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Sex- and Age-Specific Deviations in Cerebellar Structure and Their Link With Symptom Dimensions and Clinical Outcome in Individuals at Clinical High Risk for Psychosis

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***Background*: The clinical high-risk (CHR) period offers a temporal window into neurobiological deviations preceding psychosis onset, but little attention has been given to regions outside the cerebrum in large-scale studies of CHR. Recently, the North American Prodrome Longitudinal Study (NAPLS)-2 revealed altered functional connectivity of the cerebello-thalamo-cortical circuitry among individuals at CHR; however, cerebellar morphology remains underinvestigated in this at-risk population, despite growing evidence of its involvement in psychosis. *Study Design*: In this multisite study, we analyzed T1-weighted magnetic resonance imaging scans obtained from *N* = 469 CHR individuals (61% male, ages = 12–36 years) and *N* = 212 healthy controls (52% male, ages = 12–34 years) from NAPLS-2, with a focus on cerebellar cortex and white matter volumes separately. Symptoms were rated by the Structured Interview for Psychosis-Risk Syndromes (SIPS). The outcome by two-year follow-up was categorized as in-remission, symptomatic, prodromal-progression, or psychotic. General linear models were used for case-control comparisons and tests for volumetric associations with baseline SIPS ratings and clinical outcomes. *Study Results*: Cerebellar cortex and white matter volumes differed between the CHR and healthy control groups at baseline, with sex moderating the difference in cortical volumes, and both sex and age moderating the difference in white matter volumes. Baseline ratings for major psychosis-risk dimensions as well as a clinical outcome at follow-up had tissue-specific associations with cerebellar volumes. *Conclusions*: These findings point to clinically relevant deviations in cerebellar cortex and white matter structures among CHR individuals and highlight the importance of considering the complex interplay between sex and age when studying the neuromaturational substrates of psychosis risk.**

Key words: CHR/prodrome/ultra-high risk/schizophrenia/North American Prodrome Longitudinal Study/structural magnetic resonance imaging

Introduction

Among individuals with schizophrenia and other psychotic disorders, the clinical onset of psychosis is typically preceded by a prodromal period, marked by functional decline, cognitive and affective changes, and surfacing of attenuated positive symptoms.[1–5] Given this course, the prodrome offers a promising temporal window into the neurobiological precursors of psychosis.

The clinical high risk (CHR) for psychosis construct originated from findings from retrospective studies and is now used to prospectively identify individuals presenting with such "warning" signs.[6,7] Longitudinal studies using screening tools, such as the Structured Interview for

Psychosis-Risk Syndromes (SIPS)[8,9] report that 15%–35% of individuals meeting CHR criteria transition to psychosis within 2–3 years.[10–15] Hence, a substantial proportion of CHR youth are at imminent risk of developing frank psychosis. However, it is not yet possible to make personalized predictions about psychosis-onset based solely on these criteria.

Among CHR individuals who do not go on to develop psychosis, a subset experience remission, while others remain stably symptomatic or experience exacerbation,[16–25] suggesting that the CHR construct itself embodies a continuum toward frank psychosis. Consequently, considering the broader spectrum of clinical outcomes in CHR beyond conversion versus nonconversion provides more nuanced insights into variable expressions of psychosis vulnerability.

The integration of the CHR paradigm and high-resolution structural magnetic resonance imaging (MRI) has greatly advanced our understanding of brain alterations underlying psychosis risk without confounds such as disease chronicity or extended antipsychotic treatment.[26] An array of neuroanatomical abnormalities has been identified in CHR,[27–49] some of which are similar to but more subtle than those seen in psychotic disorders.[27,39,50–52] Several changes, including accelerated neocortical thinning, distinguish CHR individuals who convert to psychosis (CHR-C) from those who do not (CHR-NC),[31,32,39,40,50,53–56] and compared to CHR-NC, CHR-C shows baseline volumetric reductions in multiple structures,[27,30,34–37,39–41,56–58] including frontal and temporal regions, which has important implications for improving prognostic precision.

When these advances are reviewed collectively, it becomes apparent that most CHR studies have focused on supratentorial regions, with little attention given to the cerebellum: an infratentorial structure containing ~80% of all neurons in the brain.[59] The few that examined the cerebellum have revealed reduced gray or whole cerebellar volume in CHR, especially among those who transition to psychosis, compared to controls.[42,43,46–49] One reported increased cerebellar white matter (WM) volume in CHR converters.[44] The paucity of research on the cerebellum is partially a result of the view that cerebellar function is confined to motor control. However, recent findings indicate that the cerebellum also modulates higher cognitive and affective processes via interactions with nonmotor regions of the neocortex,[60–69] and growing evidence, with roots in early theories of "cognitive dysmetria,"[70] implicate the cerebellum in schizophrenia pathogenesis.[71–75]

Consistent with these reports, findings from the North American Prodrome Longitudinal Study (NAPLS)-2[76] revealed altered functional connectivity of the cerebellum in CHR,[77] but the cerebellar structure has not been investigated in this sample. The present study expands prior neuroimaging findings from NAPLS-2[41,55,78] and interrogates baseline differences in the cerebellar cortex and WM morphology between CHR participants and healthy controls (HCs). Although previous research has established that the cerebellar cortex and WM follow different developmental trajectories that may be sexually dimorphic,[79–92] studies of the cerebellum in CHR have not made this distinction. The inclusion of sex as a predictor is especially important, because sexual dimorphism appears to be more pronounced in the cerebellum than in any other human brain region.[81–84] Thus, we separately measure gray and WM while exploring interactions between sex and age and test for associations between baseline cerebellar volumes and psychosis-risk symptoms assessed by the SIPS. Finally, we test the prediction that baseline cerebellar volumes differ among CHR participants according to clinical outcome within the two-year study follow-up period. To our knowledge, this is the largest study of CHR to date with an explicit focus on cerebellar structure.

