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### Wired for pain, shaped by the mind

*Interactions between pain and psychopathology in pediatric and adult patient populations*

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# CHAPTER 5

REDUCED CEREBELLAR VOLUMES ASSOCIATE WITH P300  
AMPLITUDE ATTENUATION IN CHILDREN WITH CLINICAL HIGH RISK  
AND EARLY ONSET PSYCHOSIS

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# REDUCED CEREBELLAR VOLUMES ASSOCIATE WITH P 300 AMPLITUDE ATTENUATION IN CHILDREN WITH CLINICAL HIGH RISK AND EARLY ONSET PSYCHOSIS

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## **Abstract**

Patients with psychotic illnesses, including early onset psychosis (EOP), often experience cognitive impairment. The cerebellum is critically involved in neurocognitive processes, yet possible regional alterations in the cerebellum and their associations with behavioral parameters remain largely unexplored in EOP. In this preliminary study, we aimed to investigate structural morphological properties of the cerebellum as well as the supratentorial brain, and how morphological changes in the central nervous system relate to neurocognitive performance in children with EOP and clinical high-risk for psychosis (CHR). We performed whole-brain structural magnetic resonance imaging (MRI) and voxel-based morphological analyses in children with EOP (N=15), children with CHR (N=11), and healthy controls (Con, N=13). An auditory event-related potential (ERP) task to elicit a P300 response was also completed by a subset of children (N=29) as a measure of neurocognitive functioning. Linear regression analyses were performed to explore relationships between cerebellar volume, cortical thickness, and P300 amplitudes. Volumetric reductions (in bilateral Crus I, Crus II, lobule VI and VIIIa, left VIIIb, and right lobules V and IX of the cerebellum were observed ( $p < 0.05$ ). This downward trend across study cohorts was also evident for rostral middle frontal cortical (RMFC) thickness, and for centroparietal P300 amplitudes. Significant positive correlations among P300 amplitudes and cerebellar volumes were observed ( $p < 0.05$ ). Significant correlations between P300 amplitudes and RMFC thickness were not present. Robust morphological disruptions in cerebellar and frontal subdivisions were quantified in children with EOP. Structural abnormalities in these regions, particularly in the cerebellum, may signify broader brain network disruptions, potentially contributing to neurocognitive dysfunction in EOP.

**Keywords:** Early-onset psychosis; clinical high risk; cerebellum; frontal cortex, cognitive dysfunction; P300; gray matter.

## Introduction

In early onset psychosis (EOP), affected children often exhibit a broad range of cognitive impairments in areas of attention, working memory, verbal learning, among others<sup>1-5</sup>. Presentation of cognitive impairments in children with EOP can occur before the onset of psychotic symptoms, suggesting that neurocognitive phenotypes may emerge prior to onset of frank psychosis in EOP<sup>6-9</sup>. While aberrant neurobiological mechanisms facilitating cognitive deficits in late adolescents, young adults, or adults with psychotic illnesses such as schizophrenia spectrum disorder and bipolar disorders have been widely reported upon<sup>10-12</sup>, much remains unknown regarding the underpinnings of cognitive challenges experienced by patients with EOP. Specific investigation into the causes of cognitive impairments in children with EOP are warranted considering the differential neurodevelopmental status and more severe clinical course of this subpopulation of patients with psychosis<sup>13</sup>.

Prior work has demonstrated progressive and widespread supratentorial cortical thinning in patient with EOP; an effect that may in part be driven by medication usage<sup>14,15</sup>. Cortical thinning in EOP has been specifically reported in prefrontal, temporal, supplementary motor, sensorimotor and parietal cortices as well as the cerebellum; a finding in accord with our observations of suppressed (centro-)parietal P300 neurophysiological responses, neurocognitive performance, in patients with EOP<sup>16</sup>. Interestingly, an interaction between cerebellar morphological changes in EOP and exposure to pharmacological therapy is not evident<sup>15</sup>. Ventricular enlargement and subcortical (striatal, hippocampal or thalamic) morphological changes may also correlate with somatic and psychotic symptoms<sup>17</sup>. Based on multi-paradigm fMRI data from the North American Prodrome Longitudinal Study consortium, individuals at clinical high risk for psychosis (CHR) exhibit a distinctive “trait-like” abnormality in brain architecture, characterized by heightened connectivity within cerebello-thalamo-cortical circuitry<sup>18</sup>.

