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Pre-onset sub-threshold psychotic symptoms and cortical organization in the first episode of psychosis

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Abstract:

Individuals with sub-threshold psychotic symptoms (STPS) are considered at clinical high risk for psychosis (CHR). Imaging studies comparing CHR and patients shortly after a first episode of psychosis (FEP) support progressive cortical thinning by illness stage. However, at least 30% of FEP patients deny pre-onset STPS, suggesting no history of CHR. This calls into question the generalizability of previous imaging findings. To better understand the physiology of early psychosis symptomology, we investigated the relationship between pre-onset STPS and cortical thickness (CT) among FEP patients, examining regional CT and structural covariance (SC). Patients (N=93) were recruited from PEPP-Montreal, a FEP clinic at the Douglas Mental Health University Institute. The Circumstances of Onset and Relapse Schedule was administered to retrospectively identify patients who recalled at least one of nine expert-selected STPS prior to their FEP (STPS+, N=67) and to identify those who did not (STPS-, N=26). Age and sex-matched healthy controls (HC) were recruited (N=84) for comparison. Participants were scanned between one and three times over the course of two years. CT values of 320 scans (143 HC, 123 STPS+, 54 STPS-) that passed quality control were extracted for group analysis. Linear mixed effects models accounting for effects of age, sex, education, and mean thickness were applied for vertex-wise, group comparisons of cortical thickness and SC. Multiple comparison corrections were applied with Random Field Theory (p-cluster=0.001). Compared to controls, only STPS- patients exhibited significantly reduced CT in a cluster of the right ventral lateral prefrontal cortex. The vertex with the highest t-statistic within this cluster was employed as a seed in the subsequent SC analysis. After RFT-correction, STPS+ patients exhibited significantly stronger SC between the seed and right pars orbitalis compared to STPS- patients, and HC exhibited significantly stronger SC between the seed and right middle temporal gyrus compared to STPS-

patients. Our results revealed patterns of SC that differentiated patient subgroups and patterns of cortical thinning unique to STPS- patients. Our study demonstrates that the early course of sub-threshold psychotic symptoms holds significance in predicting patterns of CT during FEP.

Key Words:

Psychosis

Clinical High Risk

Structural Covariance

Cortical Thickness

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1. Introduction

The first episode of psychosis (FEP) is associated with reduced grey matter volume (GMV) and cortical thickness (CT) compared to healthy controls.[1–4] However, it is still unclear when such trends emerge in development. The advent of the clinical high risk (CHR) for psychosis, in addition to proposing a target for prevention, offers the opportunity to characterize the chronology of such grey matter changes. CHR is most commonly characterized by sub-threshold psychosis symptoms (STPS), lower in intensity and/or duration than symptoms associated with a full-blown episode,[5,6] and has been shown to indicate significantly elevated risk for a psychotic episode.[7,8] It is often assumed to precede a FEP. Cross sectional studies comparing individuals at CHR, FEP patients, and controls reveal a progression of grey matter reduction,[9,10] while longitudinal studies comparing individuals at CHR who eventually convert to a FEP (converters) versus those who do not convert (non-converters) reveal more extensive loss of grey matter among converters.[11–14] Together, these imaging studies validate a "CHR to FEP" framework for psychosis development. However, this narrative is complicated by recent findings, including our own, that at least 30% of FEP patients have no identifiable period of STPS before their FEP,[15,16] suggesting that not all FEP patients endure an earlier "at-risk" stage as it is currently defined. Furthermore, we found that a history of STPS was consequential in FEP as it predicted poorer symptomatic and functional outcomes after a year of treatment compared to FEP patients with no history of STPS.[17] As with imaging findings differentiating CHR converters and non-converters, FEP patients with and without a prior CHR stage may exhibit differences in brain maturation.

Grey matter loss is particularly pronounced early in psychosis,[18] highlighting the need to consider aspects of early illness course, including STPS. Importantly, many CHR studies include

at-risk individuals who were antipsychotic-naïve,[9,12,14] suggesting that the observed cortical changes are more likely related to the course of illness rather than an artefact of treatment effects. The importance of examining this early phase of illness is further underscored by evidence that differences in STPS severity and duration predict significant differences in magnitude and rate of grey matter loss, regardless of conversion to full-blown psychosis.[14,19,20] Together, these findings raise the possibility that FEP patients with a prior CHR state ("converters," STPS+) and patients with no such history (STPS-) may differ in these early cortical trends.

