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CEREBELLAR STRUCTURE AND COGNITIVE ABILITY IN PSYCHOSIS

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Abstract

Background: Dysconnectivity theories, combined with advances in fundamental cognitive neuroscience, have led to increased interest in characterizing cerebellar abnormalities in psychosis. Smaller cerebellar grey matter volume has been found in schizophrenia-spectrum disorders. However, the course of these deficits across illness-stage, specificity to schizophrenia (versus psychosis more broadly), and relationship to clinical phenotypes, primarily cognitive impairment, remain unclear.

Methods: The SUIT toolbox, a gold standard for analyzing human neuroimaging data of the cerebellum, was used to quantify cerebellar volumes and conduct voxel-based morphometry on structural magnetic resonance images obtained from 574 individuals (249 schizophrenia-spectrum, 108 bipolar with psychotic features, 217 non-psychiatric control). Analyses examining diagnosis (schizophrenia spectrum, bipolar disorder), illness-stage (early, chronic), and cognitive effects on cerebellum structure in psychosis were performed.

Results: Cerebellar structure in psychosis did not differ significantly from healthy participants, regardless of diagnosis and illness-stage (effect sizes (ES)=0.01-0.14). In contrast, low premorbid cognitive functioning was associated with smaller whole and regional cerebellum volumes, including cognitive (lobules VI, VII, Crus I, fronto-parietal and attention networks) and motor (lobules I-IV, V, X, somatomotor network) regions in psychosis (ES=0.36-0.60). These effects were not present in psychosis cohorts with average estimated premorbid cognition.

Conclusion: Cerebellar structural abnormalities in psychosis are related to lower premorbid cognitive functioning implicating early antecedents, atypical neurodevelopment, or both in cerebellar dysfunction. Future research focused on identifying the impact of early life risk factors for psychosis on the development of the cerebellum and cognition is warranted.

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Keywords

cerebellum; psychosis; structural MRI; bipolar disorder; schizophrenia; heterogeneity

Introduction

The cerebellum has long been included in conceptualizations of the neural underpinnings of schizophrenia. Early theories, such as Stansky's "intrapsychic ataxia," suggest that psychosis results from a dyscoordination of cognitive processes, much like uncoordinated motor functions (ataxias)(1). Aligned with this thinking, modern dysconnectivity theories, including Andreasen's cognitive dysmetria model, hypothesize that cerebellar abnormalities contribute to the mechanisms of psychosis(2, 3). Recent advances in cognitive neuroscience have provided evidence for a central and critical role of the cerebellum in various psychological processes(4–9), including cognitive and social processes, and the development of psychopathology(10, 11) that extend far beyond its traditionally circumscribed role in motor function. Indeed, "Little Brain" is a misnomer for the complex and fascinating cerebellum, a neural structure that while small in volume has been estimated to contain an upwards of 80% of the neurons in the human brain(12) and to cover 80% of the surface area of cerebral cortex(13).

Contemporary models emphasizing cerebellar dysfunction in psychosis are supported by human neuroimaging studies. Findings include smaller whole cerebellum volume, aberrant within-cerebellum and cerebellar-cerebral functional connectivity during rest and tasks, and lower activation during tasks(14–25). Neuroimaging findings are supported by neuropathological changes, including lower Purkinje cell density(26). Extensive work with cerebellar lesion patients shows region-specific cerebellar contributions to cognitive processes that overlap with deficits observed in psychosis(27). These advances are being applied to human neuroimaging studies, allowing for targeted analyses of anatomical lobules or functional divisions that may contribute to distinct aspects of psychopathology. A recent meta-analysis of 22 studies in first episode psychosis concluded that smaller cerebellar grey matter in schizophrenia is most prominent in lobules IV, V, and VII, as well as Crus I in individuals with schizophrenia (28). These lobules are significant for our understanding of psychosis, given their role in motor processes, which are widely observed as aberrant in psychosis, even preceding onset(29–31), and impaired cognitive processes(32–35). Similarly, a multi-site "mega analysis" by Moberget and colleagues(36), which included 983 individuals with schizophrenia and 1349 control participants from 12 sites, found smaller whole cerebellar grey matter volume (effect size (ES)=0.35) with the most robust effects in the posterior ("cognitive") lobules and the fronto-parietal network (ES=0.16-0.40).

While past work has supported the finding of structural cerebellar abnormalities in schizophrenia, limitations in this body of knowledge remain. Small sample sizes combined with substantial heterogeneity in psychosis phenotypes have left studies underpowered to detect effects of interest. For example, even using optimized methods such as the Spatially Unbiased Infratentorial (SUIT) Toolbox, Moberget and colleagues(36) found that the effect sizes varied substantially by site (0.11-0.69), with only 5 out of the 12 included sites

showing significant effect sizes. Consequently, three major gaps in our understanding of cerebellar structure in psychosis persist. First, studies have historically been limited to only those with a schizophrenia diagnosis and in a more chronic stage of illness, which leaves the specificity of diagnosis (schizophrenia or psychosis more broadly) and illness-stage (early vs. chronic) unclear. For example, some work suggests that smaller cerebellar grey matter volume is specific to schizophrenia (25), though others have documented similar impairments in bipolar patients(37) or reported opposite findings altogether in which bipolar and schizophrenia samples exhibit larger cerebellar volume compared to non-psychiatric control participants(38). Regarding illness-stage, findings are similarly mixed. Reports include both static abnormalities consistent with atypical early developmental processes (36) and progressive loss of total cerebellar grey matter volume, shown at 5- and 10-year intervals post first hospitalization, suggesting neuroprogression(23). Investigation of high risk groups suggests these differences precede the first episode, with smaller right cerebellum volume present only in individuals who convert to schizophrenia(39). Ultimately, to address questions regarding diagnostic and illness-stage specificity, studies have been underpowered, lacked appropriate comparison groups, or both.

Second, many studies take a whole brain approach, limiting conclusions about regional specificity. Unpredicted cerebellar differences are often reported in the context of broader cerebral findings (e.g., hippocampus, thalamus, prefrontal cortex, etc.), with cerebellum-specific studies only recently emerging. Historically, incidental cerebellar findings from whole-brain studies have resulted in unclear conclusions and subsequent work with ill-formed hypotheses on the role of the cerebellum in the development and maintenance of psychosis. Lobule-specific contributions to specific phenotypes also remain unclear outside of lesion studies. The question of regional specificity is critical, as targeted interventions are developed that rely on precise, mechanistic understanding of cerebellar circuits in disease phenomenology(40). Fortunately, advancements in cerebellar imaging, including higher resolution scanning and optimized processing tools, have equipped us to address the unique methodological challenges of cerebellar imaging(cf.(41)).