The cerebellum consists of multiple functional divisions that play key, yet overlapping roles in regulating motor, attentional, executive, default-mode, and reward processing<sup>19-22</sup>. There is increasing evidence suggesting that neurocircuitry integrating the cerebellum facilitates the expression of cognitive dysfunction as well as other symptom domains present in psychosis (e.g., negative symptoms)<sup>23,24</sup>. Structural and functional abnormalities in cerebellar subdivisions including lobule VI, lobule X, Crus I, and Crus II as well as in cortical regions (e.g., frontal cortex) have been associated with cognitive impairments in adults with psychosis<sup>25-30</sup>. In children with EOP or children with CHR, patterns of reduced frontal cortex volumes are observed and linked to poorer cognitive outcomes, yet the presence or implications of cerebellar abnormalities have been comparatively less focused upon<sup>31-36</sup>. The cerebellum undergoes considerable neuroplastic changes in late childhood (6-12 years), particularly in lateral regions involved in complex cognitive and affective processes<sup>37</sup>. Coordinated cognitive and motor abilities critically rely on both cerebellar and cortical brain development, and disruptions in either may contribute to neurodevelopmental disorders<sup>38,39</sup>.

We hypothesize that the cerebellum may on one hand facilitate cognitive impairment and on the other, remain vulnerable to maladaptive processes in children with EOP. The primary objective of this preliminary study was to probe cerebellar morphology in children with EOP or CHR, with a secondary objective to examine how structural alterations in the cerebellum and supratentorial brain regions relate to P300 amplitudes<sup>16,40</sup>. By examining cerebellar morphological properties and their relation to behavioral abnormalities, we aim to elucidate novel neurobiological insights into cognitive impairment in youth with EOP and CHR.

## **Material and Methods**

### *Participants*

The Boston Children's Hospital (BCH) Institutional Review Board approved all procedures prior to study enrollment. Written informed assent and parental consent was provided prior to study participation. Individuals with EOP (n=15), patients with CHR (n=11), and healthy controls (Con; n=13) between 5 and 17 years of age were enrolled. EOP and CHR participants recruitment sites included the psychiatry service at BCH; the Commonwealth Research Center (CRC, PI L. J. Seidman); and the Social Neuroscience and Psychopathology Laboratory (SNAP Lab, PI C. Hooker) at Harvard University. To determine EOP or CHR syndrome classification, the Structured Interview for Psychosis-risk Syndromes (SIPS; described in 2.2.1.) was utilized (McGlashan et al., 2010). Controls could not meet CHR criteria or have a current or past Axis I diagnosis or any first-, second-, or third-degree biological relative with a psychotic disorder. Exclusion criteria for all participants included a lifetime diagnosis of substance abuse or dependence, neurological disease (e.g., epilepsy) or head injury, medical illness with cognitive sequelae, sensory impairments, intellectual disability, or contraindications for undergoing MRI.

### *Imaging Acquisition*

Structural MRI data was acquired using magnetization-prepared rapid gradient-echo (MPRAGE) T1-weighted sequences with the following parameter: Repetition time (TR) = 2.52 s, echo times = [1.74, 3.6, 5.46, 7.32] ms, flip angle = 7°, TI = 1.45s, field of view (FOV) = 240 mm, matrix size = 240 × 240, slice thickness = 1 mm. Parallel imaging (GRAPPA) was employed with an acceleration factor of 2, for a total imaging time of 6:09 min. The MRI data was acquired on a Siemens scanner with a 32-channel head coil (software version: syngo MR B17) at BCH.

### *Cerebellar Volume*

Optimized voxel-based morphometry (VBM) of infratentorial structures was performed using the Spatially Unbiased Infratentorial Template (SUIT) toolbox within Statistical Parametric Mapping (SPM12)<sup>41, 42</sup>. The

workflow encompassed the following steps: visual inspection of images, alignment to the anterior commissure, segmentation of the cerebellum and brainstem, manual adjustments, normalization and reslicing to the SUIT template, and Jacobian modulation for volumetric analysis. A Gaussian smoothing kernel with a 2 mm full width at half maximum (FWHM) was applied to the data. Voxel-based analyses in SPM12 employed an ordinal regression model (0-1-2 for EOP-CHR-Con) adjusting for sex, age, and estimated total intracranial volume (eTIV). A family-wise error rate of  $p = 0.05$  was applied to correct for multiple comparisons. Volumes are expressed as a percentage of the standardized cerebellar volume derived from an independent reference population; the percentage represents the ratio of the individual's cerebellar volume to a template volume.

