Cerebellar Structure and Cognitive Ability in Psychosis

Supplementary Information

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Supplementary Note 1. Exclusion Criteria

Exclusion criteria were nearly identical across the three neuroimaging studies and included age less than 16 or older than 65 (age 55 in the case of 1R01MH102266); history of significant head trauma, medical illness or central nervous system disorder (e.g. epilepsy); substance abuse within the last one month for schizophrenia participants (three months in the case of 1R01MH102266) or lifetime history of substance abuse/dependence in healthy controls; estimated premorbid IQ less than 70 based on the Wechsler Test of Adult Reading (WTAR) (1); MRI contra-indicators; healthy subjects could not have a first degree relative with a psychotic illness.

Supplementary Note 2. Study Procedures

Individuals with a psychotic disorder were recruited from the psychiatric inpatient and outpatient clinics of the Vanderbilt University Medical Center Psychotic Disorders Program and healthy individuals were recruited from Nashville and the surrounding community via advertisements and word of mouth. Study procedures were approved by the Vanderbilt Institutional Review Board. Informed consent was obtained from all study participants.

Cognitive ability was measured using the Screen of Cognitive Impairment in Psychiatry (SCIP), consisting of five sub-tests: verbal memory (immediate and delayed), working memory, verbal fluency, and processing speed. The SCIP has been shown to be a reliable and valid measure of cognitive ability in psychotic disorders(2). SCIP subtest raw scores were converted to z-scores using normative data and averaged to create a composite z-score(3).

Psychosis symptom severity was assessed using the Positive and Negative Syndrome Scale, which rates positive, negative and general psychopathology symptoms over the past two weeks (4). Average positive and negative scale scores were used to measure positive and negative symptom severity.

Supplementary Note 3. Neuroimaging

Acquisition and Pre-Processing

Neuroimaging data were acquired on two identical 3T Philips Intera Achieva scanners (32 channel received head coil, single-band imaging) located at the Vanderbilt Institute for Imaging Sciences (VUIIS). When included as a covariate, there were no scanner by diagnosis and scanner by cognitive group interactions. The main findings remained when scanner was included as an additional covariate in the analyses. In all three studies (CT00762866; R01MH070560; R01MH102266), a high resolution T1-weighted structural scan was collected for each individual with a 3D T1 fast field echo sequence with 1 mm^3 isotropic voxels (TR/TE = 8.0/3.7, FOV=256 x 256 x 170 mm, matrix = 256 x 256 x 170, flip angle = 5°).

Voxel-Based Morphometry

Voxel-based Morphometry (VBM) was used to investigate voxel-wise volume reduction in the cerebellum using the Computational Anatomy Toolbox 12 (CAT12: Version 12.5) in Statistical Parametric Mapping 12 (SPM12: Version 7487). The modulated, normalized gray matter segmentations output from SUIT were checked with the CAT12 automated quality check protocol, which checks image inhomogeneity. All flagged images were visually inspected, and any scans with significant inhomogeneity were excluded from further analysis. Given images were used from SUIT and our a priori focus was on the cerebellum, group analyses were masked to include only voxels in the whole cerebellum.

Supplementary Note 4. Determining Cognitive Subgroups

The Wechsler Test of Adult Reading (WTAR(1)), a single-word reading measure of estimated premorbid intellectual functioning, and the Screen for Cognitive Impairment in Psychiatry (SCIP(3)), a multi subtest assessment of current cognitive function, were administered to participants. WTAR raw scores were converted to standard scores which were then used to estimate Full Scale IQ using Appendix D from the WTAR manual. The SCIP includes 4 subtests spanning (1) verbal list learning, (2) working memory, (3) phonemic verbal fluency, and (4) processing speed (cf. (4) for description of subtests). Raw scores for each SCIP subtest were converted to z scores using published norms. To capture current overall cognitive functioning, a composite z score was calculated from the average of these subtest z scores. Estimated premorbid functioning (WTAR) and discrepancies between current (SCIP composite z score) and predicted premorbid (determined in the control group (n=217) based on a regression model of SCIP, WTAR, age, race, and sex) functioning were then used to group the psychosis sample into cognitive subgroups, supported by prior work from our group(4).

Psychosis patients were classified as neuropsychologically normal if: (1) their estimated premorbid intellect was above the 10th percentile of the control distribution; and (2) their current cognitive abilities (SCIP composite z score) were consistent with expectations based on their estimated premorbid score (WTAR). The latter was tested using discrepancy analysis(5, 6). The 10th percentile was used as the cut-point for premorbid IQ and the discrepancy analysis because (1) it corresponds closely to the conventional cutoff between “low average” and “borderline” IQ ranges(7) and (2) according to the authors of the WTAR, a premorbid IQ/current neuropsychological functioning discrepancy below the 10th percentile is considered a “moderate” indicator of dysfunction(1).

Psychosis patients with a discrepancy above the 10th percentile of the control distribution were considered neuropsychologically normal. This corresponded to a 0.80 SD difference between their actual and predicted SCIP global z score.

The remaining psychosis patients (i.e., those with an estimated premorbid IQ less than 10th percentile or SCIP composite z score more than 0.80 SDs below their predicted level) were divided into “deteriorated” and “compromised” subgroups(8) based on whether their estimated premorbid IQ was above or below the 10th percentile of the control distribution.

Supplementary Note 5. Comparisons with Moberget et al., 2018

Given null findings in the current sample when comparing diagnostic groups, univariate ANOVAs comparing diagnostic groups were repeated using estimated total intracranial volume (eTIV) derived from Freesurfer, rather than SPM ICV values as performed in the primary analyses. This was done in an effort to directly replicate methods by Moberget and colleagues (9). When using Freesufer eTIV, results held; no significant group differences were observed between diagnostic groups in whole cerebellar volume, cerebellar lobular or functional ROI volumes, and voxel-based morphometry. Thus, we are confident that our inability to replicate Moberget and colleagues (9) is not due to this methodological difference.

Supplementary Note 6. Calculating Effect Sizes

Effect sizes were calculated from the F statistics produced by univariate analyses in which sex, age, TIV, and scan type were used as covariates(10). The following formula was utilized:

$$d = \sqrt{F\frac{(n_1 + n_2)}{n_1 n_2}}$$

In addition, confidence interval bounds were determined by the following formulas:

$$CI_{lower} = d - 1.959964\sqrt{\frac{(n_1 + n_2)}{n_1 n_2} + \frac{d^2}{2(n_1 + n_2)}}$$

$$CI_{upper} = d + 1.959964\sqrt{\frac{(n_1 + n_2)}{n_1 n_2} + \frac{d^2}{2(n_1 + n_2)}}$$

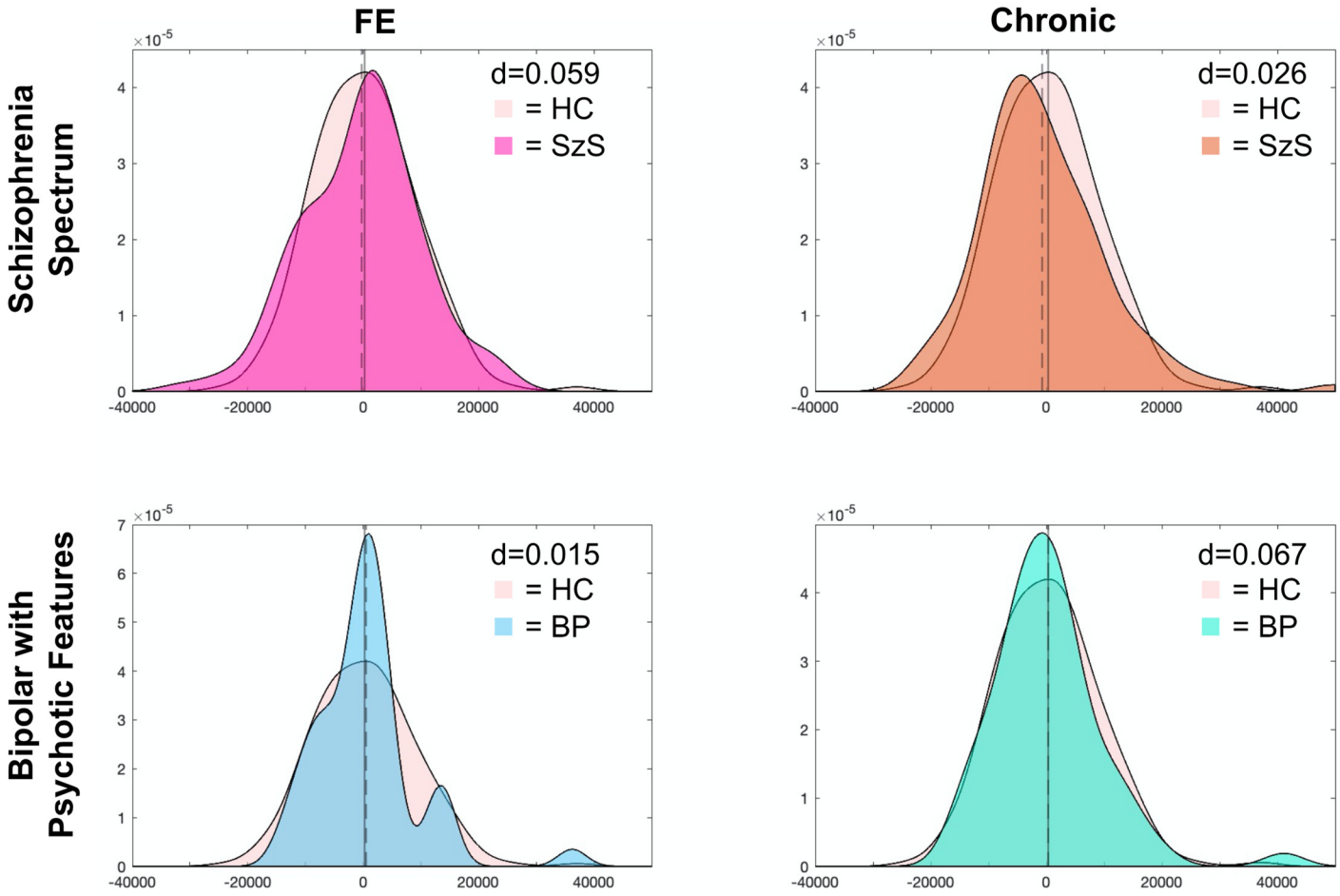
Finally, partial eta squared conversion to Cohen's d effect size was done according to:

$$d = 2\sqrt{\frac{\eta^2}{(1 - \eta^2)}}\sqrt{3\frac{(k = 1)}{(k + 1)}}$$

Supplementary Note 7. Symptom Correlates

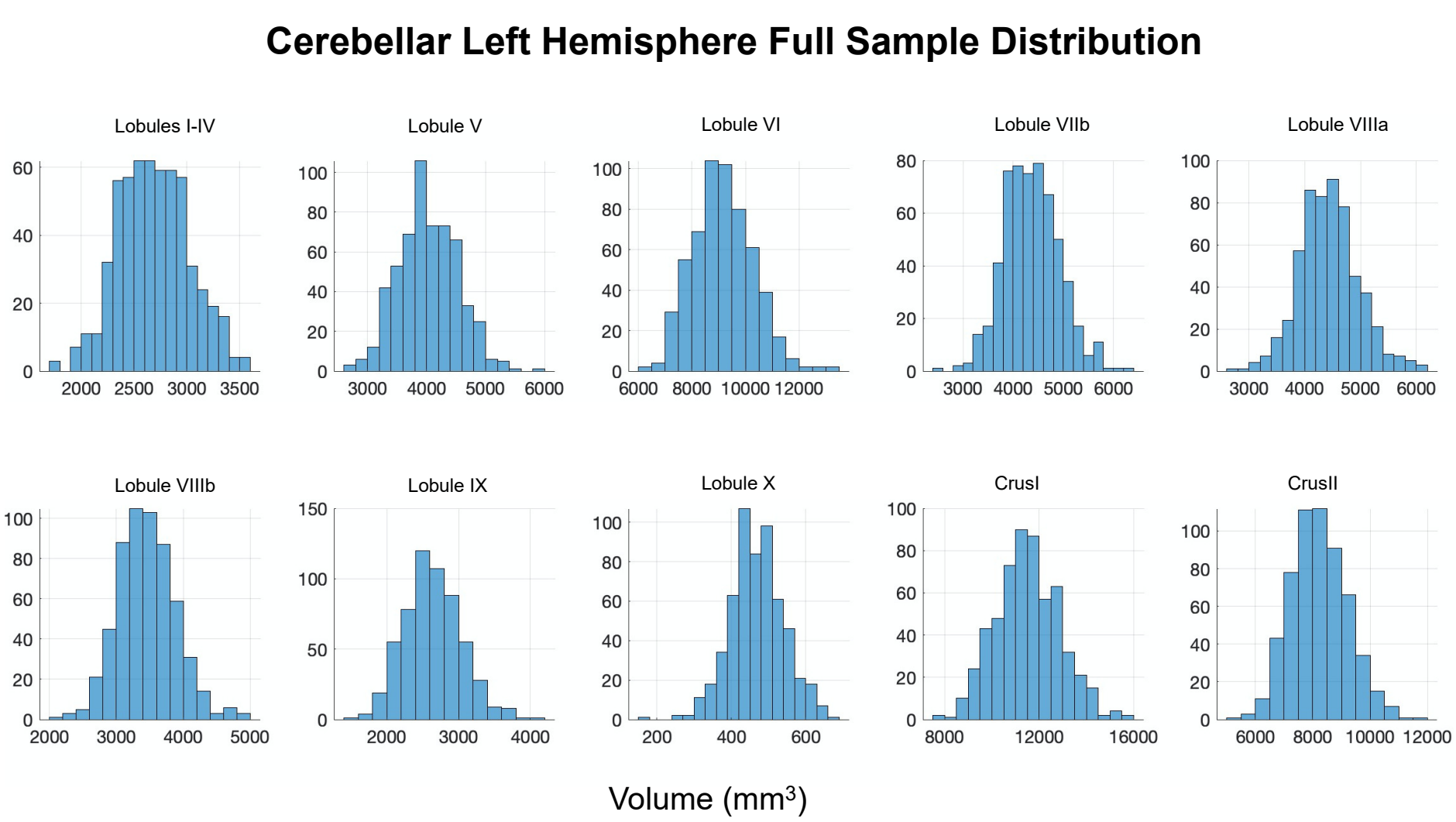
Weak (uncorrected $p < 0.05$) correlations were observed between PANSS positive scores and 2 of 11 anatomical ROIs (VIIb: r = -0.13, *p = 0.04*; X: r = -0.13, *p = 0.03*) and 2 of 7 functional ROI's (Limbic: r = -0.13, *p = 0.03*; FPN: r = -0.12, *p = 0.04*) with one trending ROI (VAN: r = -0.12, *p = 0.05*). One correlation was observed between PANSS general symptoms and an anatomical ROI (X: r = -0.15, *p = 0.02*).

Supplementary Figure 1. Density Plots of Whole Cerebellar Grey Matter Volume

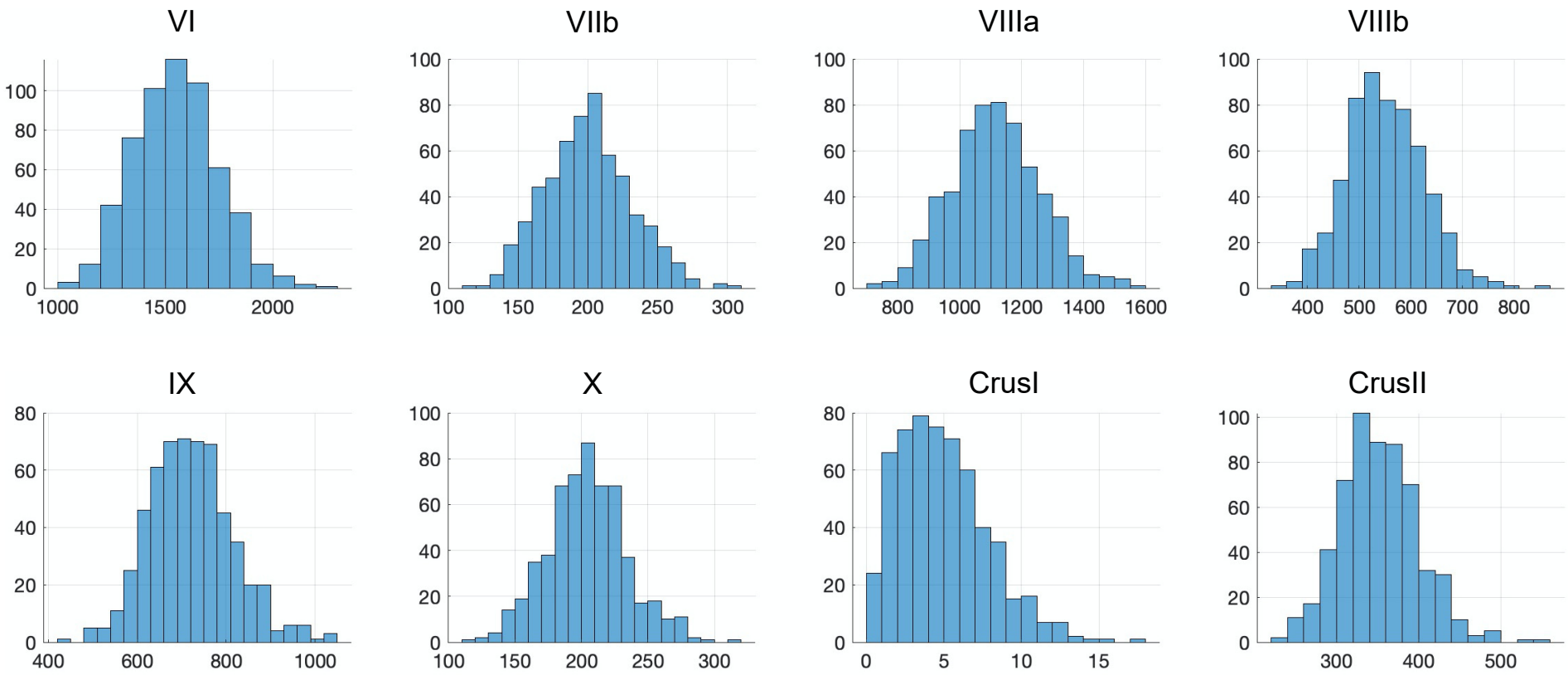


Unstandardized, residualized whole cerebellar grey matter volume using sex and age as covariates. HC = control, SzS = schizophrenia spectrum, BP = bipolar with psychotic features, FE = First Episode / early illness Stage, Chronic = chronic illness stage, d = Cohen's d Effect Size. Solid vertical line indicates mean for the HC sample; dotted vertical line indicated mean for the clinical sample.

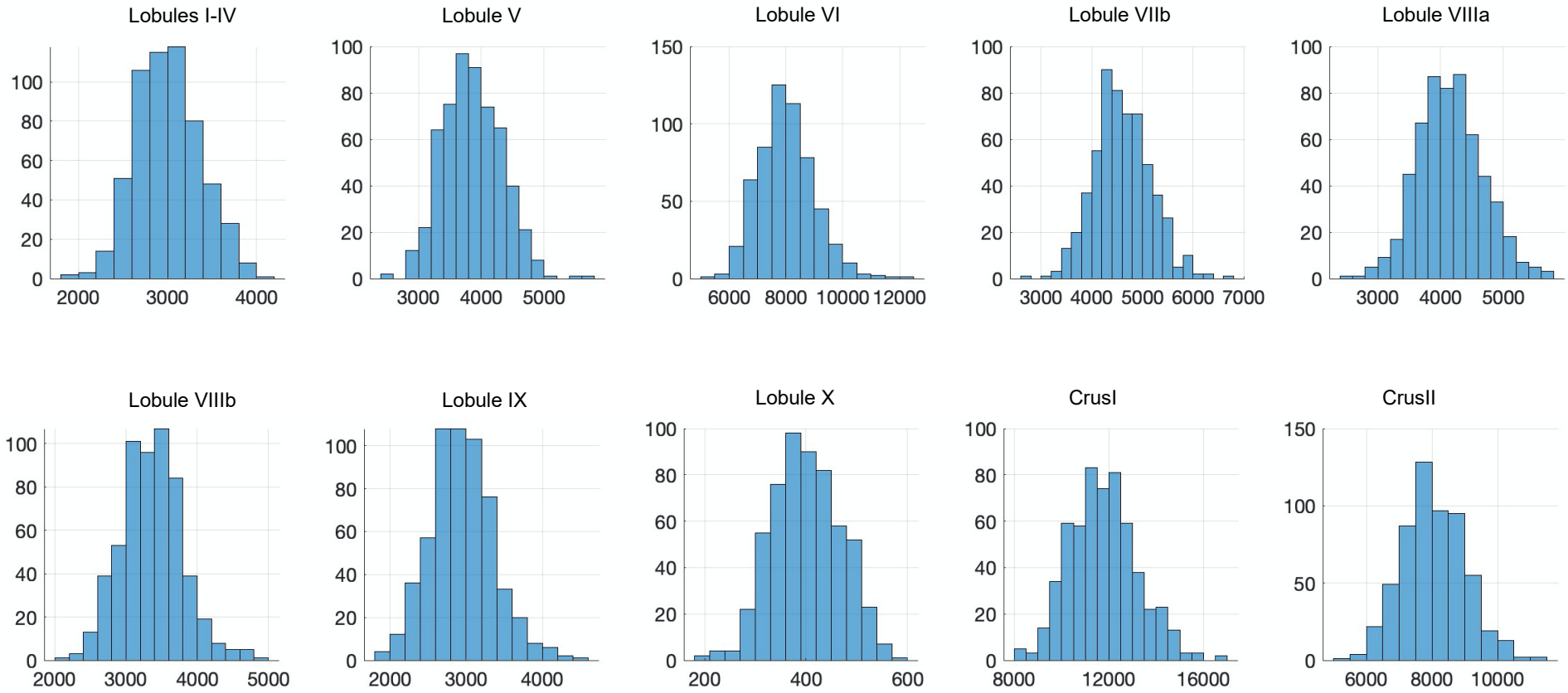
Supplementary Figure 2. Histograms of Unilateral Cerebellar Lobular Volumes in Full Sample



