Biological Psychiatry: Celebrating 50 Years

Cerebellar Gray Matter Volume Is Associated With Cognitive Function and Psychopathology in Adolescence

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ABSTRACT

BACKGROUND: Accumulating evidence supports cerebellar involvement in mental disorders, such as schizophrenia, bipolar disorder, depression, anxiety disorders, and attention-deficit/hyperactivity disorder. However, little is known about the cerebellum in developmental stages of these disorders. In particular, whether cerebellar morphology is associated with early expression of specific symptom domains remains unclear.

METHODS: We used machine learning to test whether cerebellar morphometric features could robustly predict general cognitive function and psychiatric symptoms in a large and well-characterized developmental community sample centered on adolescence (Philadelphia Neurodevelopmental Cohort, n = 1401, age 8–23 years).

RESULTS: Cerebellar morphology was associated with both general cognitive function and general psychopathology (mean correlations between predicted and observed values: r = .20 and r = .13; $p < .001$). Analyses of specific symptom domains revealed significant associations with rates of norm-violating behavior (r = .17; $p < .001$) as well as psychosis (r = .12; $p < .001$) and anxiety (r = .09; p = .012) symptoms. In contrast, we observed no associations with attention deficits or depressive, manic, or obsessive-compulsive symptoms. Crucially, across 52 brain-wide anatomical features, cerebellar features emerged as the most important for prediction of general psychopathology, psychotic symptoms, and norm-violating behavior. Moreover, the association between cerebellar volume and psychotic symptoms and, to a lesser extent, norm-violating behavior remained significant when adjusting for several potentially confounding factors.

CONCLUSIONS: The robust associations with psychiatric symptoms in the age range when these typically emerge highlight the cerebellum as a key brain structure in the development of severe mental disorders.

Keywords: Adolescence, Cerebellum, Conduct disorder, Psychopathology, Psychosis, Voxel-based morphometry

https://doi.org/10.1016/j.biopsych.2019.01.019

A growing body of research reports cerebellar involvement across a wide range of mental disorders, including schizophrenia (1), bipolar disorder (2), depression (3), anxiety disorders (4), attention-deficit/hyperactivity disorder (ADHD) (5), and autism (6). However, whereas the majority of these conditions are conceptualized as neurodevelopmental disorders (7,8), most studies investigating the role of the cerebellum in mental health research have targeted adult populations (1,9–11). Hence, it is largely unknown whether cerebellar changes can be detected in adolescence, when initial symptoms typically manifest (8,12,13), or emerge later in the disease process. Moreover, whether individual differences in cerebellar structure in adolescents are indicative of nonspecific impairments, such as cognitive deficits [present across a wide range of psychiatric disorders (14)] or general psychopathology [analogous to the g factor of intelligence (15–17)], or rather are associated with specific symptom domains (18), remains unclear. Finally, it is unknown how cerebellar associations with psychiatric symptoms in adolescence compare against such associations in other brain regions. Answering these questions will be crucial for determining the relative importance of the cerebellum during this critical period for the development of mental disorders.

In this study, we used machine learning to test whether cerebellar morphometric features could robustly predict cognitive function and psychiatric symptoms in a large and well-characterized developmental community sample centered on adolescence (19,20). Consistent with the Research Domain Criteria framework (21) proposed by the National Institutes of Mental Health, we followed a diagnostically agnostic and dimensional approach (22,23), extracting clusters of correlated symptoms from a comprehensive set of clinical assessment data using blind source separation methods (24). A similar data-driven and anatomically agnostic approach was used to decompose cerebellar gray matter maps into spatially independent components before testing for structure-function

ISSN: 0006-3223

associations using multivariate machine learning. By using 10-fold internal cross-validation of machine-learning prediction models and permutation-based statistical inference in a large community sample, we aimed to optimize the robustness and generalizability of the results (25). Furthermore, to confirm convergence across methodological approaches, we also tested for structure-function associations at the resolution levels of cerebellar lobules and voxels and performed traditional univariate analyses in addition to running the machine-learning prediction models. Finally, we evaluated the specificity of any cerebellar effects by testing for structure-function associations across brain-wide regions of interest (ROIs); tested whether associations with specific symptom domains were independent of associations with general cognitive function (26,27) and general psychopathology (15); and controlled for potentially confounding variables, such as magnetic resonance imaging (MRI) data quality (28), parental education level (29), use of psychoactive substances (30), and psychiatric assessment strategy. Based on the existing literature on adults, we hypothesized that cerebellar morphology would be associated with both cognitive function (26,31,32) and general psychopathology (15), but remained agnostic as to whether such associations would show specificity across different psychiatric symptom domains.

METHODS AND MATERIALS

Participants

The main structure-function analyses were based on data from 1401 participants (52.8% female; mean age 15.12 years; age range, 8.2–23.2) included in the publicly available Philadelphia Neurodevelopmental Cohort (PNC) (19,20) (see Supplemental Methods for inclusion criteria and demographic information). The institutional review boards of the University of Pennsylvania and the Children's Hospital of Philadelphia approved all study procedures, and written informed consent was obtained from all participants.

Collection and Processing of Cognitive and Clinical Measures

As reported previously (24), we included performance scores from the full PNC sample (N = 6487) on 12 computerized cognitive tests (20) and 129 questionnaire items from the PNC GOASSESS computerized assessment battery (20), including items adapted from several different questionnaires, such as the World Health Organization Composite International Diagnostic Interview (33), Schedule for Affective Disorders and Schizophrenia for School-Age Children (28), Structured Interview for Prodromal Syndromes (34), and PRIME Screen–Revised (35). The GOASSESS battery thus allows for a broad mapping of symptoms of anxiety, mood, behavioral, eating, and psychosis spectrum disorders, with a particular focus on psychosis. For individuals younger than 18 years of age, we relied on information from interviews with caregivers or legal guardians (20). See Supplemental Tables S1 and S2 for individual cognitive tests and clinical items. Using the full PNC sample (N = 6487), we derived general measures of cognitive performance and psychopathology by extracting the first factor scores from principal component analyses of all cognitive and clinical scores, respectively. Next, to also examine specific symptom domains, all clinical item scores (N = 6487) were submitted to independent component analysis (ICA) using Icasso software (36), decomposing them into seven independent components. For the subset of participants with MRI data (n = 1401), effects of sex and age on all cognitive and clinical measures were tested using generalized additive models as implemented in the R package "mgcv" (37), and a set of adjusted cognitive and clinical scores was computed by regressing out main effects of age and sex (see Supplemental Methods). All subsequent structure-function analyses were conducted using these age-adjusted and sex-adjusted scores.