Third, it remains unclear how heterogeneous cerebellar findings in psychosis relate to differences in cognitive in psychosis. Cognitive ability is linked to differences in brain volume in psychosis (42), and thus may provide critical insights into observed structural heterogeneity in the cerebellum. Such a link would be unsurprising given prior work showing that higher cerebellar connectivity with fronto-parietal networks predicts better cognitive outcomes in schizophrenia patients(32). A preponderance of literature in psychosis points to structural changes in cognitive regions of cerebellum, including fronto-parietal networks. This question was not addressed in prior studies, including the study by Moberget and colleagues(36) that identified robust effects in this cerebellar network.

To address these knowledge gaps, the current study investigated cerebellar grey matter volume in a large cross-sectional cohort using gold-standard volumetric and voxel-based methods. We sought to determine the specificity of cerebellar deficits to schizophrenia (versus psychosis more broadly), the specificity to stage of illness (early vs. chronic), and association between cerebellar structure and cognitive impairment. Given prior work, we hypothesized that grey matter volume would be lower in the psychosis sample overall,

with lobules I-IV and V and posterior lobule Crus I being disproportionately affected(28). We predicted that these abnormalities would be more pronounced in individuals with a schizophrenia-spectrum disorder (compared to bipolar disorder with psychotic features). We were agnostic to illness-stage given the lack of consistency in the literature. Finally, given the prominence of deficits in cerebellar cognitive lobules and networks in the literature, we predicted that individuals with impaired neuropsychological ability would show smaller cerebellar grey matter volumes, again with posterior lobules being more affected.

Methods

Study Participants and Procedures

All procedures were approved by the Vanderbilt University Institutional Review Board. Written, informed consent was provided by 643 individuals recruited for participation in one of three studies (CT00762866; R01MH070560; R01MH102266) conducted within the department of Psychiatry and Behavioral Sciences at Vanderbilt University Medical Center (VUMC). Inclusion and exclusion criteria are detailed in the Supplement (Note 1). Clinical participants were recruited from the Psychotic Disorders Program at VUMC. Diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-IV;(43)). The clinical sample was composed of individuals in early (i.e., ≤2 years) or chronic (i.e., >2 years) stages of their illness (cf. (44)). Non-psychiatric control participants (hereto forward referred to as control participants) were recruited from Nashville and the surrounding area via advertisements. Current and past psychopathology was ruled out in the control group using the SCID-IV.

Two hundred and seventeen control participants; 249 individuals diagnosed with schizophrenia-spectrum disorder including schizophrenia, schizophreniform, or schizoaffective disorder; and 108 individuals diagnosed with a bipolar disorder with psychotic features were selected for inclusion in the current study. Two individuals were further excluded due to not completing neuroimaging (no T1) for a final sample of 217 HC, 249 SZ (122 early, 127 chronic), and 108 BP participants (46 early, 62 chronic) (Table 1). No individuals were excluded due to missing cognitive data or poor imaging data or cerebellar segmentation.

Psychosis symptoms were measured using the Positive and Negative Syndrome Scale (PANSS)(45) and mood symptoms were measured using the Young Mania Rating Scale (YMRS)(46) and Hamilton Depression Rating Scale (HAMD)(47) for mania and depression, respectively. To assess estimated premorbid and current cognitive ability, the Wechsler Test of Adult Reading (WTAR)(48) and the Screen for Cognitive Impairment in Psychiatry (SCIP)(49) were administered, respectively (Supplementary Note 2).

Neuroimaging Data Acquisition and Pre-Processing

Image data storage and processing took place on the Vanderbilt University Institute of Imaging Science Center for Computational Imaging XNAT(50, 51). The processing pipelines were containerized using Singularity and were built at SingularityHub(52) (https://singularity-hub.org). Scanning was completed on one of two identical 3T Philips Intera

Achieva scanners located at Vanderbilt University Institute of Imaging Sciences (VUIIS). Scanning parameters and preprocessing steps have been described previously (cf. (53) and Supplementary Note 3). Briefly, a high resolution T1-weighted anatomical image (32-channel head coil, 1 mm^3 isotropic voxels, FOV=256 x 256 x 170 mm) was collected for each individual and visually inspected, blind to diagnosis status, for quality including head motion (e.g., blurring, ringing), brain artefacts, and incomplete coverage of the cerebellum.. No individuals meeting diagnostic criterial required exclusion following QA. Each study's scanning parameters differed slightly (e.g., minor differences in TR/TE). Accordingly, 'scan type' was included as a covariate in all neuroimaging analyses.

Structural scans were segmented into grey, white, and cerebrospinal fluid (CSF) tissue classes using the Computational Anatomy Toolbox (CAT), version 12 (http://www.neuro.uni-jena.de/cat/) for Statistical Parametric Mapping (SPM), version 12 (http://www.fil.ion.ucl.ac.uk/spm). Total grey, white, and CSF volumes were calculated and summed to determine intracranial volume (ICV), which was used as a covariate in subsequent analyses. SPM generated ICV values were used in the current study for consistency, given that the cerebellar processing toolbox (see below) is embedded within the SPM package.

Cerebellar Optimization Using the Spatially Unbiased Infratentorial (SUIT) Toolbox

The Spatially Unbiased Infratentorial (SUIT; (54–56), https://github.com/baxpr/cersuit) toolbox was used to optimize cerebellar analyses. Using pre-processed images as described above, the cerebellum and brainstem were isolated from the whole brain. Cerebellum and brainstem were then segmented into grey matter, white matter, and CSF maps. These segmentation maps are normalized to a cerebellar (SUIT-space) template which is shown to optimize alignment procedures for the cerebellum beyond standard whole-brain processes(56). These normalized grey matter maps were (1) parcellated using the SUIT anatomical probabilistic atlas and SUIT Buckner-Yeo functional atlas (57), then resliced to native space for subsequent volumetric analyses or (2) modulated with a Jacobian transformation in preparation for voxel-based morphometry (VBM) analyses. All scans were visually inspected to assure proper isolation and segmentation; no subjects required exclusion following inspection.

