

Longitudinal Gray Matter Development Associated With Psychotic Experiences in Young People

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ABSTRACT

BACKGROUND: Gray matter abnormalities are observed across the psychosis spectrum. The trajectory of these abnormalities in healthy adolescents reporting subthreshold psychotic experiences (PEs) may provide insight into the neural mechanisms underlying psychotic symptoms. The risk of psychosis and additional psychopathology is even higher among these individuals who also report childhood adversity/DSM-5 diagnoses. Thus, the aims of this longitudinal study were to investigate PE-related volumetric changes in young people, noting any effects of childhood adversity/DSM-5 diagnosis.

METHODS: A total of 211 young people 11 to 13 years of age participated in the initial Adolescent Brain Development study. PE classification was determined by expert consensus at each time point. Participants underwent neuroimaging at 3 time points over 6 years. A total of 76 participants with at least one scan were included in the final sample; 34 who met criteria for PEs at least once across all the time points (PE group) and 42 control subjects. Data from 20 bilateral regions of interest were extracted for linear mixed-effects analyses.

RESULTS: Right hippocampal volume increased over time in the control group, with no increase in the PE group ($p = .00352$). DSM-5 diagnosis and childhood adversity were not significantly associated with right hippocampal volume. There was no significant effect of group or interaction in any other region.

CONCLUSIONS: These findings further implicate right hippocampal volumetric abnormalities in the pathophysiology underlying PEs. Furthermore, as suggested by previous studies in those at clinical high risk for psychosis and those with first-episode psychosis, it is possible that these deficits may be a marker for later clinical outcomes.

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Gray matter differences are well established across the psychosis spectrum, with studies demonstrating significant abnormalities even in otherwise healthy individuals who report subthreshold psychotic experiences (PEs) (1–7).

Prevalence of PEs among the general adult population is 5.8%, compared with the 3% prevalence of psychosis (8,9). Among adolescents 13 to 18 years of age, a meta-analysis by Kelleher *et al.* (10) found the prevalence of PEs to be 7.5%. More recently, a large cohort study found that by 24 years of age, the prevalence of PEs was 8.1% (11). Study of these individuals provides a unique insight into the neural mechanisms underlying psychotic symptoms without the potentially confounding presence of a formal disorder, and without any confounding effects of antipsychotic drugs. However, despite having no formal diagnosis, longitudinal studies have shown that individuals who report PEs are at increased risk for psychosis, suicidality, additional psychopathology, and neurocognitive impairments (12–16). Thus, the study of individuals with PEs also provides a crucial opportunity to explore vulnerability for psychotic and nonpsychotic psychopathology.

Brain regions that consistently display volumetric abnormalities in individuals with PEs reflect those seen across the psychosis spectrum, including the orbitofrontal volumes (1,7), temporal regions (in particular the hippocampus and parahippocampal gyrus) (3,7,17,18), posterior cingulate and precuneus (7,19), and striatal regions including the putamen and caudate (2,3). These regions are critical components of two neural networks of interest in psychosis research: the default mode network (temporal regions, posterior cingulate, and precuneus) and the salience network (orbitofrontal regions and striatal regions) [as reviewed by O'Neill *et al.* (20)]. The default mode network is involved in internally directed thought processes, theory of mind, and memory (21), while the salience network is responsible for salience attribution and integration of sensory, emotional, and cognitive information (22). Disturbances in these networks are thought to underlie much of the core psychosis symptomology (7,23–25). Further emphasizing the importance of these structures, abnormal activation and functional connectivity of these networks has been identified in previous reports involving this cohort (1,26,27). However, their structural developmental trajectories are less clear. Recently,

interest in the role of the motor network in psychosis psychopathology has grown, beyond its role in the psychomotor impairments observed in psychotic disorders (28,29). Much like the traditional regions of interest in psychosis, structural abnormalities in motor regions have been observed across the psychosis spectrum (17,18,30–32), including a recent study in an adult PE sample (19).

Other factors for consideration include childhood adversity and DSM-5 diagnoses other than psychosis. There is a strong correlation between both factors and PEs and psychotic disorders across the spectrum (33–36). Furthermore, similar regional deficits are observed in individuals with PEs and in those who have experienced childhood adversity or histories of nonpsychotic psychiatric disorders (37–40). Thus, controlling for these factors in the current analysis could help distinguish underlying features specific to psychosis symptomology.