Neurologically, psychosis is regarded as a disorder of dysconnectivity. White mater imaging and post mortem histopathology support this claim, including studies examining abnormalities among samples at CHR.[21–25] As such, there is value in appreciating interregional relationships in addition to focal regions. In normal maturation, the structural covariance (SC) of regions within key networks including language/semantic processing, executive control, and default mode are known to change. While SC relationships evolve with age,[26–28] the pattern of change appears to be different among individuals at CHR,[29] suggesting that like psychosis-associated regional grey matter differences, psychosis-associated SC patterns emerge before onset.

In the present study, our objective was to investigate whether the STPS classification (STPS+ versus STPS-) predicts differences in cortical organization by examining cortical thickness and SC over the course of two years of FEP treatment. We hypothesized that STPS+ patients would exhibit greater reductions in cortical thickness compared to STPS- patients and that such regions of reduced cortical thickness would reveal group differences in SC.

2. Methods

2.1 Clinical Sample

The FEP patients included in the current study were recruited between 2004 and 2013, from the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal), an integrated clinical research infrastructure at the Douglas Mental Health University Institute serving a catchment area of approximately 300,000 individuals in south-west Montreal, Canada. Patients from the program were eligible to participate in PEPP-Montreal's longitudinal research neuroimaging study if they : 1) were between ages 18 and 35; 2) were diagnosed with an affective or non-affective psychotic illness (not attributable to substance use alone) based on the Structured Clinical Interview from DSM-IV;[30] 3) were medication-naïve (less than 1 month of antipsychotic medication); 4) had an IQ≥70; and 5) had no neurological disorders. The research study was approved by the Douglas Mental Health University Hospital's ethics review board. All participants provided written informed consent.

Of the 150 FEP patients recruited for study participation, 32 were excluded from the current analysis because they did not complete the Topography of Psychotic Episode (TOPE) questionnaire, the retrospective instrument used for STPS classification (described in 2.2). Among the remaining participants, 2 were excluded for having previously received CHR service for STPS, and 23 were excluded for poor structural magnetic resonance imaging (MRI) scan quality (described in 2.3). Imaging data from a total of 93 FEP patients were included in the current study.

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2.2 Healthy Control Sample

Ninety-five healthy controls between the ages of 18 and 35 were recruited and fulfilled the following inclusion criteria: 1) no Axis 1 disorder; 2) no first-degree relative with psychosis; and 3) no neurological disorder. Of the 95 age/sex-matched healthy controls recruited, data from 84 participants were included in the current analyses. One participant was excluded due to IQ<70, one did not follow through with screening, one did not participate in scanning procedures, and the remainder were excluded due to poor image quality (described in 2.3).

2.3 Defining STPS+/-

To retrospectively assess history of STPS, FEP patients were administered the Topography of Psychosis Episode (TOPE) from the Circumstances of Onset and Relapse Schedule.[31] Patients who either had health records documenting or themselves reported at least one of the following nine symptoms, which were selected by international experts as constituting STPS and indicative of symptomatic CHR (see Shah et al., 2017), were considered to have a STPS+ history: suspiciousness/odd ideas of reference, odd/bizarre ideas that are not delusional, odd/unusual/eccentric behavior, unusual perceptual experiences that are not clearly psychotic, disorganized/odd speech, inappropriate affect, hallucinations or delusions (sub-threshold), and passivity experiences. Patients with no history were considered STPS-.[16]