Volumetric and Voxel-Wise Analyses

Grey Matter Volume.—The SUIT probabilistic atlas was used to define anatomical cerebellar lobules for a total of 28 hemispheric lobules. In native space, lobular grey matter volumes were extracted and analyzed as bilateral regions of interest (ROIs; 10 lobules) and one cerebellar vermis region (total of 11 ROIs). These ROIs were summed for a measure of total cerebellar grey matter volume. In addition to anatomical ROIs, the SUIT atlas was also used to estimate cerebellar grey matter volume in functional ROIs using the Buckner-Yeo atlas (7 functional networks(57)).

Voxel-Based Morphometry.—Volumetric analyses were followed by voxel-based analyses to investigate possible regional volume changes which might be missed by gross, whole-volume analyses. Nonlinear modulated whole cerebellar grey matter images were

tested for homogeneity using CAT12's automated quality check protocol, which checks image inhomogeneity defined as the mean correlation between gray matter volumes. Flagged images were visually inspected. Eighteen participants (15 schizophrenia-spectrum, 2 bipolar, and 1 control participants) were excluded from this analysis due to significant inhomogeneity. Outputs from the SUIT toolbox (individual grey matter maps modulated with a Jacobian transformation) were entered into an ANOVA using the CAT12 toolbox.

Statistical Analyses

Volumetric group differences in whole cerebellar volume and lobular volume were investigated using univariate ANOVAs with age, sex, ICV, and scan type (to account for the three individual studies detailed above) entered as covariates. Post-hoc comparisons were used to examine group-specific effects. Comparisons were Bonferroni-corrected to $p<0.0026$ (0.05/19 ROIs including 11 lobular ROIs, 7 functional ROIs, and whole cerebellum).

Voxel-based analyses were performed using separate, independent one-way ANOVAs with preplanned between group t-tests to examine diagnosis, illness-stage, and cognitive subgroups including covariates for sex, age, ICV, and scan type. For diagnosis groups the control participants were compared to all psychosis patients and each diagnostic group (psychosis spectrum and bipolar) and, the psychosis spectrum and bipolar groups were compared. For illness-stage, t-tests were set up to compare the control group to each illness-stage (early, chronic). Finally, cognitive subgroups were compared. Individuals with psychosis were assigned to one of three cognitive subgroups: neuropsychologically normal, deteriorated, and compromised, based on their Wechsler Test of Adult Reading (WTAR(48)), Screen for Cognitive Impairment in Psychiatry (SCIP(49)), and discrepancy between their WTAR and SCIP (cf. (42); Supplementary Note 4 & Table 1). Briefly, neuropsychologically normal individuals were characterized by estimated premorbid and current cognitive ability in the normative range. The deteriorated group also had normative estimated premorbid ability, but their current ability is in the impaired range. The compromised group is notable for impaired estimated premorbid ability, with impaired current ability. T-tests were established comparing the control group to each cognitive group (neuropsychologically normal, deteriorated, compromised) and the neuropsychologically normal group to each cognitively impaired group (deteriorated, compromised). All independent samples t-tests were thresholded at cluster-level pFWE<0.05 for voxel-wise cluster-defining threshold $p=0.001$ (uncorrected).

Symptom and Medication Correlates.—To determine whether medication dose or symptoms were driving group differences, cerebellar volumes (whole, lobular, functional ROIs) were correlated with chlorpromazine equivalent (CPZ) values; PANSS positive, negative, and general scores; YMRS scores; and HAMD scores. Partial correlations were computed for these variables to control for age, sex, ICV, and scan type.

Results

Diagnosis and Illness-stage Effects

Whole Cerebellar Grey Matter Volume.—No differences were observed between individuals with psychosis and the control group (Cohen's *d* Effect Size (ES)=−0.06, negative indicates smaller in psychosis sample) (Fig. 1A & Supplemental Figure 1). No differences were observed when the psychosis sample was divided into schizophrenia spectrum and bipolar disorder with psychotic features; neither group differed from the control group (ES=−0.08 to 0.00). Similarly, chronic- and early-stage groups did not differ from the control group in whole cerebellar grey matter volume (ES=−0.08 to 0.00). No significant diagnosis by illness-stage interaction effects were present.

ROI-Based Grey Matter Volume.—Cerebellar lobular grey matter estimates were consistent with previous reports (cf.(36); Supplementary Fig. 2). For both anatomical and functional ROIs, no significant group differences were observed in comparisons between control participants and the full psychosis sample (ES=−0.14 to 0.10; Fig. 1B); control and schizophrenia-spectrum patients or bipolar groups (ES=−0.20 to 0.17), between control and first episode or chronic illness-stage groups (ES=−0.19 to 0.12); and there was no significant diagnosis by illness-stage interaction.

Voxel Based Morphometry.—No clusters passed correction for any of the planned contrasts for diagnosis and illness-stage (Fig. 1C, Supplementary Fig. 3 & 4).

Cognitive Subgroup Effects

Consistent with prior reports (42, 58) 40% of the psychosis cohort group was classified as cognitively normal, while the remaining 60% were classified as cognitively deteriorated (34%) and cognitively compromised (26%). In terms of demographics, the cognitive subgroups were similar in age, though the compromised group had the lowest personal and parental educational attainment and was more symptomatic per PANSS (Table 2). Intracranial volume (ICV) was similar across groups (Table 2, Supplementary Fig. 5), consistent with prior work, including an earlier analysis of a subset of these data (42) as well as an extension of this work by an independent group(59).

Whole Cerebellar Grey Matter Volume.—A main effect of cognitive group was observed ($F(2,542)=6.998$, $p<0.001$, ES=−0.53). Bonferroni-corrected comparisons showed smaller volume in the compromised group compared to the control ($p=0.002$, ES=−0.47), but not in the neuropsychologically normal ($p=1.00$, ES=−0.05) or deteriorated ($p=1.00$, ES=−0.14) groups (Fig. 2B).