Collection and Processing of MRI Data

As previously described (19,38,39), all magnetization prepared rapid acquisition gradient-echo T1-weighted images were collected using the same scanner with 32-channel head coil (MAGNETOM Tim Trio 3T; Siemens Healthcare, Erlangen, Germany), using the following parameters: repetition time 1810 ms, echo time 3.51 ms, field of view 180 $\times$ 240 mm, matrix 256 $\times$ 192, 160 slices, inversion time 1100 ms, flip angle 9°, effective voxel resolution 0.9 $\times$ 0.9 $\times$ 1 mm. All images were first processed using FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu), yielding estimates of total intracranial volume (eTIV) (40), volumes of eight subcortical structures (41), and mean cortical thickness of 34 cortical ROIs per hemisphere (42). Next, the bias-corrected images from the FreeSurfer pipeline were subjected to cerebellum-optimized voxel-based morphometry using the SUIT toolbox v3.2 (43,44), running on MATLAB 2014a (The MathWorks, Inc., Natick, MA). In the first step, SUIT isolates the cerebellum and brainstem, segmenting images into gray and white matter maps. To avoid including voxels from the occipital cerebral cortex in the SUIT-generated cerebellar gray matter maps, we excluded all voxels that overlapped with the FreeSurfer-generated maps of cortical gray and white matter. In the second step, SUIT normalizes these (FreeSurfer-pruned) cerebellar gray matter maps to a cerebellar template using Dartel (45), ensuring superior cerebellar alignment compared with whole-brain procedures (44). Normalized cerebellar gray matter maps were modulated by the Jacobian of the transformation matrix to preserve absolute gray matter volume, and the volumes of 28 cerebellar lobules were extracted using the SUIT probabilistic atlas. Next, maps were smoothed using a 4-mm full width at half maximum Gaussian kernel before being subjected to ICA or voxelwise general linear models. Finally, a mask for these analyses was constructed by thresholding the mean unmodulated cerebellar gray matter map at .01 and multiplying it with the SUIT gray matter template (also thresholded at .01).

Data-Driven Parcellation of Cerebellar Gray Matter

As cerebellar parcellations based on gross anatomical features (e.g., lobules) only partially overlap with functional maps of the cerebellum (46), we used a data-driven approach in our primary analyses. Specifically, we subjected the modulated cerebellar gray matter maps to ICA using FSL MELODIC (47), testing model orders from 5 to 20, and, pragmatically, selecting the model order yielding the maximal number of clearly bilateral components for further analysis. To characterize the resulting cerebellar voxel-based morphometry components, we used NeuroSynth (48) to map the full-brain functional connectivity of each component's peak voxel and decoded these full-brain connectivity maps in terms of their similarity to (i.e., spatial correlation with) meta-analytic maps generated for the 2911 terms in the NeuroSynth (48) database (see Supplemental Methods).

Analysis of Brain-Behavior Associations

Before inclusion in statistical models, all volumetric features were adjusted for effects of age, sex, and eTIV, using generalized additive models to sensitively model and adjust for potentially nonlinear effects of age (49–51) and eTIV (52,53) (see Supplemental Methods). In our primary analyses, we tested whether subject weights on cerebellar independent components could predict cognitive and clinical scores by using shrinkage linear regression (54) (implemented in the R package "care") with 10-fold internal cross-validation (i.e., based on iteratively using 90% of the sample to predict the remaining 10%), repeated 10,000 times on randomly partitioned data. Model performance was evaluated by computing the Pearson correlation coefficient between predicted and observed cognitive and clinical scores (taking the mean across iterations as our point estimate). Statistical significance was determined by comparing these point estimates with empirical null distributions of correlation coefficients under the null hypothesis (computed by running the models 10,000 times on randomly permuted clinical and cognitive scores). Results were considered significant at $p < .05$ (one-tailed), Bonferroni adjusted for the nine tested associations. To determine the relative importance of the anatomical features included in each prediction model, we computed the squared correlation-adjusted (marginal) co-relation (CAR) scores (55) for each iteration, yielding distributions of $10 \times 10{,}000$ CAR^2 estimates.

To complement these multivariate prediction models, we performed a set of univariate analyses, correlating the (age-adjusted and sex-adjusted) subject weights on each cognitive and clinical component with the (eTIV-adjusted, age-adjusted, and sex-adjusted) anatomical subject weights (see Supplemental Methods). To facilitate comparison with previously published research, we also report results from prediction models and correlation analyses using volumetric estimates of 28 cerebellar lobules as features as well as from general linear models performed at the voxel level. The voxelwise analyses tested for effects of cognitive and clinical scores while controlling for effects of sex, age, and eTIV using FSL randomise (56) with 10,000 permutations per contrast.

Next, to allow for a comparison of cerebellar and cerebral structure-function associations, all prediction models were also performed on volumetric estimates of eight bilateral subcortical structures and estimates of cortical thickness from 34 bilateral ROIs based the Desikan-Killiany atlas in FreeSurfer, respectively (Supplemental Figure S2). We chose thickness as our cortical feature of interest owing to its generally stronger and more consistent associations with psychopathology than surface area (57). All anatomical indices were adjusted for effects of age and sex (and eTIV for volumetric indices), as described above. Finally, to directly compare relative feature importance across all anatomical measures, prediction models were also fitted using *Z*-normalized versions of all morphometric features.

