Cerebellar grey matter volume in adolescence is associated with prodromal psychotic symptoms and norm-violating behavior

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Key points:

Questions: Is cerebellar morphology associated with sub-clinical psychiatric symptoms in adolescence? Do such associations show symptom domain specificity or do they rather constitute a marker of general psychopathology?

Findings: Machine learning utilizing cerebellar morphology features significantly predicted the severity of prodromal psychotic symptoms, norm-violating behavior and anxiety, but not attention deficits, depressive, manic or obsessive-compulsive sub-clinical symptoms. Associations with prodromal psychotic symptoms were stronger for the cerebellum than for cerebral subcortical and cerebro-cortical regions, and remained significant when adjusting for several potentially confounding factors.

Meaning: The cerebellum appears to play a key role in the development of severe mental illness.

Abstract:

Importance: 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 cerebellar involvement in the developmental stages of these disorders. In particular, whether cerebellar morphology is associated with early expression of specific symptom domains remains unclear.

Objective: To determine the robustness and specificity of associations between cerebellar morphology, general cognitive function, general psychopathology and sub-clinical psychiatric symptom domains in adolescence.

Design, setting and participants: Assessment of parametric structure-function associations between MR-based brain morphometric features and data-driven cognitive and clinical phenotypes in the Philadelphia Neurodevelopmental Cohort (N=1401, age-range: 8 - 23).

Main outcomes and measures: Robust prediction of cognitive and clinical symptom domain scores from cerebellar, subcortical and cerebro-cortical brain features using machine learning with 10-fold internal cross-validation and permutation-based statistical inference.

Results: Cerebellar morphology predicted both general cognitive function and general psychopathology (mean Pearson correlation coefficients between predicted and observed values: r = .20 and r = .13, respectively; corrected p-values < .0009). Analyses of specific sub-clinical symptom domains revealed significant associations with rates of norm-violating behavior (r = .17; p < .0009), prodromal psychotic symptoms (r = .12; p < .0009) and anxiety symptoms (r = .09; p =.0117). In contrast, we observed no significant associations between cerebellar features and the severity of attention deficits, depressive, manic or obsessive-compulsive symptoms (all rs =< .03, all ps => .1). Associations with norm-violating behavior and prodromal psychotic symptoms were stronger for the cerebellum than for subcortical and cerebro-cortical regions, while anxiety and general cognitive function were related to more global brain morphology patterns. The association between cerebellar volume and prodromal psychotic symptoms, and to a lesser extent norm violating behavior, remained significant when adjusting for potentially confounding factors such as general cognitive function, general psychopathology, parental education level and use of psychoactive substances.

Conclusions and relevance: The robust associations with sub-clinical 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.

Introduction

A growing body of research reports cerebellar involvement across a wide range of mental disorders, including schizophrenia[1,2], bipolar disorder[3], depression[4-7], anxiety disorders[8], attention-deficit hyperactivity disorder[9,10] and autism[11]. However, while the majority of these conditions are conceptualized as neurodevelopmental disorders[12,13], most studies investigating the role of the cerebellum in mental health research have targeted adult populations[14-16]. Hence, it is largely unknown whether cerebellar changes can be detected already in adolescence, when initial symptoms typically first present[13,17,18], or only emerge later in the disease process. Moreover, whether cerebellar alterations in adolescence are indicative of general psychopathology[19], or are associated with specific symptom domains[9], 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.

Here, we used machine learning with 10-fold internal cross-validation to test whether cerebellar morphometric features could predict sub-clinical psychiatric symptoms in a large and well-characterized developmental community sample centered on adolescence[20,21]. Consistent with NIMHs Research Domain Criteria framework[22], we followed a diagnostically agnostic and dimensional approach[23,24], extracting clusters of correlated symptoms from a comprehensive set of clinical assessment data using blind source separation methods[25]. A similar data-driven and anatomically agnostic approach was used to decompose cerebellar grey matter maps into spatially independent components, before testing for structure-function associations using multivariate machine learning. To confirm convergence across methodological approaches, we also tested for structure-function associations at the resolution levels of cerebellar lobules and voxels. We further evaluated the specificity of any cerebellar effects by comparing these to effects across brain-wide regions-of-interest (ROIs), and controlled for potentially confounding variables such as general level of cognitive function[26,27], general psychopathology[19], parental education level[28] and use of psychoactive substances[29].

Based on the existing literature on adults, we hypothesized that cerebellar morphology during adolescence would be associated with both cognitive function[26,30,31] and general psychopathology[19], but remained agnostic as to whether such associations would show specificity across different psychiatric symptom domains.