As noted earlier, previous studies from our group (Adolescent Brain Development [ABD] study) (41) have demonstrated significant PE-related neural abnormalities during adolescence. These include structural and functional abnormalities cross-sectionally (1,27,42,43), functional dysconnectivity across multiple networks including the motor network longitudinally (26), and reduced hippocampal volumes across two time points.

In the current analyses, we exploit the unique availability of data from 3 time points, spanning approximately 6 years of adolescence, making this the one of the most comprehensive studies to date exploring brain development related to PEs. The aim of this study was to explore PE-related longitudinal volumetric differences for 10 bilateral (20 in total) regions implicated in psychosis in a cohort of adolescents from the general population. In addition, we conducted sensitivity analyses to examine if childhood adversity or DSM-5 diagnosis accounted for the relationship between PEs and any volumetric changes in the regions of interest (ROIs).

METHODS AND MATERIALS

Participants

A sample of 211 young people between 11 and 13 years of age was recruited from primary schools in Dublin and Kildare, Ireland, as part of the ABD study (41). All were invited to participate in the initial neuroimaging arm of the ABD study (baseline) that took place 1 to 3 years (mean 2 years) after the original interview. A total of 100 participants with no contraindications to structural magnetic resonance imaging (MRI) completed this baseline scan. Of these 100, 69 participants returned for follow-up 1 (2 years later). For the final time point of the neuroimaging arm (follow-up 2, 4 years later), 55 of the original participants returned and were scanned. Overall, 76 participants who had been scanned at least once over the three imaging time points were included in the sample here: 34 who met criteria for a definite PE at least once across all the time points (PE group) and 42 who did not meet criteria for a PE at any time point (control group).

None of the participants in either group met the criteria for a formal psychotic disorder, and none had any history of neurological disorder (e.g., epilepsy). Written parental consent and participant assent were obtained before the study began

and at each follow-up for participants under 18 years of age. Participant consent was obtained after 18 years of age.

Clinical Measures

All participants attended a diagnostic clinical interview with trained raters [additional recruitment and interview details outlined in Kelleher *et al.* (41)]. Adolescents and parents/guardians were interviewed separately, both answering the same questions about the adolescent, using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (44) at baseline and follow-up 1. At follow-up 2, participants were interviewed using the Structured Clinical Interview for DSM-5 (45). The psychosis section of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children and the Structured Clinical Interview for DSM-5 were supplemented by additional questions from the SOCRATES instrument, which was devised to systematically assess the presence of PEs in youth populations (46). Parents/guardians were not interviewed for follow-ups 1 and 2. All interviews were reviewed by a consensus committee (2 psychiatrists and a psychologist) in order to confirm PE classification at each time point (further details in the Supplement).

Data relating to factors strongly associated with PEs and psychosis were also collected at interview. As part of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children at the baseline assessment, childhood adversity data were collected and treated as a dichotomous variable (i.e., yes/no childhood adversity reported) (details in the Supplement). During the final assessment, lifetime DSM-5 diagnoses (excluding simple phobias) were recorded and also treated as a dichotomous variable (i.e., yes/no DSM-5 diagnosis reported). Data relating to lifetime DSM-5 diagnoses were only available for participants that returned for the interview at follow-up 2 (PE group = 25, control group = 20) (breakdown of diagnoses in the Supplement).

Structural MRI Data Acquisition

Whole-brain structural MRI data were acquired for each participant using the same 3T MRI system (Philips Achieva; Philips Medical Systems) at the Trinity College Institute of Neuroscience in Dublin. High-resolution T1-weighted images were acquired with a fast field echo 3-dimensional transverse sequence, using the following parameters: echo time/repetition time = 8.4/3.9 ms; flip angle = 8°; 256 × 256 matrix; 180 × 0.9 mm slices; field of view = 230. Scan duration was 5:44 minutes.