Effects of general cognitive function and general psychopathology as well as potentially confounding variables, such as MRI data quality, parental education, use of psychoactive substances, and psychiatric assessment strategy (interviews with caregivers or self-report), were examined by running a set of univariate control analyses on subsets of subjects (n = 369–1401) with available information (see Supplemental Methods).

RESULTS

Cognitive Function and Clinical Symptoms

Results from the principal component analysis and ICA decompositions of clinical item scores are shown in Figure 1A. As reported previously (24), the ICA yielded seven components primarily reflecting symptoms of attention-deficit/hyperactivity disorder (ADHD), various anxiety disorders (anxiety), norm-violating behavior/conduct problems (conduct), psychotic symptoms (psychosis), depression (depression), mania (mania), and obsessive-compulsive disorder (OCD). See Supplemental Table S2 for a list of all clinical items and Supplemental Figure S3 for item-specific numerical principal component analysis and ICA weights. Effects of age and sex on all cognitive and clinical summary scores are displayed in Figure 1B and Supplemental Table S3. In brief, general cognitive function showed the expected strong positive association with age, with slightly higher mean scores in male participants than in female participants. General psychopathology also increased over the sampled age span but did not differ between male and female participants. All clinical scores varied as a function of age. Specifically, ADHD scores decreased with increasing age, whereas various increasing trends were observed for all other clinical components. Largely in line with population-based estimates (8,58,59), male participants scored higher on components reflecting ADHD, conduct problems, psychosis, and mania, whereas female participants had higher scores on components reflecting various anxiety disorders and OCD. No significant sex differences were observed for depression. As shown in the lower triangle of Figure 1C and Supplemental Table S4, age-adjusted and sex-adjusted subject weights on clinical independent components were only weakly correlated with each other ($r < .1$) but showed moderate positive correlations with general psychopathology (r ranging from .22 to .54). General cognitive function showed weak negative correlations with general psychopathology, ADHD, anxiety, conduct, and psychosis (r ranging from $-.1$ to $-.23$).

MRI-Based Morphometry

Data-driven decomposition of cerebellar gray matter maps using a model order of 10 yielded a set of symmetric bilateral components (Figure 2A), which tended to fuse using lower model orders and to split into unilateral components using higher model orders (see Supplemental Figures S4–S6 for