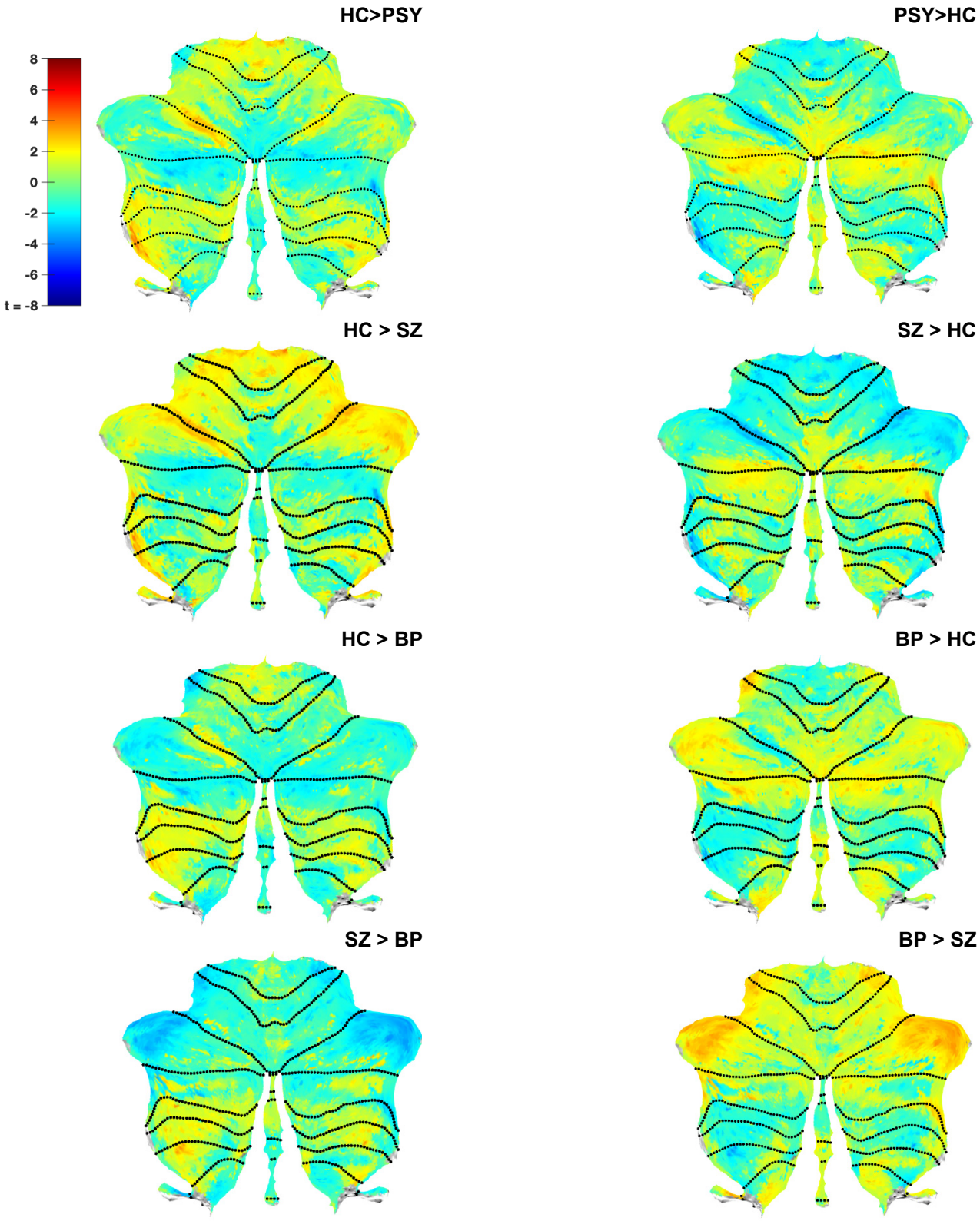
Cerebellar Vermis Full Sample Distribution



Cerebellar Right Hemisphere Full Sample Distribution

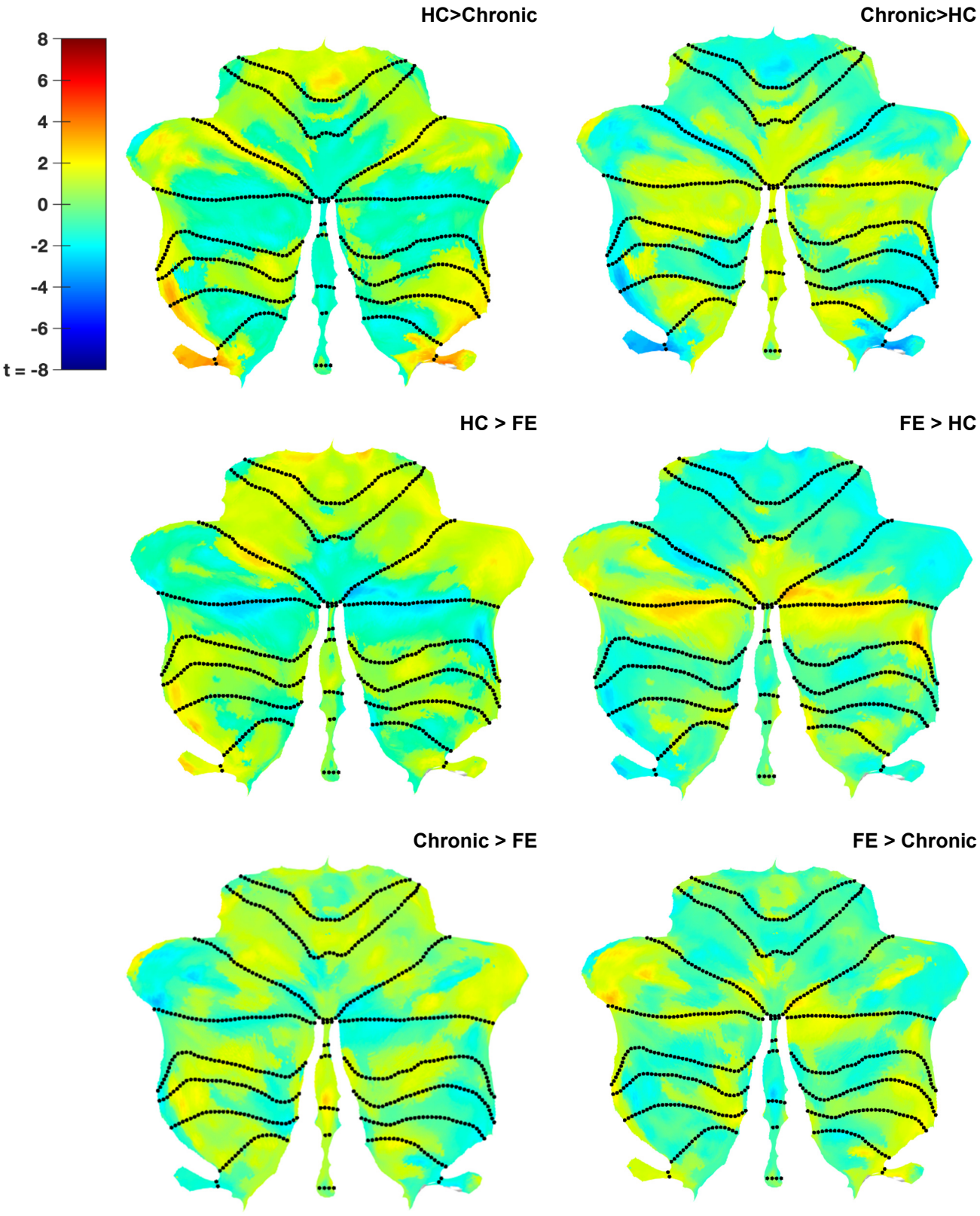


Supplementary Figure 3. Unthresholded t-Maps for VBM Analysis (Diagnosis Groups)



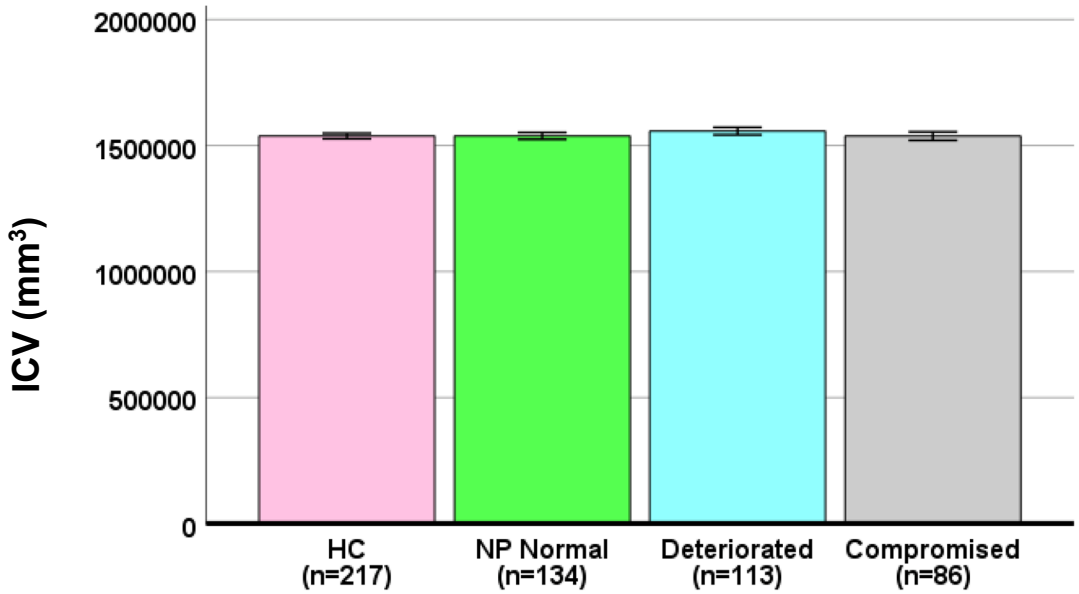
VBM results plotted on a cerebellar flatmap (11) as the uncorrected t-map of the comparison of all psychosis patients and healthy controls. PSY=psychosis, HC=control, SZ=schizophrenia spectrum, BP=bipolar with psychotic features