Preprocessing of Structural Data

Cortical and subcortical reconstruction and volumetric segmentation and parcellation were performed with the FreeSurfer image analysis suite version 6.0 and developmental toolbox for longitudinal analysis features (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in previous publications (47–54). The FreeSurfer longitudinal processing stream was used to extract reliable longitudinal volumes and thickness estimates (55). This involved the creation of an unbiased within-subject template space and image, using robust, inverse consistent registration

(56). Several processing steps, such as skull stripping, Talairach transforms, atlas registration, and spherical surface maps and parcellations, were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (55). Systematic inspection of the data including outlier identification was then performed. Outliers were defined using the first and third quartiles (Q1 and Q3) and the interquartile range, in which volumes that fell below $Q1 - 1.5$ interquartile range or above $Q3 + 1.5$ interquartile range were considered extreme outliers. Outlier detection identified 4 participants, 1 with observable structural abnormalities (a control subject) and 3 whose data were corrupted during the acquisition step (1 participant with PE and 2 control subjects). Thus, all 4 participants identified through outlier detection were removed.

Statistical Analysis

All statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing) and the lme4 v1.1.23 package (57). Bilateral cortical ROIs were as follows: lateral and medial orbitofrontal volumes (1,7), precentral volumes (17–19), posterior cingulate volumes (7), precuneus volumes (18,19), parahippocampal volumes (7), and middle temporal volumes (7,17) (Figure 1). Bilateral subcortical ROIs included caudate volumes (3), putamen volumes (2), and hippocampal volumes (3,17) (Figure 2).

Linear mixed-effects (LME) modeling was used for analysis of all the longitudinal volumetric data, with separate models computed for each ROI. LME modeling is a flexible means of analysis, allowing for the inclusion of participants with missing data points (by implementing maximum likelihood estimation), varying intervals between measurements, and combining the components of fixed effects, random effects, and repeated measures within a single model (58,59). In the current study, fixed effects of interest were group and interactions between time and group. Fixed-effects covariates were intracranial volume, time (in months since baseline), age (in months) at baseline, sex, handedness, adversity at baseline, and any DSM-5 diagnosis ever. Subjects were treated as random effects to account for within-person correlations (in brain volumes) inherent in longitudinal analyses and individual variations including random intercept (e.g., normal volumetric differences in the ROI at baseline) and random slope (e.g., normal variations in individual rates of change). Age at

baseline, age at scan, and intracranial volume were mean centered for the analysis.

Top-down model selection followed an established protocol (58). This involved fitting a forced-entry model with the greatest number of fixed effects and random effects (full model), which are then removed in a backward fashion. Specifically, for each ROI, this included a number of steps:

1. Initially fitting a full model: including the greatest number of fixed effects, and random effects of both intercept (random effects of subjects) and slope (random effects of time)
2. Selecting a random effects structure: comparing the model with and without the random effect of slope to the full model
3. Selecting a fixed-effects structure: reducing the model by removing higher-order fixed effects of interest and comparing this and the full model with the null model (which included only the intercept term but not the fixed effects of PE status and the interaction effect between PE status and time)
4. Refitting the best-fit final models: using restricted maximum likelihood estimation

Likelihood ratio tests and corrected Akaike information criterion were used to compare models and determine best fit. The default covariance structure implemented in R software is unstructured. This enables the inclusion of variation in slopes and is the most general form of covariance structure, imposing no restrictions on the covariance parameters. False discovery rate (FDR) procedures were used to correct for the multiple comparisons (20 structures).

Sensitivity Analyses

For regions where the additional variables (childhood adversity and DSM-5 diagnosis) were found to have a significant effect (in the full or null models), the relevant model was rerun to investigate whether there was effect modification or interaction effects associated with the variable and PE status (i.e., an interaction term of $\text{group} \times \text{variable}$ was added to the model).

Additional Analyses

Additional demographic analyses exploring group differences relating to sampling, selection, attrition biases, and multicollinearity are reported in the Supplement.