Methods

Participants

Participants were recruited through NAPLS-2.[76] Data from 469 help-seeking CHR participants, ages 12–36 years and 212 HCs, ages 12–34 years were included (table 1, Tables S1, and S2; figure 1A). CHR participants met the Criteria of Prodromal Syndromes,[93] or if under age 19, met the criteria for schizotypal personality disorder. HCs were excluded if they had a psychotic disorder, Cluster-A personality disorder, prodromal syndrome, first-degree family history of psychosis, or were using psychotropic medication. Individuals with IQ < 70, a central nervous system disorder, or substance dependence were excluded. Procedures were approved by the Institutional Review Boards of all sites. Project protocol and characteristics of the broader study sample, from which the current sample was drawn, have been detailed elsewhere.[25,76]

Neuroimaging

Structural MRI was performed on 3T Siemens or GE scanners with 12- or 8-channel head coils, using standardized sequence parameters optimized based on the ADNI protocol[94] (https://adni.loni.usc.edu/methods/documents/mri-protocols/). T1-weighted 3D images were acquired in the sagittal plane with a 1 × 1 mm in-plane resolution and 1.2 mm slice thickness using an MPRAGE sequence at Siemens sites and IR-SPGR sequence at GE sites: TR = 52,300 ms, TE = 2.91 ms, TI = 900 ms, FOV = 256 × 240 × 176 mm, flip angle = 9° for Siemens; TR= 57.0 ms, TE = minimum full, TI = 400 ms, FOV = 26 cm, and flip angle = 8° for GE.

Scans were processed using Freesurfer v.5.3 (http://surfer.nmr.mgh.harvard.edu/) for methodological consistency with previous work from NAPLS-2. Using automated subcortical segmentation,[95] we distinguished the

Table 1. Demographics Stratified by Sex and Diagnostic Group

	Female (N = 286)			Male (N = 395)		
Demographic Variables	CHR (N = 185)	HC (N = 101)	Test Statistics	CHR (N = 284)	HC (N = 111)	Test Statistics
Age at baseline (years)						
Mean (SD)	18.91 (4.17)	21.55 (4.01)	W = 12,860,	19.56 (3.88)	19.88 (4.77)	W = 16,146,
Median	18.05	21.41	r = 0.31 (moderate ES),	18.80	19.67	P-value[a] = .71
Range	12.08–33.54	12.26–30.29	P-value[a] ≤ .001	12.77–36.35	12.25–34.38	
Ethnicity, *n (%)*						
Non-Hispanic or Latino	157 (84.87%)	90 (89.11%)	X^2 = 1.00,	233 (82.04%)	86 (77.48%)	X^2 = 1.07,
Hispanic or Latino	28 (15.13%)	11 (10.89%)	P-value[b] = .32	51 (17.96%)	25 (22.52%)	P-value[b] = .30
Race, *n (%)*						
White	106 (57.30%)	50 (49.51%)	X^2 = 8.73,	178 (61.59%)	66 (59.47%)	X^2 = 5.14,
Black	29 (15.68%)	21 (20.79%)		40 (13.84%)	18 (16.22%)	P-value[b] = .74
Interracial	24 (12.97%)	9 (8.91%)	P-value[b] = .46	28 (9.69%)	11 (9.91%)	
Central/South American	4 (2.16%)	3 (2.97%)		18 (6.23%)	5 (4.50%)	
South Asian	5 (2.70%)	5 (4.95%)		8 (2.77%)	1 (0.90%)	
Southeast Asian	7 (3.79%)	4 (3.96%)		4 (1.38%)	2 (1.80%)	
East Asian	4 (2.16%)	7 (6.93%)		5 (1.73%)	5 (4.50%)	
First Nations	2 (1.08%)	1 (0.99%)		6 (2.08%)	3 (2.70%)	
West/Central Asia and Middle East	2 (1.08%)	1 (0.99%)		2 (0.69%)	0 (0.00%)	
Native Hawaiian/Pacific Islander	2 (1.08%)	0 (0.00%)		0 (0.00%)	0(0.00%)	
Maternal education score						
Mean (SD)	6.33 (1.60)	6.71 (1.39)	W = 10640,	6.40 (1.60)	6.86 (1.54)	W = 18,050,
Median	7.00	7.00	r = 0.12 (small ES),	7.00	7.00	r = 0.12
Range	2.00–9.00	2.00–9.00	P-value[a] = .05	2.00–9.00	3.00–9.00	(small ES), P-value[a] = .02
Handedness,[c] *n (%)*						
Right	145 (79.67%)	87 (87.00%)	X^2= 2.74,	229 (82.97%)	94 (85.46%)	X^2 = 1.24,
Left	16 (8.79%)	7 (7.00%)	P-value[b] = .25	17 (6.16%)	8 (7.27%)	P-value[b] = .54
Mixed	21 (11.54%)	6 (6.00%)		30 (10.87%)	8 (7.27%)	

Note: CHR, clinical high-risk for psychosis; HC, healthy control; ES, effect size; SD, standard deviation.
[a]Wilcoxon rank-sum test.
[b]Pearson's chi-squared test.
[c]For handedness, CHR female N = 182, HC female N = 100, CHR male N = 276, HC male N = 110.