### *Cortical Thickness*

Automated cortical reconstruction and volumetric segmentation were performed using the FreeSurfer software package (version 7.1.1). T1-weighted MRI scans underwent motion correction and alignment to Talairach space. Non-brain tissues were removed through skull stripping, followed by intensity normalization to address bias field inhomogeneities and cortical reconstruction. Cortical parcellation was carried out using the Desikan-Killiany atlas, which delineates regions of interest (ROIs) based on gyral and sulcal anatomy. This process yielded estimates of cortical thickness (mm) for each ROI and volumetric data ( $\text{mm}^3$ ) for both cortical and subcortical structures. VBM analysis was carried out through a higher level general linear model (GLM), applying a three-group ordinal regression model (0-1-2 for EOP-CHR-Con) to compare cortical metrics (e.g. volume, thickness) across the groups. Age, sex, and eTIV were included as covariates in the regression analysis to control for potential confounding variables, and a Monte Carlo simulation cluster analysis (10,000 iterations) to achieve a cluster-corrected threshold of  $p < 0.05$  was employed.

### *Auditory Event-Related Potential Paradigm for the P300*

The paradigm that was used to assess P300 amplitude in this cohort of participants as well as subsequent data analysis plan has previously been reported on <sup>16</sup>. Electroencephalography (EEG) data were acquired using a 128-channel Geodesic Net System while participants sat in a quiet room, with muted videos played to help maintain their focus. Auditory stimuli included 500 tones, of which 15% were infrequent, to elicit a differential P300 response. The tones were 1000 Hz (frequent) and 1500 Hz (infrequent) sinusoidal pulses, presented with a varying interstimulus interval to avoid rhythm artifacts. Participants pressed a button in response to the infrequent tones, which required attention and elicited a P3b response. EEG data were processed to remove artifacts, and P300 amplitudes and latencies were measured across midline electrodes during the 200-450 ms window post-stimulus. A subset of individuals (EOP N = 10, CHR N = 10, Con N = 9) was able to complete both MRI and EEG assessments. In the previous study of EEG data, the right centroparietal electrode also revealed significant amplitude reductions between EOP and CHR patients, thus providing the rationale for a focus on the centroparietal (CP) electrodes in the current study <sup>16</sup>.

### *Statistical Analysis*

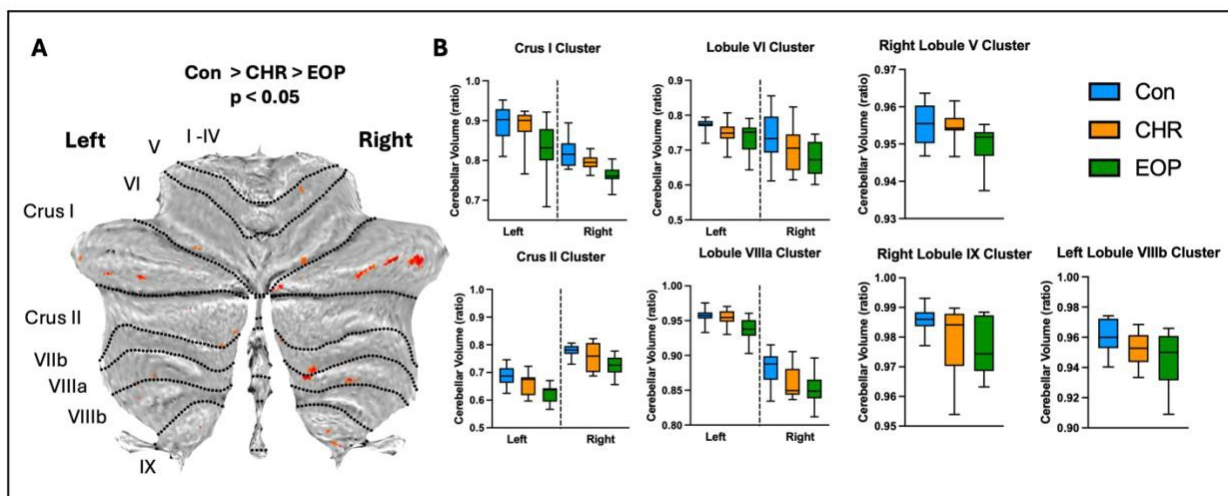
Demographic differences among the groups were evaluated by a one-way analysis of variance model (ANOVA), and post hoc Tukey-Kramer test when ANOVA model was significant. Categorical demographic variables were analyzed using Fisher's exact test. The association between P300 amplitudes with cortical thickness and cerebellar morphology was summarized with the use of the Pearson correlation coefficient ( $r$ ). These results were not adjusted for multiple comparisons, to reduce the probability of type II error due to the small sample size. Linear regression analyses were used to determine differences between groups with the morphological and ERP measures as an outcome while controlling for age, sex, eTIV, and antipsychotic medication chlorpromazine equivalent (CPZ) equivalence. P values of less than 0.05