ROI-Based Grey Matter Volume.—Significant differences were present in 9 of 10 cerebellar lobules (lobules I-IV, V, VI, VIIb, VIIIa, VIIIb, X, Crus I, and Crus II) and 5 of 7 networks (DAN, VAN, limbic, FPN, and DMN), with post hoc comparisons revealing these differences were driven by smaller volume in the compromised group (ES=−0.60 to −0.34, Fig. 2C, Supplementary Fig. 8) compared to all other groups (control, neuropsychologically normal, and deteriorated, ES=0.00 to 0.20, Supplementary Fig. 6–8).

Voxel Based Morphometry.—VBM results were consistent with lobular and functional ROI analyses; the compromised group showed smaller regional volumes compared to all other groups (Fig. 3, Table 3). No clusters survived correction for contrasts in the other direction (e.g., compromised > neuropsychologically normal; Supplementary Fig. 9).

Symptom and Medication Correlates

Positive and general PANSS scores correlated weakly with several ROI volumes; however, none survived correction for multiple comparisons (Supplementary Note 7). No significant correlations were observed between volumes and PANSS negative scores, chlorpromazine equivalents, HAMD, or YMRS scores.

Discussion

While the cerebellum has been identified as a key node in dysconnectivity theories of schizophrenia, the specificity of these deficits to psychosis-spectrum diagnostic groups, specificity to illness-stage, and contributions of cognitive function to heterogeneity has been unclear. The current study used a large cross-sectional dataset to localize cerebellar deficits among these groups. Moreover, this study aimed to parse some of the heterogeneity present throughout the literature by investigating cerebellar structural changes within psychosis cognitive subgroups, given findings indicating robust deficits of cerebellar cognitive (posterior) regions in psychotic disorders(30, 32).

Differences in cerebellar structure, including grey matter volume (Fig. 1A and 1B) and voxel-based morphometry (Fig. 1C), were not present when looking at diagnostic groups (schizophrenia-spectrum, bipolar with psychotic features) or illness-stage (early, chronic). This was in stark contrast to findings by Moberget and colleagues(36) that individuals with a schizophrenia diagnosis show smaller cerebellar volume in posterior (cognitive) lobules and functional networks. One major difference is that the current study used ICV calculated by CAT12, compared to Moberget and colleagues' study(36) which used eTIV estimated in Freesurfer. Here, this was done to maintain consistency in analysis packages given that SUIT and CAT12 both utilize SPM. Although it is unclear why ICV and eTIV values are poorly correlated (Supplementary Note 5 & Fig. 12), confidence in the current findings in enhanced by observations of a similar trend in effects when using eTIV (Freesurfer), though marginally weaker than effects from ICV (CAT12) (Supplementary Fig. 13–15). In addition, the current work is highly powered (96.4%) to replicate findings by Moberget and colleagues(36). Given the robust findings in the current work, it is possible that the effects are largely driven by heterogeneity across samples. Moberget and colleagues reported large effect sizes for the pooled sample (Moberget et al. ES=0.35; current study ES=0.08), though there was substantial variability across the 14 sites(36) with only 5 sites showing significant effects. It is likely that cognitive impairment contributes to this heterogeneity and may explain the inconsistent findings across studies. Aligned with this hypothesis, Moberget's study highlighted the robustness of effects in cognitive cerebellar lobules(36) and prior work has shown that cognitive performance is associated with cerebellar findings in psychosis samples(37).

To better elucidate these effects, the current work used cognitive ability to define psychosis types. Individuals with a compromised neuropsychological profile show markedly smaller cerebellar volume compared to all other groups (whole cerebellum ES=−0.47; Fig. 2B and 2C). Deficits were pronounced in cognitive lobules, with moderate effect sizes in lobule VI (ES=−0.47), Crus I (ES=−0.42), and the fronto-parietal (ES=−0.45) and attention (ES=−0.42 to −0.48) networks. (Fig. 2C & 3). The compromised group is distinguished from the other cognitive subgroups (neuropsychologically normal and deteriorated) by a low estimated premorbid IQ (Fig. 2A). This suggests an early developmental process contributing to these anatomical deficits that is supported by prior work. In a neurodevelopmental sample, cerebellar structural features spanning anterior and posterior lobules were shown to be predictive of general cognitive function in youth aged 8-23 (33), with more circumscribed cerebellar deficits (lobule VI and Crus I) relating to psychotic-like experiences and symptoms. A developmental model is also supported by fundamental impairments in the motor system. Studies rating childhood home movies of individuals who then go on to develop psychosis have noted motor impairments present early in development(29, 30, 60). These motor system phenotypes are squarely in line with the current observations of cerebellar abnormalities. In fact, the current study identified the strongest effects in motor ROIs, including lobules I-IV (ES=−0.60), lobule V (ES=−0.50), lobule X (ES=−0.56), and the somatomotor network (ES=−0.52). These motor regions tend to develop earlier in life, quickly reaching their peak by birth to young childhood, compared to cognitive regions that slowly continue to develop into mid adulthood(61–63). Taken together with our findings, this work provides evidence for a formative role of early developmental processes, cognition, and cerebellar development in psychosis, though causal mechanisms remain unclear.

The current work has several limitations. First, alcohol and cannabis use were not included in our models. Both substances have a high density of receptors in the cerebellum and alter cerebellar volume with chronic use(64–67). Prior work in a subset of the current sample has shown that a lifetime history of cannabis or alcohol abuse or dependence does not significantly influence grey matter estimates, including in cerebellum(68). Moberget and colleagues(36) did report on harmful alcohol use. In analysis of a subset of their sample with no alcohol use, effect sizes increased marginally. Accordingly, this suggests that if harmful alcohol consumption did impact our findings, then the current work is likely underestimating the effects in our sample. Future work should seek to better characterize these effects using high resolution data on dose (frequency, volume, potency) and timing of use to clarify brain effects, including social determinants of substance use on cerebellar structure.

Second, the current work was restricted to structure and did not investigate cerebellar function. The cerebellum alone may contribute to some low-order cognitive processes(69), performing timing, prediction, and model updating(70). Stemming from these basic processes, a broader role for the cerebellum in higher-order processes lies in its ability to coordinate and regulate (through timing, predicting, and modeling) the cerebral regions that more directly perform high-order computations and outputs. For example, a compelling and growing literature in rodent models has shown that Purkinje cell firing rates in the Crus I region of the cerebellum modulate neural oscillations within hippocampus and PFC(71). In humans, non-invasive stimulation of the cerebellum has been shown to increase

theta oscillations in frontal regions(72). In psychosis specifically, transcranial magnetic stimulation of the cerebellum has shown promise in reducing negative symptoms(40, 73). It remains unclear how anatomical changes reported here relate to cerebello-cerebral connectivity changes and associated symptom and behavior profiles.

