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Structural Brain Abnormalities in Youth with Psychosis-Spectrum Symptoms

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Abstract

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—The Philadelphia Neurodevelopmental Cohort (PNC) is a prospectively accrued community-based sample of nearly 10,000 youths who received a structured psychiatric evaluation. A subsample of 1,601 subjects underwent neuroimaging including structural magnetic resonance imaging.

Setting—The PNC is a collaboration between The Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania.

Participants—Youths ages 8–22 years identified through structured interview as having psychosis-spectrum features (PS, n=391), and typically developing comparison subjects without significant psychopathology (TD, n=400).

Main Outcomes and Measures—Measures of brain volume derived from T1-weighted structural neuroimaging at 3T. Analyses were conducted at global, regional, and voxelwise levels. Regional volumes were estimated with an advanced multi-atlas regional segmentation procedure; voxelwise volumetric analyses were conducted as well. Nonlinear developmental patterns were

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examined using penalized splines within a general additive model. PS symptom severity was summarized using factor analysis and evaluated dimensionally.

Results—Compared to the TD group, the PS group had diminished whole brain gray matter volume and expanded white matter volume. Voxelwise analyses revealed significantly lower gray matter volume in the medial temporal lobes as well as in frontal, temporal, and parietal cortex. Reduction of medial temporal lobe volume 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.

Keywords

psychosis; development; neuroimaging; MRI; adolescence; brain

INTRODUCTION

Psychotic disorders have a devastating impact on the lives of patients and families, producing substantial morbidity and mortality.[1–3] Based on the early age of 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 relatively modest samples, large recent meta-analyses have yielded consistent findings.[11,13,15,16] Recently, the ENIGMA-SZ consortium[19] examined subcortical volumes from a sample totaling over 2,000 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] Sub-cortical and cortical volume reduction 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. Recently, the NAPLS[9] consortium demonstrated that clinical high risk youth who later convert to psychosis have accelerated gray matter loss in frontal cortex compared to non-converters 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%) in the general

population.[35,36] PS symptoms can impact functioning,[36,37] are associated with increased risk of conversion to a psychotic disorder,[38] and have been associated neuroimaging abnormalities.[39–42]

Here 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).[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 sub-clinical psychotic symptoms may be valuable for elucidating the neurodevelopmental etiology of psychosis, as it allows investigation of brain abnormalities at an earlier stage.[44–47] To our knowledge there has been only one small study of developmental structural abnormalities in community youth with PS symptoms,[42] 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 psychosis symptomatology,[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 PS youth would show reduced gray matter volume in similar regions 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 PS youth that show parallels to those seen in adults with clinically diagnosed psychotic disorders.

METHODS

Participants

Of the 1,601 participants imaged as part of the PNC, 172 were excluded due to co-morbidity including medical illness that could impact brain function (n=73), incomplete data (n=1), non-psychiatric medication with potential CNS effects (n=78), or an incidentally-encountered structural abnormality that distorted normal brain anatomy (n=20).[50] Of the remaining n=1,429, psychosis-spectrum (PS) symptoms were present in 408 participants, which was defined as in prior reports[36,37,39,40,51] using the GOASSESS interview,[36] which includes elements of the K-SADS, PRIME screen, and SOPS (see eMethods).[52–54] Notably, this community-based ascertainment strategy is distinct from studies of help-seeking ultra-high risk youth. A minority of the PS youths (n=69) were being treated psychoactive medication at the time of scan (see eMethods for details). PS youths were compared to 416 typically developing (TD) youths, who had no significant psychiatric symptoms, were not taking psychotropic medication, and no history of psychiatric hospitalization. Following image quality assurance, the final sample was comprised of 391 PS youths and 400 TD youths. Cognition was assessed using the Penn computerized neurocognitive battery, and summarized as a general cognitive factor as previously reported.[52,56,57] Dimensional

psychosis severity in the PS group was estimated using a previously described factor analysis of psychosis assessments.[37]

Demographic characteristics are detailed in Table 1. While TD and PS samples were matched on sex ($p>0.9$), TD and PS samples differed on age, race, and maternal education ($p<0.01$); these variables were included as covariates in group-level analyses and further evaluated in supplementary analyses (see below). All study procedures were approved by the Institutional Review Boards of the University of Pennsylvania and Children's Hospital of Philadelphia. Adult participants provided informed consent; minors provided assent and their parent or guardian provided informed consent.