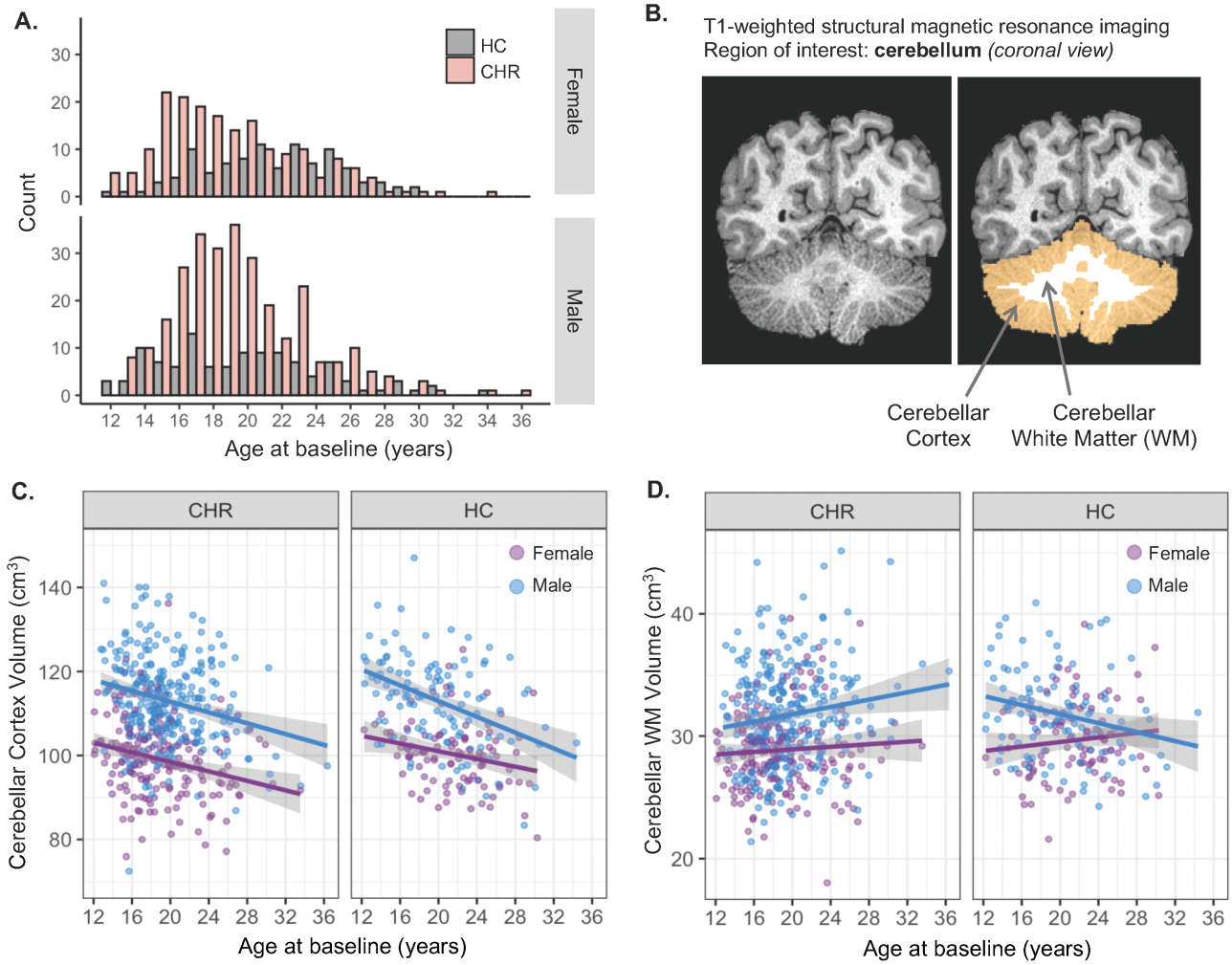

Fig. 1. (A) Histogram showing age distributions of study participants. (B) Example cerebellar segmentation mask. (C) and (D) Cerebellar cortex and WM volume distributions across age. Solid lines: line of linear fit, error bands: 95% confidence interval. CHR, clinical high-risk; HC, healthy control; WM, white matter.

two primary tissue types of the cerebellum and extracted volumetric measures for the cerebellar cortex and WM (figure 1B). To correct for variability in head size,[96,97] we used estimated intracranial volume (eICV).[98] To improve between-site reliability a traveling-subject design was implemented, and scanner-related variance was corrected as reported previously[41,99] (see Supplemental Methods and Figure S1 for details). Quality control is described elsewhere.[41,55,99]

Clinical Measures

Dimensional Symptom Ratings at Baseline. SIPS was administered at baseline to rate symptom severity along positive, negative, and disorganization symptom dimensions.[8,9] Individual items were summed to produce a total score for each dimension. Only participants with complete SIPS data across all domains (CHR N = 466, HC N = 210) were included in corresponding analyses. Assessments were performed by trained personnel, with high inter-rater reliability.[9,25]

Clinical Outcome at Follow-up. CHR participants were followed for up to two years to determine illness progression based on Current Clinical State criteria.[22] To reduce attrition-related bias, clinical outcome was determined based on the last observation carried forward (LOCF) method commonly used in longitudinal research.[100] Resulting clinical outcomes were (1) in-remission (full remission from prodromal syndromes, N = 121), (2) symptomatic (continues to exhibit prodromal symptoms, but not meeting prodromal syndrome criteria, N = 130), (3) prodromal-progression (continues to meet prodromal syndrome criteria, N = 109), or (4) psychotic (converted to psychosis, N = 68) (Table S3). LOCFs were relatively evenly distributed across outcome groups (Figure S2).