2.4 MRI protocol

Participants were scanned on a 1.5T Siemens Sonata whole body MRI System at the Montreal Neurological Institute. Structural T1-weighted volumes were acquired for each

participant using a three-dimensional gradient echo pulse sequence with sagittal volume excitation (resolution=1mm^3, repetition time=22ms, echo time=9.2ms, flip angle=30°, 180 1mm contiguous sagittal slices). The rectangular field of view (FOV) for the images was 256mm (AP) 204mm (SI). Scans were collected at three time points: baseline, one and two-year follow-ups. Throughout study participation, medication dosage (recorded in chlorpromazine (CPZ) equivalents) and percent adherence were measured for patients in the last month prior to their MRI scan. T1-weighted images were visually inspected for motion artefact. All scans were processed through the CIVET pipeline (version 2.1; http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET) for extraction of grey/white matter surfaces.[32] This method has been described previously by our group.[33] Main processing steps include: 1) Registration of T1-weighted images to standardized space[34] and correction for non-uniformity artefacts;[35] 2) segmentation of gray, subcortical gray and white matter, and cerebral spinal fluid;[36,37] 3) extraction of the white matter surface using a marching-cubes algorithm and extraction of the gray matter surface using the CLASP algorithm;[32] 4) surface registration to a template for inter-subject correspondence;[38] 5) reverse transformation (initially done in step 1) to estimate CT in native space for each subject at 81,924 vertices using the t-laplace metric;[39] and 6) smoothing the data in native space with a 30mm FWHM Gaussian kernel to diminish the impact of noise.[40] CT was estimated using the Laplacian distance between the two surfaces[41] across 81,924 vertices. Processed images were quality controlled for accurate grey/white matter extraction by visual inspection, using a rating system where 0=fail, 1=questionable, and 2=pass. A total of 177 participants completed between 1 and 3 MRI scans that passed (rating of 2) quality control inspection (84 HC, 67 STPS+, 26 STPS-), for a total of 323 scans (146 HC, 123 STPS+, 54 STPS-).

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2.5 Statistical Analyses

2.51 Medication

Medication exposure among FEP patients included in the imaging analysis was calculated by multiplying medication dosage by estimated adherence. A linear mixed effects model (shown below) controlling for the random effect of subject was applied to medication use (CPZ dose x adherence) among patients to evaluate any group (STPS+/-) differences:

$$M = intercept + \alpha + \beta(Group) + random(subject) + e$$

where M = CPZ equivalent dose x adherence, α represents random within-subject effects, β represents the regression coefficient for group and e represents residual error. Statistics were performed on SPSS version 22.[42]

2.52 Cortical Thickness

Imaging analyses were conducted using the SurfStat package for Matlab (http://www.math.mcgill.ca/keith/surfstat/). All analyses were performed using a vertex-wise approach across 81,924 vertices. For analyses of cortical thickness, a general linear model was applied with covariates that were selected using Akaike Information Criterion (AIC). The AIC method uses a likelihood function, rewarding goodness of fit and penalizing as the number of parameters increase.[43] The best fit for the cortical thickness data (the combination of variables with the smallest AIC value) included age, sex, years of education, and mean cortical thickness:

$$Y = intercept + \beta_1(Group) + \beta_2(Age) + \beta_3(Sex) + \beta_4(Years\ Education) + \beta_5(Mean\ CT) + e$$

where Y represents CT, $\beta_{1\text{-}5}$ represent regression coefficients, and e represents residual error.

Vertex-wise F-tests were performed to probe for main group effects at baseline. Pairwise t-tests were then applied post-hoc and corrected for multiple comparisons using Random Field Theory (RFT).[44] The following pairwise contrasts were considered in both directions: HC vs. STPS+ ; HC vs. STPS-; STPS+ -vs. STPS-. Aggregated data across time points were used to test for a group by age interaction, allowing us to examine whether there were any group differences in age-related trajectories of cortical thickness. This was achieved using a linear mixed effects model using the same covariates as above, and additional terms to include random within-subject effects (α, *random(Subjects)*) and (β_0*(Group x Age)*) for interaction. The group by age interaction was tested with vertex-wise F tests. In the event that the group by age interaction yielded no significant results, main effects of group were tested using the aggregated longitudinal data using the same statistical approach that was used for baseline data. This allowed us to determine whether baseline group effects were durable over two years of a FEP.

