ARTICLE

Developmentally divergent sexual dimorphism in the cortico-striatal–thalamic–cortical psychosis risk pathway

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Structural and functional cortico-striatal–thalamic–cortical (CSTC) circuit abnormalities have been observed in schizophrenia and the clinical high-risk state. However, this circuit is sexually dimorphic and changes across neurodevelopment. We examined effects of sex and age on structural and functional properties of the CSTC circuit in a large sample of youth with and without psychosis spectrum symptoms (PSS) from the Philadelphia Neurodevelopmental Cohort. T1-weighted and resting-state functional MRI scans were collected on a 3T Siemens scanner, in addition to participants' cognitive and psychopathology data. After quality control, the total sample (aged 11–21) was $n = 1095$ (males = 485, females = 610). Structural subdivisions of the striatum and thalamus were identified using the MAgE Brain segmentation tool. Functional seeds were segmented based on brain network connectivity. Interaction effects among PSS group, sex, and age on striatum, thalamus, and subdivision volumes were examined. A similar model was used to test effects on functional connectivity of the CSTC circuit. A sex by PSS group interaction was identified, whereby PSS males had higher volumes and PSS females had lower volumes in striatal and thalamic subdivisions. Reduced functional striato-cortical connectivity was found in PSS youth, primarily driven by males, whereby younger male PSS youth also exhibited thalamo-cortical hypo-connectivity (compared to non-PSS youth), vs. striato-cortical hyper-connectivity in older male PSS youth (compared to non-PSS youth). Youth with PSS demonstrate sex and age-dependent differences in striatal and thalamic subdivision structure and functional connectivity. Further efforts at biomarker discovery and early therapeutic intervention targeting the CSTC circuit in psychosis should consider effects of sex and age.

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INTRODUCTION

Disorders that involve psychosis symptoms, such as schizophrenia, are debilitating and largely neurodevelopmental in origin, with etiologies still poorly understood. Many of the cognitive, functional, and brain abnormalities associated with schizophrenia are present to some degree at earlier stages of illness in help-seeking and clinical high-risk (CHR) groups [1].

One important priority related to uncovering the neurobiology of psychosis onset is that of sex-related neurodevelopmental differences between males and females [2–4]. It remains unclear whether there are similar or different neural circuit risk pathways for psychosis between the sexes. It is well-known that men and women with schizophrenia show a number of differences including prevalence, age of onset, cognitive burden, and functional outcomes [5]. There is also evidence that similar sex differences in symptoms, functioning, and brain structure exist in CHR groups [6, 7]. Sex differences in brain structure and function may themselves be age-dependent. Childhood and adolescence are important periods of brain maturation and reorganization, involving increasing functional modularity and long-range

connections [8–10]. Puberty is also a period when there is a large shift in decision-making, sensory associations, attention, reward processing, and motivation that are related to changing brain structure and functioning [11].

The striatum and thalamus, and specifically the cortico-striatal–thalamic–cortical (CSTC) circuit is involved in these processes and is consistently implicated in psychosis, and other neurodevelopmental disorders. In healthy youth, recent work has shown sexual dimorphism in development of CSTC structure, including (1) rates of change across age and timing of striatal and thalamic volume peaks [4] and (2) increased differences between sexes across age [3]. Significant abnormalities in overall measures of striatal and thalamic structure, as well as within subdivisions (known to be diversely connected across the cortex structurally and functionally [12, 13]) have been observed in schizophrenia [14, 15], including sex-dependent differences [16]. Functional imaging studies have also found maturational changes between children and adults in thalamo–cortical and striato–cortical connectivity, which differ based on the subdivision of subcortical structures examined [17, 18]. Striato–cortical

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Table 1. Demographic summary statistics by psychosis spectrum symptoms group and sex for structural analyses of striatal and thalamic subdivision volumes