Third, the lack of longitudinal data hindered a more nuanced investigation of the progressive nature of cerebellar aberrations in psychosis. Cross-sectionally, this study did not show effects of illness-stage. Prior work in samples with a longer course of illness have identified a degenerative effect on the cerebellum in schizophrenia(23). Investigating these questions in longitudinal samples that can track individual changes in cerebellum will be helpful to the field. Moreover, future work may seek to better characterize the cognitive subgroups, including the neuropsychologically normal and deteriorated groups. In the current study, the cognitively compromised group exhibited lower parental education compared to the other groups. An individual's cognitive ability is highly related to parental cognitive ability and is also associated with critical social determinants, including socioeconomic status and education. While race was included in our estimates of cognitive ability, future work should use large scale, developmental datasets to parse the roles and interactions of education, socioeconomic status, race, and related social determinants in cognitive and cerebellar development, broadly and within the context of psychosis(cf. (74, 75)). Uncovering such risk and protective factors in neurodevelopment, as well as the association with onset and maintenance of psychosis will be critical for the development of targeted, large-scale prevention and intervention strategies and will require longitudinal designs.

Conclusions

The current study suggests that cerebellar aberrations are not tied to a specific diagnosis or the stage of illness alone. Rather, this work confirms the substantial heterogeneity within psychosis broadly and suggests that developmental factors, indexed here by premorbid cognitive disturbances, are key contributors to the cerebellar aberrations observed in psychosis. Future work would benefit from further parsing this heterogeneity and identifying risk and protective factors to aberrant cerebellar development. Moreover, the field will benefit from a clearer understanding of how specific cerebellar deficits contribute to key phenotypic profiles within psychosis and related disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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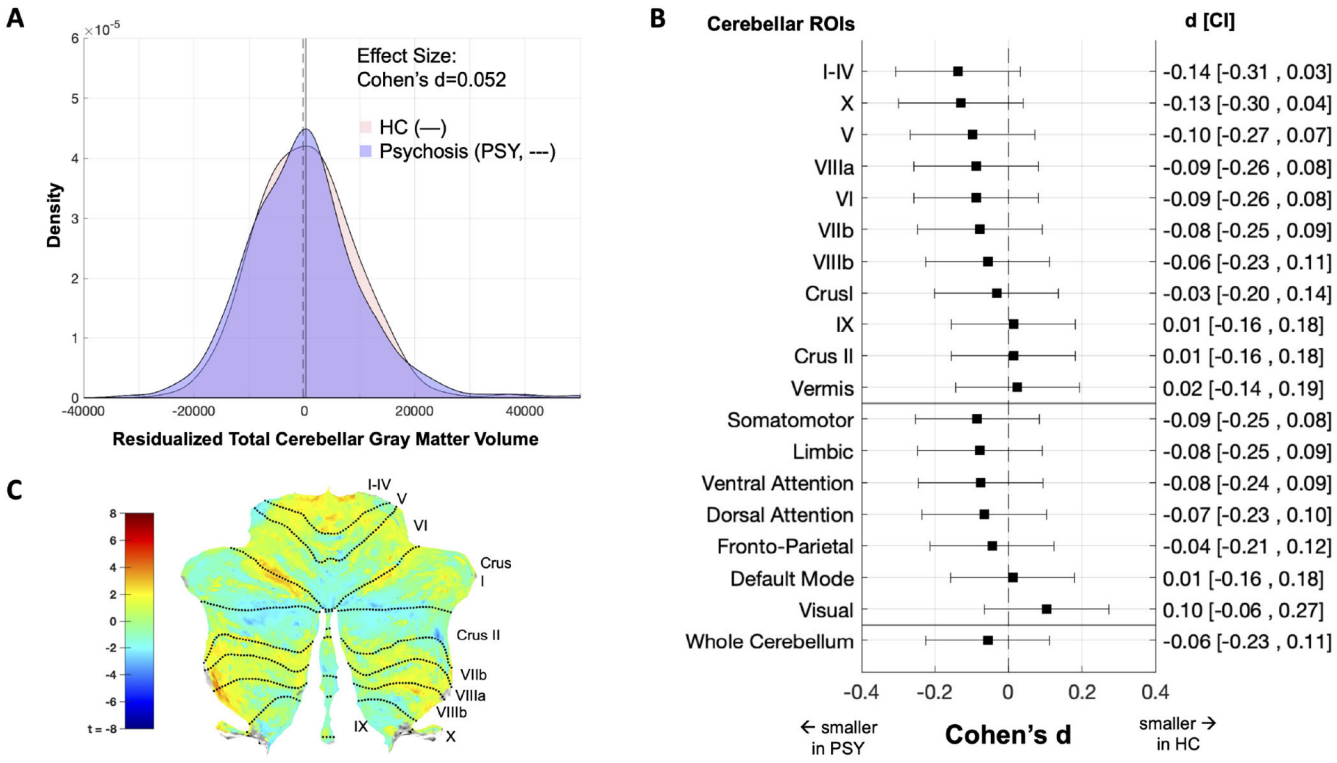

Figure 1. Diagnosis-Based Findings.

Effects from diagnosis-based comparisons. (**A**) unstandardized, residualized whole cerebellar grey matter volume using sex and age as covariates. HC = control, PSY = psychosis. (**B**) cerebellar volume for 10 bilateral lobules, cerebellar vermis, and 7 functional networks ((57). Left axis indicates the ROI, right axis displays the Cohen's d effect size with confidence interval (see Supplementary Note X for calculation) based on the univariate test comparing all psychosis patients with the control group, using sex, age, ICV, and scan type as covariates. Effect sizes <0 indicate that the region is smaller in the psychosis group. (**C**) VBM results plotted on a cerebellar flatmap (55) as the uncorrected t-map of the comparison of all psychosis patients and healthy controls. No significant group differences were observed in whole cerebellar volume (**A**), ROI volume (**B**), or voxel-based regional (**C**).