2.53 *Post-hoc* Structural Covariance analysis

Structural covariance is a metric derived from grey matter metrics (i.e. CT and GMV) that serves as a limited proxy for connectivity. Strong SC between cortical regions may reflect co-maturation or coupling; evidence suggests that functionally related regions are also more likely to exhibit stronger SC.[45] Although SC is not a direct measure of connectivity, significant overlap between patterns of SC and patterns of structural and functional connectivity suggest that these metrics are sensitive to common underlying mechanisms.[46,47] *Post-hoc* linear mixed effects

models were applied to assess group effects (HC, STPS+, and STPS-) on SC using a seed-based approach, informed by results from analyses above. Because regions of reduced cortical thickness have been shown to predict significant relationships in SC,[48] the peak vertex of any significant cluster(s) revealing a significant group difference in cortical thickness was employed as a seed in the SC analysis. SC analysis was performed using baseline scan with a general linear model, and again with scans pooled across time points with a linear mixed effects model as described above. This entailed adding the cortical thickness of the seed vertex as an additional term to the linear mixed effects model used in the primary analysis, shown below, allowing us to examine a main effect of seed by group interaction. The following model was employed:

$$Y = intercept + \alpha + \beta_1(Seed\ x\ Group) + \beta_2(Seed) + \beta_3(Group) + \beta_4(Age) + \beta_5(Sex) + \beta_6(Years\ Education) + \beta_7(Mean\ CT) + random(Subjects) + e$$

where Y_1 is the slope relating seed CT to CT of other brain regions, representing SC. Omnibus F-tests followed by RFT-corrected vertex-wise t-tests were similarly applied for pairwise comparison of groups.

3. Results

3.1 Medication by Group

Across time points, STPS+ and STPS- patients did not differ in medication exposure (CPZ equivalents prescribed x adherence) ($p>0.05$). Baseline sociodemographic characteristics are reported in Table 1. A more thorough clinical characterization of this sample at baseline and

12 months is provided in previous work by Shah and colleagues[16] and Rosengard and colleagues,[17] respectively.

Table 1: Baseline sociodemographic and clinical characteristics of healthy controls, patients with (STPS+) and without (STPS-) a history of sub-threshold psychotic symptoms. CPZ=chlorpromazine equivalents.

	STPS+	STPS-	Healthy Control
	N=67	N=26	N=84
Age, mean (sd)	24.2, 3.8	24.0, 3.5	24.4, 3.4
Female, n (%)	20 (30%)	8 (31%)	31 (37%)
Years of education, mean (sd)	12.1, 2.5	12.1, 2.3	14.4, 2.5
CPZ baseline (mean, sd)	2406, 2780	1771, 4109	n/a
CPZ 1 year (mean, sd)	1258, 2799	1278, 961	n/a
CPZ 2 year (mean, sd)	912, 853	642, 569	n/a

3.2 Cortical Thickness

Vertex-wise F-tests revealed no significant group by age interactions, but did reveal group effects at both baseline and longitudinally with peak statistics in the right prefrontal cortex (PFC). Post-hoc vertex-wise t-tests (RFT corrected) revealed that group effects were driven by a group difference between HC and STPS- patients where HC exhibited significantly thicker cortex in a cluster of the right ventral lateral PFC (vlPFC), capturing anterior regions of the middle and inferior frontal gyri (Figure 1). The group effect persisted longitudinally, in a smaller cluster (Figure 1B). No significant group differences were found between HC and STPS+ patients and between the two FEP groups across time points. Cortical thickness of the peak vertex in the longitudinal cluster (MNI space X=43; Y=45; Z=-5.8) is plotted by group over time in Figure 1 with accompanying images of the baseline and longitudinal p-maps.