	Demographics for structural volume analyses									
	PSS females (<i>n</i> = 167)		PSS males (<i>n</i> = 133)		Diff (<i>p</i> value)	Non-PSS females (<i>n</i> = 443)		Non-PSS males (<i>n</i> = 352)		Diff (<i>p</i> value)
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age (years)	15.3	2.6	14.9	2.8	<i>t</i> = 1.4, n.s	15.9	2.8	15.5	2.7	<i>t</i> = 2.0, <i>p</i> < 0.05
IQ estimate	95.6	15.8	99.8	17.9	<i>t</i> = 2.1, <i>p</i> = 0.03	103.2	17.1	105	17.0	<i>t</i> = 1.4, n.s
Global functioning	72.1	12.7	71.1	13.6	<i>t</i> = 0.5, n.s	82.0	9.9	82.2	9.8	<i>t</i> = 0.24, n.s
Positive symptom severity	24.8	14.0	24.7	14.4	<i>t</i> = 0.1, n.s	4.2	6.1	4.9	6.6	<i>t</i> = 1.3, n.s
Negative/disorganized symptom severity	4.7	4.4	5.6	4.8	<i>t</i> = 1.8, <i>p</i> = 0.07	1.4	1.7	1.6	2.0	<i>t</i> = 2.0, <i>p</i> = 0.02
Medication use (%)	13.2%		18.0%		χ^2 = 0.9, n.s	5.4%		7.1%		χ^2 = 0.5, n.s

IQ was measured using standardized Wide Range Achievement Test 4 (WRAT) scores and functioning was measured using the Global Assessment of Functioning (GAF). Positive symptom severity was calculated as an accumulated score of severity across symptoms assessed using the PRIME Screen-Revised and negative/disorganized symptom severity was calculated using severity measures from the Scale of Prodromal Symptoms (SOPS). Continuous variables were analyzed for PSS group differences within sex using a two-tailed Welch two sample *t* test, while a Pearson chi-squared test (two-tailed) was used for medication use. See also Table S1 for demographic summary statistics for participants included in functional connectivity analyses

and thalamo-cortical dysconnectivity are replicated findings in both chronic schizophrenia and those in the prodrome or at CHR for psychosis [19–21], indicating a marker of illness that emerges from early stages.

Those with psychosis spectrum symptoms (PSS), defined in studies of the Philadelphia Neurodevelopmental Cohort (PNC), may exhibit an even earlier potential risk phenotype than the prodrome. Based on studies of CHR individuals, presence of PSS symptoms captures a risk for psychosis spectrum disorders as well as general psychopathologies [1]. Accumulating evidence indicates that youth with PSS have impairments in cognition, general everyday functioning [22], and altered brain structure and connectivity [23, 24]. Like sex, age (and associated neurodevelopment) may play a crucial role in dictating the timing of neurobiological changes that predispose a young person toward experiencing PSS. Investigating divergences related to sex and age in youth with PSS, may provide insight into varying risk trajectories that explain differences observed in adults with more severe presentations of psychosis spectrum disorders.

In a large population sample of youth, we aimed to examine structural and functional properties of the CSTC circuit considering PSS, biological sex, and age. Due to the known diversity in connectivity and functioning of subdivisions of both the striatum and thalamus [12, 13], we investigated characterizations of both whole structures and subdivisions. We compared four groups: females with and without PSS, and males with and without PSS. We anticipated that there would be CSTC circuit abnormalities in PSS youth compared to non-PSS youth, but that those differences will be primarily driven by males. Specifically, we hypothesized (1) sex-dependent volumetric differences between PSS and non-PSS groups would be present within subdivisions of the striatum and thalamus, (2) sex-dependent functional connectivity differences with subdivisions would be present between PSS and non-PSS groups, and (3) age-related effects would emerge within sex-dependent patterns in PSS and non-PSS groups in both volume and functional connectivity.