Statistical Analyses

Case-Control Comparison of Cerebellar Volume at Baseline. Statistical analyses were performed using R v.4.0.3.[101] Demographics were compared using Pearson's chi-squared and Wilcoxon rank-sum tests. Baseline volumes of cerebellar cortex and WM were compared between CHR and HC using multiple linear regression, correcting for age, sex, maternal education, and eICV. Covariate selection was informed by correlation analyses prior to model construction (Tables S4–9, Figures S3 and 4). Maternal education was included as a covariate given its association with offspring outcomes.[102–105] Higher degree polynomials of age were additionally tested; consistent with the age range, linear models were found more appropriate to prevent overfitting (figure 1C and D).

We checked for two-way and three-way interactions between sex, age, and diagnostic group and determined best-fit models using analyses of variance (ANOVA). In cases where a significant product term was identified, data were stratified by sex and/or age for post hoc analysis. In supplemental analyses, bilateral volumes were substituted with hemisphere-specific counterparts with handedness[106] added as an additional covariate.[107] Results indicate parallel trends between models testing bilateral versus unilateral measures (Table S10). Hence, downstream analyses focus on bilateral volumes.

Relationship between Cerebellar Volume and Symptom Dimensions of Psychosis Risk. We investigated the dimensional relationship between positive, negative, and disorganization symptoms and cerebellar cortex and WM volumes among CHR participants at baseline in separate multiple linear regression models, correcting for age, sex, maternal education, and eICV. Using the same procedure outlined above, we checked for two-way and three-way interactions between sex, age, and cerebellar volumes. Descriptive statistics for SIPS ratings are provided in Table S11 and Figure S5. Covariate selection was informed by supplemental correlation analyses (Tables S12–14 and Figure S6).

Relationship between Cerebellar Volume and Future Clinical Outcomes. Baseline demographics of the four clinical outcome groups that CHR participants met criteria for at follow-up were compared using Pearson's chi-squared, Kruskal–Wallis, and Dunn's tests. Multiple linear regression was used to test for baseline differences in the cerebellar cortex and WM volumes of CHR participants with varying clinical outcomes, correcting for age, sex, maternal education, and eICV. Clinical outcome was treated as an ordered predictor (in-remission < symptomatic < prodromal-progression < psychotic); one fewer orthogonal polynomials than ordered levels were fit, and interactions between sex, age, and clinical outcome were tested. Since a linear trend was observed across its ordinal levels, clinical outcome was treated as continuous in post hoc analyses to maximize power.

Standard diagnostics were performed for statistical assumptions; to address ordinary least squares violations, heteroscedasticity-robust estimates were calculated using the HC1 robust standard error estimator.[108] All analyses were two-tailed. Benjamini–Hochberg procedure[109] was used to control the false discovery rate (FDR) within families of hypotheses. See Supplemental Materials for details.

Results

Case-Control Differences in Cerebellar Cortex and WM Volumes Change as a Function of Sex and Age at Baseline

We first compared the cerebellar volumes of CHR and HC participants at baseline (Table S15). There was a significant effect of diagnostic group ($b = -2.78$, P-value = .002, adjusted P-value = .01) and a two-way interaction between sex and diagnostic-group on cerebellar cortex volumes ($b = 2.79$, P-value = .03, adjusted P-value = .04). Simultaneously, there was a significant two-way interaction between sex and diagnostic-group ($b = -5.65$, P-value = .02, adjusted P-value = .03) and a three-way interaction between sex, age, and diagnostic group ($b = 0.32$, P-value = .01, adjusted P-value = .03) on cerebellar WM volumes, as well as a two-way interaction between sex and diagnostic groups ($b = 0.56$, P-value = .02, adjusted P-value = .03) and a three-way interaction between sex, age, and diagnostic group ($b = -0.03$, P-value = .02, adjusted P-value = .03) on cerebellar cortex-to-WM ratios.

In post hoc analyses (Table S16), there was a significant reduction in the cerebellar cortex of CHR compared with HC participants ($b = -2.53$, P-value = .005, adjusted P-value = .02), among females only (figure 2A). There was also a significant effect of diagnostic-group ($b = -6.38$, P-value ≤ .001, adjusted P-value ≤ .001; $b = 0.53$, P-value ≤ .001, adjusted P-value = .004) and a two-way interaction between diagnostic group and age ($b = 0.32$, P-value ≤ .001, adjusted P-value ≤ .001; $b = -0.03$, P-value ≤ .001, adjusted P-value = .004) on cerebellar WM volumes and cerebellar cortex-to-WM ratios, among males only (figure 2B and C). The crossover of these two-way interactions (ie, the point of intersection for regression lines in figure 2B and C) occurred around age 20, coinciding with the period of transition from adolescence to young adulthood. Partitioning males into younger (age ≤ 20) versus older (age > 20) age cohorts (Table S17) revealed a significant reduction in the cerebellar WM of younger CHR males than HCs ($b = -1.14$, P-value = .02, adjusted P-value = .03), whereas cerebellar WM was significantly larger in older CHR males than HCs ($b = 1.36$, P-value = .02, adjusted P-value = .03) (Table S18).