Image processing

All data were acquired on the same scanner using the same imaging sequences.[43,55] To maximize sensitivity to detect effects in PS youth, advanced structural image processing and registration procedures were employed. The T1 image was skull-stripped using a multi-atlas procedure[56] followed by multiplicative intrinsic component optimization for bias correction.[57] Multi-atlas regional segmentation (MARS)[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)[60] was used to register images to a study-specific template.[61] RAVENS maps were down-sampled to 2mm and smoothed (8 mm FWHM) prior to 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, see eMethods).[65,66] The GAM assesses a penalty (using restricted maximum likelihood) on nonlinearity in order to avoid over-fitting. 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-by-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] In order to enhance interpretability, dimensional associations with symptom severity were limited to voxels where a nominal ($p<0.05$, uncorrected) group difference was present. Type I error for voxelwise analyses was controlled using AFNI AlphaSim[70] (cluster

height z>2.3, corrected cluster significance p<0.01). Cortical projections were displayed using Caret;[71] subcortical images were projected to the Montreal Neurological Institute 1mm 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 analysis of global, lobar, and regional medial temporal lobe volumes in three sub-samples. In the first sub-sample (n=722), we excluded PS youth who were taking psychoactive medication. In the second sub-sample (n=665), as prior,[39,40] we excluded PS youth younger than age 11 whose status was assessed only by collateral interview. In the third sub-sample (n=478), we used propensity score matching[72] to create groups that were exactly matched on age, sex, race, and maternal education. Finally, in order to examine the specificity of PS results,[51] we compared TD participants to 591 youth imaged as part of the PNC who had other psychopathology (and not PS symptoms) while controlling for covariates as above.

RESULTS

PS youth have lower gray matter volume and greater white matter volume

PS youths had reduced ICV compared to TD youth (p=0.002). Global gray, white, and CSF volumes were thus evaluated with and without ICV correction; ICV was included as a covariate in all other analyses. PS youth had marked reductions in total gray matter volume (Figure 1A), regardless of whether ICV was included as a covariate (ICV-corrected: $p=1.8x10^{-10}$; without ICV correction: $p=6.3x10^{-9}$). This difference was larger in older participants, producing a significant group-by-age interaction (ICV-corrected: $p=1.13x10^{-5}$; without ICV correction: $1.58x10^{-5}$). When accounting for diminished ICV, PS youth had greater white matter volume than TD comparators ($p=2.8x10^{-11}$; Figure 1B), which was larger at older ages ($p=6.6x10^{-8}$). When ICV was not included in the model, the main white matter effect was present as a trend (p=0.10), while the age by group interaction remained significant (p=0.02). When examined on a lobar level while accounting for ICV, gray matter differences were widespread and most significant within frontal cortex (eFigure 1).

Distributed gray matter volume reduction is maximal in medial temporal lobes

In order to delineate the spatial pattern of volumetric deficits in more detail, we next conducted whole-brain voxelwise analyses. As displayed in Figure 2 and detailed in eTable 1, voxelwise analyses revealed significant clusters of reduced volume in PS youth in a network of regions including bilateral medial temporal lobe, ventromedial prefrontal cortex, orbitofrontal cortex, and posterior cingulate. 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 the right inferior cerebellum where the PS group had larger gray matter volume. Significant group-by-age interactions were present in bilateral medial temporal lobe (Figure 3; eTable 2), where higher volume in PS youth during childhood is followed by lower volume in adolescence. No other regions demonstrated a significant age by group interaction.

Dimensional psychosis severity is associated with medial temporal volume loss

Having identified regions of reduced volume in PS youth, we next evaluated whether the severity of symptoms in PS participants was related to the magnitude of structural abnormalities. Greater severity of PS symptoms was associated with volume reduction in bilateral medial temporal lobe (Figure 4, see also eTable 3). Follow-up analyses revealed that these medial temporal effects were driven by positive ($p<0.001$) but not negative symptoms (NS). These results suggest that lower volume in the medial temporal lobe is related not just to the presence of PS symptoms, but also their severity.

Supplementary analyses

Supplementary analyses in three sub-samples that excluded medicated subjects, removed subjects under age 11, or used groups matched on demographic covariates provided convergent results (eTable 4). Effect sizes in all samples were small (d=0.4 or lower; see eTable 4). Finally, PNC participants with other psychopathology did not show similar volumetric deficits to those seen in PS youths (eTable 5).