METHODS

Sample

The publicly available PNC dataset consists of a sample of children and youth aged 8–21 characterized with multimodal magnetic resonance imaging (MRI), cognitive and psychopathology

assessments (Table 1, Table S1). Recruitment procedures for this catchment area cohort have been previously described [22]. All participants provided written informed consent. For youth under 18, both written informed consent and parental/legal guardian permission were acquired. The University of Pennsylvania and the Children's Hospital of Philadelphia Institutional Review Boards approved all procedures. Use of the PNC data for this study was approved by the Centre for Addiction and Mental Health research ethics board. Participants were administered the structured interview GOASSESS, which screened for psychopathologies and medical history. It is a modified and abbreviated version of the National Institute of Mental Health Genetic Epidemiology Research Branch Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) [25]. Categorization to be included in the PSS group was calculated as previously outlined [22] and screening was evaluated using the PRIME Screen-Revised to assess subpositive symptoms [26], the K-SADS to assess positive symptoms [27], and the Scale of Prodromal Symptoms (SOPS) to assess negative/disorganized symptoms [28] (see Supplemental Materials). The PSS group in the PNC is distinct from a CHR sample as it encompasses a wider range of symptom severity and is not limited to youth that are help-seeking. A portion of the sample (~20%) were taking medications for problems related to their mood or behavior. Medication names/classes and dose were not disclosed.

We excluded participants aged 8–10 years old from our analyses because of increased motion, a reduction in prevalence of PSS in this lower age range (resulting in a greater skew than the remainder of the sample) and unavailability of self-reported clinical data (Fig. S1).

Image acquisition and processing

T1-weighted structural and resting-state (120 TRs, TR = 3000 ms, TE = 32 ms) functional MRI, all collected on a single 3T Siemens TIM Trio whole-body scanner, were acquired as previously described [29] (Supplemental Materials).

Structural

The striatum was segmented into five bilateral subdivisions including the nucleus accumbens, anterior caudate, posterior caudate, anterior putamen and posterior putamen. The thalamus was segmented into 11 bilateral fields, including the medial dorsal, pulvinar, anterior, ventral anterior, ventral posterior, ventral lateral, lateral posterior, lateral dorsal, central, lateral and medial geniculate nuclei. The Colin27 subcortical atlas [30] was used and

Fig. 1 Structural and functional parcellation labels for striatal and thalamic subdivisions and seeds. **a** shows the structural segmentation using the MAGEt. Brain algorithm shown in (**b**) as adapted from Chakravarty et al. [31], using an atlas created from the 3D reconstruction of serial histological data [30] to create anatomically distinct regions within the striatum and thalamus. **c** shows functional segmentation of the striatum [35] and thalamus [36] into seven seeds based on their intrinsic resting-state functional connectivity with the seven networks from Ye et al. [34] (**d**)

subdivisions were labeled from a 3D reconstruction of a serial histological dataset [31] using Multiple Automatically Generated Templates (MAGEt) Brain [32] (Fig. 1a and b). Further details are provided in Supplemental Materials. Intracranial volume was calculated using the Freesurfer toolkit (v.5.3) for use as a covariate. T1-weighted images ($n = 1598$) and segmentation labeling were all visually examined and removed if there was significant motion, artifacts, or incorrect subcortical segmentation to control for data quality ($n = 204$). Further exclusion criteria included presence of neurological disorders, head injuries resulting in a skull fracture, or other potential abnormalities that could affect brain development ($n = 67$), as well as an age below 11 ($n = 232$).

Functional

Resting-state functional MRI (fMRI) scans ($n = 1395$) were preprocessed using a combination of FSL and AFNI packages as described in detail in the Supplemental Materials. Following this, fMRI images were non-linearly transformed to MNI space,

and then resampled to MNINonLinear-fsaverage_LR32 grayordinates space using a workflow adapted from the Human Connectome Project Minimal Processing Pipeline to register data into a combined volume and cortical surface-based analysis format (cifti format) [33]. Cortical surfaces were defined using FreeSurfer's recon-all pipeline (v.5.3). The fMRI data were smoothed along the cortical surface using a 2 mm full-width half-max Gaussian kernel. In-scanner motion for each individual was calculated as an average of framewise displacement across TRs and was included as a covariate in all functional analyses. Scans were excluded if they had too much motion, determined by a loss of more than 50 TRs during preprocessing ($n = 293$), as well as if youth had similar neurological conditions as described above ($n = 50$) or were below the age of 11 ($n = 143$).