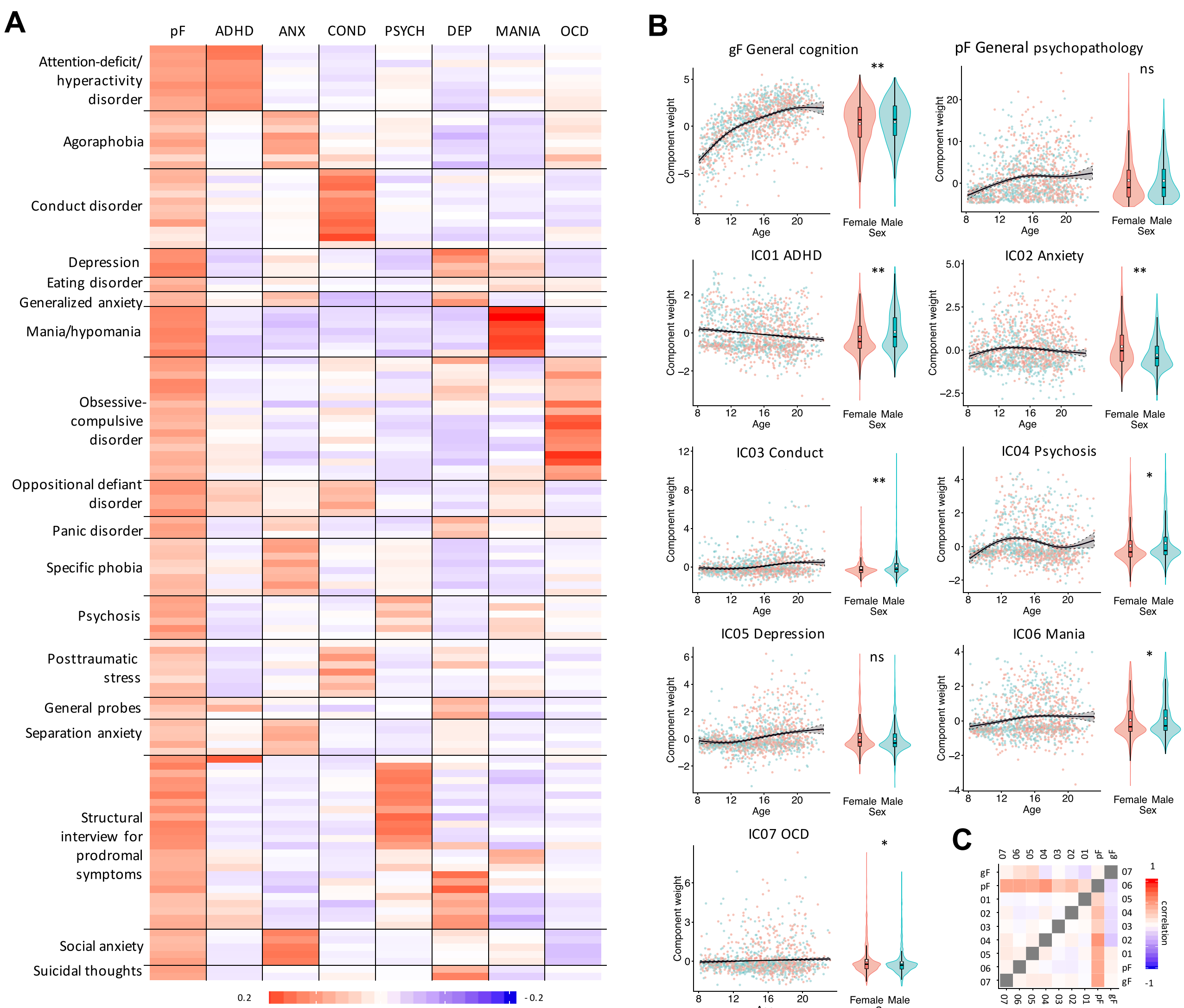

Figure 1. Behavioral indices. **(A)** Loadings of 129 clinical items from 18 questionnaires on the general psychopathology factor (pF) and the seven clinical independent components (ICs), primarily reflecting symptoms of attention-deficit/hyperactivity disorder (ADHD), anxiety (ANX), norm-violating behavior/ conduct disorder (COND), psychosis (PSYCH), depression (DEP), mania (MANIA), and obsessive-compulsive disorder (OCD). Clinical conditions targeted by each questionnaire are listed on the y-axis. Supplemental Table S2 lists all 129 individual items, and Supplemental Figure S3 shows numeric principal component analysis and independent component analysis weights for each item. **(B)** Effects of age and sex on cognitive and clinical scores (asterisks denote significant sex differences: *$p < .05$, **$p < .001$). **(C)** Correlations between all cognitive and clinical scores before (upper triangle) and after (lower triangle) correcting for effects of age and sex. gF, general cognitive function factor.

results using model orders of 5, 15, and 20). We consequently chose the 10-component decomposition for all further analyses. Of note, the Neurosynth analyses revealed that voxels at the peak coordinates of each cerebellar component (marked with an asterisk in Figure 2A) showed distinct patterns of whole-brain functional connectivity (Figure 2B, C), which were associated with different functional terms in the neuroimaging literature (Figure 2D). In brief, the connectivity maps of four independent components (IC02, IC05, IC06, and IC09) were most closely associated with motor control, whereas the remaining connectivity networks showed stronger associations with various cognitive functions. See Supplemental Figures S7–S10 and Supplemental Tables S5–S8 for estimated effects of age, sex, and eTIV on all anatomical features.

Structure-Function Associations

Results from the main structure-function analyses are presented in Figure 3. As hypothesized, cerebellar morphological features predicted both general cognitive function (mean correlation between observed and predicted scores: $r = .20$; Bonferroni-corrected $p < .001$) and general psychopathology ($r = .12$, $p < .001$). When using cerebellar features to predict clinical components, we observed significant results for conduct

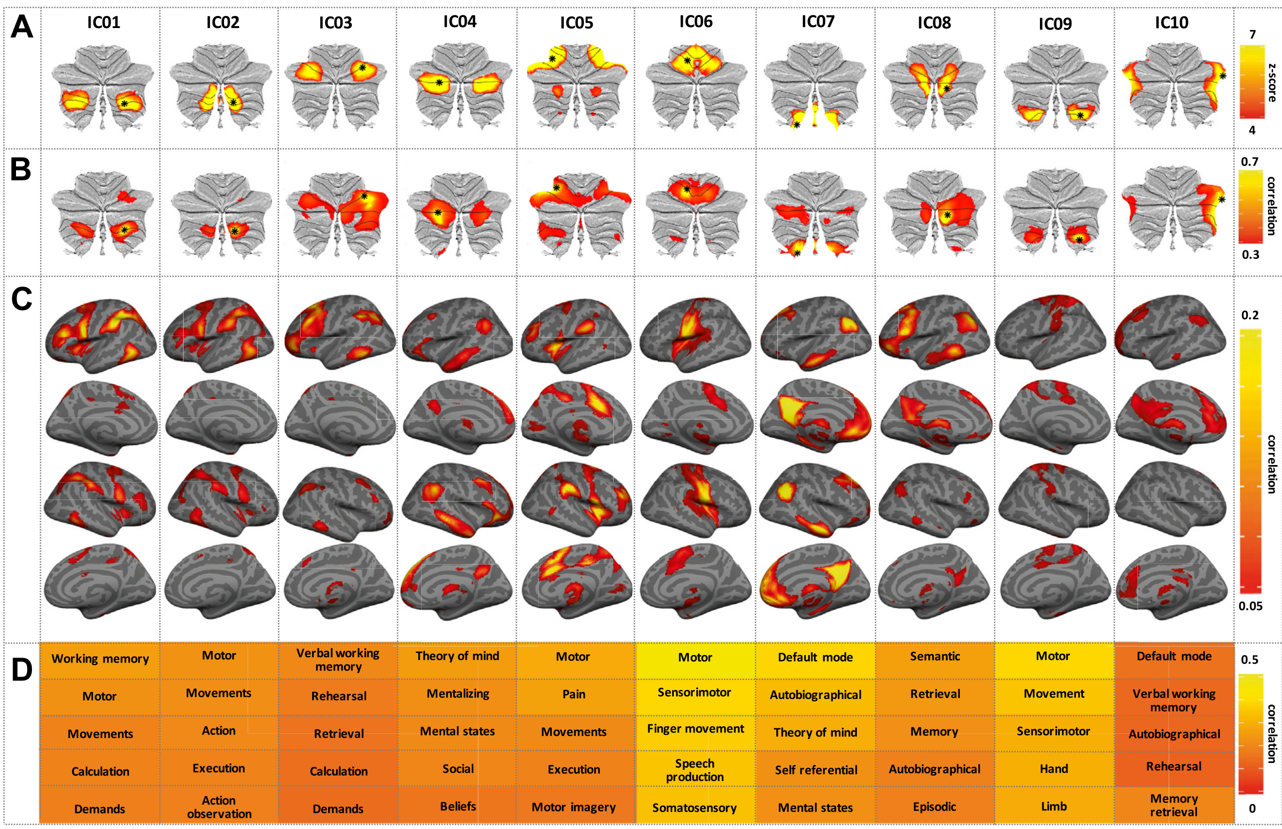

Figure 2. Cerebellar anatomical indices. **(A)** The 10 independent components (ICs) resulting from data-driven decomposition of cerebellar gray matter maps projected onto flat maps of the cerebellar cortex (43). Asterisks denote the peak voxel for each component. **(B, C)** Cerebellar and cerebrocortical functional connectivity maps [determined using NeuroSynth (46,48)] for each of the peak voxels shown in panel **(A)**. **(D)** Top five functional terms associated with each of the full-brain cerebellar connectivity maps shown in panels **(B, C)**.