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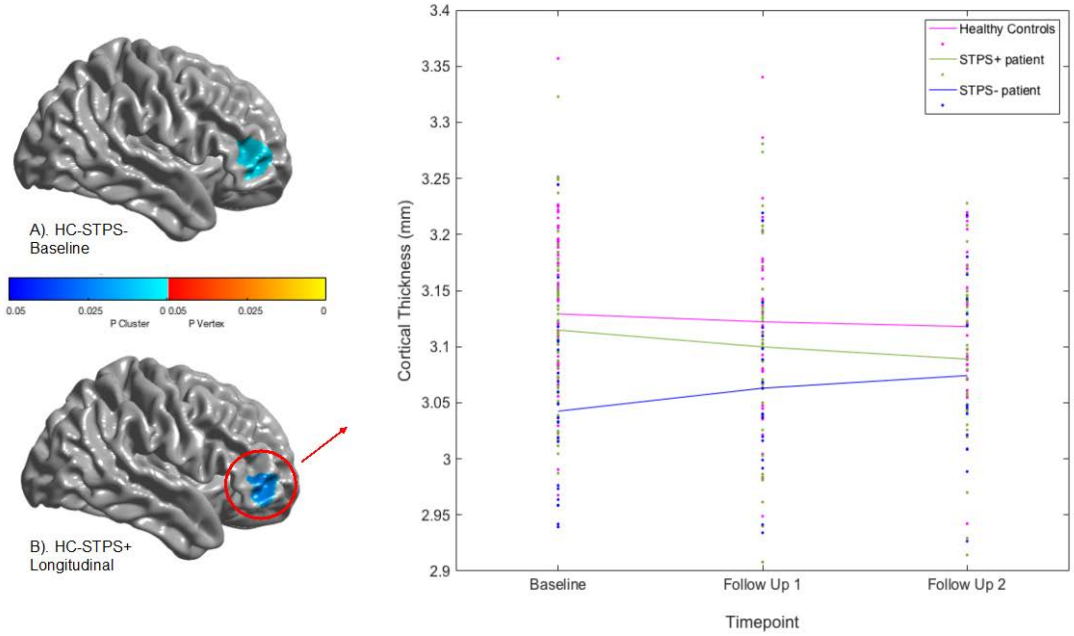

Figure 1: **Whole brain, vertex-wise cortical thickness group analysis.**
Sagittal view of RFT-corrected ($p < 0.001$) p-value map of baseline data with significant cluster in which healthy controls exhibited greater cortical thickness than patients with no history of pre-onset subthreshold psychotic symptoms (A); RFT-corrected p-value map of data across all time-points with significant cluster in which healthy controls exhibited greater cortical thickness than patients with no history of pre-onset subthreshold psychotic symptoms (B); Cortical thickness of peak vertex in longitudinal cluster (B; MNI space X=43; Y=45; Z=-5.8) plotted by group across time-points. Cortical thickness values are adjusted for age, sex, education, and mean whole-brain cortical thickness. HC=healthy controls; STPS- =patients with no history subthreshold psychotic symptoms; STPS+ =patients with history of pre-onset subthreshold psychotic symptoms.

3.3 Structural Covariance

The peak vertex of the significant right vlPFC cluster that emerged between HC and STPS- patients (MNI space X=43; Y=45; Z=-5.8) was employed as a seed (Figure 1B) in the SC analysis. Whole-brain, vertex-wise F-tests comparing all three groups revealed peaks in the right PFC and right temporal lobe. Post-hoc t-tests, corrected with RFT for multiple comparison, revealed a significant group difference between STPS+ and STPS- patients in the SC of seed cortical thickness and cortical thickness of the right pars orbitalis (Figure 2A; MNI space: X=47, Y=32, Z=-12). STPS+ patients exhibited a stronger association in cortical thickness between

regions, illustrated by a more positive slope in (Figure 2A). Post-hoc tests also revealed a significant group difference between HC and STPS- patients in SC between the cortical thickness of the seed region and cortical thickness of the right middle temporal gyrus (Figure 2B; MNI Space: X=68, Y=-35, Z=-4). HC exhibited a positive association between regions while STPS- patients exhibited a negative association (Figure 2B).