DISCUSSION

In a large, community-based sample of PS youth, we identified abnormalities of brain structure. Gray matter volume loss was globally reduced and focused in regions including 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 PS youth that in part mirrors that seen in both adults with clinically diagnosed psychotic disorders and youth at clinical risk.

Structural brain abnormalities in PS youth

We examined gray matter volume in PS youth at multiple scales, including tissue class, lobar, and voxelwise analyses. Throughout, we maximized sensitivity by using advanced image processing techniques: regional volumes were estimated using cutting-edge multi-atlas segmentation,[58] while voxelwise analyses used a highly accurate deformable registration[60] in combination with a study-specific template. These analyses provided convergent results, and demonstrated that PS youth have diminished GM volume, with lobar deficits that were most prominent in frontal cortex. It should be noted that as in prior meta-analyses of adult clinical samples,[15,20] PS youth also had significantly lower ICV; all regional and voxelwise analyses co-varied for ICV and thus represent volumetric decrements above and beyond such a global effect. Voxelwise analyses 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 impacted 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 deficits[13,20,78] of default mode regions

have been widely documented in psychosis. Indeed, in a prior report from this cohort we described default mode hyper-connectivity in PS youth.[39] The current results thus provide convergent evidence for multi-modal structural and functional abnormalities of default mode regions in PS youth.

These results show substantial concordance with other studies of psychosis and risk across the lifespan, 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 relatively 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 here is also consistent with premature acceleration of brain development, this finding has not typically been reported in clinical samples. To our knowledge, only one prior study has examined structural brain abnormalities in youth with PS symptoms: Jacobson et al. (2010) documented increases in gray matter density in a small sample (n=11) of children ages 11–13.[42] Differences among these results may be accounted for by the difference in dependent measure (density versus volume) and the small sample size of the prior work.

Medial temporal lobe volume deficits in PS youth

Volumetric deficits in PS youth 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, in particular 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 including 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, recently Small et al. 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.[98] Such changes may potentially be linked to GABA-ergic deficits in the medial temporal lobe in psychosis.[99] In the present data, 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 PS youth 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 an series of allosteric compensatory responses to an initial deficit.[100] Future studies employing dedicated imaging techniques sensitive to hippocampal neurogenesis and injury may provide further insight.[91]

Community-based research of PS symptoms: Opportunities and limitations

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, and also to accrue a substantially larger sample size at a single site and scanner. However, the effect sizes of observed effects are relatively small (i.e., d=0.4 or below) and large samples may be required to detect such effects. Further, it should be noted that the correspondence with abnormalities in adult clinical samples is descriptive, and observed abnormalities are partially, though not completely, similar to those identified in meta-analysis of schizophrenia.[11,87,101]

Additionally, the present cross-sectional analysis does not allow us to evaluate the degree to which observed abnormalities are driven by individual participants who will later become overtly psychotic.[34] Given the higher prevalence of PS symptoms compared to population rates of schizophrenia, it seems likely that PS symptoms are themselves associated with structural brain abnormalities. This would support a dimensional view of the psychosis spectrum, and accord closely with the NIMH Research Domain Criteria approach.[48,49] As suggested by such a multi-dimensional view of psychopathology, it should be noted that participants with PS symptoms also have elevated levels of co-morbid symptoms from other psychopathology dimensions.[36] While specificity analyses established that youth with other non-PS psychopathology did not have the same deficits as PS youths, 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 PS youth.[51,104] Finally, it should be noted that despite our efforts to control for relevant covariates, un-modeled confounding variables remain a persistent concern in psychiatric neuroimaging.