(r = .16; Bonferroni-corrected p < .001), psychosis (r = .12; Bonferroni-corrected p < .001), and anxiety (r = .09; Bonferroni-corrected p = .012), but not for ADHD (r = .01; uncorrected p = .242), depression (r = −.02; uncorrected p = .350), mania (r = .03; uncorrected p = .373), or OCD (r = −.01; uncorrected p = .078). The relative feature importance (i.e., CAR score) for each cerebellar component used in the five significant prediction models is presented in Figure 3B. Briefly, IC03 contributed most strongly to the prediction of cognitive function, general psychopathology, and psychotic symptoms, whereas IC01 was the most important feature when predicting conduct problems.

This pattern was confirmed in the univariate analyses (Figure 3C). Specifically, general cognitive function was positively correlated with subject weights on IC01, IC03, and IC05, whereas overall psychopathology was negatively correlated with subject weights on IC03. Of the seven clinical independent components, conduct was negatively correlated with cerebellar IC01 and IC09, whereas psychosis was negatively correlated with cerebellar IC03. No other associations survived correction for multiple comparisons. Prediction models and univariate analyses using cerebellar lobular volumes yielded very similar results (Supplemental Figure S12).

Results from the voxel-based analyses are given in Figure 3D and Supplemental Table S9. In line with the main findings, we observed anatomically widespread positive associations with general cognitive function, whereas general psychopathology scores were associated with a more restricted pattern of cerebellar gray matter volume reduction, encompassing bilateral lobule VI and crus I. Psychotic symptoms were associated with a largely overlapping pattern, whereas conduct problems were associated with a partially overlapping region in left crus I as well as additional clusters in more inferior and midline regions. Anxiety was negatively associated with a small cluster in left lobule VI (11 voxels, not shown). No other clinical component yielded significant voxelwise results.

Prediction Models Using Cerebral Anatomical Features

Figure 4A–C presents the performance of prediction models using volumetric estimates of eight bilateral subcortical structures, cortical thickness estimates from 34 bilateral cerebral ROIs, and scaled versions of all anatomical measures (see Supplemental Figures S13 and S14 for CAR scores). In brief, the subcortical model performed worse than the cerebellar model, with a notable exception for OCD (r = .08; p = .042), where pallidum volume emerged as the most important feature. The cortical thickness model performed better than the cerebellar