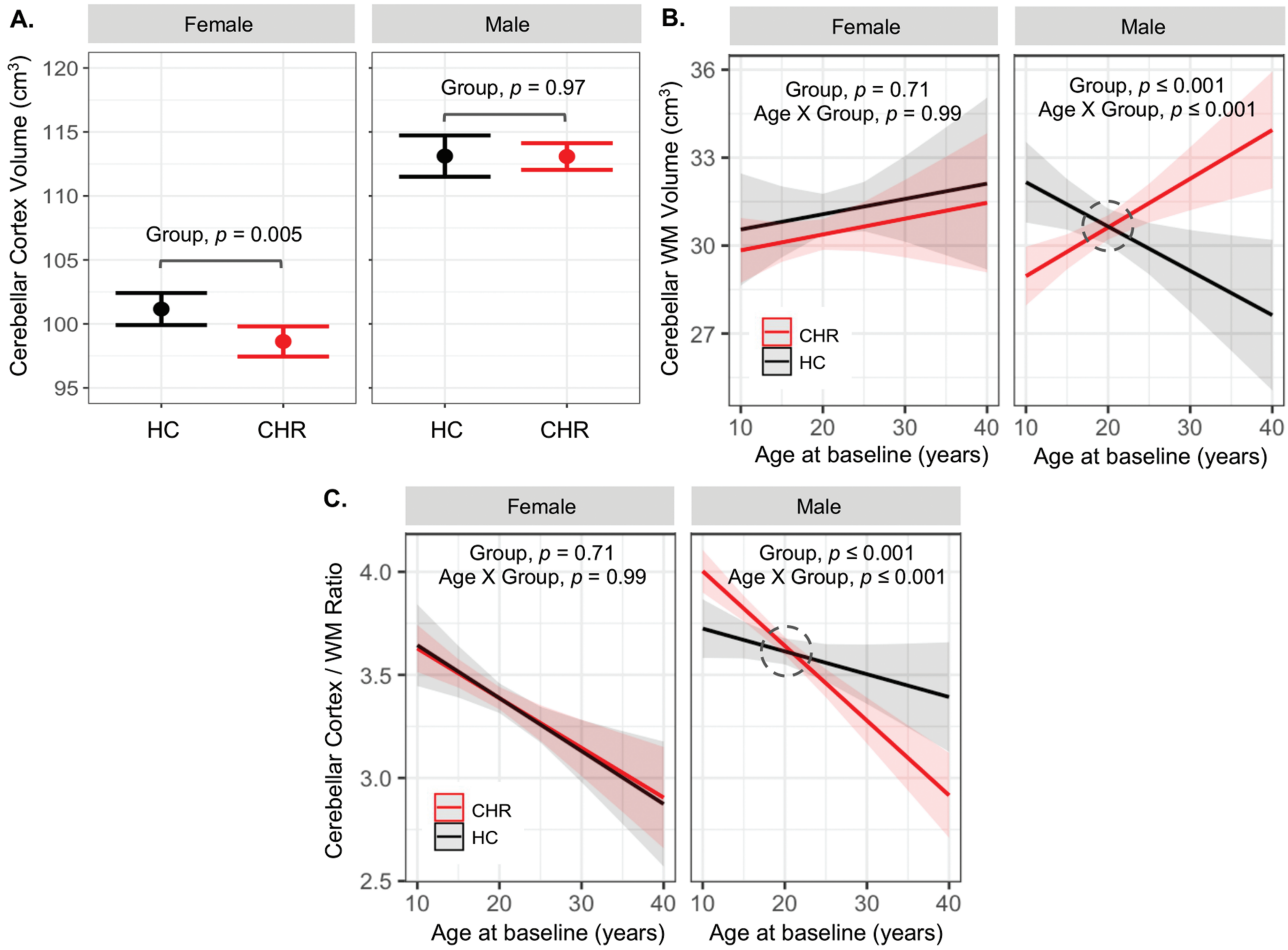

Fig. 2. (A)–(C) Predictor effect plots illustrating sex- and age-specific differences in baseline cerebellar cortex and WM volumes between CHR and HC participants. Error bands: 95% confidence interval, dashed circles: crossover point of interaction. CHR, clinical high-risk; HC, healthy control; WM, white matter.

Disorganization and Negative Symptoms Covary with Baseline Cerebellar Cortex Volumes in CHR

We next tested whether cerebellar volumes were associated with positive, negative, or disorganization symptom ratings among CHR participants at baseline (Table S19). There was a significant effect of cerebellar cortex volume ($b = -0.06$, P-value = .01, adjusted P-value = .02) and a two-way interaction between cerebellar cortex volume and sex ($b = 0.11$, P-value ≤ .001, adjusted P-value = .004) on disorganization symptoms. Similarly, there was a significant two-way interaction between cerebellar cortex volume and sex on negative symptoms ($b = 0.16$, P-value = .01, adjusted P-value = .02), but no association between cerebellar volumes and positive symptoms.

When stratified by sex (Table S20; figure 3), a significant inverse relationship was identified between cerebellar cortex volume and disorganization symptoms among CHR females ($b = -0.07$, P-value = .01, adjusted P-value = .02), whereas the direction of this relationship was positive among CHR males ($b = 0.05$, P-value = .02, adjusted P-value = .04). Similarly, there was a nominally significant positive relationship between cerebellar cortex and negative symptoms among CHR males that did not survive FDR correction ($b = 0.09$, P-value = .04, adjusted P-value = .10), and a trend-level inverse association between these variables among CHR females ($b = -0.08$, P-value = .10).

Future Clinical Outcomes in CHR are Associated with Baseline Cerebellar WM Volumes

To investigate prognostic relations, we tested for baseline differences in the cerebellar cortex and WM volumes of CHR participants as a function of clinical outcomes by the end of the two-year study follow-up period (Table S21). Results indicated a relation with clinical outcome ($b = -5.30$, P-value = .02, adjusted P-value = .04), a two-way interaction between sex and clinical outcome ($b = 9.94$, P-value = .01, adjusted P-value = .03), a two-way interaction between age and clinical outcome ($b = 0.30$, P-value = .03, adjusted P-value = .04), and a three-way interaction between sex, age, and clinical outcome