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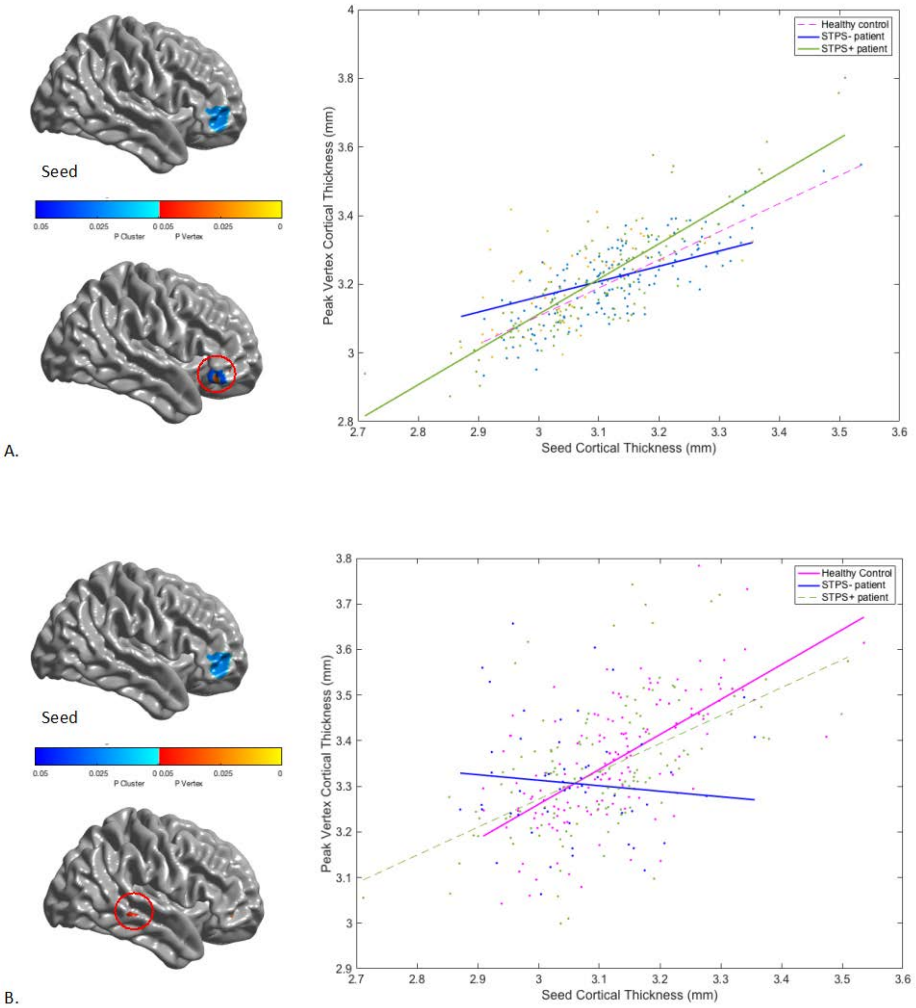

Figure 2: **Structural covariance analyses.**
A. Top: Sagittal view of cluster whose peak vertex (MNI space X=43; Y=45; Z=-5.8) was employed as a seed in whole-brain, vertex-wise structural covariance (SC) analyses, Bottom: Random Field Theory (RFT) corrected p-statistic map displaying regions where STPS+ patients exhibited significantly greater SC compared to STPS- patients, Right: Cortical thickness of seed vertex plotted against peak vertex of significant cluster of right prefrontal cortex (MNI space: X=47, Y=32, Z=-12) from SC analysis, by group. **B.** Top: Sagittal view of cluster whose peak vertex (MNI space X=43; Y=45; Z=-5.8) was employed as a seed in whole-brain, vertex-wise structural covariance (SC) analyses, Bottom: Random Field Theory (RFT) corrected p-statistic map displaying regions where healthy controls exhibited significantly greater SC compared to STPS- patients, Right: Cortical thickness of seed vertex plotted against peak vertex of significant cluster of right middle temporal gyrus ((MNI space: X=68, Y=-35, Z=-4) from SC analysis, by group.

4. Discussion

The current study explored the association between pre-onset STPS and cortical thickness over two years of a FEP. Most notably, we found that FEP patients with a history of STPS exhibited stronger SC within regions of the right prefrontal cortex (PFC), suggesting greater co-maturation between sub-regions compared to patients with no history of STPS. Specifically, cortical thickness of regions within the right vlPFC, including the pars orbitalis, were found to correlate more strongly among STPS+ patients compared to STPS- patients. This group difference was drawn from data pooled over two years of FEP services despite no group differences in potential confounding factors such as exposure to antipsychotic medication (Table 1). Overall, the results reveal differential patterns of cortical thickness among FEP patients predicted by history of STPS.

