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Structural Brain Abnormalities in Youth With Psychosis Spectrum Symptoms

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☐ **Supplemental content**

IMPORTANCE Structural brain abnormalities are prominent in psychotic disorders, including schizophrenia. However, it is unclear when aberrations emerge in the disease process and if such deficits are present in association with less severe psychosis spectrum (PS) symptoms in youth.

OBJECTIVE To investigate the presence of structural brain abnormalities in youth with PS symptoms.

DESIGN, SETTING, AND PARTICIPANTS The Philadelphia Neurodevelopmental Cohort is a prospectively accrued, community-based sample of 9498 youth who received a structured psychiatric evaluation. A subsample of 1601 individuals underwent neuroimaging, including structural magnetic resonance imaging, at an academic and children's hospital health care network between November 1, 2009, and November 30, 2011.

MAIN OUTCOMES AND MEASURES Measures of brain volume derived from T1-weighted structural neuroimaging at 3 T. Analyses were conducted at global, regional, and voxelwise levels. Regional volumes were estimated with an advanced multiatlas regional segmentation procedure, and voxelwise volumetric analyses were conducted as well. Nonlinear developmental patterns were examined using penalized splines within a general additive model. Psychosis spectrum (PS) symptom severity was summarized using factor analysis and evaluated dimensionally.

RESULTS Following exclusions due to comorbidity and image quality assurance, the final sample included 791 participants aged youth 8 to 22 years. Fifty percent (n = 393) were female. After structured interviews, 391 participants were identified as having PS features (PS group) and 400 participants were identified as typically developing comparison individuals without significant psychopathology (TD group). Compared with the TD group, the PS group had diminished whole-brain gray matter volume ($P = 3.4 \times 10^{-4}$) when not accounting for intracranial volume and relatively expanded white matter volume when accounting for intracranial volume ($P = 2.2 \times 10^{-3}$). Voxelwise analyses revealed significantly lower gray matter volume in the medial temporal lobe (maximum z score = 5.2 and cluster size of 1225 for the right and maximum z score = 4.5 and cluster size of 310 for the left) as well as in frontal, temporal, and parietal cortex. Volumetric reduction in the medial temporal lobe was correlated with PS symptom severity.

CONCLUSIONS AND RELEVANCE Structural brain abnormalities that have been commonly reported in adults with psychosis are present early in life in youth with PS symptoms and are not due to medication effects. Future longitudinal studies could use the presence of such abnormalities in conjunction with clinical presentation, cognitive profile, and genomics to predict risk and aid in stratification to guide early interventions.

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P sychotic disorders have a devastating effect on the lives of patients and families, producing substantial morbidity and mortality.[1-3] Based on the early age at onset and convergent evidence from animal models, psychosis is increasingly conceptualized as a downstream product of abnormal neurodevelopment.[4-7] A better understanding of the developmental antecedents of psychosis may lead to both early identification and novel targeted interventions.[8-10]

Adults with psychotic disorders, such as schizophrenia, have significant abnormalities of brain structure.[11-18] While initial studies examined modest samples, large meta-analyses have yielded consistent findings.[11,13,15,16] Recently, the ENIGMA-SZ (Enhancing NeuroImaging Genetics Through Meta-Analysis–Schizophrenia) Consortium[19] examined subcortical volumes from a sample totaling more than 2000 patients with schizophrenia and found reduced volume that was maximal in the hippocampus.[20] These results accord with a long line of research documenting structural and functional medial temporal lobe abnormalities.[21-27] Both meta-analyses and large-scale single-site studies examining cortical deficits have additionally provided evidence for diminished volume in frontal, temporal, and parietal brain regions.[11,13,15,16] Subcortical and cortical volume reductions have also been reported in unaffected family members,[28-30] suggesting that structural deficits are a heritable intermediate phenotype.