Supplementary Figure 4. Unthresholded t-Maps for VBM Analysis (Illness Stage Groups)



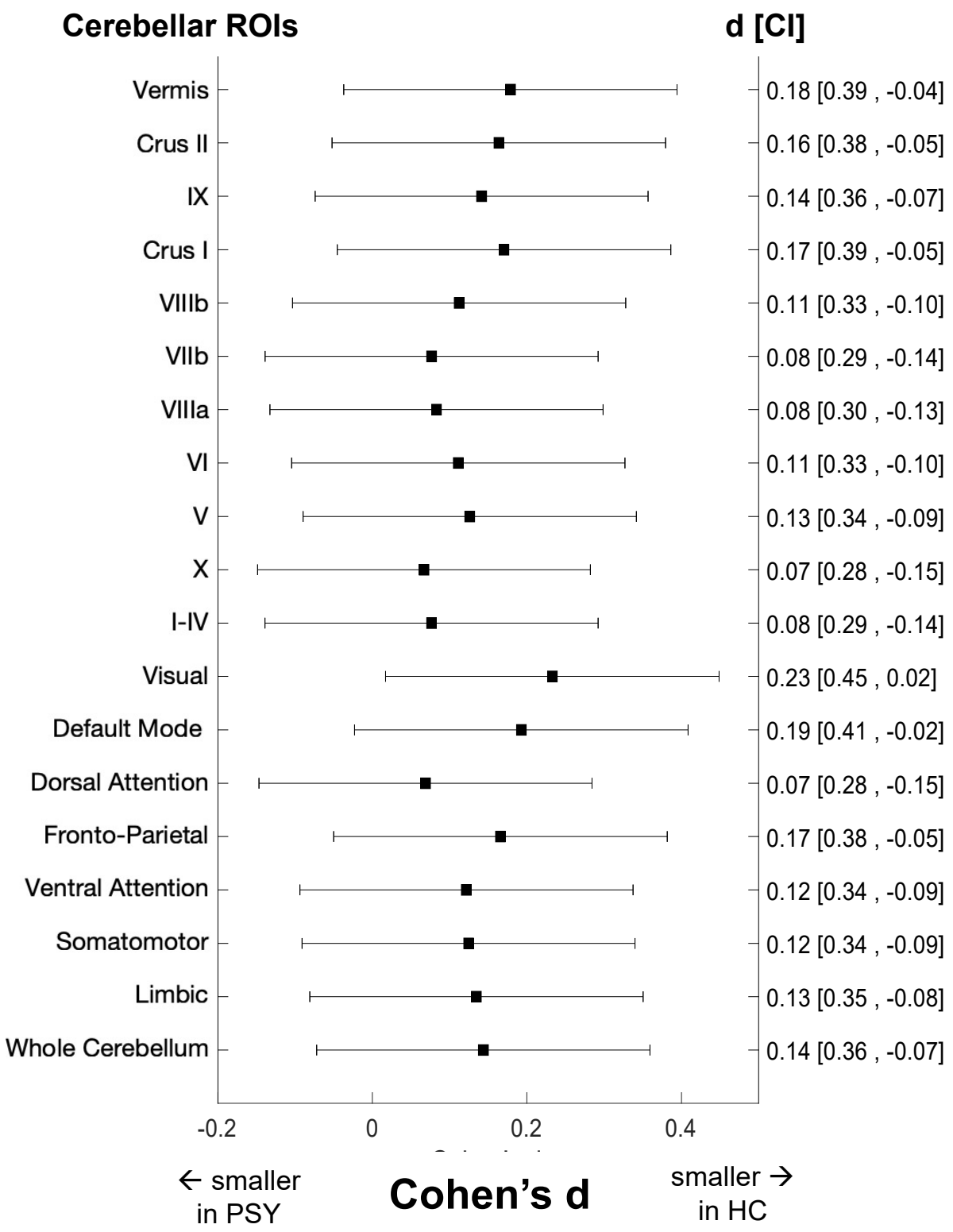
VBM results plotted on a cerebellar flatmap (11) as the uncorrected t-map of the comparison of all psychosis patients and healthy controls. HC=control, FE=first episode, early stage, Chronic=chronic stage illness

Supplementary Figure 5. ICV for Cognitive Subgroups



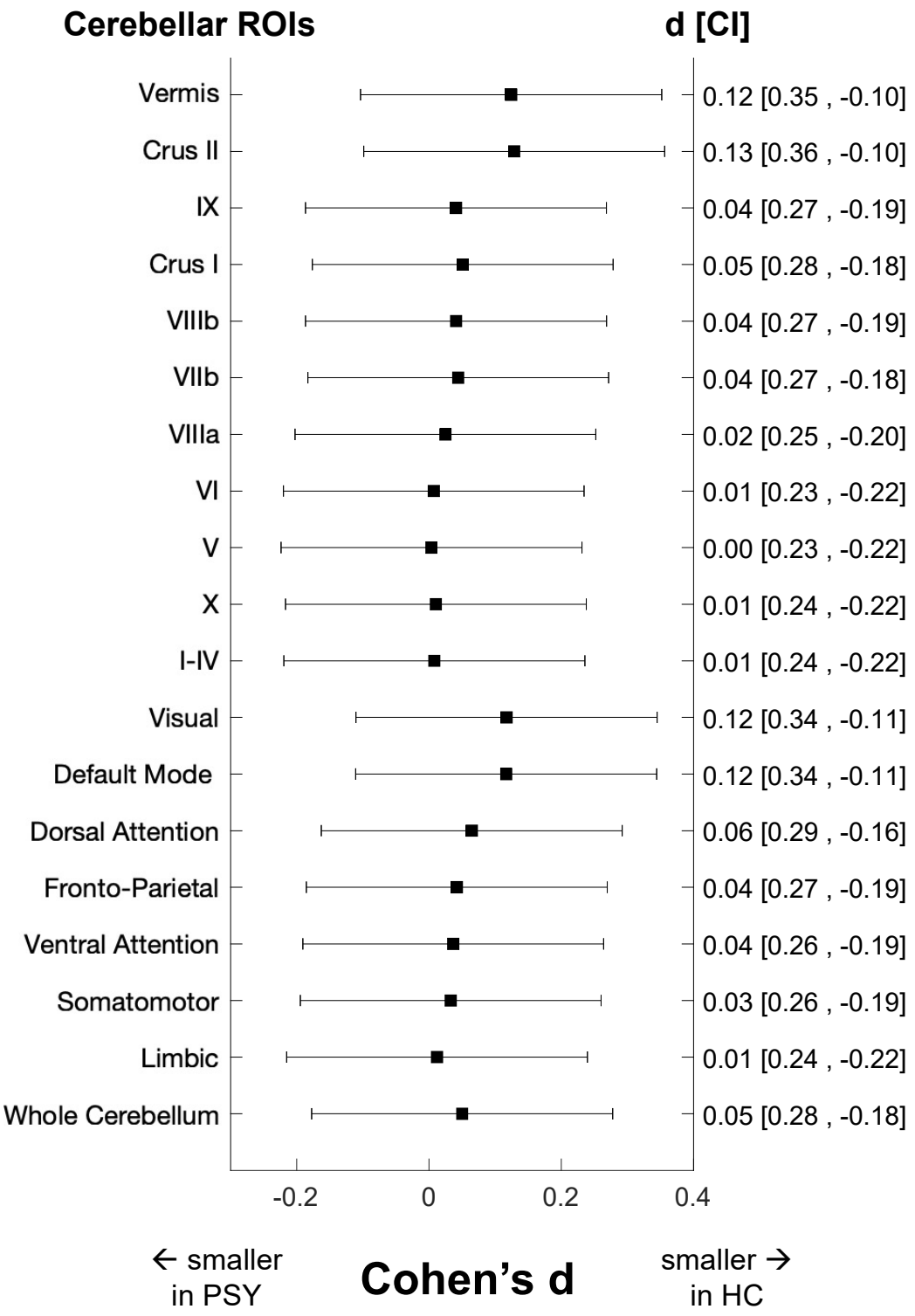
Unstandardized, residualized intracranial volume (ICV) using sex, age, and scan type as covariates. See Supplementary Note 4 for additional details on the generation of cognitive subgroups. No significant group differences were observed for this model, or for total ICV (CAT12) without covariates. HC=control, NP Normal = neuropsychologically normal cognitive group.

Supplementary Figure 6. Effect Size Plot with Confidence Intervals – Neuropsychologically Normal vs. Control



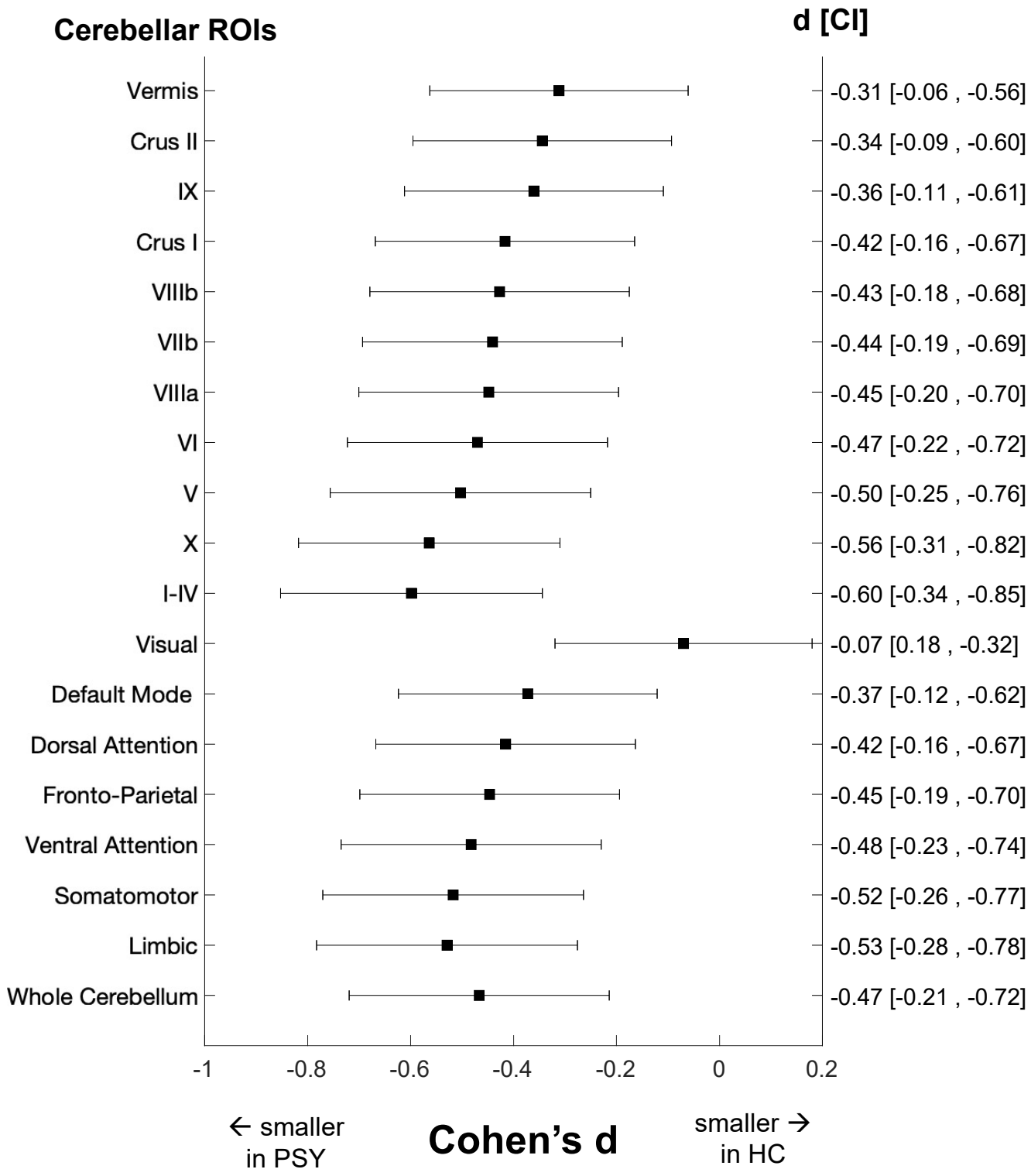
ROI effect sizes. All effects plotted for the neuropsychologically normal cognitive group compared to the control (HC) group; right axis displays the corresponding effect size. Figure depicts effect sizes for cerebellar volume of 10 bilateral lobules, cerebellar vermis, and 7 functional networks (12) 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 (PSY) cognitive subgroup.