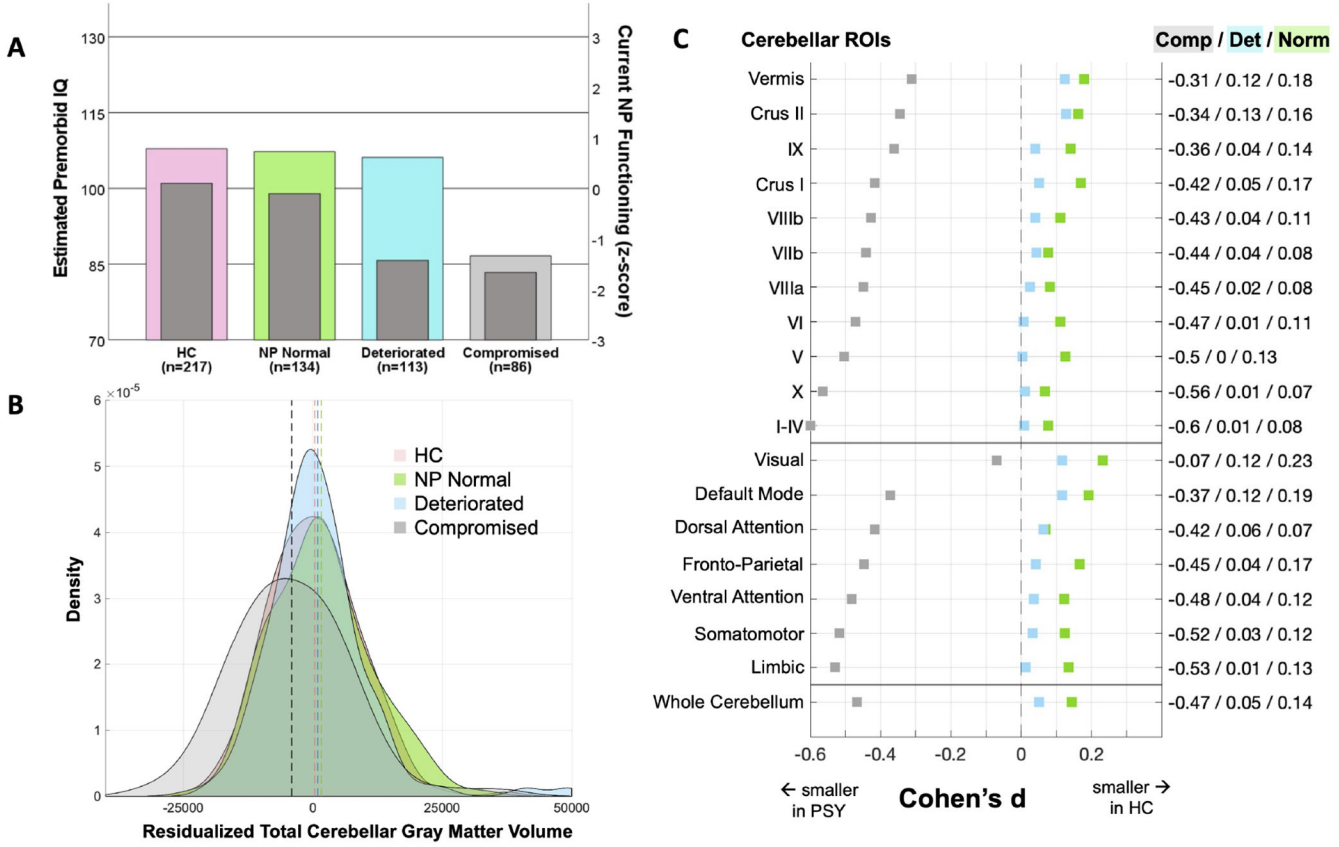

Figure 2. Cognitive Subgroups Findings

Three psychosis cognitive subgroups were generated (**A**) according to Woodward & Heckers (42) using estimated premorbid IQ (left axis, colored bars) and current neuropsychological functioning (right axis, dark grey bars). (**B**) unstandardized, residualized whole cerebellar grey matter volume using sex and age as covariates indicated that the compromised (comp, light grey) group had significantly smaller volume compared to the healthy control (HC, pink), neuropsychologically normal (NP Normal/Norm, green), and deteriorated (Det, blue) groups. (**C**) ROI analyses showed significant effects for the compromised group only. All effects plotted are for the indicated group compared to the HC group; right axis displays the corresponding effect size. Figure depicts effect sizes for cerebellar volume of 10 bilateral lobules, cerebellar vermis, and 7 functional networks (57). based on the univariate test using sex, age, ICV, and scan type as covariates. Effect sizes <0 indicate that the region is smaller in the psychosis cognitive subgroup. For subgroup effects with associated confidence intervals, see Supplementary Figs. 6–8.