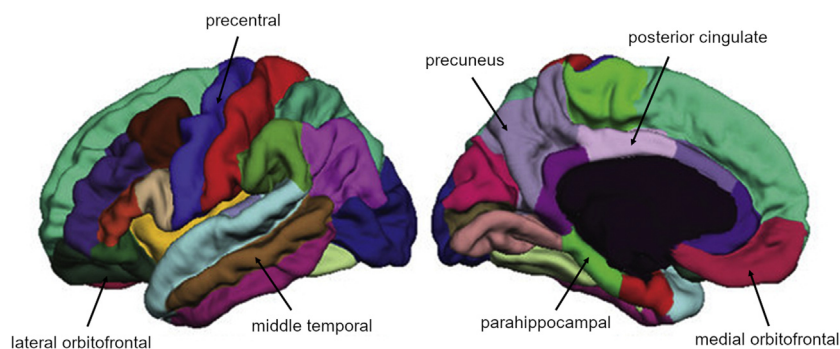


Figure 1. Representation of the seven cortical regions of interest included in this study (for the right and left hemispheres). Regions of interest follow the Desikan-Killiany-Tourville atlas protocol and are displayed on the lateral (left) and medial (right) views of the left hemisphere of the FreeSurfer average brain template. Cortical regions of interest include the lateral and medial orbitofrontal, precentral, middle temporal, precuneus, posterior cingulate, and parahippocampal regions.

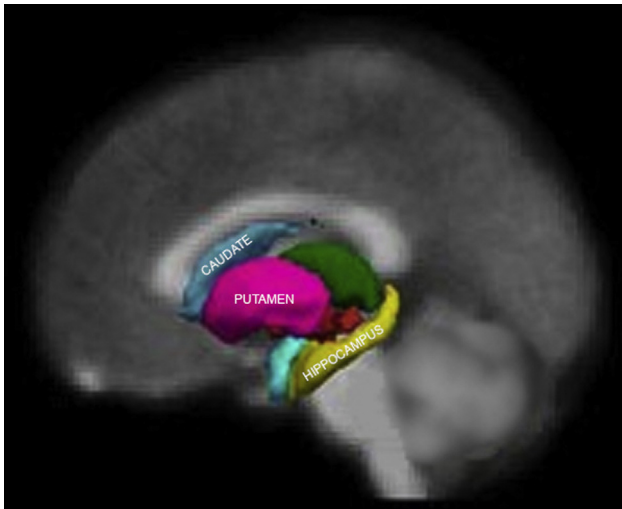


Figure 2. Representation of the three subcortical regions of interest included in this study (for the right and left hemispheres), extracted through FreeSurfer segmentation. Regions of interest are displayed on the medial view of the right hemisphere. Subcortical regions of interest include the caudate nucleus, hippocampus, and putamen.

RESULTS

Demographics

Participant demographic information is summarized in Table 1. Mean age at baseline was 13.9 years in the PE group and 14.2 years in the control group. Mean age at follow-up 1 was 16.1 years (PE group) and 16.22 years (control group). Mean age at follow-up 2 was 19.76 years (PE group) and 20.24 years

(control group). All participants were antipsychotic naïve across all time points. At baseline, 2 of the 76 included participants were taking medication for attention-deficit/hyperactivity disorder. By the final follow-up, 2 participants reported taking antidepressant medication. All 4 of these participants were in the PE group. Of the 34 participants who met the criteria for a PE at some point, 21 participants met the criteria for a PE at one time point, 6 participants met the criteria at two time points, and 7 participants met the criteria at three time points. In the PE group, 8 participants had one scan, 10 had two scans, and 16 had three scans. In the control group, 11 participants had one scan, 14 had two scans, and 17 had three scans. There were no significant differences between the groups in terms of number of scans; age at baseline, follow-up 1, or follow-up 2; sex; handedness; or socioeconomic status. Significantly more of the participants with PEs had received a DSM-5 diagnosis at some point in their lives than the control subjects ($p = .001$). Similarly, significantly more of the participants with PEs had experienced adversity by the baseline assessment than the control subjects ($p = .031$).

Model Selection Process

Random-Effects Structure. The model including slope was found to be most appropriate for the following volumes: left lateral orbitofrontal, left posterior cingulate, bilateral pre-cuneus, and right parahippocampal. For all other volumes, only the intercept was included in the random-effects structure.