In contrast to large studies of adults with psychosis, studies of youth remain smaller. Most studies have examined either first-episode psychosis[10,12,17,18,31-33] or youth at clinical high risk.[10,12,31-33] These studies typically document attenuated patterns of gray matter volume reductions similar to those seen in adults with schizophrenia. The North American Prodrome Longitudinal Study consortium[9] reported in 2015 that clinical high-risk youth who later convert to psychosis have accelerated gray matter loss in frontal cortex compared with nonconverters and healthy comparators.[34] Beyond such studies of high-risk youth, it is also increasingly recognized that subtle psychosis spectrum (PS) symptoms are prevalent (5%-10%) among the general population.[35,36] Psychosis spectrum symptoms can impact functioning,[36,37] are associated with increased risk of conversion to a psychotic disorder,[38] and have been associated with neuroimaging abnormalities.[39-42]

Herein, we used a community-based approach to examine brain structure in a large sample of non–help-seeking youth with PS symptoms imaged as part of the Philadelphia Neurodevelopmental Cohort (PNC) of 9498 youth who received a structured psychiatric evaluation.[43] While such a design will likely produce lower rates of transition to frank psychosis than studying help-seeking clinical high-risk youth, understanding early subclinical psychotic symptoms may be valuable for elucidating the neurodevelopmental etiology of psychosis because it allows investigation of brain abnormalities at an earlier stage.[44-47] To our knowledge, there has been only one small study[42] of developmental structural abnormalities in community youth with PS symptoms, and it is unknown whether PS symptoms in this population demonstrate patterns of volume reduction similar to those found in clinical risk and adult psychosis samples. Similarities to adult clinical phenotypes would provide support for a dimensional view of psychotic

symptoms[4,48,49] and support examination of these phenotypes at younger ages and milder severity levels.[44-47]

We hypothesized that youth with PS symptoms would demonstrate abnormalities of structural brain development. Specifically, we expected that youth with PS symptoms would show reduced gray matter volume in regions similar to those impacted in adults with frank psychosis, such as the medial temporal lobe. We used nonlinear analyses of developmental patterns to investigate structural deficits on multiple scales, including analyses of global volumes, lobar volumes, and high-resolution voxelwise analyses. As described below, this approach yielded novel evidence for structural brain abnormalities in youth with PS symptoms that show parallels to those seen in adults with clinically diagnosed psychotic disorders.

Methods

Participants

Of the 1601 participants imaged as part of the PNC, 172 were excluded due to comorbidity, including medical illness that could affect brain function (n = 73), incomplete data (n = 1), nonpsychiatric medication with potential central nervous system effects (n = 78), or an incidentally encountered structural abnormality that distorted normal brain anatomy (n = 20).[50] Of the remaining 1429, PS symptoms were present in 408 participants, as defined in prior reports[36,37,39,40,51] using the GOASSESS interview,[36] which includes elements of the K-SADS (Schedule for Affective Disorders and Schizophrenia for School-Age Children), PRIME screen, and Scale of Prodromal Symptoms (eMethods in the Supplement).[52-54] Notably, this community-based ascertainment strategy is distinct from studies of help-seeking ultra high-risk youth. A minority of the youth with PS symptoms (n = 69) were being treated with psychoactive medication at the time of scan (eMethods in the Supplement). Youth with PS symptoms were compared with 416 typically developing (TD) youth, who had no significant psychiatric symptoms, were not taking psychotropic medication, and had no history of psychiatric hospitalization.

Following image quality assurance, the final sample comprised 391 youth with PS features (PS group) and 400 TD youth (TD group) 8 to 22 years old. Cognition was assessed using the University of Pennsylvania computerized neurocognitive battery and summarized as a general cognitive factor as previously reported.[52,55,56] Dimensional psychosis severity in the PS group was estimated using a previously described factor analysis of psychosis assessments.[37]

Demographic characteristics are summarized in the **Table**. While TD and PS samples were matched on sex (P > .90), they differed on age, race, and maternal education (P < .01). These variables were included as covariates in group-level analyses and further evaluated in supplementary analyses (see the Supplementary Analyses subsection below). All study procedures were approved by the institutional review boards of the University of Pennsylvania and The Children's Hospital of Philadelphia. Adult participants provided written informed consent. Minors provided assent, and their parent or guardian provided written informed consent.