indicated statistical significance. All the statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

## Results

### *Demographics*

Structural interviews confirmed psychosis or prodromal diagnoses, and comorbid diagnoses in the CHR and EOP participants included attention-deficit disorder (ADHD), obsessive compulsive disorder (OCD), anxiety disorders, depressive disorders, post-traumatic stress disorder (PTSD) and Tourette's disorder. A summary of the demographic data for each study participant can be found in **Table 1**. No significant differences were observed between the groups for age and sex and eTIV, while antipsychotic medication dosage was significantly higher in the EOP group compared to controls ( $p = 0.01$ ). No significant effect of CPZ equivalent on RMFC thickness or on any of the cerebellar cluster volumes were observed based on linear regression analyses, while CPZ did have an effect on left and right CP P300 amplitudes (**Supplemental Table 1**).

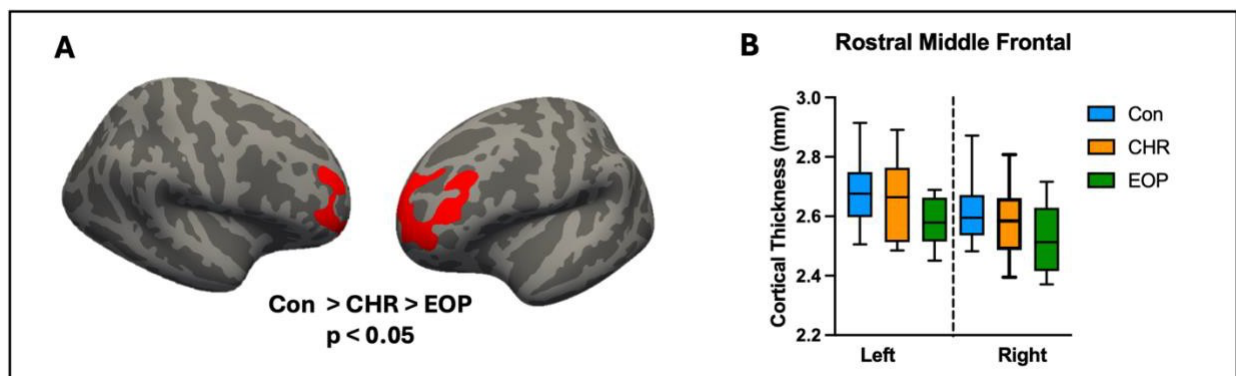


**Figure 1. Reduced Cerebellar Volume in Children with EOP.** Clusters of reduced cerebellar volume in children with early-onset psychosis (EOP,  $N = 15$ ) vs. Clinical High Risk (CHR,  $N = 11$ ) vs. healthy controls (Con,  $N = 13$ ) (A). Voxel-based morphological analysis was performed using the SUI ToolBox. Cerebellar volumetric properties were corrected for age, gender, and total intracranial volume and thresholded at  $p < 0.05$  and cluster corrected at  $p$  (family

wise error rate) FWE < 0.05. Significant clusters were not detected in left lobule V or lobule IX cerebellar subdivisions. The cerebellar volumes of individual subjects were normalized to a standardized template using the SUI toolbox. Volumes are expressed as a percentage of the standardized cerebellar volume derived from an independent reference population; the percentage represents the ratio of the individual's cerebellar volume to a template volume. Cerebellar volume of bilateral left crus I, II, VI, VIIIa, and right VIIIb, V, and VI are plotted to demonstrate the trend of Con>CHR>EOP (B).