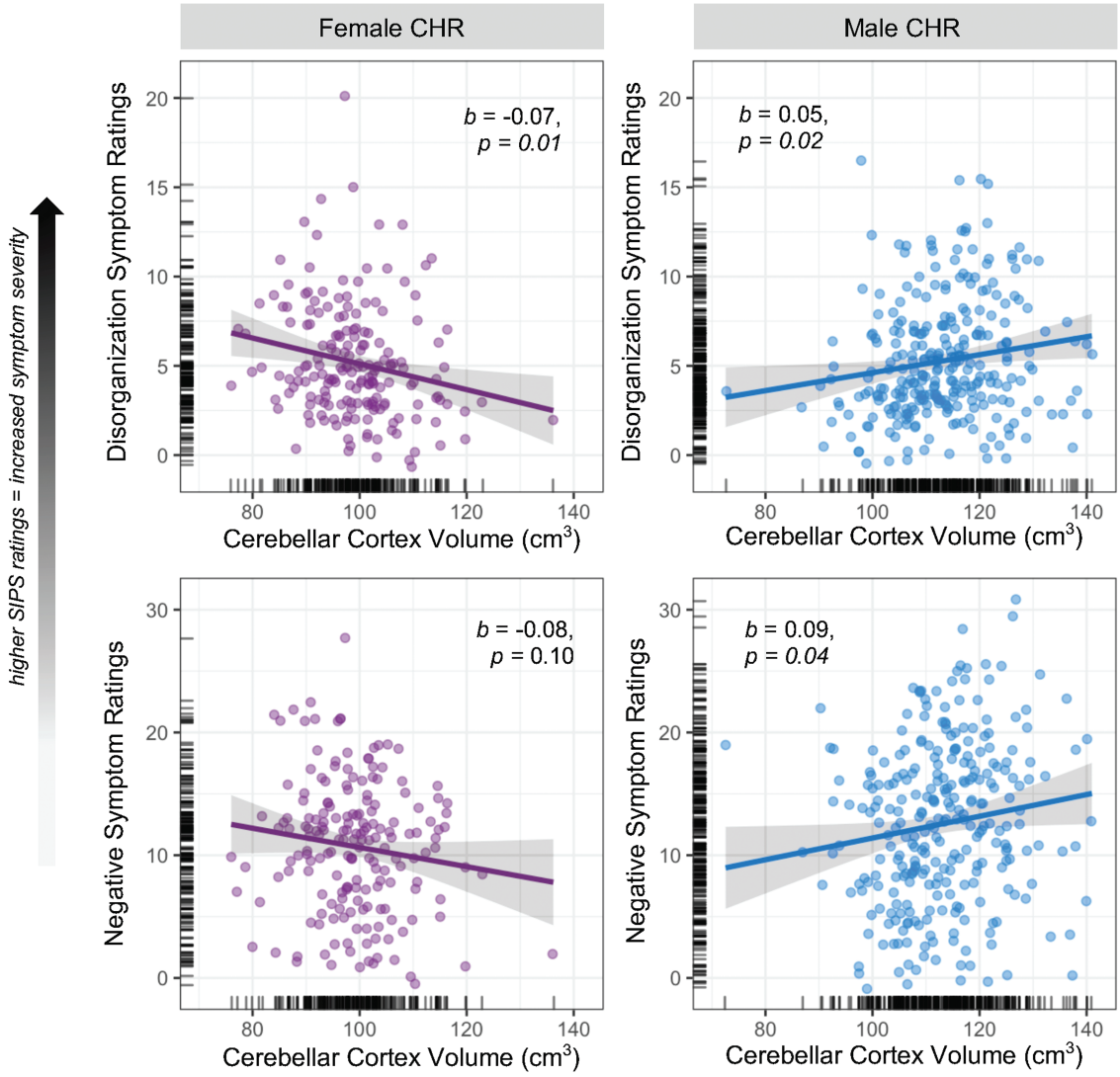

Fig. 3. Predictor effect plots illustrating sex-specific associations between baseline cerebellar cortex volumes and symptom ratings among CHR participants. Error bands: 95% confidence interval. CHR, clinical high-risk.

(b = −0.60, P-value = .004, adjusted P-value = .03) on cerebellar WM volumes.

In post hoc analyses (Table S22; figure 4), there was a significant relation of clinical outcome (b = −2.01, P-value = .02, adjusted P-value = .04) and a significant interaction between age and clinical outcome (b = 0.12, P-value = .02, adjusted P-value = .04) for cerebellar WM among CHR females. Similarly, there was a trend-level effect of clinical outcome (b = 2.04, P-value = .10) and a nominally significant interaction between age and clinical outcome on WM among CHR males (b = −0.13, P-value = .04, adjusted P-value = .06).

To parse these interactions, we partitioned CHR participants into two age groups (age ≤ 20 vs > 20) (Table S23). In older CHR males, participants with more severe clinical outcomes had significantly smaller cerebellar WM at baseline (b = −0.96, P-value = .03, adjusted P-value = .04). Among older CHR females, a trend-level association was identified between clinical outcome and cerebellar WM, but the direction of this relationship was positive (b = 0.83, P-value = .07). No link was identified between clinical outcome and cerebellar volumes among younger CHR participants. A similar pattern was observed when the clinical outcome was treated as an unordered categorical variable (Table S24), but power was expectedly reduced.