We used the six thalamic and six striatal subdivisions as defined by assigning each voxel to one of seven functional networks (visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal, and default mode network) [34] based on vertex-

wide cortical surface connectivity (Fisher's Z-transformed Pearson's r) as outlined in Choi et al. [35] and Ji et al. [36] (Fig. 1c and d). Visual network connectivity for the striatum and limbic connectivity for the thalamus were negligible and thus these subdivisions were excluded from analyses (Supplemental Materials). These subdivisions were each used as seeds to compute whole-brain functional connectivity maps. This included first extracting the mean BOLD time-series across all voxels within a given subject for each of the seeds. Next, the correlation (Pearson's r) between the seed mean and the BOLD time-series of every vertex on the surface of the brain was calculated and transformed to Fisher's Z-values. This yielded six thalamic and six striatal whole-brain Fisher's Z-values maps for each subject ($n = 909$).

Structural statistical analyses

A two-way and three-way analysis of covariance (ANCOVA) for each subdivision was used to examine the interaction between PSS group and sex, as well as PSS group, sex, and age on volume. Intracranial volume (ICV) and an estimate of IQ, the Wide Range Assessment Test 4 [37] (WRAT), were included as covariates for all analyses, and age was included for the two-way ANCOVAs. A linear fit was first tested, followed by quadratic and cubic fits for continuous covariates. ICV was the only covariate included in the model using a quadratic function, because it led to an increased model R^2 and decreased variance. For thalamic and striatal subdivisions observed to have a significant interaction between PSS group and sex, follow-up analyses of pairwise t tests were carried out to assess volume differences between the four groups. Correction for multiple comparisons of the 32 subdivisions and follow-up t tests within subdivision were conducted using a false discovery rate (FDR) of 5%.

Functional statistical analyses

Parallel and independent analyses were conducted for the striatum and thalamus. Primary analyses included examining connectivity with whole striatal and thalamic structures, individual seeds, as well as interactions across age. Within-subject and between-group differences in striato-cortical and thalamo-cortical functional connectivity were formally tested across seeds by entering all vertex-wise seed-based maps for each structure (six per participant) into a three-way ANCOVA (PSS group by sex by seed). F tests were used to test for significant differences between sexes and PSS groups across all functional seeds of the striatum and the thalamus, as well as for interaction effects between PSS group and seed, PSS group and sex, or PSS group, seed and sex. Interactions, as well as main effects of PSS group and sex for individual seeds were also examined using t -tests. Further, interactions between age and PSS group, as well as between PSS group, sex, and age for both whole structures and individual striatal and thalamic seeds were evaluated to determine the effects of age on group differences. In addition, in-scanner motion (mean framewise displacement) and WRAT score were mean-centered by group and included as covariates to be regressed out of analyses. All statistical effects were evaluated non-parametrically using FSL's permutation analysis of linear models with 2000 permutations and tail approximation [38]. Threshold-free cluster enhancement (TFCE) [39] was applied to avoid using arbitrary thresholds when testing for statistically significant regions. Because spatial statistics such as TFCE inherently depend on spatial properties of the particular representation of the brain (e.g., surface or volume), we permuted the left and right cortical components separately and applied a family-wise error rate (FWER) correction for multiple vertex-wide comparisons to each component. Lastly, to keep the family-wise alpha for the entire family of comparisons (left and right cortices) at 0.05, a Šidák-Bonferroni correction for the two independent components

was applied to threshold resulting statistical images. Visualizations were conducted using Connectome-Workbench software [40].

Following findings of connectivity changes across age, secondary post-hoc analyses were performed to further investigate differences between youth with and without PSS, to help determine whether important findings were missed by examining the entire sample together. The sample was divided into younger (age 11–15, $n = 401$) and older adolescents (age 16–21, $n = 508$) based on age interaction findings and all analyses (except age interactions) were repeated (Tables S2 and S3).