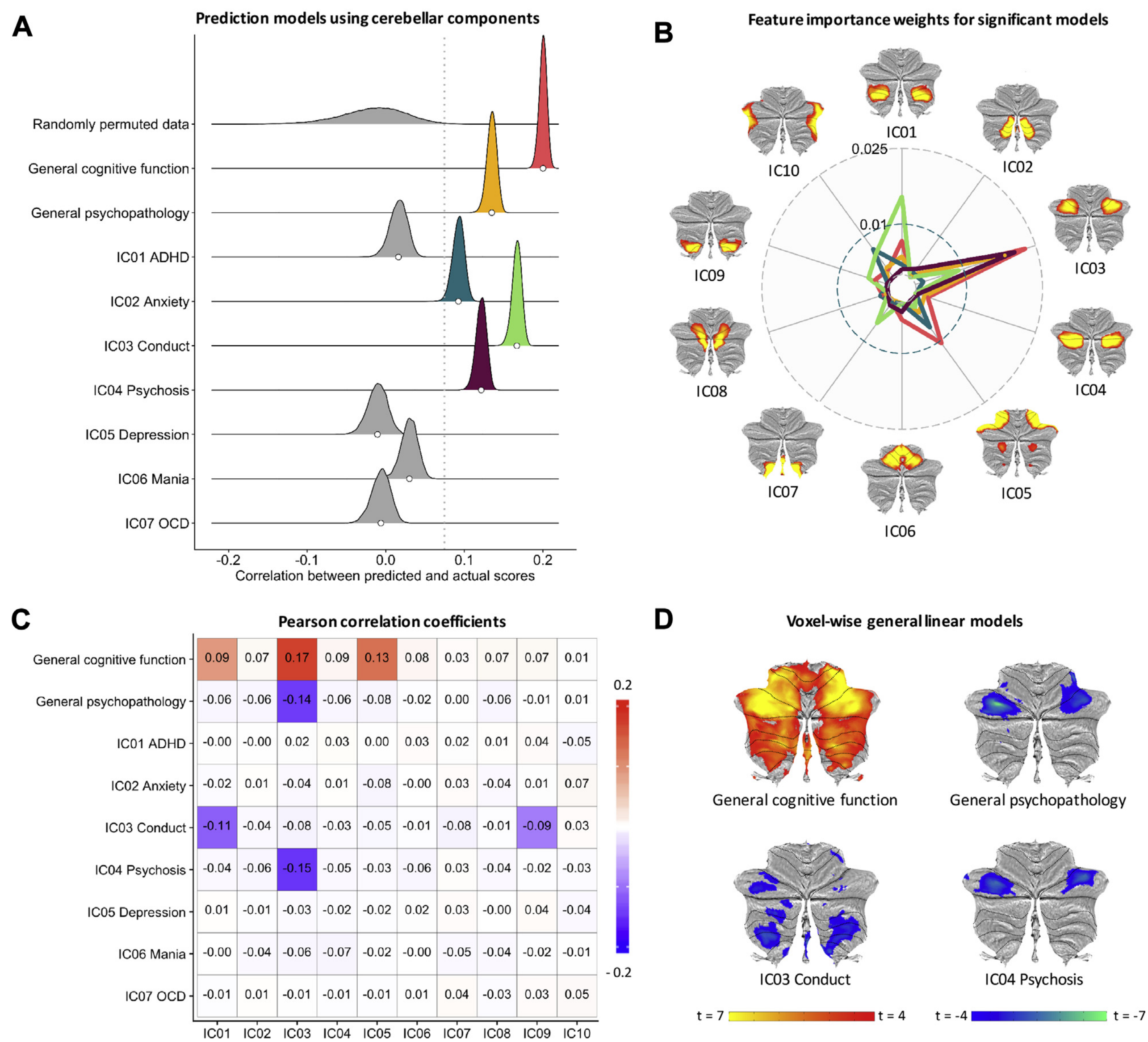

Figure 3. Cerebellar structure-function associations. **(A)** Distributions of correlations between predicted and actual cognitive and clinical scores across 10,000 iterations of the 10-fold cross-validated model. White dots denote the mean, used as point estimates for comparison with each model's empirical null distribution (computed by fitting the predictive models to randomly permuted cognitive and clinical data, across 10,000 iterations). For illustrative purposes, we plot the empirical null distribution summed across all prediction models. The dotted gray line represents the one-tailed .05 threshold, Bonferroni adjusted for nine tests. **(B)** Feature importance weights (correlation-adjusted [marginal] co-relation scores) for the five significant models [color code as in panel **(A)**]. **(C)** Univariate correlations between cerebellar independent components (ICs) and cognitive and clinical scores. Colored tiles mark significant associations (corrected for multiple comparisons across the matrix). **(D)** *T* statistics from the voxelwise general linear models, thresholded at $p < .05$, two-tailed (based on 10,000 permutations). ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder.

model for general cognitive function (r = .26; $p < .001$) and yielded comparable results for anxiety (r = .09; p = .023) but performed worse than the cerebellar model in predicting general psychopathology, conduct and psychosis (all $r < .08$; all $p \geq .072$). Models using all anatomical features significantly predicted general cognitive function (r = .29; $p < .001$), general psychopathology (r = .13; $p < .001$), anxiety (r = .10; p = .015), conduct (r = .14; $p < .001$), and psychosis (r = .10; p = .016). Univariate analyses yielded similar results (Supplemental Figures S15 and S16).

Figure 5 shows the feature importance weights for significant models using all anatomical features. Of note, cerebellar features emerged as the most important in several of these models, especially general psychopathology, conduct, and psychosis.

Control Analyses

See Supplemental Results and Supplemental Figure S17 for detailed results. In brief, the negative correlation between

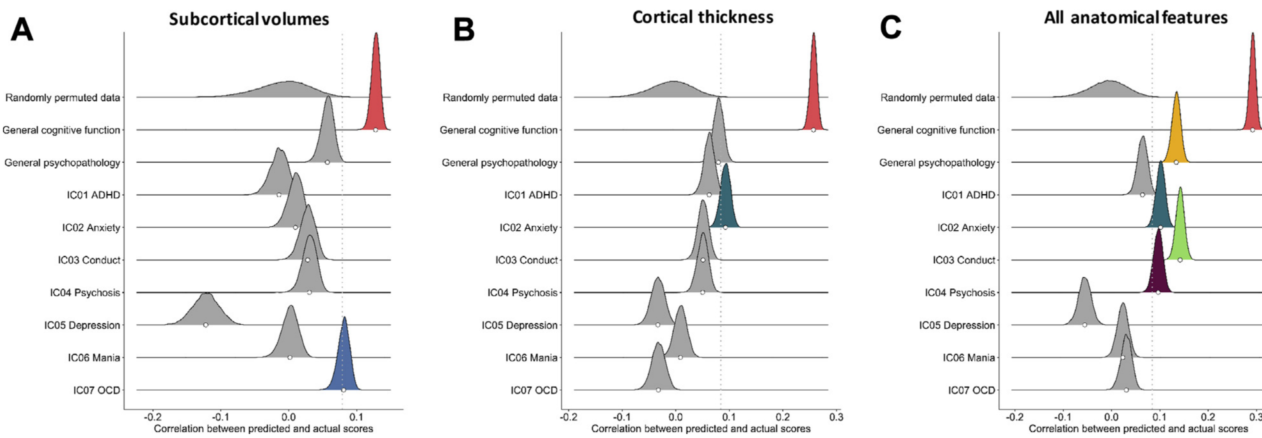

Figure 4. Predictive performance of cerebral models. Predictive performance of machine-learning models using **(A)** subcortical volumes, **(B)** mean thickness for 34 bilateral cerebrocortical regions of interest, and **(C)** *Z*-normalized versions of all anatomical features. ADHD, attention-deficit/hyperactivity disorder; IC, independent component; OCD, obsessive-compulsive disorder.

cerebellar IC03 and psychotic symptoms remained significant when controlling for general cognitive function, general psychopathology, MRI data quality, and parental education level as well as in the subsets of participants with no evidence of substance abuse or assessed using only collateral information from caregivers (all corrected p values $< .05$). The negative correlation between cerebellar IC01 and conduct problems was no longer significant when controlling for parental education level or substance abuse.