Discussion

Structural neuroimaging has been pivotal in identifying the types of brain abnormality observed across individuals at CHR for psychosis. However, not all parts of the brain have received equal attention in this pursuit, partially stemming from the neocorticocentric bias in studying higher-order capacities of the human brain.[110] Work suggesting that cerebellar abnormalities occur in

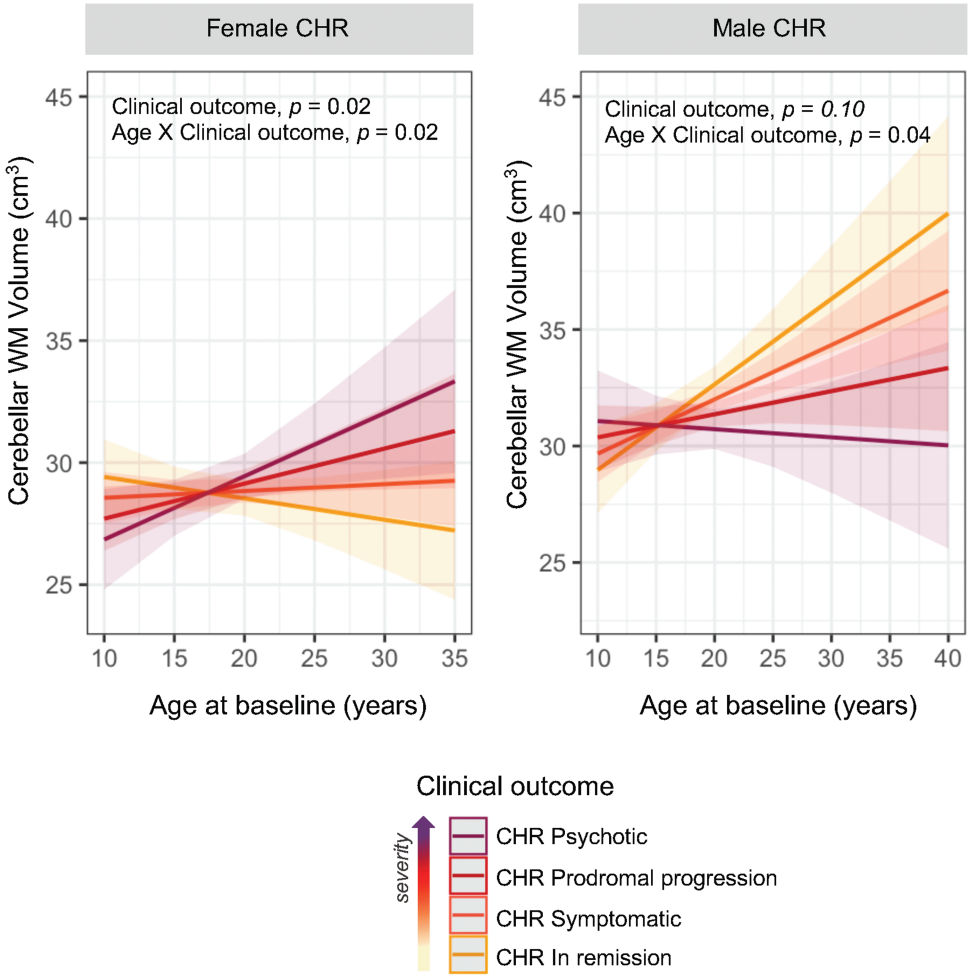

Fig. 4. Predictor effect plots illustrating sex- and age-specific associations between baseline cerebellar WM volumes and future clinical outcomes among CHR participants. Error bands: 95% confidence interval. CHR, clinical high-risk; WM, white matter.

schizophrenia and other psychoses are accumulating,[111,112] but only a limited number of studies with relatively small sample sizes, and in some cases with no HC comparisons, have investigated the morphology of the cerebellum in CHR.[35,42–49,54,56] Due to insufficient data, the cerebellum was excluded from multiple meta-analyses in this population,[113,114] hindering our ability to assess the full extent of neuropathology associated with vulnerability for psychosis.

To our knowledge, no large-scale study of CHR has ever jointly investigated the distinct volumetric profiles and clinical correlates of cerebellar cortex and WM, while considering sex and age-related differences beyond so-called "nuisance" variation. Using high-resolution T1-weighted MRI, standardized clinical assessments, and the NAPLS-2 multicenter design, here we report the largest study of CHR to date with an explicit focus on sex-, age-, and tissue-specific deviations in the volumetric properties of this long-overlooked brain region.

Consistent with previous reports of normative sex differences, in our HC group, males showed larger cerebellar cortex volumes than females across ages, as well as a significant age-by-sex interaction, with females showing an earlier peak volume and less protracted age-related volumetric declines in adolescence/young adulthood.[80,83] In a study of both cerebellar gray and WM volumes in healthy youth aged 12–22, age-by-sex interactions were also found; controlling for sex differences in overall volume, gray matter volume declined faster in male youths than in female youths with age, but WM volume increased faster in females than in males.[85] To date, we are aware of one report on sex and age differences in cerebellar WM using diffusion tensor imaging, with results also showing a significant age-by-sex interaction, due to males only with an age-related increase during childhood.[115] Because the sample age ranges in the above-cited studies differ from the present study, with minimums from 7 to 12 years and maximums to the early/mid-1920s, we would not expect replications of the age-related trends. Nonetheless, all find age-by-sex interactions.

Present findings suggest that the CHR group showed sex differences similar to those observed in HCs, but the volumes and age trajectories differed by diagnostic group. First, we found a significant diagnostic-group-by-sex

interaction on baseline volumes of the cerebellar cortex, which contains almost all neuronal cell bodies (gray matter) in the cerebellum and more than half of the neurons in the entire brain. The average size of the cerebellar cortex was smaller in CHR females compared with HC females, while this effect was not observed among males and did not change as a function of age.