### Cerebellar Volume

Cerebellar voxel-wise morphological analysis revealed clusters of volumetric reductions within bilateral Crus I, Crus II, lobule VI and VIIIa, as well as in left lobule VIIIb and right lobules V and IX of the cerebellum ( $p < 0.05$ ) in children with EOP, and to a lesser extent, in CHR, compared to controls (**Figure 1.**) No significant differences were detected in left lobule V or lobule IX cerebellar subdivisions.

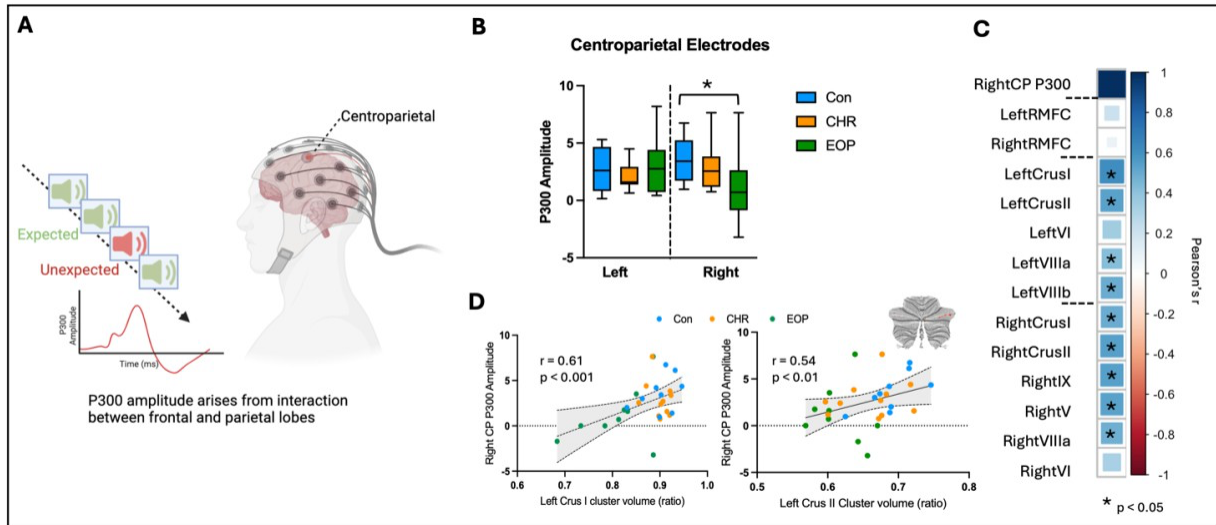


**Figure 2. Reduced Frontal Cortex Cortical Thickness in Children with EOP.** Clusters of reduced cortical thickness in the bilateral rostral middle frontal regions in children with EOP (N = 15) vs. CHR (N = 11) vs. Con (N = 13) (A). Cortical thickness analysis was performed using the Freesurfer Toolbox. Significant clusters ( $p < 0.05$ ) in the rostral middle frontal cortex are shown. Cluster-wise probability threshold correction for multiple comparisons (cwp = 0.05) was implemented and measures of cortical thickness were corrected for age, gender, and total intracranial volume. Left and right RMFC thickness are plotted to demonstrate the trend of Con>CHR>EOP thickness (B).

### Cortical Thickness

Whole-brain voxel-wise morphological analysis demonstrated clusters of significantly ( $p < 0.05$ ) decreased cortical thickness in the bilateral rostral middle frontal cortex (RMFC) in children with EOP, and

to a lesser extent in CHR, compared to controls (**Figure 2.**). No other significant clusters of differential cortical thickness between cohorts were observed.



**Figure 3. Reduced P300 Amplitude in Children with EOP associated with Cerebellar Volumes.** P300 Auditory Oddball Paradigm (A) demonstrated reduced P300 amplitudes in the right centroparietal electrode but not in the left in children with EOP (N = 10) compared to Con (N = 9) with a non-significant trend of reduced amplitudes in CHR (10) compared to Con when controlling for age, sex, and CPZ use (B). Positive associations between P300 amplitude and cerebellar cluster volumes but not RMFC thickness, were observed (C). Two example correlation plots are shown of P300 amplitudes and right Crus I and Crus II cluster volume (D).