Supplementary Figure 7. Effect Size Plot with Confidence Intervals – Deteriorated vs. Control



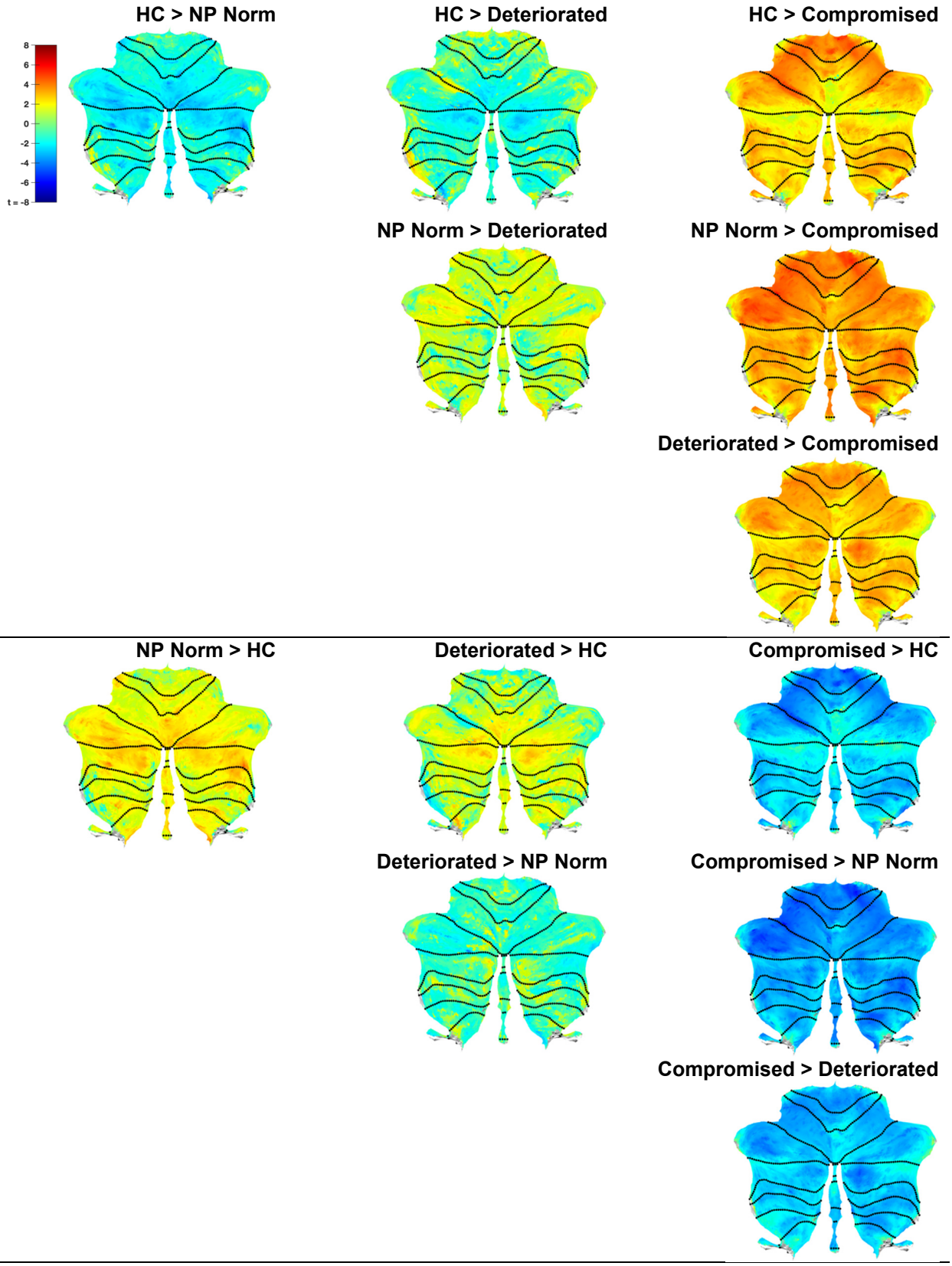
ROI effect sizes. All effects plotted for the deteriorated cognitive group compared to the control (HC) group; right axis displays the corresponding effect size. Figure depicts effect sizes for cerebellar volume of 10 bilateral lobules, cerebellar vermis, and 7 functional networks (12) based on the univariate test using sex, age, ICV, and scan type as covariates. Effect sizes <0 indicate that the region is smaller in the psychosis (PSY) cognitive subgroup.

Supplementary Figure 8. Effect Size Plot with Confidence Intervals – Compromised vs. Control



ROI effect sizes. All effects plotted for the compromised cognitive group compared to the control (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 (12) 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 (PSY) cognitive subgroup.

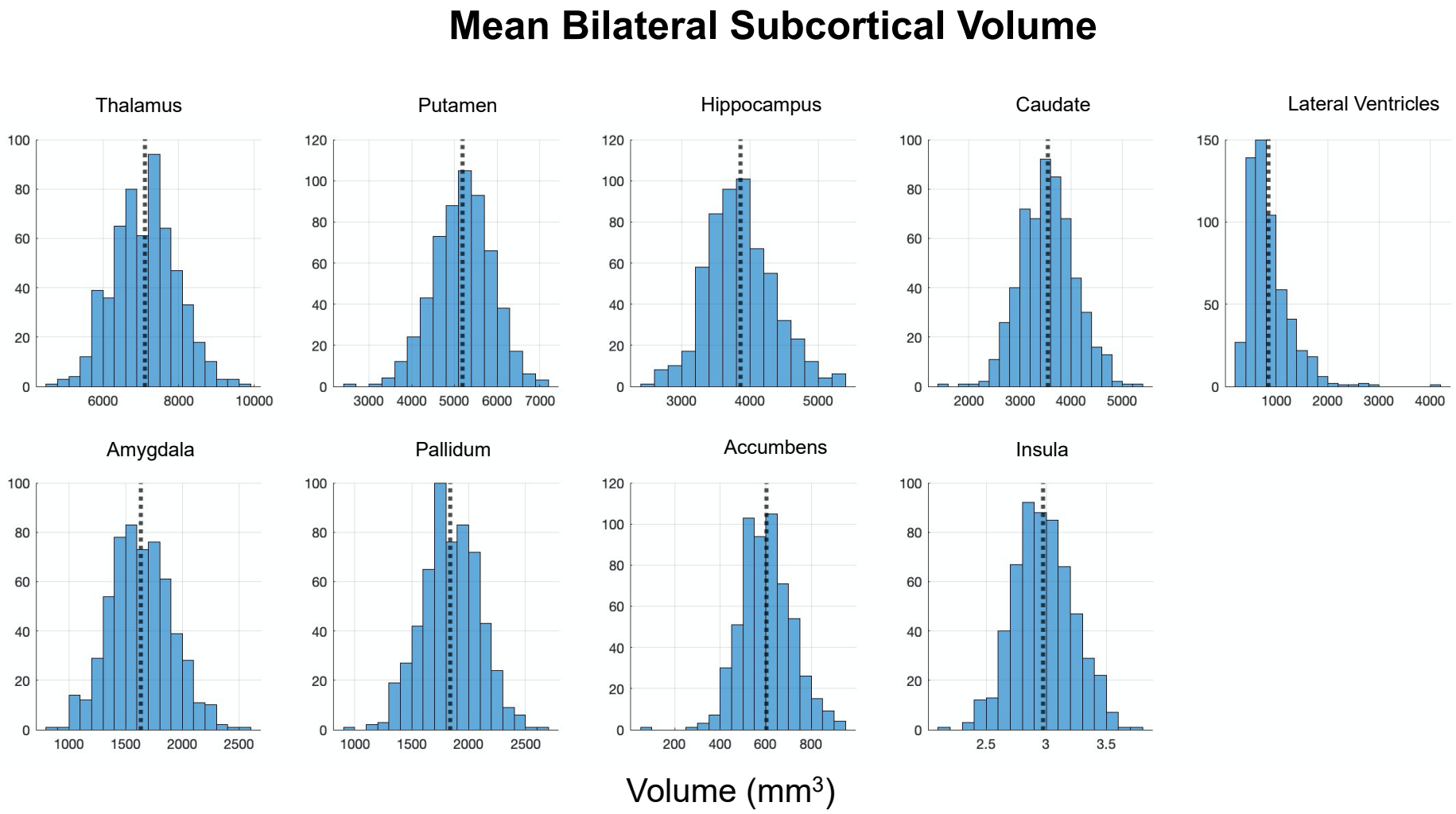
Supplementary Figure 9. Unthresholded t-Maps for VBM Analysis (Cognitive Subgroups)