Simultaneously, we found a significant diagnostic-group-by-sex-by-age interaction on baseline volumes of cerebellar WM, which mostly contains myelinated axons connecting the cerebellum with the central nervous system. There was a male-specific reduction in the cerebellar WM volumes of CHR participants compared with HCs among those aged 20 or younger, while CHR males older than 20 had larger WM than HCs. This male-specific effect was also mirrored in cerebellar cortex-to-WM ratios. Altogether, these results implicate abnormal cerebellar structure as a baseline neuroanatomical marker of CHR, but with substantial sex- and age-specific heterogeneity in the direction of diagnostic-group effects that support the importance of harnessing sex- and age-related variability in future precision medicine approaches[116–119]

Furthermore, our results revealed sex-specific relationships between baseline cerebellar cortex volumes and disorganization symptoms. Among CHR females, smaller cerebellar cortex volumes were associated with more severe disorganization symptoms, while the inverse was observed among males. Concurrently, among CHR males, larger cerebellar cortex volumes showed a nominally significant association with more severe negative symptoms, while an inverse trend was observed among females. We found no association between baseline cerebellar volumes and positive symptom ratings among CHR participants, although caution is warranted in interpreting this finding, given the range restriction imposed on this dimension by SIPS eligibility criteria.

These findings are broadly consistent with growing evidence indicating many cognitive and affective processes map onto neural networks involving the cerebellum.[120–123] Following cerebellar lesion, a cognitive/affective syndrome is known to unfold, which includes impairments in working memory, verbal fluency, attention, and abstract reasoning, as well as blunted affect, and disinhibited or inappropriate behavior,[124] which are highly consistent with the phenomenology of disorganization and negative symptoms.

We also showed that baseline cerebellar WM volumes display a sex- and age-specific association with clinical outcome at follow-up, suggesting prognostic utility. Among CHR males older than 20, those with smaller baseline cerebellar WM volumes developed more severe clinical outcomes, while among CHR females older than 20, larger cerebellar WM showed a trend-level association with more severe clinical outcomes. These associations were not observed among younger CHR participants.

Previous findings from NAPLS-2 revealed that the degree to which CHR cases manifest deviance from age-normative neuroanatomical profiles depends on age-of-ascertainment, with marked differences observed between those ascertained during early adolescence versus late adolescence/early adulthood.[41,78] These findings were interpreted as a pattern consistent with differential vulnerability for insidious versus acute forms of psychosis-onset,[41,78] which may be relevant to the age-specific findings observed in this study. However, compensation attempts in WM microstructure, which can be maladaptive,[125] may also be at play. We note that the approximate point of crossover for these age-dependent effects was 20, as opposed to 18 in earlier extra-cerebellar findings from NAPLS-2[41,78] (see Supplemental Materials for an extended discussion); this may be due to slight differences in age ranges or protracted development of the cerebellum.[126,127] Here, we highlight that age 20 is only an approximate marker that was derived from the corresponding interactions to demarcate the age dependence of group effects (similar to[128]). A sliding window approach should be employed in future work with larger sample sizes to re-evaluate the reproducibility of this split.

Literature on neuroanatomical sex differences in CHR is scarce. Similar to our findings, at least one prior study identified sex-by-diagnosis interactions in the cerebrum, with opposite directions of effect observed in CHR males, and females relative to same-sex HCs.[129] Interestingly, Gur and colleagues reported a positive association between amygdala volume and negative symptom severity among males with schizophrenia, while the inverse was identified among females. This was interpreted as indicative of increased "feminization" among men and "masculinization" among women with schizophrenia.[130] More research is needed to determine whether the reversal of normative sexual dimorphism during neurodevelopment contributes to the opposite pattern of cerebellar findings identified in CHR males and females.

We highlight that Purkinje cells of the cerebellar cortex are a major site of neurosteroid synthesis.[131–134] Cerebellar sex differences in synaptic physiology,[135] gene and protein expression, and functional associations have been reported.[136–140] It has been further suggested that cerebellar synaptic pruning is linked with puberty, the timing of which differs by sex.[80] These data, together with our findings demonstrate an imperative for including sex and sex-by-age interactions as variables of interest in future studies of the cerebellum's role in neuropsychopathology. In this context, the extent to which variations in the timing of puberty[141] might influence the age- and sex-specific findings reported herein remains to be explored.

Finally, as shown in some previous studies of healthy participants,[79–90] we found that age-related changes in HCs differ for the cerebellar cortex and WM, with the cortex showing a greater age-related decline. Differences in the timing of neuromaturational processes governing

the development of these two tissue types likely confer different susceptibilities to cerebellar cortex versus WM development, which may partially explain the tissue-specific findings reported herein. We expect that previous studies of the cerebellum in clinical populations that did not distinguish between white and grey matter have missed differences in their respective developmental trajectories, as well as developmental moderation of their changes.

Several limitations should be considered. The complexity of cerebellar architecture introduces methodological challenges; our gray and WM classifications lack the resolution to differentiate thinner WM branches and the deep cerebellar nuclei. Emerging findings indicate that distinct cerebellar subregions subserve different motor and nonmotor functions mediated by their connectivity patterns with extracerebellar regions; however, it is unclear whether functional subdivisions coincide with lobular boundaries.[142–148] Given these intriguing circuit-level links, future work should determine whether differing pathologies in CHR can be localized to variations in distinct subregions of the cerebellum. In this context, integrating a neurocognitive battery may provide more refined insights. Age-of-ascertainment does not necessarily reflect age-of-onset for CHR symptoms, but determining the latter requires reliance on retrospective memory which is frequently disrupted in CHR.[149] Finally, findings do not necessarily reflect causation; longitudinal tracking of changes in cerebellar morphology and replication of results in a larger sample is needed. Nonetheless, present findings point to the importance of the cerebellum in the neuropathological processes involved in at least some forms of psychosis. They also highlight sexual dimorphisms in normative cerebellar developmental trajectories that must be taken into consideration in future research.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin.

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