Conclusions

These results establish that community youths with PS symptoms have similar patterns of structural brain abnormalities seen in clinically ascertained samples from the psychosis spectrum. 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 dysconnectivity in PS youths,[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 PS youth will accelerate translation to clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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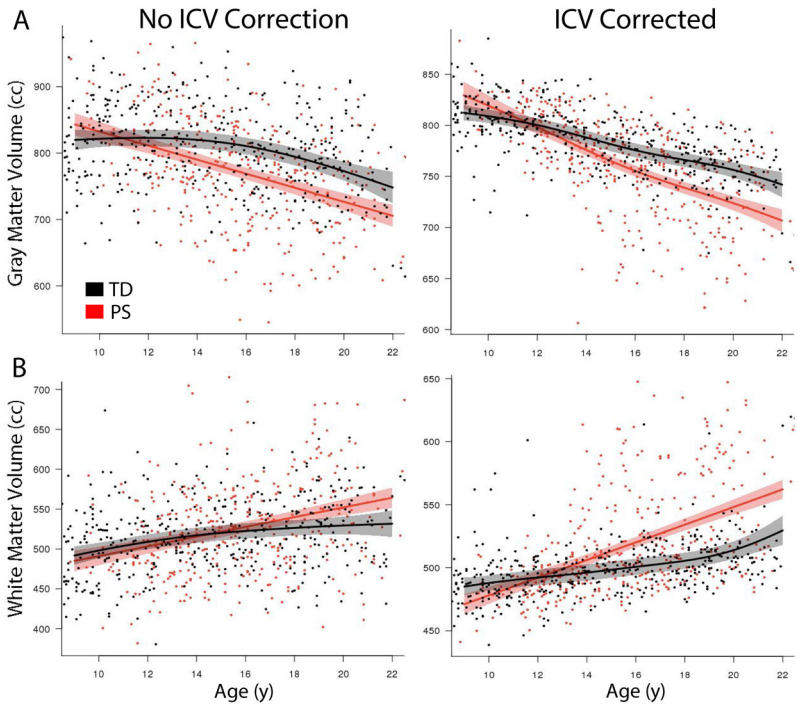

Figure 1.

Psychosis spectrum youth have volumetric deficits that progress with age. PS youth have diminished gray matter volume (**A**) regardless of whether ICV is included as a model covariate. Additionally, PS youth have expanded white matter volume (**B**) when smaller head size is accounted by covarying for ICV. In both gray and white matter, these abnormalities become more marked at later ages in adolescence and young adulthood. Shaded regions represent 95% confidence intervals.

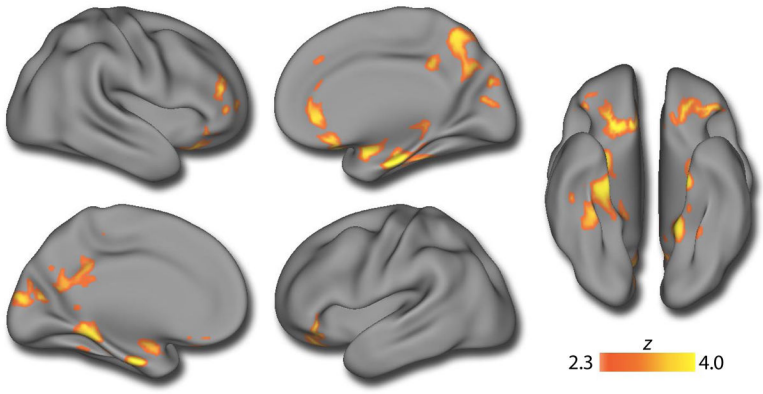

Figure 2.

Multifocal gray matter volume reduction in psychosis-spectrum youth. A voxelwise between-group analysis of gray matter volume reveals that PS youth have diminished GM volume across multiple brain regions, including the precuneus, posterior cingulate, bilateral medial temporal lobes, frontal pole, and orbitofrontal cortex. Image thresholded at $z>2.3$, corrected $p<0.01$; minimum cluster size: $k>255$ voxels. See eTable 1 for further details.

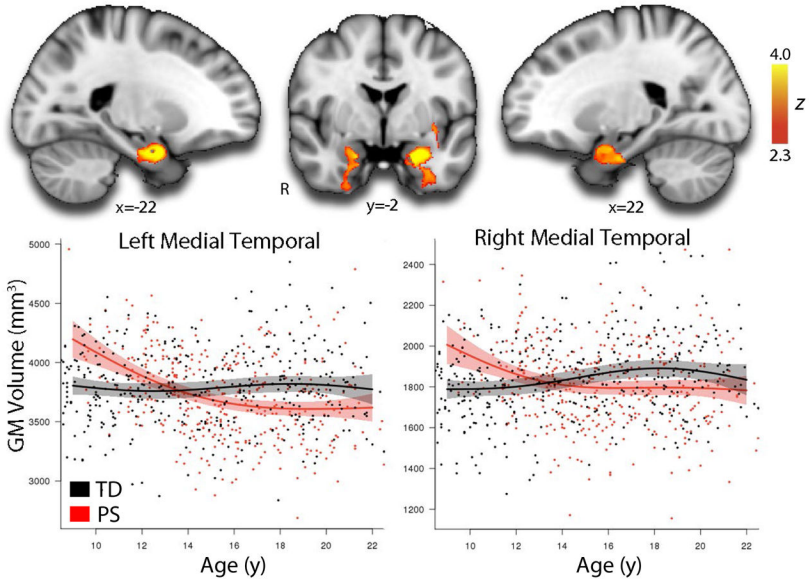

Figure 3.