RESULTS

Sex-dependent striatal and thalamic subdivision volume differences in youth with PSS

There was a significant interaction effect between sex and PSS group when covarying for age, ICV and WRAT score in total thalamic volume ($F = 7.1$, $p < 0.009$), but not total striatal volume. Analyses comparing striatal and thalamic subdivision volumes showed significant FDR thresholded interaction effects between sex and PSS group in nine regions. Significant thalamic subdivisions included the bilateral pulvinar (left: $F = 12.0$, $p_{FDR} < 0.02$, right: $F = 7.5$, $p_{FDR} < 0.04$), left ventral posterior nucleus ($F = 9.9$, $p_{FDR} < 0.03$), bilateral medial dorsal (left: $F = 8.1$, $p_{FDR} < 0.04$, right: $F = 6.7$, $p_{FDR} < 0.04$), bilateral lateral geniculate nuclei (left: $F = 6.2$, $p_{FDR} < 0.05$, right: $F = 6.7$, $p_{FDR} < 0.04$), and left medial geniculate nucleus ($F = 7.4$, $p_{FDR} < 0.04$) in addition to the right posterior putamen of the striatum ($F = 7.0$, $p_{FDR} < 0.04$). Across all subcortical subdivisions showing a significant PSS group by sex interaction effect, there were higher volumes in PSS males compared to non-PSS males, while lower volumes were found in PSS females compared to non-PSS females (Fig. 2, Table S4).

In addition, all significant differences in volumes were observed when original analyses were repeated in a subsample of youth that overlapped for inclusion in both structural and functional analyses ($n = 880$).

Increased striatal subdivision volume differences between PSS groups across age

Investigations of three-way interactions between PSS group, sex, and age showed trending findings restricted to (and only present before FDR correction) the left ($F = 3.46$, $p < 0.053$) and right ($F = 3.74$, $p < 0.062$) posterior putamen. With increasing age, there was an increasing difference in volume between PSS and non-PSS groups both in females and males. The difference between PSS groups was greater with increased age in males compared to females (Fig. S2).

Medication use associated with lower thalamic subdivision volumes in males with PSS

When youth taking medication ($n_{PSS} = 46$, $n_{non-PSS} = 49$) were excluded in a follow-up analysis, effect sizes and the number of subdivisions meeting significance for an interaction between PSS group and sex on volume increased to fourteen regions, including the bilateral central nuclei (left: $F = 7.2$, $p_{FDR} < 0.02$, right: $F = 7.4$, $p_{FDR} < 0.02$) of the thalamus.

This impact on the results appeared to be driven by the existence of lower subdivision volumes in males with PSS taking medications, as opposed to the higher volumes seen in unmedicated PSS males. When the sexes were evaluated separately, and ICV, WRAT, and age were included as covariates, there was a significant interaction between PSS group and medication use in males in five thalamic subdivisions (Fig. S3), including the right central nucleus ($F = 9.5$, $p < 0.003$) and right medial dorsal ($F = 6.3$, $p < 0.02$). These findings did not survive FDR correction.

Fig. 2 Volumes for thalamic subdivisions (**a**) and striatal subdivisions (**b**) shown in females and males with and without PSS. Significant PSS group by sex interactions are indicated by an asterisk and significance bars indicate post hoc tests comparing volumes of the four groups. Graphs indicate volume Z-score averages and standard error after adjustment for age, ICV, and WRAT score. ** = significant differences that survived a 5% FDR correction, * = survival of a 10% FDR correction. See also Table S4 for a summary of statistical differences between sex and PSS groups

Sex-dependent altered functional striato-cortical connectivity in youth with PSS
 There were no significant differences between PSS groups, or interactions between PSS group and sex in striato-cortical

and thalamo-cortical connectivity when examining the whole structures across seeds and covarying for age, motion, and WRAT score. However, comparisons of individual striatal and thalamic seed connectivity with cortical surfaces

Fig. 3 Significant functional differences between PSS groups in all youth and only within males where there was a significant decrease in connectivity between the striatal dorsal and ventral attention seeds with the visual cortex. Scale bar indicates Z-scores of significant correlation differences after a FWER correction for vertex-wise analysis and a Šidák-Bonferroni correction for separate analyses of each hemisphere