### Centroparietal P300 Amplitude

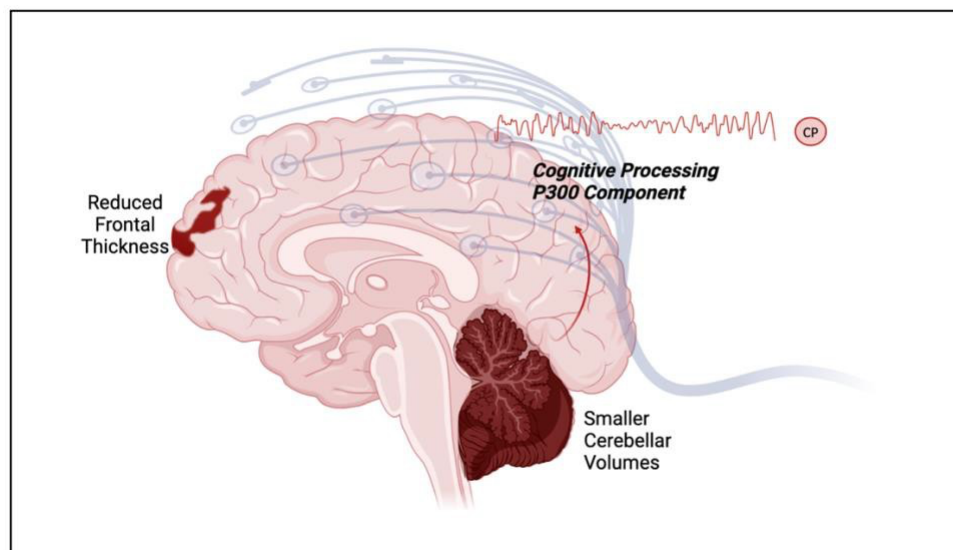
Consistent with what was found in the previous investigation of this EEG dataset, attenuated P300 amplitudes ( $p = 0.001$ ) during the auditory oddball task in the right centroparietal electrode was evident between EOP (N=10) and controls (N = 9) in the current cohort, while CHR (N = 10) did not differ significantly from EOP or controls, corrected for age, gender and CPZ score (**Figure 3A, B**). Left centroparietal P300 amplitudes did not demonstrate significantly altered amplitudes between groups. A significant effect of CPZ equivalents on both left ( $p = 0.031$ ) and right ( $p = 0.0006$ ) centroparietal P300 amplitudes was observed, while age and gender did not significantly impact P300 amplitudes.

### Association among Morphology Measures and P300 Amplitudes

To explore the relationship between morphology and neurocognitive functioning, linear regression analyses were performed among study measures. Significant associations of various cerebellar cluster volumes to RMFC thickness were observed, further confirming the link between the cerebellum and the frontal cortex (**Supplemental Table 2**). Moreover, significant positive correlations between right centroparietal P300 and cerebellar cluster volumes in bilateral Crus I, Crus II and lobule VIIIa, as well as left lobules IX and V and right lobule VIIIb were observed (**Figure 3C, D, Supplemental Table 3**).

## Discussion

The current study aimed to investigate cerebellar and supratentorial morphology in children with EOP or CHR and the relationship between structural alterations and neurocognitive functioning as captured by an auditory ERP paradigm. The current results, though preliminary, provide a more granular understanding on specific cerebellar subdivisions that may be implicated in EOP and in the context of neurocognitive functioning (**Figure 4**).



**Figure 4. Altered Cerebellar and Frontal Cortex Morphology and P300 Amplitudes in Children with EOP.** Abnormalities within cerebellar lobules and frontal cortex regions are indicated in relation to cognitive deficits, as represented by reduced right centroparietal P300 amplitudes, in children with EOP and CHR.

The volumetric reductions reported herein are in line with the few studies that explored cerebellar structural properties in EOP, which have pointed to volumetric reductions of the anterior lobes and the vermis, and noted associations with IQ scores<sup>33, 36</sup>. In the current cohort of EOP patients, reduced volumes were mainly observed in lobule VI, Crus I, lobule VIIb, and lobule VIIIa. Lobule VI and Crus I are linked with frontoparietal and default mode functional networks, but also task-based networks that regulate working memory, language, and reward processing<sup>19, 22, 43-45</sup>. Lobule VIIb and lobule VIIIa appear to more so align with ventral and dorsal attention networks. Our results further indicate that morphological disruptions in the cerebellum integrate with the cognitive dysfunction in children with EOP, as quantified by auditory oddball task P300 amplitudes, a marker of impaired attention and working memory. Interestingly, significant correlations among P300 amplitudes and cortical thickness in frontal cortices were not present.