Image Processing

All data were acquired on the same scanner using the same imaging sequences.[43,57] To maximize sensitivity to detect effects in youth with PS, advanced structural image processing and registration procedures were used. The T1-weighted image was skull stripped using a multiatlas procedure,[55] followed by multiplicative intrinsic component optimization for bias correction.[56] Multiatlas regional segmentation[58] was performed, which yields regional, lobar, and tissue class volume estimates. Voxelwise analyses were conducted using regional analysis of volumes in normalized space (RAVENS maps).[59] A deformable registration (DRAMMS [Deformable Registration via Attribute Matching and Mutual-Saliency Weighting])[60] was used to register images to a study-specific template.[61] RAVENS maps were downsampled to 2 mm and smoothed (8 mm full-width at half maximum) before voxelwise analyses.

Group-Level Analyses

Prior work has demonstrated that brain development is not a linear process.[62-64] Accordingly, group-level analyses of regional and voxelwise data were flexibly modeled using penalized splines within a general additive model (GAM) (eMethods in the Supplement).[65,66] The GAM assesses a penalty (using restricted maximum likelihood) on nonlinearity to avoid overfitting. This approach allowed us to estimate group differences and also ascertain whether the pattern of age-related changes was significantly different between groups.[64,67] We examined group differences and group × age interactions for global, lobar, and voxelwise volume measurements. In all models, we controlled for potentially confounding covariates, including sex, race, and maternal education. Intracranial volume (ICV) was included as a covariate in all regional and voxelwise models.[68,69] Tissue class volumes were modeled with and without ICV.

In addition to group differences, we examined the relationship between overall dimensional psychosis symptom severity (as defined by a previously completed factor analysis of PS symptoms)[37] and voxelwise gray matter volume within the PS group while controlling for covariates as above (sex, race, maternal education, and spline of age). Clusters demonstrating a significant association with overall psychosis symptom severity were further evaluated versus previously defined factors corresponding to positive and negative symptoms.[37] To enhance interpretability, dimensional associations with symptom severity were limited to voxels where a nominal (uncorrected $P < .05$) group difference was present. Type I error for voxelwise analyses was controlled using AFNI AlphaSim[70] (cluster height z score > 2.3, corrected cluster significance $P < .01$). Cortical projections were displayed using Caret.[71] Subcortical images were projected to the Montreal Neurological Institute 1-mm template for display.

Supplementary Analyses

We conducted several supplementary analyses to ensure that potentially confounding variables did not drive the observed results. Specifically, we conducted analyses of global, lobar, and regional medial temporal lobe volumes in 3 subsamples. In the first subsample (n = 722), we excluded youth with PS symptoms who were taking psychoactive medication. In the second subsample (n = 665), as in prior work,[39,40] we excluded youth

Table. Sample Demographics

Variable	Typically Developing (n = 400)	Psychosis Spectrum (n = 391)
Female sex, No. (%)	195 (48.8)	198 (50.6)
White race, No. (%)	221 (55.3)	121 (30.9)
Age, mean (SD), y	14.57 (4.03)	15.73 (3.11)
Maternal education, mean (SD), y	14.68 (2.56)	13.78 (2.23)
Psychosis z score, mean (SD)	−0.6 (0.7)	1.1 (0.8)
Cognitive performance, mean (SD)[a]	0.23 (0.76)	−0.18 (0.99)
Psychoactive medication use, No.	0	69
ICV, mean (SD), mm³	1485.69 (138.55)	1436.70 (155.04)

Abbreviation: ICV, intracranial volume.

[a] Cognitive performance is reported as a z score of scores from a factor analysis of the Penn Computerized Neurocognitive Battery, where a higher score denotes better performance.

with PS symptoms younger than 11 years whose status was assessed only by collateral interview. In the third subsample (n = 478), we used propensity score matching[72] to create groups that were exactly matched on age, sex, race, and maternal education. Finally, to examine the specificity of PS results,[51] we compared TD participants with 591 youth imaged as part of the PNC who had other psychopathology (and not PS symptoms) while controlling for covariates as above.