(regressing out age, motion, and WRAT score) revealed significant hypo-connectivity between the striatal dorsal attention seed ($p_{\text{FWER}} < 0.008$) and ventral attention seed ($p_{\text{FWER}} < 0.02$) with predominantly the occipital cortex (visual and dorsal attention networks) [34] in youth with PSS. This effect was driven by significant striato-cortical connectivity reductions in males with PSS ($p_{\text{FWER}} < 0.007$, Fig. 3).

Changing connectivity across age in early and late adolescence Although there were no main effects of PSS group on whole striatal and thalamic connectivity across seeds when covarying for age (as above), there was a significant PSS group by sex by age interaction effect observed between the whole thalamus and similarly the occipital cortex (visual and dorsal attention networks, Fig. 4a). Following analyses comparing individual striatal and thalamic seed connectivity with cortical surfaces (as described above), it was found that within male youth only, there were significant PSS group by age interaction effects between cortical areas and the thalamic visual ($p_{\text{FWER}} < 0.004$), somatomotor ($p_{\text{FWER}} < 0.009$), and ventral attention ($p_{\text{FWER}} < 0.002$) seeds, as well as striatal ventral attention seed ($p_{\text{FWER}} < 0.02$).

Younger males with PSS appeared to have decreased average connectivity compared to younger non-PSS males, whereas older PSS males demonstrated increased connectivity compared to older non-PSS males. (Fig. 4b). To further investigate differences across age that emerged, secondary analyses repeating previous testing were done after dividing the sample into younger adolescents (age 11–15, $n = 401$) and older adolescents (age 16–21, $n = 508$). This showed significant interactions between PSS group and sex in several striatal and thalamic seeds with mainly the visual cortex in younger adolescents. This prominent effect of hypo-connectivity was specific to younger PSS males, with younger PSS females having significantly greater connectivity than this group in many of these same regions. Alternatively, in late adolescence, there was increased connectivity in PSS males compared to non-PSS males between the striatal default mode network seed and somatomotor cortex ($p_{\text{FWER}} < 0.02$). Further

details and figures are provided in Supplemental Materials (Figs. S4–S6).

DISCUSSION

Using structural and functional MRI, we examined the effects of PSS, sex, and age on structural and functional properties of the CSTC circuit. By including biological sex as a variable, we found vulnerability pathways in the CSTC circuit associated with PSS that would not have been revealed in a main effect analysis. Further, consideration of age effects provided additional vulnerability pathways in the CSTC circuit that differed by developmental time point. By studying both brain structure and function, our results illuminate CSTC circuit vulnerability during brain development in a manner not possible with either approach alone. Striatal and thalamic volumes were affected in both PSS males and PSS females, but in opposing directions. Functional connectivity of many of these same overlapping subdivisions and seeds were altered in the same direction, but more prominently in PSS males. Age interactions in functional connectivity of striatal and thalamic seeds in PSS males were marked by hypo-connectivity to predominantly the visual cortex in younger males vs. hyper-connectivity with somatomotor regions in older males.

Sex-dependent alterations in striatal and thalamic subdivision volumes in youth with PSS

Our findings of striatal and thalamic subdivision volume abnormalities in PSS youth are consistent with observations in schizophrenia [14, 15] and youth with psychosis [41, 42]. Specifically, the thalamic changes that we found in the pulvinar and medial dorsal nucleus have been reported in schizophrenia with a previously identified similar increase in medial dorsal thalamic volume in males compared to females with schizophrenia [16]. Opposite volume differences between PSS groups in sexes is consistent with findings of alterations in CHR youth in other subcortical and cortical areas [7]. Sex differences have not been formally examined in thalamic subdivisions in CHR youth to