The current observation in children with EOP finds parallels in studies of adult psychosis. Reduced volumes in Crus I, Crus II and lobules VI, VIIb, VIII and IX have been reported, and smaller volumes of Crus I and II and lobules V, VI, VIIb and X have been associated with cognitive performance in adults with psychosis<sup>21, 26, 30, 46-48</sup>. Our current study extends these findings to children with EOP, examining how cerebellar morphological disruptions may influence cognitive and behavioral outcomes in this population, thereby contributing to a more nuanced understanding of the neurodevelopmental underpinnings of psychosis in younger individuals.

Cerebellar and cortical development follows distinct but interrelated trajectories, reflecting their unique roles in brain functioning. Gaining insight into these developmental processes is key to understanding both the unique features and shared characteristics of EOP compared to adult psychosis. As outlined previously, the developmental trajectory of the cerebellum persists into adolescence, particularly in

regions involved in non-motor functioning, thereby supporting increasingly complex cognitive and affective processes<sup>37</sup>. The cerebral cortex, particularly the prefrontal regions, undergoes rapid synaptogenesis and pruning during early childhood, with peak gray matter volume occurring around early adolescence<sup>49, 50</sup>. Prefrontal and orbitofrontal cortical thinning has been linked to worsening cognitive impairments such as working memory, reasoning and emotional intelligence in adolescents and adults with first-episode psychosis, as well as individuals at high risk<sup>14, 51-53</sup>. Typically, cortical thinning is a part of normal aging, but this process might be altered or accelerated in EOP and thinning of the frontal cortex may reflect abnormal developmental trajectories in EOP and CHR youth<sup>54</sup>. Considering that the cerebellum and frontal cortex are crucial to the development of coordinated cognitive and motor abilities, disruptions in either may contribute to neurodevelopmental disorders, including psychosis<sup>38, 39</sup>.

The P300 ERP is a well-established neurophysiological marker used to assess cognitive function, particularly attention and working memory<sup>55</sup>. In adults with schizophrenia, reduced P300 amplitude and prolonged latency have been consistently reported, regardless of symptom severity or medication status<sup>56-59</sup>. These alterations seem to reflect deficits in attentional resource allocation and working memory, both of which are compromised in psychosis. Similar P300 abnormalities have been observed in children and adolescents with psychosis, where localized amplitudes yielded significant reductions in amplitude not only between EOP and Con but also EOP and CHR patients<sup>16, 40</sup>. There is an added complexity to extrapolating P300 findings from adults to childhood populations due to the developmental trajectories of the P300. Typically, the latency decreases, and amplitude increases from childhood to adolescence, reflecting maturation of cognitive processes<sup>60, 61</sup>. Although the association between the P300 and gray and white matter aberrancies has been reported in adults with psychosis and CHR, the research on P300 amplitude and brain morphology in childhood psychosis is sparse<sup>62-65</sup>. While contributing valuable insights to the current body of evidence about cerebellar structural abnormalities relating to cognitive functioning

in patients with EOP, it is important to acknowledge certain limitations of our study that could impact the interpretation of our findings, and the relatively small sample size may limit the generalizability of our results. Not all participants had P300 data available, which impacts our ability to draw more comprehensive conclusions regarding the relationship between cerebellar morphology and neurocognitive functioning. Moreover, due to the lack of functional MRI data, either in resting-state or during performance of a specific cognitive task, this study could not decipher the link between morphological changes in cerebellar subdivisions and alterations in the functional topology in the cerebellum in patients with EOP. Additionally, our cross-sectional data does not lend itself to determining causality among cognitive dysfunction and psychosis, and to whether there are neuropathological mechanisms that are unique to each of these constructs. Despite these limitations, the significance of our findings demonstrates a clear association between cerebellar abnormalities and cognitive deficits in this population.

## **Conclusions**

The current preliminary study found morphological abnormalities in cerebellar subdivisions and frontal subdivisions in children with CHR and EOP. The cerebellar abnormalities were associated with cognitive dysfunction as reflected by diminished auditory oddball P300 amplitudes. Larger cohort sizes are needed to refute or support and refine these findings. However, the current study suggests that despite the challenges inherent in studying patients during the rapid developmental changes of childhood and adolescence, it can lead to better understanding of neural correlates of psychosis early in its course when there is more opportunity to change its trajectory and enhance patient outcomes.