Results

Youth With PS Symptoms Have Lower Gray Matter Volume and Greater White Matter Volume

Youth with PS symptoms had reduced ICV compared with TD youth ($P = .002$). Global gray, white, and cerebrospinal fluid volumes were thus evaluated with and without ICV correction, and ICV was included as a covariate in all other analyses. Youth with PS symptoms had reduced total gray matter volume ($P = 3.4 \times 10^{-4}$), which was present at a trend level ($P = .058$) when covarying for ICV. This difference was larger in older participants, producing a significant group × age interaction ($P = .02$); this was not significant while covarying for ICV. When accounting for diminished ICV, youth with PS symptoms had greater white matter volume than TD comparators ($P = 2.2 \times 10^{-3}$); no age by group interaction was present. When ICV was not included in the model, PS participants demonstrated a trend towards reduced white matter volume ($P = .08$); no age by group interaction was present.

Distributed Gray Matter Volume Reduction Is Maximal in the Medial Temporal Lobe

To delineate the spatial pattern of volumetric deficits in more detail, we next conducted whole-brain voxelwise analyses. As shown in **Figure 1** and summarized in eTable 1 in the Supplement, voxelwise analyses revealed significant clusters of reduced volume in youth with PS symptoms in a network of regions, including bilateral medial temporal lobe, ventromedial prefrontal cortex, orbitofrontal cortex, and posterior cingulate.

Figure 1. Multifocal Gray Matter Volume Reduction in Youth With Psychosis Spectrum Symptoms
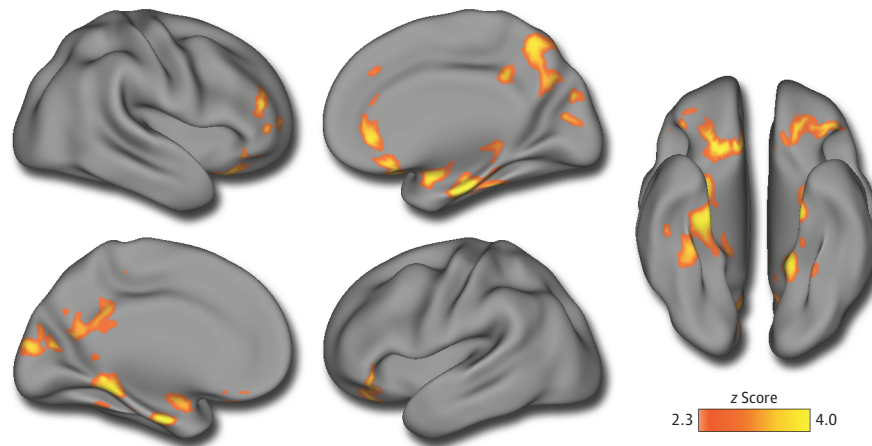
Voxelwise between-group analysis of gray matter volume reveals that youth with psychosis spectrum symptoms have diminished gray matter volume across multiple brain regions, including the precuneus, posterior cingulate, bilateral medial temporal lobe, frontal pole, and orbitofrontal cortex. The image was thresholded at z score > 2.3, corrected P < .01. The minimum cluster size is 255 voxels. Further details are listed in eTable 1 in the Supplement.