Our study is the first to address whether brain anatomy in a FEP differs by history of STPS consistent with CHR. We build on previous work where data drawn from the same setting support different CT trends by other dimensions of illness including negative symptomology.[33,49] In our analysis, we compared the CT of FEP patients to controls, and thus re-examined a contrast that has been explored in existing literature with our novel sub-grouping for patients. This novelty warranted a whole-brain approach, and with that, strict multiple comparison corrections that we acknowledged could lower sensitivity for subtle group effects. Even though our primary analysis of CT only revealed a significant group effect in the comparison of HC and STPS- patients, visualization of the data (Fig. 1) supported a trend of increasing cortical thickness between STPS- patients, STPS+ patients, and HC in the right vlPFC. We further investigated this brain region with a *post hoc* SC analysis, allowing us to appreciate interregional relationships by

group. This was an appropriate *post hoc* analysis because it employed a new metric, thus offering sensitivity for group differences that the primary analysis may have lacked. The SC analysis revealed a significantly stronger correlation in CT between regions within the right PFC among STPS+ patients compared to STPS-. In addition to providing the first piece of evidence that FEP patients with and without a prior syndrome consistent with CHR exhibit neural differences, this analysis recapitulates the added value of studying the interaction between brain regions in the psychosis population.

The baseline and longitudinal pooled analyses both supported a fixed difference in right vlPFC cortical thickness between HC and STPS- patients where STPS- patients had comparatively thinner measurements. It is noteworthy that this group difference did not change by age, evidenced by the lack of significant group by age interactions across all vertices. Together, the results support a comparable age-related trajectory in CT across all groups, with fixed differences in CT that are durable over time. Since the group effect was observable even at baseline (Figure 1A), this trend may have emerged prior to the onset of FEP – alongside nonspecific prodromal symptomatology (rather than the CHR state). Our results offer a valuable contribution because literature on cortical thickness prior to the onset of FEP has been contextualized with the CHR state. It is also noteworthy that the cortical thickness of STPS+ patients did not differ significantly from that of controls in any of the tested brain regions, in contrast to what has been reported by previous studies comparing HCs to both FEP and CHR samples. Taken together, these results support an association between an acute onset of threshold-level psychotic symptoms (STPS-) and abnormal right prefrontal development. Cannon and colleagues reported that among CHR converters to FEP (i.e. STPS+ patients), those with a shorter duration of STPS before transition to a full-blown presentation (a more acute

onset) exhibited steeper rates of cortical thinning, notably in the right PFC.[14] Along with our results, these findings implicate the right PFC as a critical substrate for onset of STPS and FEP.

Our analysis of SC revealed a significant effect between patient groups, with differences in cortical organization localized to the right PFC. Specifically, SC between a seed within the right ventrolateral prefrontal cortex and the right pars orbitalis of the inferior frontal gyrus (IFG) differed between groups, with a steeper, stronger positive association between these two regions among STPS+ patients compared to STPS- patients (Figure 2A). Structurally, it is likely that short association fibers, which facilitate communication between adjacent cortical regions,[50] are responsible for differences in covariance between these prefrontal regions. The integrity and abundance of fibers between the seed and pars orbitalis may be greater or more preserved among STPS+ patients. Structural differences may also reflect concurrent differences in cognition and behavior. Our study revealed findings in the right hemispheric homologue of areas associated with language.[51] Patients with psychosis have previously been shown to exhibit right-hemisphere recruitment during verbal tasks, suggesting a shift away from typical left-lateralized language processing.[52,53] It is possible that our sample has captured differences in this more widely observed process, however we cannot make this claim without behavioral data. The presented results provide evidence for two prefrontal relationships, distinct in strength, offering a neurobiological substrate for the STPS construct. The results build on previous work with the same cohort showing that STPS+ history was predictive of poorer longitudinal clinical and functional outcomes.[17]

Unlike STPS- patients, STPS+ patients exhibited preserved SC between the right vlPFC and right middle temporal gyrus (MTG). The superior longitudinal fasciculus, a major long association fiber tract connecting ipsilateral frontal, parietal, occipital, and temporal cortices,[54]