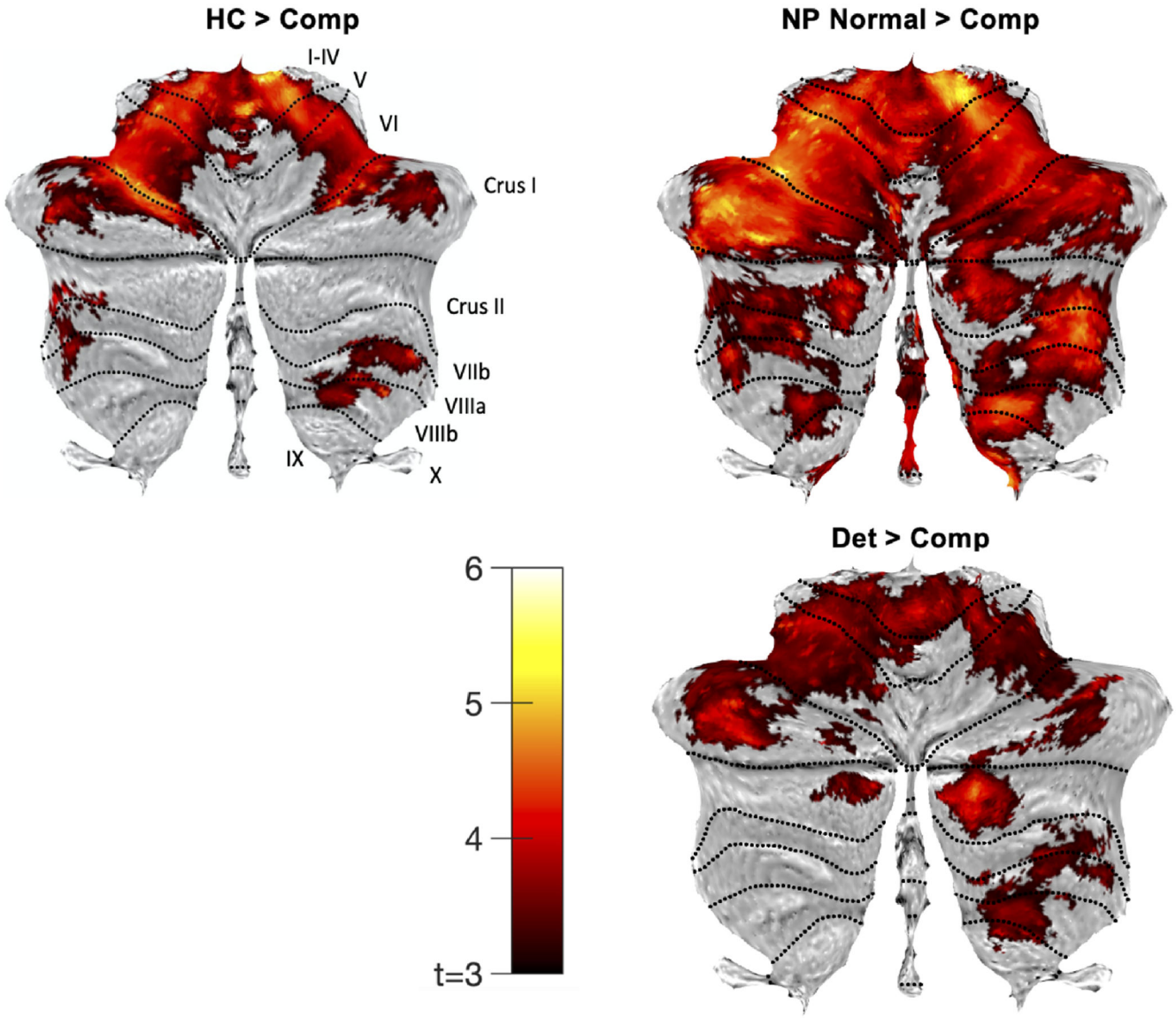

Figure 3. Cognitive Subgroups Voxel-Based Morphometry Analysis

Cerebellar flatmaps (57) indicating significant effects of comparisons between the compromised (Comp) psychosis subgroup and other cognitive subgroups (control, HC; neuropsychologically normal, NP Normal; and deteriorated, Det), thresholded at cluster-level pFWE < 0.05 for voxel-wise cluster-defining threshold $p = 0.001$ (uncorrected).

Table 1.

Sample Demographics – Diagnostic Subgroups

	Schizophrenia Spectrum (SzS; n=249)	Bipolar w/ Psychotic Features (BP; n=108)	Control (HC; n=217)	Statistics (F or χ^2)	*p*-value (post-hoc)
Sex (% male)	70.3	50.0	61.3	13.77	*0.001*
Race (C/B/O)	157/82/10	87/11/10	152/52/13	27.70	*<0.001*
Age (years ± SD)	29.7 ± 11.2	31.2 ± 11.7	29.3 ± 10.1	1.21	0.30
Education (years)					
Personal	13.2 ± 2.2	14.1 ± 1.9	15.2 ± 2.1	48.18	*<0.001 (HC >BP >SzS)*
Parental	14.4 ± 2.7	14.8 ± 2.2	14.5 ± 2.3	0.85	0.43
Handedness (%R)	89.2	91.7	91.7	0.79	0.67
ICV (cm^3)	1536.7 ± 161.8	1561.4 ± 163.6	1537.3 ± 152.8	1.03	0.36
Illness-Stage					
Chronic/Early Stage	127/122	61/47	--	--	--
Duration (months)[†]	102.2 ± 133.9	86.3 ± 107.5	--	1.17	0.24
Age Onset (years)	21.1 ± 5.3	24.1 ± 8.5	--	3.37	*0.001 (BP > SzS)*
Clinical Symptoms					
Positive (PANSS)	18.0±8	15.1±9	--	3.07	*0.002 (SZ > BP)*
Negative (PANSS)	15.8±7	10.3±4	--	9.58	*<0.001 (SZ > BP)*
Mania (YMRS)	4.9±7	8.0±12	--	−2.51	*0.003 (BP > SzS)*
Depression (HAMD)	11.3±9	10.4±9	0.7±2	71.84	*<0.001 (SzS/BP > HC)*
WTAR (standardized)	99.6 ± 15.8	106.7 ± 12.5	111.0 ± 10.8	41.51	*<0.001 (HC >BP >SzS)*
SCIP (z-score)	−1.10 ± 0.9	−0.67 ± 0.9	0.09 ± 0.6	114.51	*<0.001 (HC >BP >SzS)*
Cognitive Subgroups (Norm/Det/Comp)	82/81/73	52/32/13	--	14.29	*0.001*

WTAR, Wechsler Test of Adult Reading (48); SCIP, Screen for Cognitive Impairment in Psychiatry (49), ICV, transcranial volume as determined using the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/) for SPM (http://www.fil.ion.ucl.ac.uk/spm); for race, C=Caucasian, B=Black, and O=other race (e.g., Hispanic, Asian, Mixed-Race); PANSS, Positive and Negative Syndrome Scale (45); YMRS, Young Mania Rating Scale (46); HAMD, Hamilton Depression scale (47); Norm=neuropsychologically normal cognitive subgroup, Det=deteriorated cognitive subgroup; Comp=compromised cognitive subgroup. *Italics* indicate significant *p*-values.

[†]Duration of illness was defined as the time at which an individual first met criteria for psychosis (based on extensive interview, review of medical records, and collateral reports) until the date of study enrollment.

[≠]For comprehensive demographic breakdown of the cognitive subgroups, please see Table 2.

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Table 2.