Figure 2. Reduced Medial Temporal Volume in Youth With Psychosis Spectrum Symptoms Develops in Early Adolescence
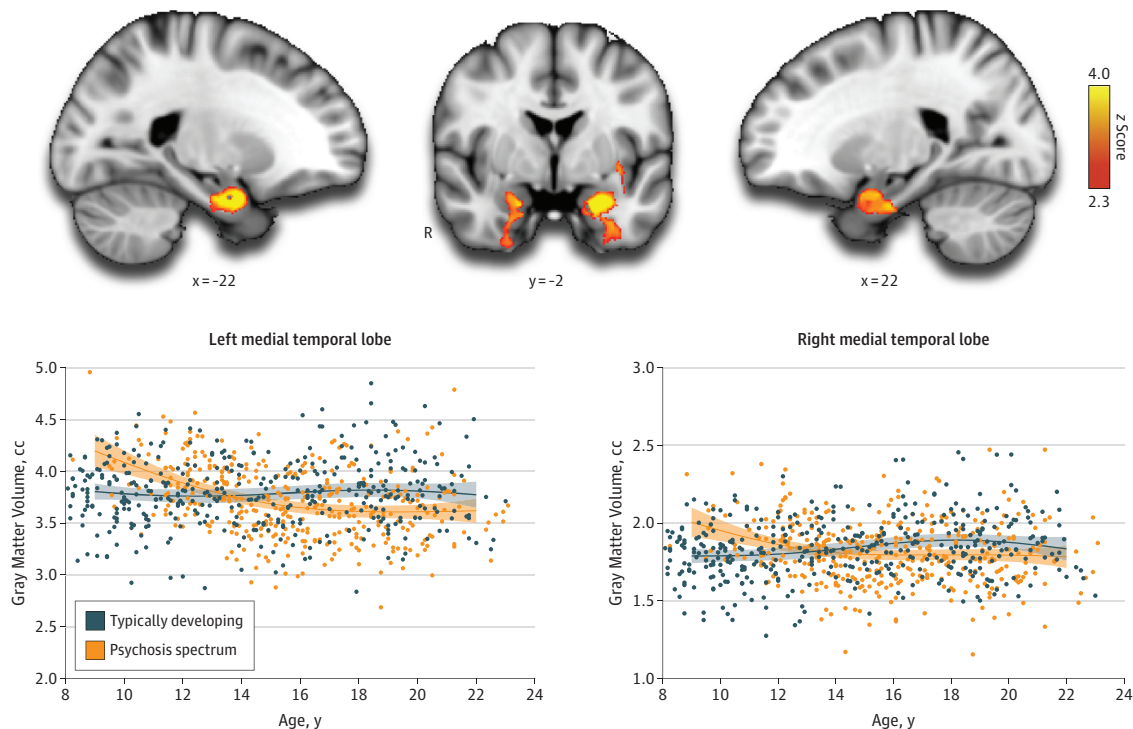
A, Voxelwise examination of nonlinear group × age interactions reveals significant differences in the developmental pattern of bilateral medial temporal lobe. Whereas intracranial volume–adjusted medial temporal volumes are stable in typically developing youth, youth with psychosis spectrum symptoms lose medial temporal volume in late childhood and early adolescence, resulting in lower medial temporal lobe volumes bilaterally by mid-adolescence. The image was thresholded at z score > 2.3, corrected P < .01. The minimum cluster size is 255 voxels. The x and y coordinates are in MNI. B, The mean volume is plotted within these clusters vs psychosis spectrum symptom severity while adjusting for covariates. Shaded regions represent 95% CIs. Further details are listed in eTable 2 in the Supplement.

Reduced volume was also seen in right dorsolateral prefrontal cortex and superior parietal cortex. Peak deficits were found in the medial temporal lobe. There was a single cluster in right in-ferior cerebellum where the PS group had larger gray matter volume. Significant group × age interactions were present in bilateral medial temporal lobe (**Figure 2** and eTable 2 in the Supple-

