cognitive predictors. This might also explain our lack of significant findings (after multiple comparison correction) for CAPE-cognition associations. Future efforts should, therefore, achieve wider PLE variance and compare metrics of local GI with mean curvature. Additionally, weaknesses regarding the present IQ estimate needs to be pointed out. IQ estimation based on the MWT-B and educational level are not independent,<sup>58</sup> and global estimates from comprehensive neuropsychological batteries could increase robustness. Also, other cognitive tests such as those tapping into visuospatial and motor skills, which were not included in our test battery

despite showing heritability in schizophrenia,<sup>100</sup> might be useful for future studies. The cross-sectional design allows for inferences about the natural state of cortical gyrfication at an average age of about 30 years when the influence of time-invariant subclinical psychotic traits reaches a peak,<sup>101</sup> but not across the lifespan.<sup>67</sup> Using the gyrfication metric as a proxy measure of early genetic influence on cytoarchitecture, its stability may be tested in PLE combined with cumulative risk burden and clinical trait-state markers. Longitudinal designs with increased PLE variability are required to address such time variants and effects of PLE heterogeneity. Despite limited understanding of cytoarchitectural mechanisms involved in gyrfication in the psychosis spectrum, this study together with previous neuroimaging research suggests that differences in PLE dimensionality correspond to distinctive genetically determined neurobiological characteristics.

Besides previously mentioned limitations, our explicit investigation of the subclinical spectrum warrants some considerations. To our knowledge, few studies including different patient groups across the psychosis spectrum, eg, schizotypal personality disorder,<sup>41</sup> exist, which calls for further research in the subclinical range. Here, we operationalized CAPE symptom dimensions derived by a 3-factor solution. However, further partitioning of subscales resulting in more PLE phenotypes in exchange for lower indices of construct validity<sup>102</sup> offers an alternative research avenue to these dimensions. Future studies might also consider white matter changes related to PLE, which have been linked to symptom dimensions in schizophrenia.<sup>103,104</sup>

In conclusion, we report evidence for a relationship between variation in cortical gyrfication and subclinical psychosis phenotypes in the nonclinical spectrum. If cognition influences psychotic pathogenesis, interactions between cognitive and neurobiological endophenotype levels may be associated with attenuated PLE on the clinical spectrum end.

### Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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