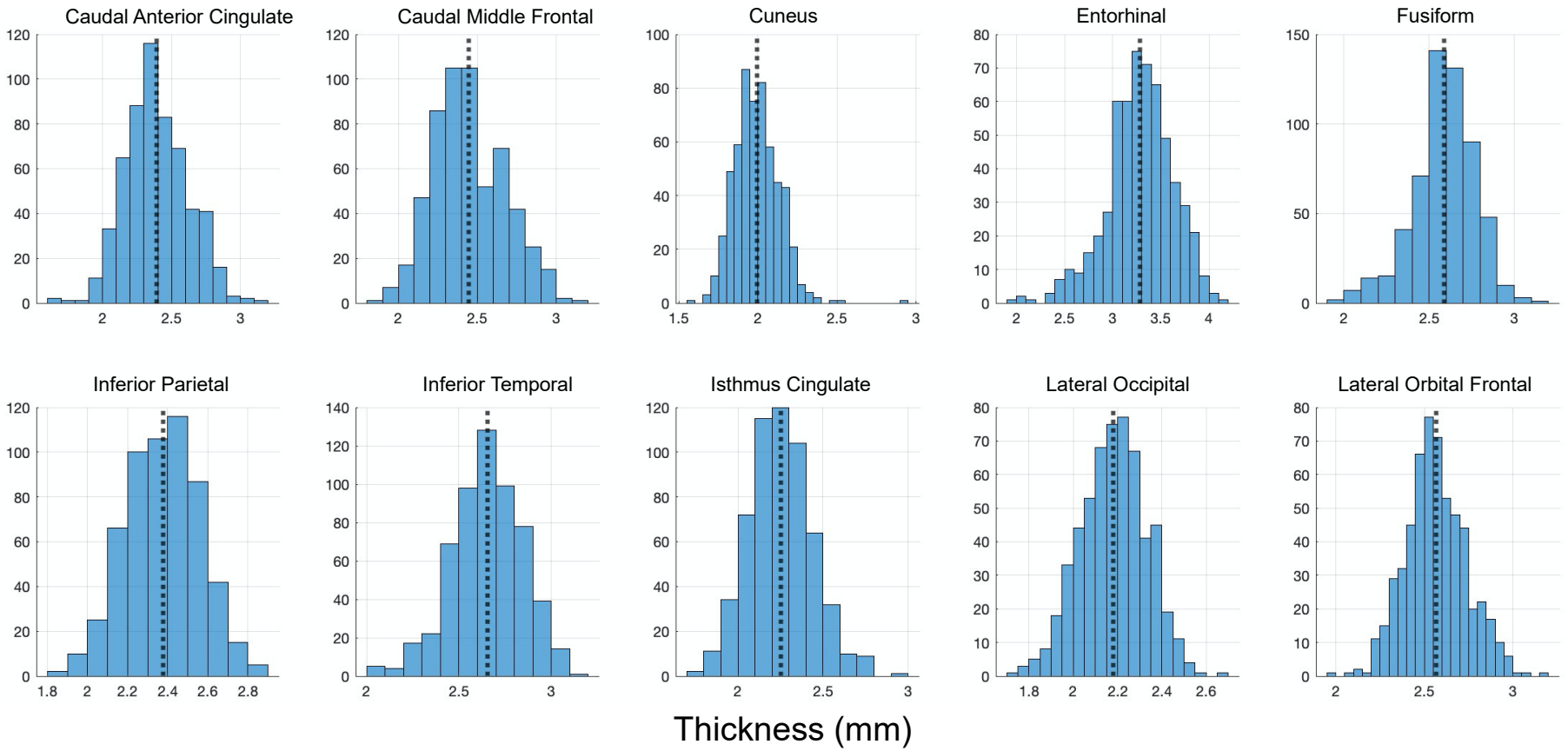
VBM results plotted on a cerebellar flatmap (11) as the uncorrected t-map of the comparison of all psychosis patients and healthy controls. HC=control, NP Norm = neuropsychologically normal cognitive group

Supplementary Figure 10. Histograms of Cerebral Morphometric Features

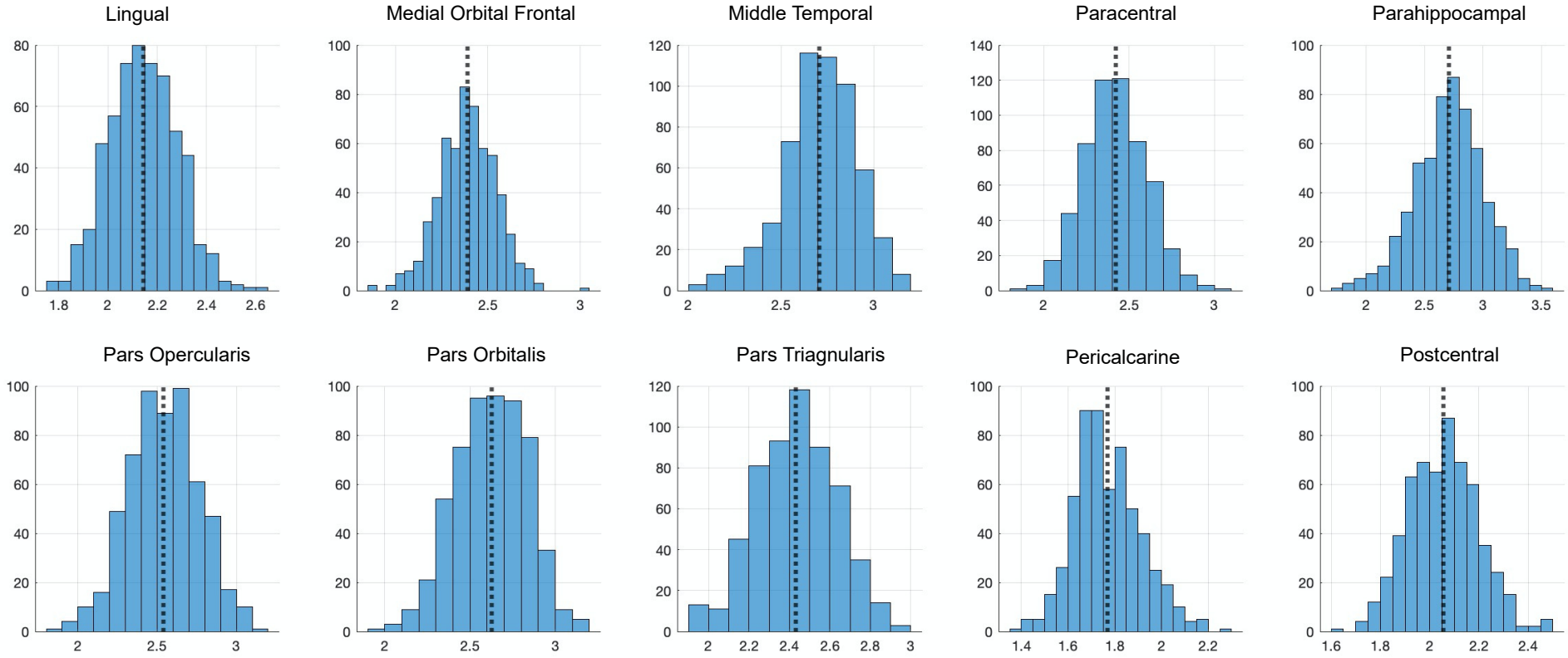
Given that cerebellar comparisons between diagnostic groups were inconsistent with prior studies (cf. (9)), we report here cerebral cortical thicknesses and subcortical volumes to help readers better compare the current dataset and cerebellar findings in the context of other studies and the whole brain.