Fixed-Effects Structure. The full model (including all higher-order fixed-effects of interest) was found to be most appropriate (significantly better than the null model) and subsequently was fitted for the right hippocampal volume and bilateral precentral volumes. For all other volumes, the null

Table 1. Participant Sociodemographic Information

Variable	PE Group ($n = 34$)	Control Group ($n = 42$)	Statistics	95% CI
Number of Scans, Mean (SD)	2.23 (0.82)	2.14 (0.81)	$p = .62$	-0.28 to 0.47
1 scan	8 subjects	11 subjects	-	-
2 scans	10 subjects	14 subjects	-	-
3 scans	16 subjects	17 subjects	-	-
Age at BL, Months, Mean (SD)	167.06 (14.51)	169.9 (16.7)	$p = .44$	-10.16 to 4.47
Age at FU1, Months, Mean (SD)	193.25 (14.89)	194.67 (17.32)	$p = .76$	-10.56 to 7.73
Age at FU2, Months, Mean (SD)	237.1 (18.45)	242.95 (21.73)	$p = .36$	-18.75 to 7.054
Sex, Male, %	67.6%	45.2%	$p = .05$	-0.002 to 0.445
Right-handed, %	94.1%	92.7%	$p = .81$	0.0 to 0.45
Socioeconomic Status ^a , Mean (SD)	2.2 (0.96)	2.18 (0.94)	$\chi^2 = 0.049, p = 1$	-
Adversity at BL, Yes, %	67.6%	42.9%	$p = .031^b$	-0.47 to -0.023
DSM-5 Diagnosis Ever ^c , Yes, %	76%	25%	$p < .001^b$	-0.77 to -0.24
PE Recurrence Across Time Points, n				
1 time point	21	N/A	-	-
2 time points	6	N/A	-	-
3 time points	7	N/A	-	-

BL, baseline; FU, follow-up; N/A, not applicable; PE, psychotic experience.

^aSocioeconomic status was established via highest parental occupation level, categorized as follows: 1 = professional work, 2 = managerial and technical work, 3 = nonmanual work, 4 = skilled manual work, 5 = semiskilled work, 6 = unskilled work, 7 = unemployed.

^bSignificant p value.

^cDSM-5 diagnosis ever data were only available for those participants who returned at FU2 (PE group = 25, control group = 20).

Table 2. Results of the Mixed-Effects Model Analyses for GM Volumes in the PE Group and the Control Group

GM Volumes of Interest	Intracranial Volume			Sex			Age at BL			Handedness			Time Since BL			Adversity at BL			DSM-5 Diagnosis Ever			Group × Time Since BL						
	B	t	p	B	t	p	B	t	p	B	t	p	B	t	p	B	t	p	B	t	p	B	t	p				
R Hippo-campus	0.00067 (0.00025)	2.67	.011 ^a	-0.28 (0.11)	-2.54	.015 ^a	0.0057 (0.00027)	2.12	.041 ^a	-0.34 (0.26)	-1.31	.2	0.00067 (0.00018)	3.78	.00034 ^b	-0.14 (0.09)	-1.56	.13	0.034 (0.088)	0.38	.7	-0.035 (0.096)	-0.36	.72	-0.0014 (0.00035)	-3.87	.00025 ^b	(FDR p = .0053 ^b)
R Precentral	0.006 (0.0013)	4.56	<.0001 ^b	0.15 (0.57)	0.27	.79	-0.0034 (0.014)	-0.25	.81	3.23 (1.36)	2.37	.023 ^b	-0.025 (0.0018)	-14.078	<.0001 ^b	0.46 (0.47)	0.98	.33	0.62 (0.46)	1.34	.19	-1.025 (0.51)	-2.016	.051 ^b	0.0041 (0.0036)	1.15	.25	(FDR p = 1)

B is the estimate of the fixed-effect coefficient. FDR-corrected p is reported for variables of interest significant at the uncorrected level; all other values displayed are uncorrected.

BL, baseline; FDR, false discovery rate; GM, gray matter; PE, psychotic experiences; R, right.

^aSignificant p value.

^bTrend-level effect.

model was most appropriate, indicating no significant effects on volume due to the fixed measures of interest.

Between-Group Differences

The significant mixed-model analyses results for the covariates of interest are shown in Table 2. Full results for all regions (including nonsignificant results) are displayed in the Supplement.

The right hippocampus was the only region that displayed a significant group × time interaction that survived correction (FDR-corrected p = .0055, Cohen’s d = -0.96). This effect was such that the right hippocampal volume increased in the control group and remained relatively constant in the PE group (Figure 3).

In terms of group effects regardless of time, the PE group displayed smaller right precentral volumes at a trend level (uncorrected p = .051, Cohen’s d = -0.6) (Figure 4). This effect did not survive correction, although it demonstrated a moderate-to-large effect size.