DISCUSSION

The current machine-learning approach using 10-fold internal cross-validation in a large developmental MRI sample yielded three main findings. First, cerebellar morphological features could significantly predict both general cognitive function and general psychopathology in adolescence. Second, the analyses of independent component scores computed from clinical symptoms revealed a pattern of diagnostic specificity, in that significant results were observed for psychosis symptoms, rates of norm-violating behavior (i.e., conduct problems), and, to a lesser extent, anxiety, whereas symptoms of ADHD, depression, mania, and OCD were unrelated to cerebellar morphology. These patterns also showed anatomical specificity, with volume reductions in bilateral lobule VI and crus I most strongly related to psychosis symptoms, and volume reductions in more inferior cerebellar regions (lobules VIIb and VIII) most highly correlated with norm-violating behavior. Third, associations with psychotic symptoms and norm-violating behavior were stronger for the cerebellum than for subcortical volumes or regional cortical thickness. Together, these findings provide compelling evidence for an association between cerebellar structure and the early expression of core phenotypes of severe mental illness.

The associations with general cognitive function and general psychopathology were expected based on previous research in adults (26,31,32) and add to the growing database supporting a cerebellar role in cognition and affect (60). Of note, the voxelwise analyses (Figure 3D) revealed an anatomically widespread pattern for general cognitive function, whereas general psychopathology showed a more restricted pattern, largely overlapping with that seen for the psychosis domain. One possible explanation for this overlap is that psychosis symptoms lie at the very extreme end of a putative continuum going from more benign to more severe psychopathology (16,17). Thus, participants with high scores on the psychosis component would also be expected to express high symptom levels more generally. In line with this notion, Caspi *et al.* (17) observed a very high correlation (.997) between a thought disorder factor (reflecting symptoms associated with psychotic disorders) and their general psychopathology factor (reflecting overall psychopathology) calculated based on extensive structured interviews in a large longitudinal sample. Consistent with their results, across the seven clinical components, we also observed the highest correlation with general psychopathology for psychosis (IC04). Of note, measures of general psychopathology have recently been associated with a range of brain phenotypes (24,61,62), including white matter integrity and gray matter volume of the cerebellum (15).

The majority of existing structural MRI studies on psychosis have focused on cerebral structures (63), but our findings on psychotic symptoms are nonetheless in general agreement with an emerging body of research. For instance, we have recently shown that cerebellar volume reductions are one of the strongest and most consistent morphological alterations in a large multisite sample of patients with schizophrenia (N = 983) and healthy control subjects (N = 1349) (1). Of note, both in our previous patient study (1) and in the current study of premorbid symptoms, the strongest effects of the psychosis domain converged on cerebellar regions that show functional connectivity with the frontoparietal cerebral network, which has been strongly implicated in cognitive control processes (64). Indeed, previous functional MRI studies of working memory using the PNC sample found that activation of cerebellar crus I was associated with task performance (65) and that reduced activation in this region was associated with overall level of psychopathology (66). Structural alterations in this cerebellar region also emerged as one of the strongest predictors of transition to psychosis in a recent study of