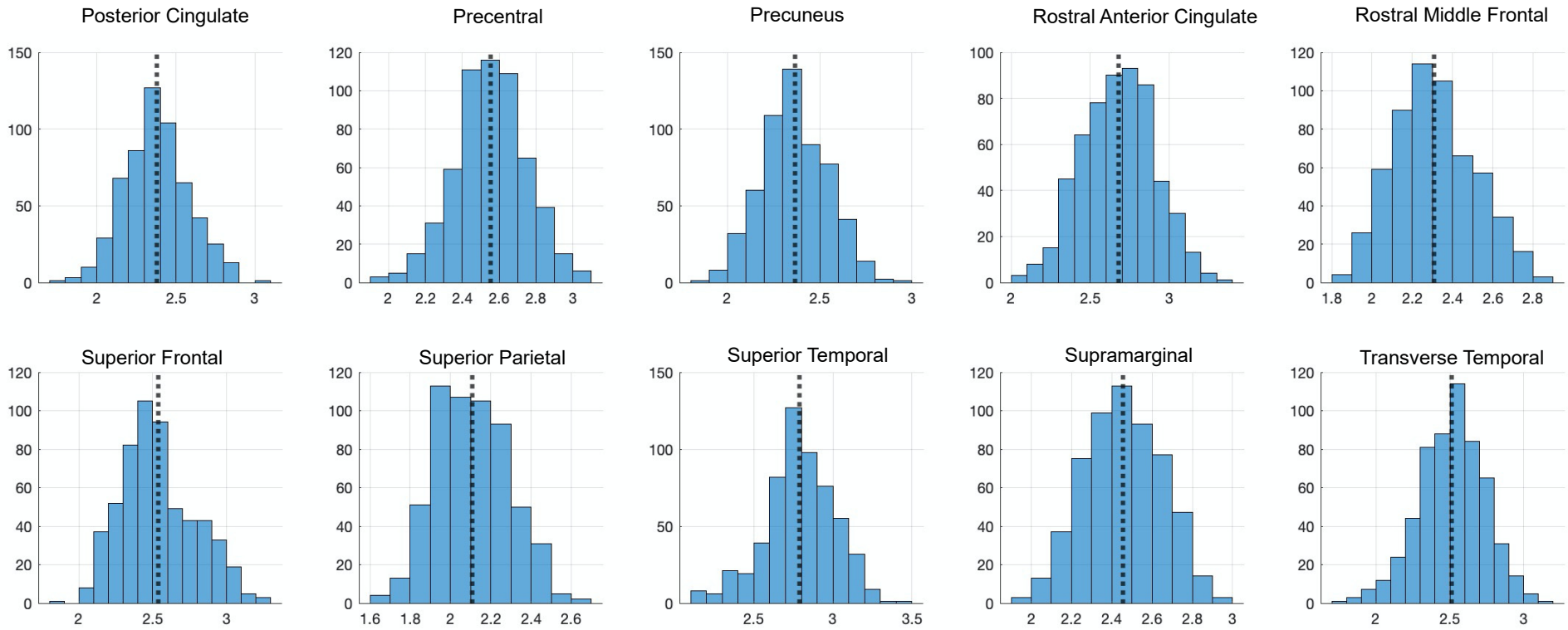
Mean Bilateral Cortical Thicknesses



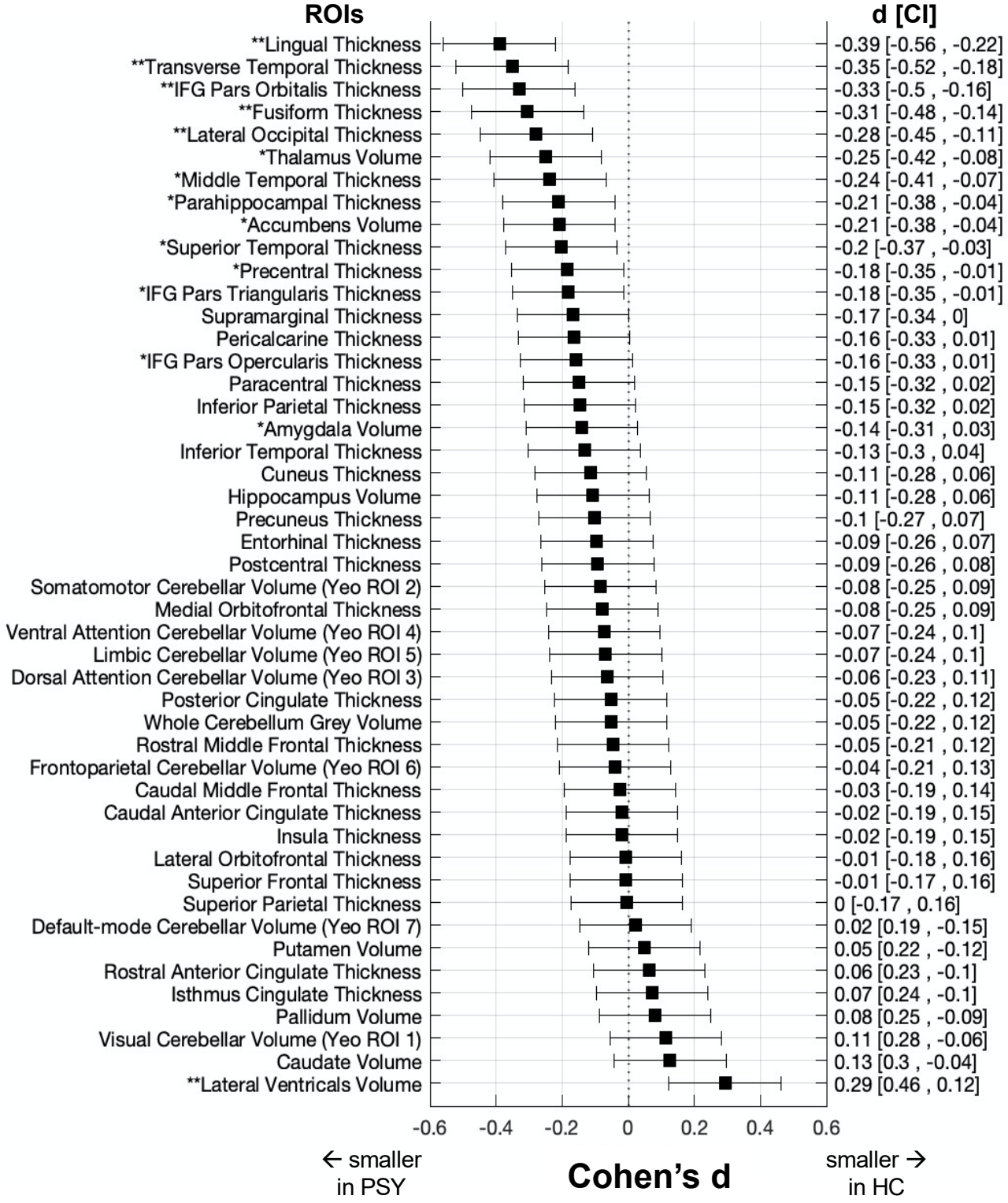
Mean Bilateral Cortical Thicknesses



Mean Bilateral Cortical Thicknesses

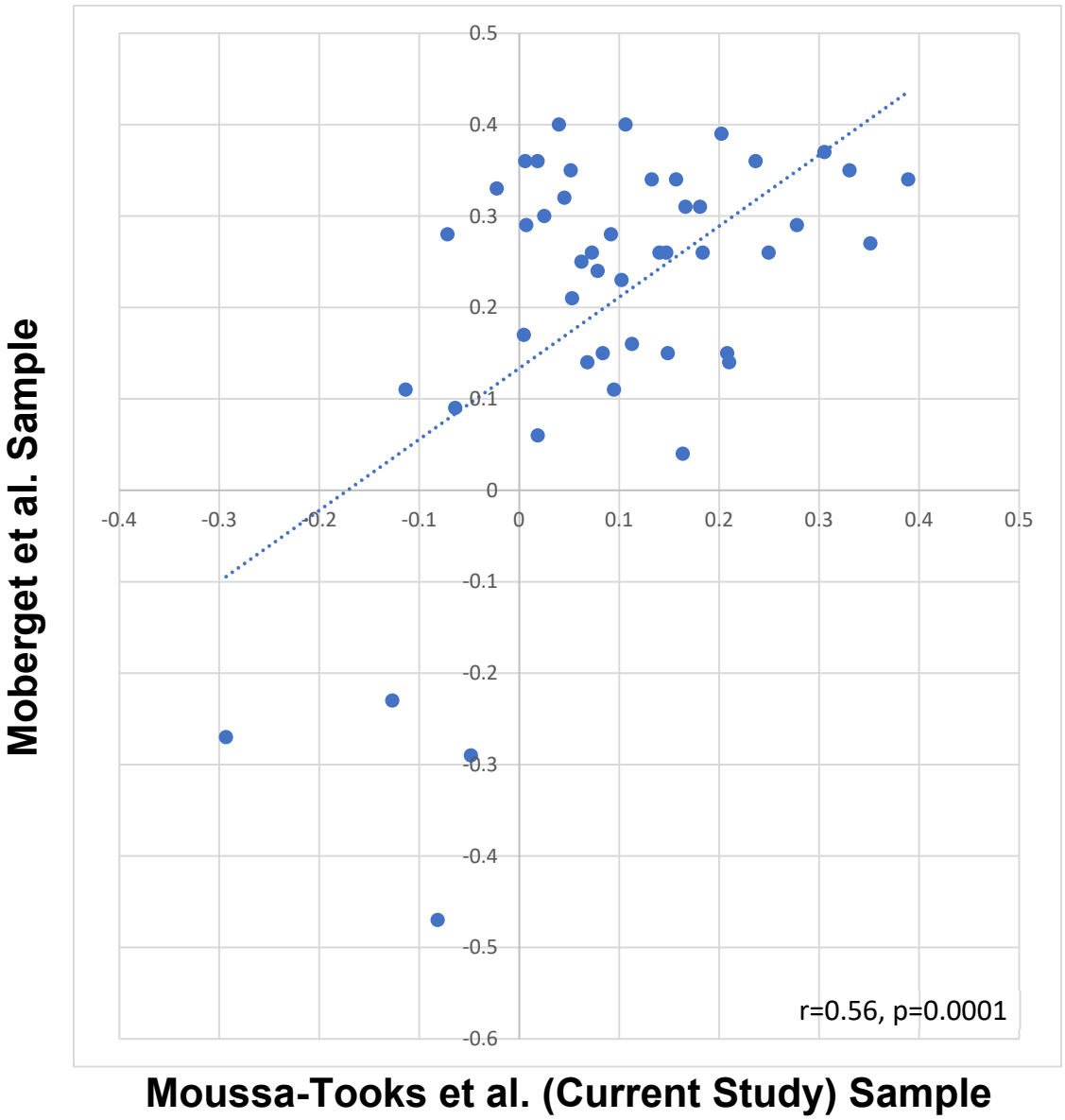


Supplementary Figure 11. Effect Size Plot with Confidence Intervals – Cerebral Morphometric Features



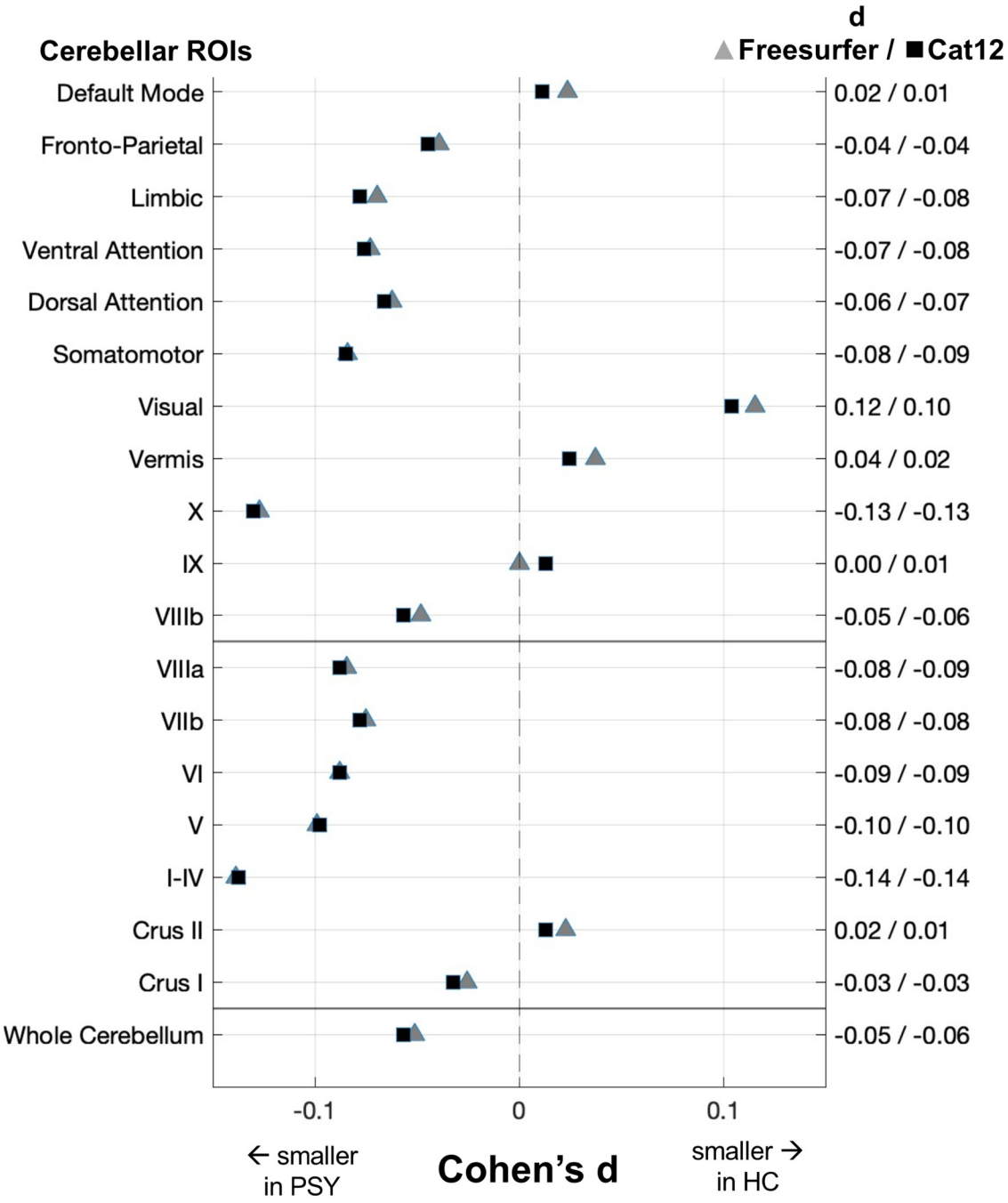
Effect sizes from comparisons between diagnostic groups (control [HC] vs. schizophrenia spectrum [PSY]) for cerebral cortical thicknesses and subcortical volume data for the current dataset. Notably, for many regions often implicated in psychosis our dataset is consistent with the literature (e.g., in psychosis sample, smaller hippocampus, thalamus, etc.; larger lateral ventricles). We hope this will help readers better compare the current dataset and cerebellar findings (highlighted in green for ease of identification) in the context of other studies and the whole brain. Right axis displays the corresponding effect size and confidence interval. 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 (PSY) group.