Fig. 4 Significant findings of functional connectivity interactions between PSS group and age both in the entire thalamus in (a) as well as individual seeds in (b). Age interactions in males show differences in functional connectivity between PSS groups in early versus late adolescence. Graphs show average Fisher Z transformed correlations between the seeds and highlighted cortical areas for each individual. Scale bar indicates Z-scores of significant correlation differences after a FWER correction for vertex-wise analysis and a Šidák–Bonferroni correction for separate analyses of each hemisphere

our knowledge, and although whole volume reductions tend to be observed in CHR and first-episode groups [43], these samples are often significantly older than the PSS youth studied here (mean age 15.4 ± 2.6). Higher striatal volumes have been observed in childhood onset schizophrenia (mean age 17.6 ± 3.9), in a predominantly male sample [36]. In normal development, volumes of the striatum and thalamus increase in childhood, peak in early adolescence (earlier for females), and then begin declining [4]. Opposing volume differences by sex in our PSS groups may be indicative of maturational delays that onset at different stages of development related to diverging mechanisms involved in PSS. Striatal and thalamic structures in females with PSS may not reach their peak volumes resulting in lower volumes across adolescence. Striatal and thalamic structures in males with PSS may be exhibiting delayed development later via a lack of volumetric decline, which is typically more pronounced in males compared to females [3] during normal maturation.

Reductions in functional connectivity with the visual cortex in youth with PSS

Alterations in functional connectivity between striatal and thalamic seeds with the visual cortex are consistent with several studies in schizophrenia [36, 44, 45]. However, our observed hypo-connectivity findings in PSS youth, while consistent with some findings [46], conflict with the hyper-connectivity found in schizophrenia between these regions. In addition, reductions in either striatal or thalamic connectivity with frontal cortical regions found in schizophrenia [36, 44, 45, 47], first-episode psychosis [45] and CHR [19, 21] were not seen in either PSS males or females. Our findings of altered connectivity with sensory regions might be consistent with the primarily adolescent developmental time period of our sample and the maturation of these connections [13, 17]. Samples older than the present study may display the altered connectivity with frontal regions identified due to the later maturation [9] of the frontal cortex and subcortical connectivity to frontal regions [10].

Amplified brain abnormalities observed in males is consistent with findings in psychosis and may be related to elevated negative and cognitive symptoms, as well as an eventual poorer course of illness [1, 5]. Sex-dependent differences identified in males with PSS might also relate to age of onset, with an earlier onset in males coinciding with earlier emergence of circuit abnormalities. Fewer women develop schizophrenia by early adulthood, and disease expression is often milder; this improved outcome may be reflected in more similar neural functioning to youth without PSS at earlier stages related to diverging neurodevelopment trajectories and sex-dependent risk for psychosis.

Overlapping structural and functional CSTC pathway abnormalities in PSS

Both alterations in volume and connectivity of the CSTC pathway found in youth with PSS were localized to striatal and thalamic subdivisions principally involved in sensory and motor processing [12, 13]. In the striatum, volumes were altered in the posterior putamen (involved in sensorimotor functioning), which overlaps with the dorsal and ventral attention striatal seeds located in the posterior and anterior putamen (involved in social and language functioning) [13]. Thalamic subdivision volumes significantly altered in youth with PSS also overlap anatomically with the seeds we found demonstrating altered functional connectivity. These subdivisions, such as the lateral and medial geniculate nuclei primarily connect functionally to sensory processing areas, while the ventral posterior nucleus connects to motor processing areas, and the medial dorsal and pulvinar nuclei connect to both sensorimotor and executive functioning regions [12]. Reductions in cortical thickness in regions of the occipital and parietal cortex overlapping with areas observed to have functional connectivity

differences in this study have previously been found in PSS youth in the PNC [24]. Taken with present findings, this supports overlapping structural and functional abnormalities in the CSTC circuit specifically involving striato-occipital and thalamo-occipital pathways.