Figure 3. Dimensional Severity of Psychosis Spectrum Symptoms Is Associated With Diminished Volume in Bilateral Medial Temporal Lobe
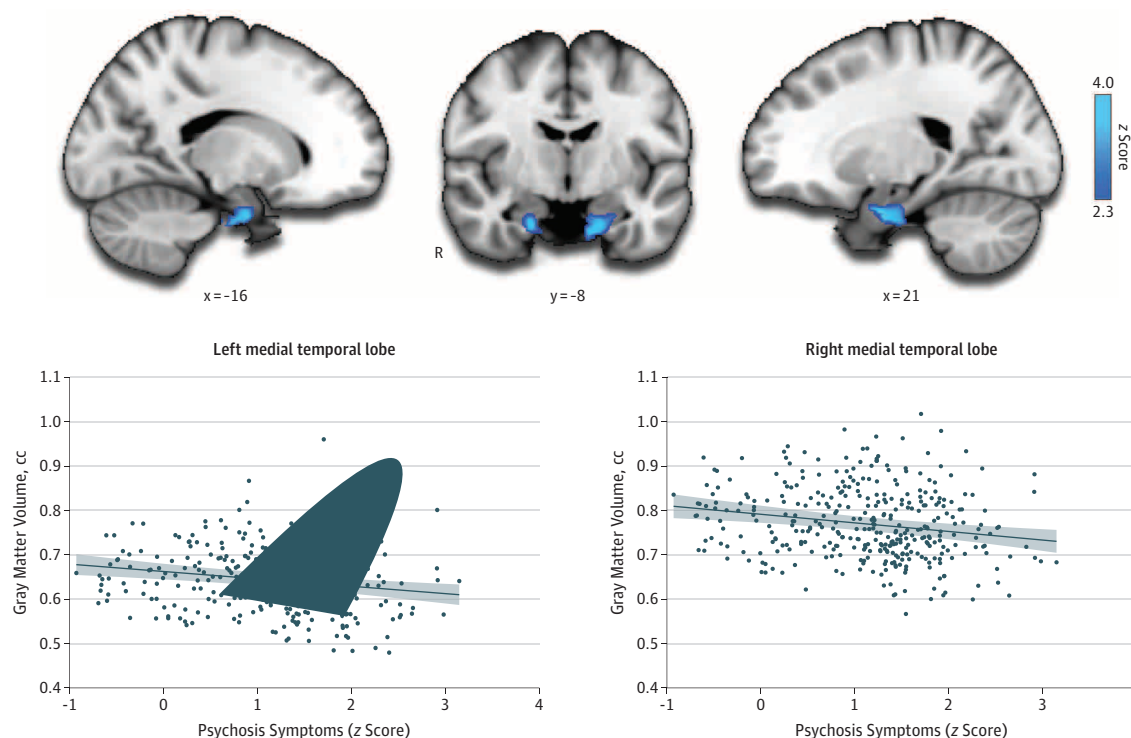
A, Voxelwise regression of dimensional psychosis spectrum symptoms within the psychosis spectrum sample reveals bilateral clusters of diminished volume in the medial temporal lobe. The image was thresholded at z score > 2.3, corrected P < .01. The minimum cluster size is 150 voxels. The x and y coordinates are in MNI. B, The mean volume is plotted within these clusters vs psychosis spectrum symptom severity while adjusting for covariates. Shaded regions represent 95% CIs. Further details are listed in eTable 3 in the Supplement.

ment), where higher volume in youth with PS symptoms during childhood is followed by lower volume in adolescence. No other regions demonstrated a significant group × age interaction.

Dimensional Psychosis Severity Is Associated With Medial Temporal Volume Loss

Having identified regions of reduced volume in youth with PS symptoms, we next evaluated whether the severity of symptoms in the PS group was related to the magnitude of structural abnormalities. Greater severity of PS symptoms was associated with volume reduction in bilateral medial temporal lobe (**Figure 3** and eTable 3 in the Supplement). Follow-up analyses revealed that these medial temporal effects were driven by positive symptoms (P < .001) but not negative symptoms. These results suggest that lower volume in the medial temporal lobe is related to not only the presence of PS symptoms but also their severity.

Supplementary Analyses

Supplementary analyses in 3 subsamples that excluded participants taking psychoactive medication, removed individuals younger than 11 years, or used groups matched on demographic covariates demonstrated significant group differences, but only when not covarying for ICV (eTable 4 in the Supplement). The effect sizes in all samples were small (Cohen d = 0.3 or lower; eTable 4 in the Supplement).