Supplementary Figure 12. Correlation of Current Study and Moberget Cerebral and Cerebellar ROIs/Features



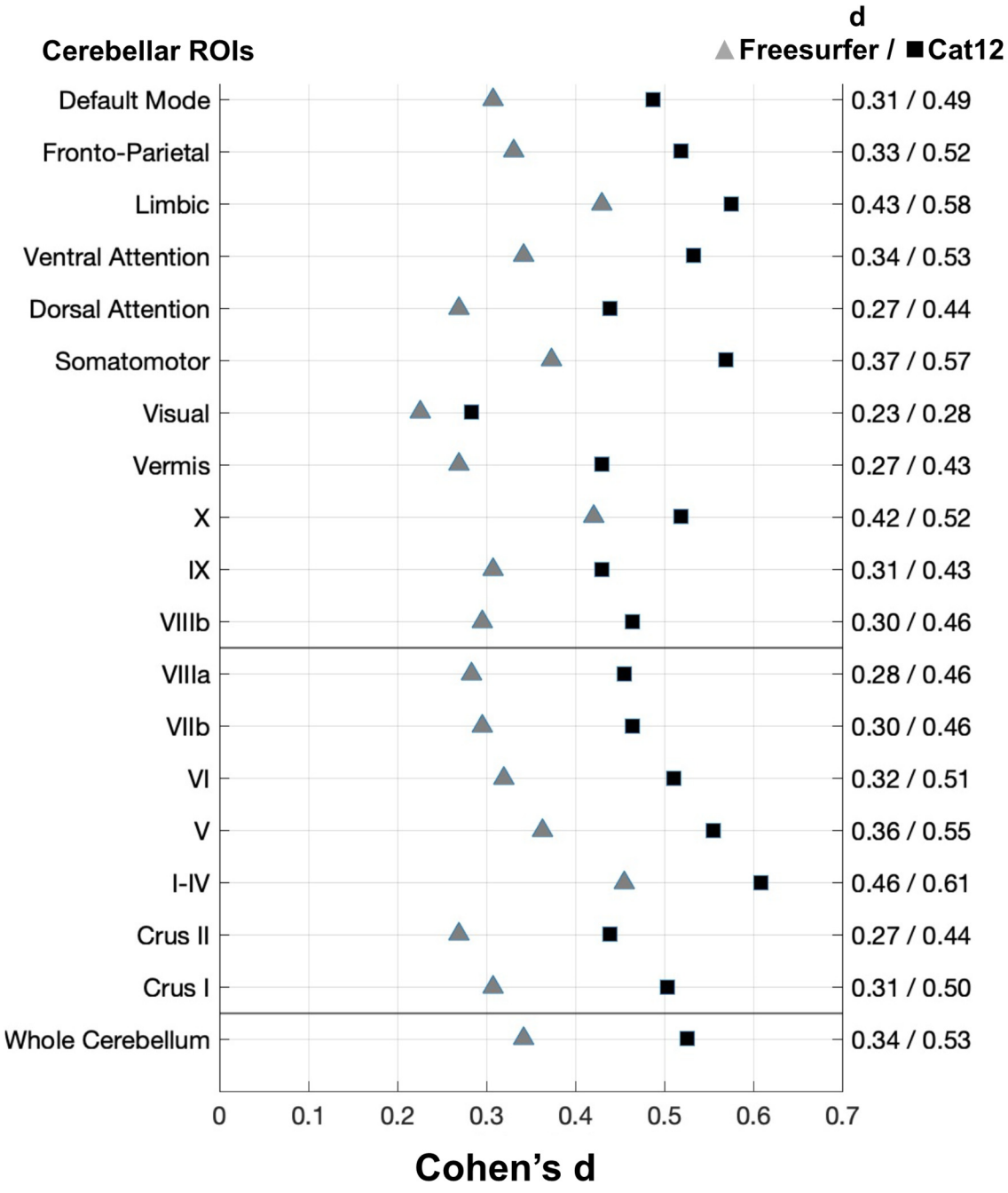
Differing cerebellar findings were observed for the diagnostic group comparison (healthy control vs. schizophrenia spectrum) between the current study and that by Moberget and colleagues (9). When looking at reported effect sizes for all cerebellar and cerebral ROIs, there is a moderate positive correlation observed between the effect size outcomes from the Moberget study and the current study. Effect sizes for the current sample are reported in Supplementary Figure 11.

Supplementary Figure 13. Cat12 and Freesurfer Effect Size Comparison: Psychosis vs. Control Analysis



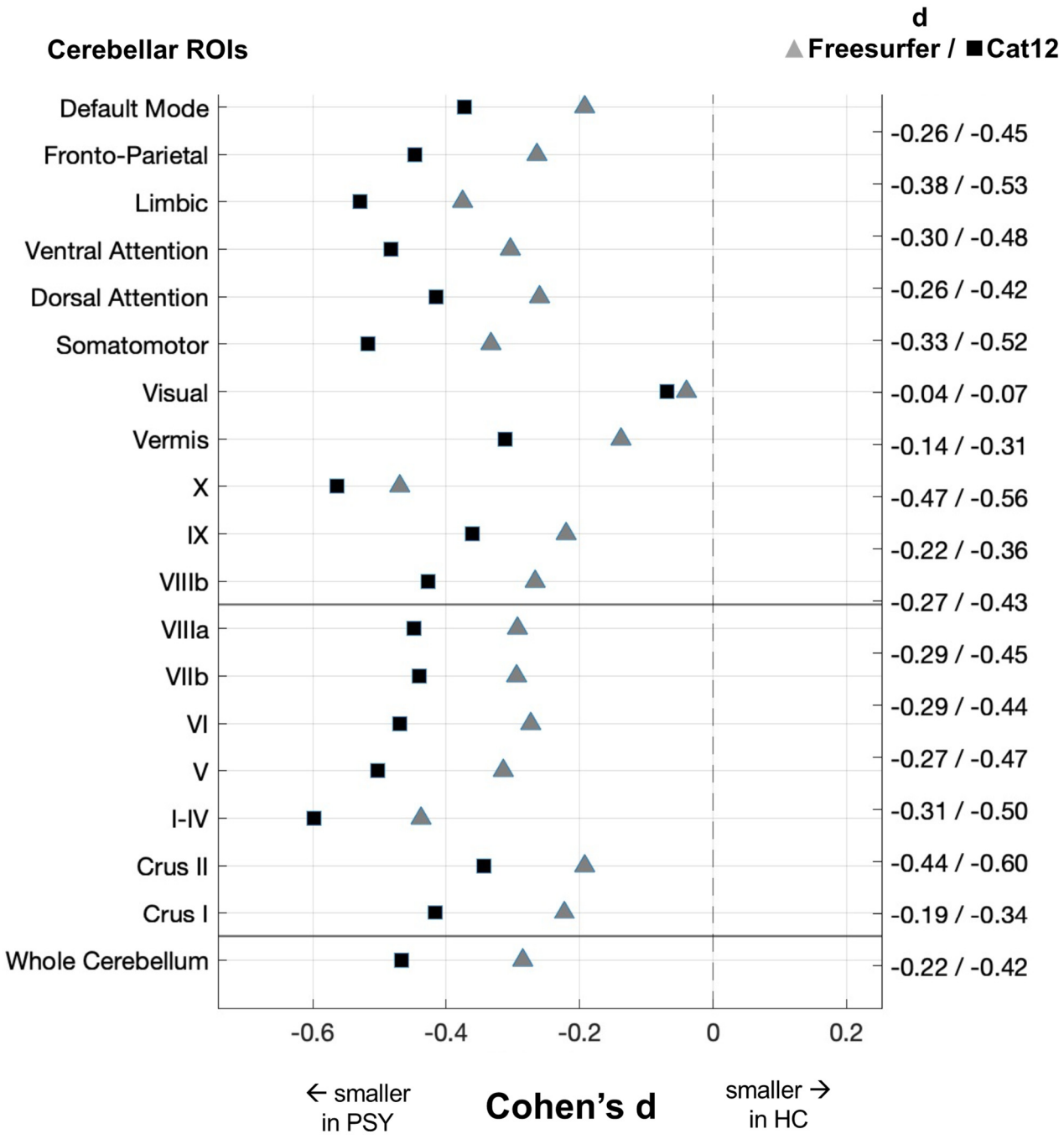
ROI effect sizes. All effects plotted for the full psychosis group compared to the control (HC) group; right axis displays the corresponding effect size. Figure depicts effect sizes for cerebellar volume of 10 bilateral lobules, cerebellar vermis, and 7 functional networks (12) based on the univariate test using sex, age, ICV (CAT12 ■) or eTIV (Freesurfer ▲), and scan type as covariates. Effect sizes <0 indicate that the region is smaller in the psychosis (PSY) cognitive subgroup.

Supplementary Figure 14. Cat12 and Freesurfer Effect Size Comparison: Cognitive Subgroups 4-Group Analysis



ROI effect sizes. All effects plotted for the 3 psychosis cognitive groups (compromised, deteriorated, and neuropsychologically normal) compared to the control (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 (12) based on the univariate test using sex, age, ICV (CAT12 ■) or eTIV (Freesurfer ▲), and scan type as covariates. Effect sizes <0 indicate that the region is smaller in the psychosis (PSY) cognitive subgroup. Effect sizes are not directional due to 4-way comparison.

Supplementary Figure 15. Cat12 and Freesurfer Effect Size Comparison: Cognitively Compromised vs. Control Group



ROI effect sizes. All effects plotted for the psychosis cognitively compromised group compared to the control (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 (12) based on the univariate test using sex, age, ICV (CAT12 ■) or eTIV (Freesurfer ▲), and scan type as covariates. Effect sizes <0 indicate that the region is smaller in the psychosis (PSY) cognitive subgroup.

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