Reduced medial temporal volume in PS youth relative to TD youth develops in early adolescence. Voxelwise examination of nonlinear group-by-age interactions reveals significant differences in the developmental pattern of bilateral medial temporal lobes. Whereas ICV-adjusted medial temporal volumes are stable in TD youth, PS youth lose medial temporal volumes in late childhood and early adolescence, resulting in lower MTL volumes bilaterally by mid-adolescence. Image thresholded at $z>2.3$, corrected $p<0.01$; minimum cluster size: $k>255$ voxels. See eTable 2 for further details. Shaded regions represent 95% confidence intervals.

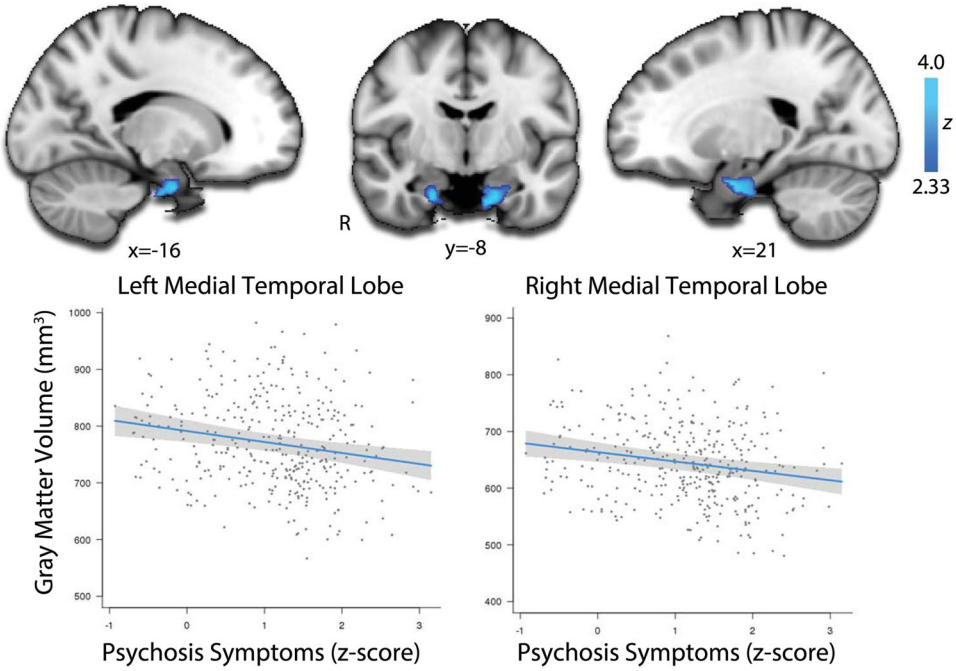

Figure 4.

Dimensional severity of psychosis-spectrum symptoms is associated with diminished volume in bilateral medial temporal lobe in PS youth. Voxelwise regression of dimensional PS symptoms within the PS sample reveals bilateral clusters of diminished volume in the medial temporal lobe (top panels). Image thresholded at $z>2.3$, corrected $p<0.01$; minimum cluster size: $k>150$ voxels. Bottom panels plot the mean volume within these clusters versus PS symptom severity, while adjusting for covariates. Shaded regions represent 95% confidence intervals. See eTable 3 for details.

Table 1

Sample demographics.

	Typically Developing	Psychosis Spectrum
n	400	391
Number Female (%)	195 (49%)	198 (51%)
Number Caucasian (%)	221 (55%)	121 (31%)
Mean Years Age (SD)	14.57 (4.03)	15.73 (3.11)
Mean Years Maternal Education (SD)	14.68 (2.56)	13.78 (2.23)
Mean Psychosis Score (SD)	−0.56 (0.73)	1.12 (0.81)
Mean Cognitive Performance (SD)	0.23 (0.76)	−0.18 (0.99)
Psychoactive Medication (n)	0	69
Mean ICV, cubic mm (SD)	1485.69 (138.55)	1436.7 (155.04)