Sensitivity Analyses

Across the whole group, those who experienced adversity at baseline had significantly larger left precuneus volumes (uncorrected p = .025, Cohen’s d = 0.75), regardless of time (Table S1). Across the whole group, those who had received a DSM-5 diagnosis by the final time point had significantly larger right posterior cingulate volumes than those who did not (uncorrected p = .022, Cohen’s d = 0.79), regardless of time (Table S2).

After rerunning these models with an interaction term of group × variable, no significant interaction effects were observed between group and adversity for the precuneus volume (p = .66, Cohen’s d = -0.15) or between group and DSM-5 diagnosis for the posterior cingulate volume (p = .71, Cohen’s d = 0.13).

DISCUSSION

In this study, we performed a comprehensive longitudinal volumetric analysis of the effects of adolescent PEs on 20 bilateral regions implicated in established psychotic disorders. After FDR correction, the only region that displayed any significant differences in the primary analysis was the right hippocampus. Specifically, right hippocampal volumes increased in the control group over time and remained relatively stable in the PE group. Before correction, the PE group displayed reduced right precentral volumes compared with the control group, regardless of time. However, this effect did not survive correction. Childhood adversity and DSM-5 diagnosis did not affect any of the volumes differently between the two groups even though PE group had higher rates of both.

The hippocampus plays a crucial role in many cognitive processes including memory, learning, executive functions, and emotional processing—all functions that are notably impaired in psychosis (60). As such, hippocampal abnormalities are strongly implicated in the pathophysiology of psychosis (60) and are well established through different modalities across the psychosis spectrum (6,61–66). Volumetric reductions of the hippocampus and overall temporal lobe in particular are evident in young people and adults with

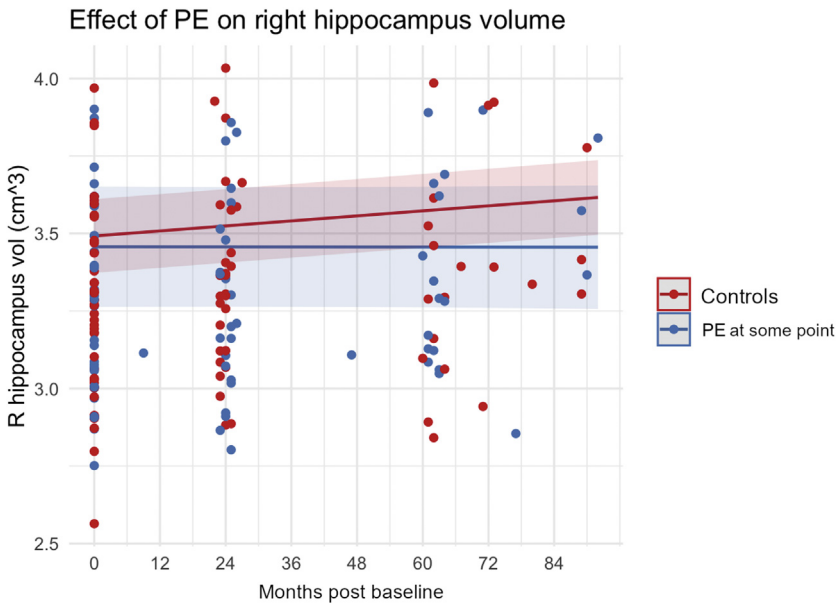


Figure 3. Right hippocampal development in the participants with and without psychotic experiences (PEs) from baseline to follow-up 2. A significant group \times time interaction effect was observed, such that right hippocampal volume increased in the control group and remained relatively stable in the PE group. R, right.

PEs and those at clinical high risk (CHR) for psychosis (7,67–69). However, the trajectory of these deficits is less clear. One CHR study found that hippocampal atrophy at baseline predicted progression to psychosis after 2 years (59). Another study in early psychosis found that those who developed

schizophrenia after 2 years displayed smaller baseline hippocampal volumes that did not change over time compared with healthy control subjects, while those who maintained a diagnosis of schizophreniform disorder displayed normal hippocampal volumes over time (70). Calvo *et al.* (71) explored