may underlie alterations in SC observed in this study. Indeed, reduced white matter integrity within this tract has been reported among patients with psychosis.[55] The superior longitudinal fasciculus is associated with language articulation, and auditory and somatosensory information processing,[54,56] processes that have all been shown to be impaired to some degree in psychosis. Our results however, suggest that coupling between regions, potentially mediated by the right superior longitudinal fasciculus, is preserved among STPS+ patients and not in STPS- patients. Overall, the SC analyses suggest that STPS+ patients may be on a different trajectory of interregional organization. We show that differences in cortical organization are related to earlier exposure to sub-threshold psychotic symptoms, whose duration at sub-threshold levels predicts differences in rates of cortical thinning,[14] and whose severity at a subsequent threshold level FEP predicts differences in cortical thickness in the PFC.[57] Compared to controls, only STPS- patients exhibited significant differences across the metrics we examined. We are hesitant to call STPS+ status-- that is, a history of symptoms consistent with CHR prior to FEP – "protective" without behavioral data to qualify use of this term, however there appear to be preserved trends in cortical organization and cortical thickness associated with this group. Another group found that with longer duration of illness, the cortical thickness of patients with schizophrenia tended to deviate less from that of controls and attributed such changes in group dynamics to reorganization.[58] The notion of STPS prior to FEP suggests that STPS+ patients have endured psychotic illness for longer. The relationship between illness duration and cortical reorganization may explain why they compare to HC differently than STPS- patients.

The retrospective design of the current study introduces several limitations. First, because STPS history was assessed in a FEP setting (i.e. after transition to psychosis), no scans were acquired before the first episode, preventing extrapolation beyond the data presented.

Nevertheless, the results suggest that the STPS+/- construct deserves further exploration, perhaps through comparison of FEP STPS+ youth with those being treated in a CHR and/or general youth mental health service settings. These groups, each followed prospectively for future transition to FEP, would shed light on whether the temporal aspects of cortical differences observed between STPS+ and STPS- patients extend to non-FEP populations observed over time while also eliminating recall bias that is a limitation of retrospective study design.[15,16] This bias may contribute to underrepresentation of STPS+ patients, limiting our power to analyze the relationship between STPS and brain structure. Nevertheless, retrospective work is a necessary step for identifying relevant premorbid factors in psychosis. Second, our work offers neurodevelopmental insights into differential early illness courses that converge on FEP presentation. In its current application, the STPS construct does not consider variability within the STPS+ population in term of STPS duration, intensity, or continuity leading up to a FEP. Given evidence for variability among converters, it would be worthwhile to expand our current results by exploring differences in cortical thickness and SC among STPS+ patients in relation to important clinical variables.

While our results suggest reduced cortical thickness and reduced right fronto-temporal regional coupling are related to a more acute onset of threshold level symptoms (i.e. STPS-), our study lacks behavioral correlates that would allow us to understand the impact of these anatomical trends. In future work, it would be meaningful to examine differences in neuroanatomy as they relate to cognitive function. Since our results were localized to the right vlPFC, it would be meaningful to examine groups differences in performance on verbal tasks and tasks of attention and inhibition, thus targeting functions associated with left and right vlPFC function respectively.[59]

Despite these limitations, our study design offers many strengths. The study population consisted of participants recruited from the sole provider of specialized FEP services in Southwest Montreal, Canada. Because our sample was catchment-based and the study design was observational, our results are likely more generalizable than comparable studies limited by differences in access to care. Importantly, our study employed stringent quality control of MRI scans. It has been shown that low quality scans yield under-estimations of cortical thickness in somatosensory areas and over-estimations of cortical thickness in prefrontal regions,[60,61] highlighting the need for stringent quality in cortical thickness analyses. While a substantial number of scans were not included because of failed quality control, this selectivity was paramount given the exploratory nature of the STPS+/- construct.

5. Conclusion

The current study provides novel evidence suggesting neural differences between FEP patients who do and do not experience pre-onset STPS, consistent with a CHR state, before the onset of psychosis. The right vlPFC emerged as a region of particular importance, revealing significantly greater SC in its sub-regions among STPS+ patients compared to STPS- patients. In addition, STPS- patients exhibited significantly reduced right vlPFC CT and right prefronto-temporal SC compared to controls while STPS+ were spared. Our results suggest the value of considering the STPS+/- construct in other explorations of neuroanatomy and functioning in FEP.

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Ethical Statement

The research in the manuscript entitled "**Pre-onset sub-threshold psychotic symptoms and cortical organization in the first episode of psychosis,**" was conducted with approval from the Ethics Committee of the Douglas Mental Health University Hospital. Participants provided written informed consent.

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