**Table 1. Overview of participant demographics and completed study assessments.**

<b>Demographics</b>	<b>Con</b>	<b>CHR</b>	<b>EOP</b>
<b>Sex (N)</b>			
Male	9	5	9
Female	4	6	6
<b>Age in years</b>	12.1 ± 3.4	12.2 ± 2.7	10.9 ± 3.1
<b>CPZ</b>	-	29.7 ± 64.0	84.6 ± 112.1
<b>eTIV (mm<sup>3</sup>)</b>	1.6E10 <sup>6</sup> ± 2.1E10 <sup>5</sup>	1.5E10 <sup>6</sup> ± 9.1E10 <sup>4</sup>	1.6E10 <sup>6</sup> ± 1.4E10 <sup>5</sup>
<b>Data Collected (N)</b>			
MRI	13	11	15
P300	9	10	10

*Con Healthy Controls, CHR Clinical High Risk, EOP Early Onset Psychosis, CPZ Chlorpromazine equivalent, eTIV Estimated Total Intracranial Volume. Data are presented as mean score ± standard deviation.*

**Supplemental Table 1. Effect of Chlorpromazine (CPZ) Equivalent on outcome measures for linear regression analysis.**

<b>Outcome Measure</b>	<b>CPZ (p-value)</b>
Left RMFC Thickness	0.49
Right RMFC Thickness	0.43
Left Crus I	0.61
Left Crus II	0.63
Left VI	0.17
Left VIIIa	0.76
Left VIIIb	0.19
Right Crus I	0.95
Right Crus II	0.86
Right VI	0.43
Right VIIIa	0.18
Right IX	0.47
Right V	0.29
<b>Left CP P300 Amplitude</b>	<b>0.03</b>
<b>Right CP P300 Amplitude</b>	<b>&lt;0.001</b>

**Supplemental Table 2. Correlations among RMFC thickness and cerebellar cluster volumes.**

RMFC		Left CrusI	Left CrusII	Left VI	Left VIIIa	Left VIIIb	
<b>Left</b>	R	0.22	0.21	<b>0.38</b>	<b>0.36</b>	<b>0.34</b>	
	p	0.20	0.24	<b>0.02</b>	<b>0.04</b>	<b>0.02</b>	
<b>Right</b>	R	0.14	0.27	0.28	0.29	<b>0.41</b>	
	p	0.43	0.12	0.10	0.10	<b>0.02</b>	
		Right CrusI	Right CrusII	Right VI	Right VIIIa	Right IX	Right V
<b>Left</b>	R	0.28	0.15	0.26	<b>0.44</b>	0.16	<b>0.46</b>
	p	0.11	0.39	0.13	<b>&lt;0.01</b>	0.35	<b>&lt;0.01</b>
<b>Right</b>	R	0.32	0.10	0.11	<b>0.42</b>	0.19	<b>0.50</b>
	p	0.06	0.58	0.52	<b>0.01</b>	0.28	<b>&lt;0.01</b>

Prob > |r| under H0: Partial Rho=0

**Supplemental Table 3. Correlations among morphological measures and P300 amplitudes.**

P300		Left RMFC	Left CrusI	Left CrusII	Left VI	Left VIIIa	LeftV IIIb	
<b>Left</b>	R	-0.06	0.24	0.14	0.12	-0.03	0.10	
	p	0.77	0.24	0.51	0.34	0.89	0.61	
<b>Right</b>	R	0.22	<b>0.61</b>	<b>0.54</b>	0.34	<b>0.42</b>	<b>0.49</b>	
	p	0.29	<b>&lt;0.001</b>	<b>&lt;0.01</b>	0.09	<b>0.03</b>	<b>0.01</b>	
		Right RMFC	Right CrusI	Right CrusII	Right VI	Right VIIIa	Right IX	Right V
<b>Left</b>	R	-0.03	-0.07	0.22	0.08	<b>0.41</b>	<b>0.52</b>	0.17
	p	0.88	0.74	0.28	0.69	<b>0.04</b>	<b>&lt;0.01</b>	0.40
<b>Right</b>	R	0.09	<b>0.50</b>	<b>0.55</b>	0.32	<b>0.48</b>	<b>0.55</b>	<b>0.53</b>
	p	0.68	<b>0.01</b>	<b>&lt;0.01</b>	0.11	<b>0.01</b>	<b>&lt;0.01</b>	<b>&lt;0.01</b>

Prob > |r| under H0: Partial Rho=0

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