Decreases in connectivity observed between these striatal and thalamic seeds with the visual and dorsal attention networks in the occipital and parietal cortex could indicate impaired or delayed maturation of sensorimotor integration, as shown across a spectrum of psychotic symptoms [48]. Widespread deficits in visual and sensory perception are found in schizophrenia [49], as well as in CHR youth [50]. In addition, these abnormalities localized to connectivity with the dorsal attention network may underlie impaired decision-making related to top-down attention to visual stimuli [51]. The increased presence of negative and cognitive symptoms in males with PSS compared to females with PSS (consistent with sex differences in CHR [1] and schizophrenia [5]), including attention and focus deficits may be related to sex-dependency of connectivity abnormalities.

Differences in CSTC functional connectivity alterations in early and late adolescence

The significant interactions across age for thalamic seed connectivity further support age-dependent functional changes in the CSTC circuit associated with PSS during development. Reductions in connectivity between the visual cortex and subcortical regions were predominantly found in younger PSS males, with most effects not significant in older PSS males (compared to non-PSS older males). This is in contrast to the hyper-connectivity between the striatal default mode seed and somatomotor cortex present only in older PSS males that is more consistent with the schizophrenia and psychosis literature. These shifting, age-dependent alterations might relate to a compensatory or developmental mechanism consisting of earlier hypo-connectivity with sensory areas (specifically the visual cortex) potentially related to early altered processing of sensory information, that leads to derailment of normal circuit development and later overcompensation. Unlike in adults with schizophrenia, no change or a directional decrease (although not significant) [20] in subcortical connectivity with the visual cortex in CHR [19, 20] and first-episode psychosis [45] has been reported. These phases of illness might be an intermediate stage (between milder PSS and 'full-blown' psychosis) where alterations in connectivity are transitioning from under to over-connectivity. In addition, timing of these circuit changes coincide with puberty in adolescence when sex hormones impact behavior and the brain through reorganization of sensory, association and reward systems [11]. Findings of sexual dimorphic CSTC circuit abnormalities could also be related to differing distributions of sex hormone androgen and estrogen receptors within subdivisions of the striatum and thalamus. Overlapping with our observed sex-dependent altered volumes in the pulvinar, ventral posterior nucleus, and medial geniculate nucleus, androgen receptors have been found with an absence of estrogen receptors in these same areas in rodents [52]. Furthermore, it is well-known that estrogen and dopamine systems interact to modulate striatal functioning [53].

Strengths and limitations

This study examined non-help-seeking youth with PSS from a community sample that largely avoids confounding factors such as medication use, long-term substance use, and duration of illness. The PNC sample also offers other advantages such as its large size and collection of imaging data on a single scanner. The PNC draws from a sample with a wide range of symptom severity, and an unknown (but likely low) specificity for PSS preceding development of schizophrenia over other psychiatric illnesses with psychosis and impaired functioning in general. Only a minority of participants were taking medication, but we were unable to more

precisely investigate effects of type and dosage as such information was not made available. We were also unable to examine pubertal status and its relationship with the observed sexual dimorphism and changes across age in the CSTC circuit as the pubertal data for this sample is not available. Further, interpretations of age effects are limited by the cross-sectional data. Another limitation is the inherent bias introduced into a sample due to correction or exclusion of participants for in-scanner head motion. Alterations in connectivity and biased exclusion are related to factors such as age, sex, and psychopathology [54], and led to the inclusion of proportionately more females in analyses, and exclusion of some of the most symptomatic participants.

CONCLUSION

In conclusion, structural and functional sex-dependent alterations in the CSTC circuit indicate early abnormalities in youth with PSS, with a clear pattern of structural sexual dimorphism. Some of the observed changes were age-dependent, particularly functional connectivity abnormalities in males with PSS. These male driven findings may point towards protection against these connectivity abnormalities in females, which might explain lower prevalence or later onset of more severe illnesses such as schizophrenia.

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AUTHOR CONTRIBUTIONS

Conceptualization: ANV and AA; methodology: GRJ, JLJ, JDV, EWD, and SS; formal analysis: GRJ and JLJ; resources, ANV and AA; writing—original draft: GRJ, ANV, EWD, and JDV; writing—review and editing: all authors; visualizations: GRJ; supervision: ANV, SHA, and ALW.

ADDITIONAL INFORMATION

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