Sample Demographics – Cognitive Subgroups

	Control (n=217)	NP Normal (n=134)	Impaired		Statistics (F or χ^2)	*p*-value (post hoc) †
			Deteriorated (n=113)	Compromised (n=86)		
Sex (% male)	61.3	66.4	63.7	65.1	1.046	0.790
Race (C/B/O)	152/52/13	105/25/4	90/18/5	38/42/6	38.845	*<0.001*
Age (years ± SD)	29.27 ± 10.13	28.70 ± 10.47	30.10 ± 11.50	31.51 ± 12.40	1.354	0.256
Education (years)						
Personal	15.21 ± 2.10	14.33 ± 2.11	13.41 ± 2.12	12.33 ± 1.62	44.757	*<0.001* (HC > NP Norm > Det > Comp)
Parental	14.48 ± 2.35	15.26 ± 2.46	14.96 ± 2.64	12.89 ± 1.98	16.698	*<0.001* (NP Norm > HC/Det > Comp)
Handedness (%R)	91.7	87.3	91.2	91.9	2.198	0.532
ICV (cm^3)	1537.33 ± 152.79	1540.36 ± 155.00	1557.26 ± 166.09	1536.72 ± 167.05	0.449	0.718
Diagnostic Groups						
SzS (Chronic:FE)	--	82 (35:27)	81 (41:40)	73 (44:29)	4.784	0.091
BP (Chronic:FE)	--	52 (25:27)	32 (21:11)	13 (9:4)	4.663	0.324
Age Onset (years)	--	22.78 ± 6.20	21.77 ± 6.40	21.05 ± 7.03	1.943	0.145
Clinical Symptoms						
Positive (PANSS)	--	15.93 ± 8.45	17.55 ± 8.81	18.12 ± 7.31	3.358	*0.019* ‡
Negative (PANSS)	--	12.36 ± 5.45	13.64 ± 5.85	17.36 ± 8.14	12.558	*<0.001* (Comp > NP Norm / Det)
Mania (YMRS)	--	4.40 ± 1.03	3.92 ± 0.95	3.47 ± 1.03	12.147	*<0.001* (NP Norm > Det > Comp)
Depression (HAMD)	0.71 ± 1.52	9.82 ± 8.53	11.79 ± 8.44	11.26 ± 8.93	48.381	*<0.001* (HC < NP Norm / Det / Comp)
WTAR (standardized)	111.01 ± 10.84	110.11 ± 9.31	108.52 ± 8.46	81.45 ± 7.91	218.029	*<0.001* (Comp < NP Norm / Det / HC)
SCIP (z-score)	0.09 ± 0.63	−0.10 ± 0.54	−1.43 ± 0.57	−1.66 ± 0.93	240.530	*<0.001* (HC > NP Norm > Det > Comp)

WTAR, Wechsler Test of Adult Reading (1); SCIP, Screen for Cognitive Impairment in Psychiatry (3), TIV, transcranial volume as determined using the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/) for SPM (http://www.fil.ion.ucl.ac.uk/spm); for race, C=Caucasian, B=Black, and O=other race (e.g., Hispanic, Asian, Mixed-Race); PANSS, Positive and Negative Syndrome Scale (11); YMRS, Young Mania Rating Scale(12); HAMD, Hamilton Depression scale(13); Szs, schizophrenia spectrum; BP, bipolar with psychotic features; NP Normal/NP Norm, neuropsychologically normal; Comp, compromised; Det, deteriorated; HC/Control, healthy control; FE, first-episode/early stage psychosis. Italics indicate significant *p*-values.

Table 3.

Cognitive Subgroups VBM Analysis Findings

Contrast	Cluster size (voxels)	MNI coordinates			t-value	*p*-value †	Region‡
		x	y	z			
HC > Impaired	639	9	−39	−21	5.64	<0.001	Right I-IV
	711	−25	−60	−32	5.46	<0.001	Left VI
	234	24	−68	−34	4.54	0.016	Right VI
	178	3	−52	−23	4.34	0.043	Right I-IV
	323	−11	−37	−19	4.14	0.004	Left I-IV
HC > Compromised	17198	9	−47	−23	5.66	<0.001	Right I-IV
	1295	25	−48	−49	4.42	<0.001	Right VIIIb
	799	48	−57	−28	4.20	<0.001	Right Crus I
	245	−37	−47	−44	4.10	0.006	Left Crus II
NP Normal > Impaired	2636	−28	−56	−33	5.31	<0.001	Left VI
	1910	14	−42	−27	4.83	<0.001	Right I-IV
	1998	−37	−74	−24	4.80	<0.001	Left Crus I
	440	10	−51	−37	4.74	<0.001	Right IX
	799	42	−58	−54	4.21	<0.001	Right VIIb
	475	5	−61	−52	4.17	<0.001	Right IX
	663	36	−54	−21	3.86	<0.001	Right VI
NP Normal > Compromised	49315	−28	−56	−33	5.86	<0.001	Left VI
Deteriorated > Compromised	16559	17	−85	−36	4.86	<0.001	Left Crus II
	152	−16	−77	−31	4.30	0.047	Left Crus I
	2335	14	−60	−57	4.15	<0.001	Right VIIIb
	447	−8	−86	−32	4.14	<0.001	Left Crus II

HC = control group; Impaired = cognitively compromised and cognitively deteriorated subgroups; NP Normal = neuropsychologically normal cognitive group

† thresholded at cluster-level *p*FWE < 0.05 for voxel-wise cluster-defining threshold $p = 0.001$ (uncorrected)

‡ region is determined by the location of peak activation

KEY RESOURCE TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use "this paper" if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Other	3T Philips Intera Achieva Scanner	Philips Healthcare, Inc.		T1 Structural Image
Software; Algorithm	Freesurfer 6	PMID: 9931268; PMID: 11832223		Pre-Processing; Cerebral Volumes
Software; Algorithm	Statistical Parametric Mapping (SPM)	Wellcome Centre for Human Neuroimaging (https://www.fil.ion.ucl.ac.uk/spm/)		Volumetric and VBM Analyses
Software; Algorithm	Computational Anatomy Toolbox v12 (Cat12 Toolbox) for SPM	Structural Brain Mapping Group (http://www.neuro.uni-jena.de/cat/)		VBM Analysis
Software; Algorithm	Spatially Unbiased Intfratentorial (SUIT) Toolbox for SPM	PMID: 16904911; PMID: 26230510; PMID: 19457380; Diedrichsen Lab (https://www.diedrichsenlab.org/imaging/suit.htm)		Cerebellum-specific isolation and segmentation
Software; Algorithm	MATLAB v2019a	Mathworks		Statistics and Figures
Software; Algorithm	SPSS v28	IBM		Statistics