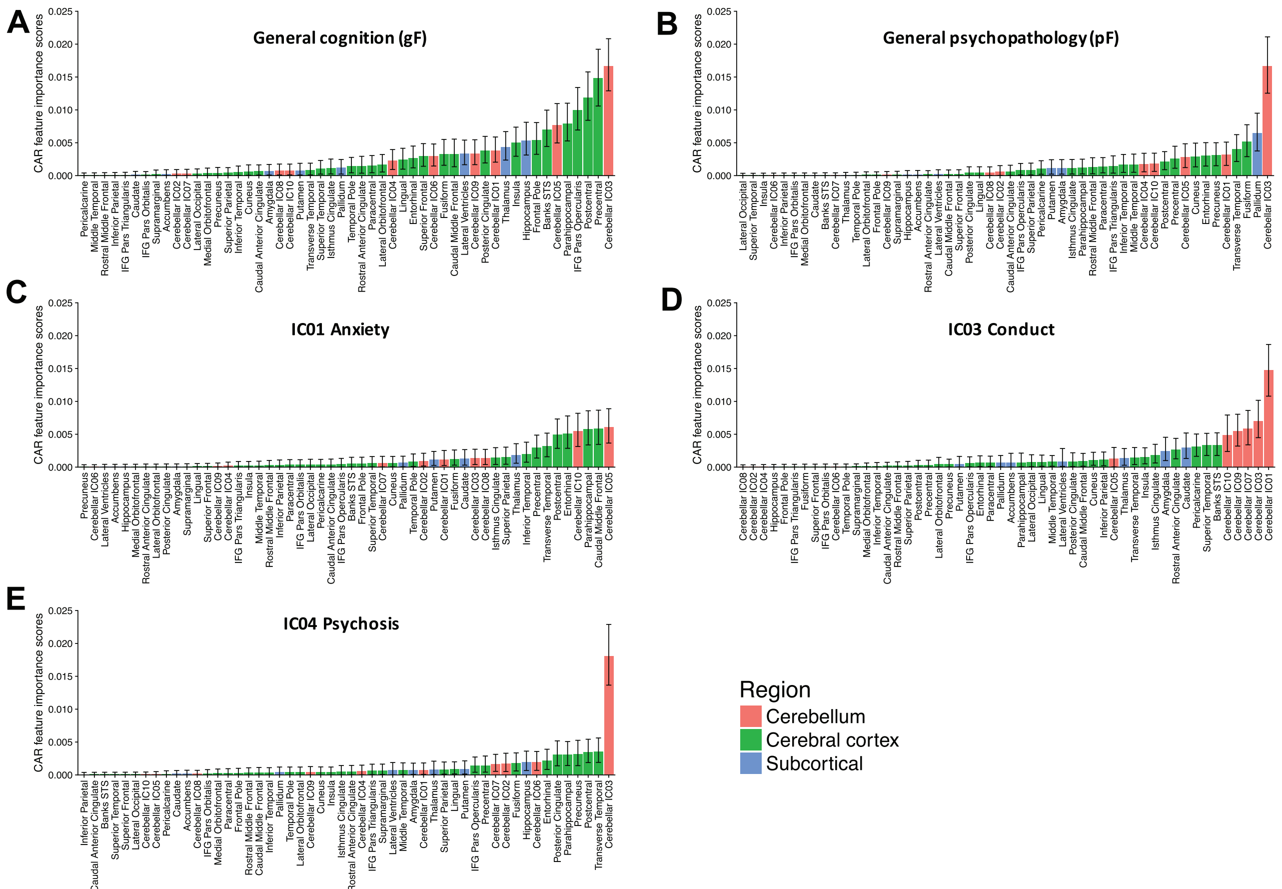

Figure 5. Relative feature importance across brain regions. Feature importance weights (correlation-adjusted [marginal] co-relation [CAR] scores) for the five significant prediction models using all anatomical features. **(A)** General cognition; **(B)** general psychopathology; **(C)** anxiety; **(D)** conduct; and **(E)** psychosis. CAR scores were computed for each of 10,000 iterations of the model on randomly 10-fold partitioned data, yielding 100,000 estimates for each model. Colors indicate the general anatomical classification of each feature, and error bars denote the 2.5th and 97.5th percentiles of these CAR score distributions. gF, general cognitive function factor; IC, independent component; IFG, inferior frontal gyrus; pF, general psychopathology factor, STS, superior temporal sulcus.

high-risk populations (67). Considered together, these findings provide converging evidence for cerebellar crus I as a key node involved in both high-level cognition and severe psychopathology. More broadly, functional neuroimaging studies consistently report reduced cerebellocerebral connectivity in patients with schizophrenia (68,69) and high-risk groups (70,71), whereas behavioral studies find impaired cerebellar learning in both patients with schizophrenia (72–74) and their first-degree relatives (75).

Of note, our findings differ in some respects from a previous study of structural brain alterations in a partially overlapping sample of youths with psychosis spectrum symptoms (38), which reported the strongest group effects in medial temporal, posterior cingulate, and frontal regions. We highlight two possible sources of these discrepancies. First, only the current study employed analysis pipelines optimized for both the cerebellum (44) and the cerebrum (76). Second, whereas the previous study employed an extreme group design (38), we tested parametric associations across the full phenotypic range.

The associations between cerebellar volume and rates of norm-violating behavior are consistent with some recent reports of altered cerebellar white matter microstructure (77) and functional activation (78) in conduct disorder. However, as our control analyses suggested that these associations may be partially confounded by parental education level and substance abuse, they should be interpreted with caution.

While the current results do not allow inferences regarding the pathophysiological mechanisms underlying these changes in cerebellar morphology, we observe that genes associated with schizophrenia have been shown to be highly expressed in the human cerebellum (79), suggesting a direct or indirect genetic impact. Furthermore, cerebellar volume, similar to hippocampal volume (80), has been shown to be very sensitive to stress hormone exposure. Whereas this effect is especially strong during infancy (81), it has also been observed in adults with very high levels of circulating corticosteroids due to Cushing's disease (82). These latter observations may provide a possible link, to be tested in future research, between our findings and the well-documented role of stressful life events in the development of psychopathology (83).

Strikingly, associations with psychotic symptoms and norm-violating behavior were stronger for the cerebellum than for subcortical volumes or regional cortical thickness. As this pattern was not observed across all examined phenotypes (e.g., cortical thickness was the best predictor of general cognitive function, whereas subcortical volumes showed stronger associations with OCD symptoms), we believe these brain-wide comparisons reveal a crucial cerebellar involvement with respect to these specific symptom domains.

From a methodological point of view, it is worth mentioning that our data-driven cerebellar decomposition yielded components that only partially overlapped with standard anatomical parcellations. In particular, borders between several components were primarily organized along the medial-to-lateral dimension, and one component could span parts of several lobules. Together with results from recent functional MRI studies (84,85), these results suggest that traditional cerebellar subdivisions do not optimally capture either the intersubject structural variability or the functional heterogeneity of the cerebellum.

Notable strengths of the current study include the use of a large sample and internal cross-validation methods, which should reduce the risk of overfitting and thus ensure more generalizable effect estimates (25). Its main limitation is the cross-sectional design, which prevents direct tests of causal relationships. We observe, however, that results from previous studies using smaller longitudinal samples do suggest that cerebellar structure and function can predict later progression of psychotic symptoms (71) or conversion to frank psychosis (67). A second limitation is that only a subset of participants had information on parental education and substance abuse, resulting in a reduced sample size for some of the control analyses. Third, although a previous study has found that cerebellocerebral connectivity patterns are largely developed and similar to patterns seen in adults by middle childhood (86), the extent to which results from a young adult sample (46) can be generalized to the current adolescent sample remains unknown. Finally, although the reported structure-function associations were robust and highly significant, cerebellar morphology explained only a limited part of the variance in clinical scores. Although not surprising, given the multiple factors that influence the expression of psychiatric symptoms (83,87,88), this caveat must be kept in mind when interpreting the results.

In conclusion, our findings highlight the cerebellum as a key brain structure for understanding the development of mental disorders, in particular, psychosis.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the European Commission Seventh Framework Programme (Grant No. 602450 to IMAGEMEND), Research Council of Norway (Grant Nos. 213837, 223273, 229129, 204966/F20, 249795, and 251134), South-Eastern Norway Regional Health Authority (Grant Nos. 2013-123, 2014-097, 2015-073, 2016-083, and 2017112), and K.G. Jebsen Foundation. The Philadelphia Neurodevelopment Cohort sample is a publicly available data set. Support for the collection of the data sets was provided by the National Institute of Mental Health (Grant No. RC2MH089983 to Raquel Gur, M.D., Ph.D., and Grant No. RC2MH089924 to Hakon Hakonarson, M.D., Ph.D.). All participants were recruited through the Center for Applied Genomics at Children's Hospital of Philadelphia.

This article was published as a preprint on bioRxiv (doi: https://doi.org/10.1101/288134).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Sep 19, 2018; revised and accepted Jan 18, 2019.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2019.01.019.

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