Finally, PNC participants with other psychopathology did not show volumetric deficits similar to those seen in youth with PS symptoms that were observed when not covarying for ICV (eTable 5 in the Supplement).

Discussion

In a large community-based sample of youth with PS symptoms, we identified abnormalities of brain structure. Gray matter volume loss was identified globally as well as in specific regions that included the medial temporal lobe, ventromedial and orbital frontal cortex, posterior cingulate, and dorsolateral prefrontal cortex. Volume reduction was maximal in the medial temporal lobe, where deficits became apparent in mid-adolescence and were correlated with the severity of PS symptoms. Taken together, these findings delineate a pattern of abnormal structural brain development in youth with PS symptoms that in part mirrors that seen in both adults with clinically diagnosed psychotic disorders and youth at clinical risk.

Structural Brain Abnormalities in Youth With PS Symptoms

We examined gray matter volume in youth with PS symptoms at multiple scales, including tissue class, lobar, and voxelwise analyses. Throughout, we maximized sensitivity by using ad-

vanced image processing techniques: regional volumes were estimated using cutting-edge multiatlas segmentation,[58] while voxelwise analyses used a highly accurate deformable registration[60] in combination with a study-specific template. It should be noted that, as in prior meta-analyses[15,20] of adult clinical samples, youth with PS symptoms also had significantly lower ICV. Global, lobar, and regional analyses were conducted with and without ICV included in the model. In these analyses, we only found evidence of significant gray matter reduction in PS youth when ICV was not included as a covariate. In contrast, all voxelwise analyses covaried for ICV and revealed significant areas of lower volume that were maximal in the medial temporal lobe and also present in ventromedial prefrontal cortex, orbitofrontal cortex, posterior cingulate, and dorsolateral prefrontal cortex.

Many of the regions affected are part of the default mode network, a large-scale functional network that is critical for internally directed attention, theory of mind, social cognition, and memory.[73,74] Both functional[75-77] and structural[13,20,78] deficits of default mode regions have been widely documented in psychosis. Indeed, in a prior report[39] from this cohort, our group described default mode hyperconnectivity in youth with PS symptoms. The present results thus provide convergent evidence for multimodal structural and functional abnormalities of default mode regions in youth with PS symptoms.

These results show substantial concordance with other studies of psychosis and risk across the life span, including adults with chronic schizophrenia,[13,15,16,20] childhood-onset schizophrenia,[79,80] and first-episode psychosis.[10,12,31-33] Our results indicate that structural abnormalities seen in clinical populations are also present in youth with PS symptoms and suggest that abnormalities of structural brain maturation may arise early in the course of development. Early loss of gray matter is consistent with prior reports of "accelerated aging" in schizophrenia.[81-83] While expansion of white matter observed herein is also consistent with premature acceleration of brain development, this finding has not typically been reported in clinical samples. It should be noted that such white matter expansion is only apparent when considering reduced ICV in PS youth; uncorrected white matter volumes did not differ significantly between groups. Thus, PS is characterized by an absolute reduction in gray matter volume and a relative expansion of white matter volume. To our knowledge, only one prior study has examined structural brain abnormalities in youth with PS symptoms. Jacobson et al[42] documented increases in gray matter density in a small sample (n = 11) of children 11 to 13 years old. Differences among these results may be accounted for by the difference in dependent measure (density vs volume) and the small sample size of the prior work.