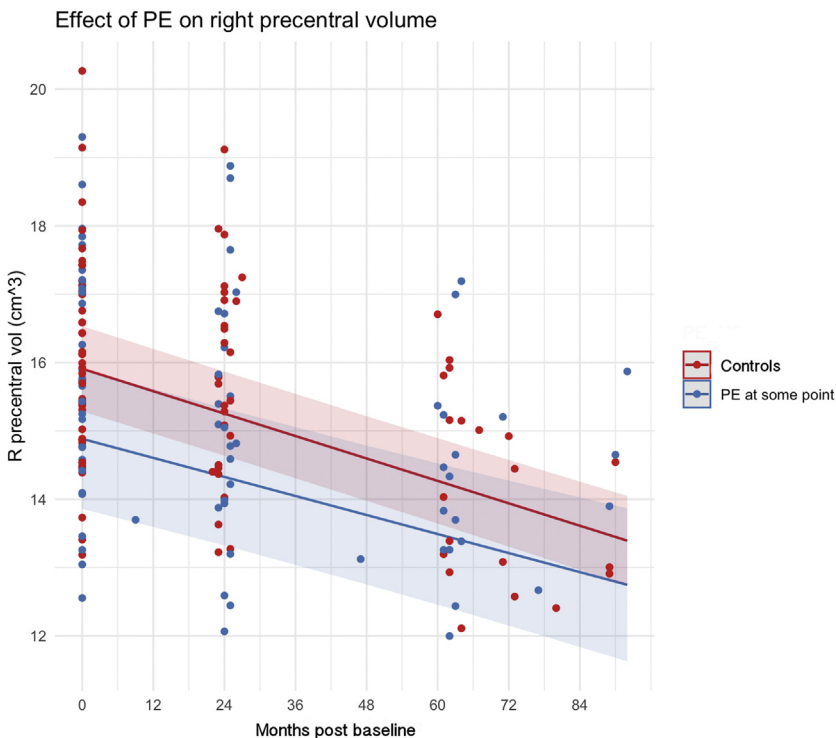


Figure 4. Right precentral development in the participants with and without psychotic experiences (PEs) from baseline to follow-up 2. A group effect was observed, with the control group displaying greater right precentral volumes compared with the PE group, regardless of time. This effect did not survive false discovery rate correction.

hippocampal volumes in a matched case-control subsample of the current ABD cohort (PE group = 19, control group = 19), and over the first two time points, smaller bilateral hippocampal volumes were observed in the PE group at both time points. Consistent with this, in the current extended analysis, we identified a deficit in the development trajectory of the right hippocampus in the PE group. These findings give a broader perspective of our previous findings, contextualizing them in the wider population over a longer period and emphasizing the importance of the right hippocampus. Indeed, the current findings may suggest that more significantly impaired right hippocampal development in those with subthreshold symptoms could be a marker for poorer clinical prognosis overall, as in previous CHR and early psychosis studies (69,70). This is further supported by a recent meta-analysis that described a trend specifically toward right hippocampal volume predicting transition to psychosis in CHR groups (72).

Reduced precentral volumes (which encompass the primary motor cortex) support similar recent findings in an adult study of PEs (19) and in a CHR study (17). This is in keeping with the extensive motor network dysconnectivity observed in a previous longitudinal study in this sample (26), and similar findings in an independent cross-sectional study of PEs in young people (73) and in a cross-sectional study of CHR individuals (74). There is mounting evidence supporting a role for motor network dysfunction in the pathophysiology and etiology of psychosis (28,29). Less is known about the role of volumetric changes of the motor regions in PEs. However, motor network dysfunction has been identified as a potential predictive marker for transition to psychosis (75–77). Although this effect did not survive FDR correction, the effect size makes this finding noteworthy. Notably, spatial processing and acquisition of spatial knowledge have also been strongly linked with hippocampal volume (78,79) and are thought to be potential risk markers for psychosis (80,81). Future studies should consider this link between hippocampal and precentral deficits in relation to PEs and spatial processing, and more broadly in terms of childhood spatial exploration and motor activity.

In keeping with our recent longitudinal functional connectivity study that demonstrated greater changes in connectivity over time in the typically developing group, compared with the PE group (26), these findings may also support neurodevelopmental delay [e.g., inefficient synaptic pruning during adolescence, in line with the neural efficiency threshold model (82)] as a potential mechanism underlying PEs. Similar delays in neurocognitive growth for individuals with PEs have been described in childhood and early adolescent development studies (83) and in white matter growth for siblings of patients with childhood-onset schizophrenia (84).