Medial Temporal Lobe Volume Deficits in Youth With PS Symptoms

Volumetric deficits in youth with PS symptoms were observed in the medial temporal lobe, including the hippocampal head, amygdala, and parahippocampal cortex. Critically, reduced volume in these regions also correlated with symptom severity, particularly positive symptoms. These results are concordant with a large literature of both structural[18,20,26,27,84-90] and functional[24,91-96] medial temporal deficits in psychosis. Medial temporal volume loss has previously been documented in samples that included adults with chronic schizophrenia,[17,18,20,24,88] first-episode psychosis,[17,18,32,33] and youth at clinical risk for psychosis[26,27,32,97] but has not previously been reported in association with PS symptoms in a population-based sample. While the exact mechanism of injury to the hippocampus in psychosis is as yet unknown, Schobel et al[98] recently documented hypermetabolism at baseline in hippocampus CA1 in youth at clinical high risk for psychosis, which was linked to both elevated levels of extracellular glutamate and subsequent volume loss. Such changes may potentially be linked to γ-aminobutyric acid deficits in the medial temporal lobe in psychosis.[99] In the present data, the medial temporal lobe volumes showed a marked nonlinear developmental pattern, with volumetric deficits only becoming apparent in mid-adolescence. While speculative, the nonlinear pattern of medial temporal volume reduction in the youth with PS symptoms seen in our data may be consistent with the ongoing effects of glutamate-related toxicity following a period of both higher metabolism and volume. Potentially, both structural and functional changes could be phase specific[100,101] and represent a series of allostatic compensatory responses to an initial deficit.[100] Future studies using dedicated imaging techniques sensitive to hippocampal neurogenesis and injury may provide further insight.[91]

Opportunities and Limitations of Community-Based Research of PS Symptoms

In this study, we examined PS symptoms present in the community. In comparison with other strategies, such as studying help-seeking youth at clinical high risk, this approach comes with both advantages and disadvantages. The community-based approach allowed us to study younger participants who were largely unmedicated as well as to accrue a substantially larger sample size at a single site and scanner. However, the effect sizes of the observed effects are small (ie, Cohen d = 0.3 or lower), and large samples may be required to detect such effects. Furthermore, it should be noted that the correspondence with abnormalities in adult clinical samples is descriptive, and the observed abnormalities are partially, although not completely, similar to those identified in meta-analyses of schizophrenia.[11,87,101]

In addition, the present cross-sectional analysis does not allow us to evaluate the degree to which the observed abnormalities are driven by individual participants who will later become overtly psychotic.[34] Given the higher prevalence of PS symptoms compared with population rates of schizophrenia, it seems likely that PS symptoms are themselves associated with structural brain abnormalities, which would support a dimensional view of the PS and accord closely with the National Institute of Mental Health Research Domain Criteria approach.[48,49] As suggested by such a multidimensional view of psychopathology, it should be noted that individuals with PS symptoms

also have elevated levels of comorbid symptoms from other psychopathology dimensions.[36] While specificity analyses established that youth with other non-PS psychopathology did not have the same deficits as youth with PS symptoms, additional work will be necessary to evaluate the unique impact of PS symptoms in the context of other symptom dimensions. The necessity of further research to establish specificity is underlined by prior reports of cortical and medial temporal lobe abnormalities in both other psychiatric disorders[102,103] and in association with cognitive deficits, such as those seen in youth with PS symptoms.[51] Finally, it should be noted that, despite our efforts to control for relevant covariates, unmodeled confounding variables remain a persistent concern in psychiatric neuroimaging.[104]

Conclusions

These results establish that community youth with PS symptoms have patterns of structural brain abnormalities similar to those seen in clinically ascertained samples. Together with recent reports from this sample regarding cognitive deficits,[36,37,51] reduced executive activation,[40] exaggerated amygdala threat responsivity,[40] and functional network disconnectivity in youth with PS symptoms,[39] these findings suggest that brain abnormalities are associated with PS symptoms at a young age before clinical high-risk symptoms are typically identified. Such deficits are not dependent on disease chronicity or the confounding influence of psychotropic medication. These brain phenotypes may become a biomarker that can be used in genomic studies, drug discovery, and clinical trials of novel therapeutics.[34,105-108] Especially when used in combination with cognitive testing and measures of polygenic risk,[109-112] imaging phenotypes may help evaluate risk and target interventions for youth with PS symptoms before frank psychosis occurs and negative outcomes accrue. Moving forward, development of data-driven analytic techniques to parse heterogeneity[113] within the psychosis spectrum will accelerate translation to clinical practice.

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