Despite the association between the variables included in the sensitivity analyses (childhood adversity and DSM-5 diagnoses) and psychotic symptoms/psychopathology (11,12,35,36,85–87), and similarly between these variables and reduced hippocampal volumes (88,89), neither of these variables was found to have a significant effect on any brain region in the current analysis (after correction). In relation to the hippocampus specifically, this is supported by a recent study in adults with PEs, which found that volumetric reductions in regions including the temporal lobe were not accounted for by psychotic or depressive illness or by childhood adversity (67).

These findings further distinguish and implicate abnormal neurodevelopment of the hippocampus in the mechanisms underlying PEs.

To further clarify the mechanisms of hippocampal dysfunction underlying PEs, it will be important to parse out the effects of PEs among the functionally discrete subfields of the hippocampus. Previous studies frequently report abnormalities in the CA regions in CHR, first-episode psychosis, and chronic schizophrenia (61,68,69,90,91). One theory suggests that abnormalities in the CA1 region initially lead to attenuated psychotic symptoms, and that as psychotic illness progresses, these neural abnormalities spread to other hippocampal regions and projection fields in other areas (92). The current findings support this hypothesis, further endorsing the investigation of hippocampal subregion development in individuals with PEs.

The findings are strengthened by the use of LME statistics, which allow the inclusion of all valid participant datapoints. As with all longitudinal studies, biases cannot be ruled out entirely. However, the findings of the additional comparative analyses suggest that these effects are limited, and support the generalizability of the volumetric findings overall. The inclusion of time since baseline and age at baseline as separate variables is an additional strength, as this approach to time has been shown to produce more accurate representations of the effects of time, while simultaneously accounting for differences in baseline age (93). Further methodological strengths include the population-based sample, the consensus-based criteria for PEs, the well-matched control participants, the neuroimaging data all being acquired from the same scanner, and the use of the FreeSurfer longitudinal processing stream. As we had no specific hypotheses related to hemispheric laterality and asymmetry, each region was treated as an independent region of interest (hence the correction of the p threshold for 20 ROIs). Given the current findings, future research should consider laterality and asymmetry components in their analyses for additional insight. A potential limitation of the study is the restricted data relating to lifetime DSM-5 diagnoses and childhood adversity (DSM-5 diagnoses data were only available for participants who took part in follow-up 2, and childhood adversity data were only collected at baseline). While the overall grouping of DSM diagnosis did not significantly affect the main findings, it is possible that this approach overlooks any associations between specific diagnoses, brain morphology, and PEs. As it stands, our sample was too limited to specifically examine this breakdown. Subsequent studies should examine any effects of specific disorders/groupings of disorders (according to Hierarchical Taxonomy of Psychopathology) (94). Furthermore, although it was not within the scope of the current work, future studies should consider a multidimensional approach to adversity including timing, severity, and type of adversity, in line with compelling recent evidence (95). As such, the covariate analyses should be interpreted with caution. Additionally, given the moderate numbers of participants who experienced PE recurrence, it was not possible to conduct separate analysis on transient vs persistent PEs. Finally, there is growing interest in the reconceptualization of psychotic disorders as occurring on a spectrum, similar to those spectrum phenotypes covering autism and addiction (96). In the current study, the categorization of weak/strong

PEs from the original protocol limits the implementation of a spectral analysis of this sort. The “weak” category represents experiences not convincing enough to be classified as a definite psychotic experience. Thus, inclusion of these participants could lead to misleading results owing to mislabeling of non-PEs. In the future, more nuanced approaches to categorization of experiences should be considered, to better represent the spectrum of experiences.

Previous studies exploring neurocognition within this cohort suggest that young people reporting PEs are functioning relatively normally (97,98). The current volumetric findings generally support this. Notably, the only neurocognitive deficits found in this cohort were observed in the domains of fine motor skill and processing speed—potentially linking to the subthreshold differences in the precentral volumes observed here, and adding further support to the precentral-hippocampal association with spatial processing. Given the effect sizes for these regions, it is possible that the moderate sample size of the current cohort, number of participants with a single scan, and/or the restriction of the LME models to linear analyses (as opposed to quadratic or cubic) could have resulted in type II errors. Nonetheless, the minimal functional and cognitive deficits of the group support the limited volumetric abnormalities observed in the current study.

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