Methods

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 to 23.2) included in the publicly available Philadelphia Neurodevelopmental Cohort (PNC)[20,21](see Supplementary 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[25], we included performance scores from the full PNC sample (n=6,487) on 12 computerized cognitive tests[21] and 129 questionnaire items assessing symptoms of anxiety, mood, behavioral, eating and psychosis spectrum disorders, with collateral informants for individuals below 18 years of age[21]. We derived general measures of cognitive performance (gF) and psychopathology (pF) by extracting the first factor scores from principal component analyses (PCA) of all cognitive and clinical scores, respectively. Next, in order to examine specific symptom domains, all clinical item scores were submitted to independent component analysis (ICA) using ICASSO[32], decomposing them into seven independent components. Effects of gender and age on all cognitive/clinical measures were tested using generalized additive models (GAMs) as implemented in the r-package "mgcv"[33], and a set of adjusted cognitive/clinical scores were computed by regressing out main effects of age and sex (see Supplementary Methods).

Collection and processing of MRI data:

As previously described[20,34,35], all data were acquired on the same 3 Tesla scanner using the same MRI sequence (See Supplementary Methods). All images were first processed using FreeSurfer version v5.3 (http://surfer.nmr.mgh.harvard.edu), yielding estimates of total intracranial volume (eTIV)[36], volumes of eight subcortical structures[37] and mean cortical thickness of 34 cortical regions-of-interest (ROIs) per hemisphere[38]. Next, the bias-corrected images from the FreeSurfer pipeline were subjected to cerebellum-optimized voxel-based morphometry (VBM) using the SUIT-toolbox (v3.2[39,40]), running on MATLAB 2014a. In brief, SUIT isolates the cerebellum and brainstem, segments images into grey and white matter maps and normalizes these maps to a cerebellar template using Dartel[41], ensuring superior cerebellar alignment compared with whole-brain procedures[40].

Normalized cerebellar grey matter maps were modulated by the Jacobian of the transformation matrix to preserve absolute grey matter volume, and the volumes of 28 cerebellar lobules were extracted using the SUIT probabilistic atlas. Next, maps were smoothed using a 4 mm FWHM Gaussian kernel before being subjected to ICA or voxel-wise general linear models. Finally, a mask for these analyses was constructed by thresholding the mean unmodulated cerebellar grey matter map at .01 and multiplying it with the SUIT grey matter template (also thresholded at .01).

Data-driven parcellation of cerebellar grey matter

Since cerebellar parcellations based on gross anatomical features (e.g., lobules) only partially overlap with functional maps of the cerebellum[42-50], we used a data-driven approach in our primary analyses. Specifically, we subjected the modulated cerebellar grey matter maps to ICA using FSL MELODIC[51], testing model orders from 5 to 20.

In order to characterize the resulting cerebellar VBM-components, we used NeuroSynth[52] to map the full-brain functional connectivity of each components 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[52] database, reporting the top five functional terms (see Supplementary Methods).

Analysis of brain-behavior associations

Before inclusion in statistical models, all volumetric features were adjusted for effects of age, sex and eTIV, using GAMs to sensitively model and adjust for potentially non-linear effects of age[53-55] and eTIV[56,57] (see Supplementary 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[58] (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/clinical scores (taking the mean across iterations as our point estimate). Statistical significance was determined by comparing these point estimates to empirical null distributions of correlation coefficients under the null hypothesis (computed by running the models 10,000 times on randomly permuted clinical/cognitive scores). Results were considered significant at $p < .05$ (one-tailed), Bonferroni-adjusted for the 9 tested associations. In order to determine the relative importance of the anatomical

features included in each prediction model, we computed correlation-adjusted marginal correlation (CAR) scores[59] for each iteration, and used the mean CAR scores as measures of relative feature importance.

To complement these multivariate prediction models, we performed a set of univariate analyses, correlating the (age- and sex-adjusted) subject weights on each cognitive/clinical component with the (eTIV- age- and sex-adjusted) anatomical subject weights (see Supplementary Methods).

In order to facilitate comparison with previously published research, we also report results from prediction models and correlation analyses using 28 cerebellar lobules as features and general linear models performed at the voxel level. The voxel-wise analyses tested for effects of cognitive/clinical scores while controlling for effects of sex, age, and eTIV using FSLs randomise[60] with 10,000 permutations per contrast.

Next, to allow for a direct 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 ROI based the Desikan-Killany atlas in FreeSurfer. We chose thickness as our cortical feature of interest, due to its generally stronger and more consistent associations with psychopathology than surface area[61,62]. All anatomical indices were adjusted for effects of age and sex (and eTIV for volumetric indices), as described above. Prediction models were also fitted using z-normalized versions of all morphometric features, in order to directly compare the relative feature importance of all anatomical measures.

Finally, on subjects with available information, we ran a set of univariate control analyses examining potentially confounding variables, such as general cognitive function, general psychopathology, parental education and use of psychoactive substances (see Supplementary Methods).

Results

Cognitive function and clinical symptoms

Results from the PCA and ICA decompositions of clinical item scores are shown in Figure 1a. As reported previously[25], the ICA yielded seven components, primarily reflecting symptoms of attention deficit hyperactivity disorder (IC01 ADHD), various anxiety disorders (IC02 Anxiety), norm violating behavior/conduct problems (IC03 Conduct), prodromal psychotic symptoms (IC04 Psychosis), depression (IC05 Depression), mania (IC06 Mania) and obsessive-compulsive disorder (IC07 OCD).

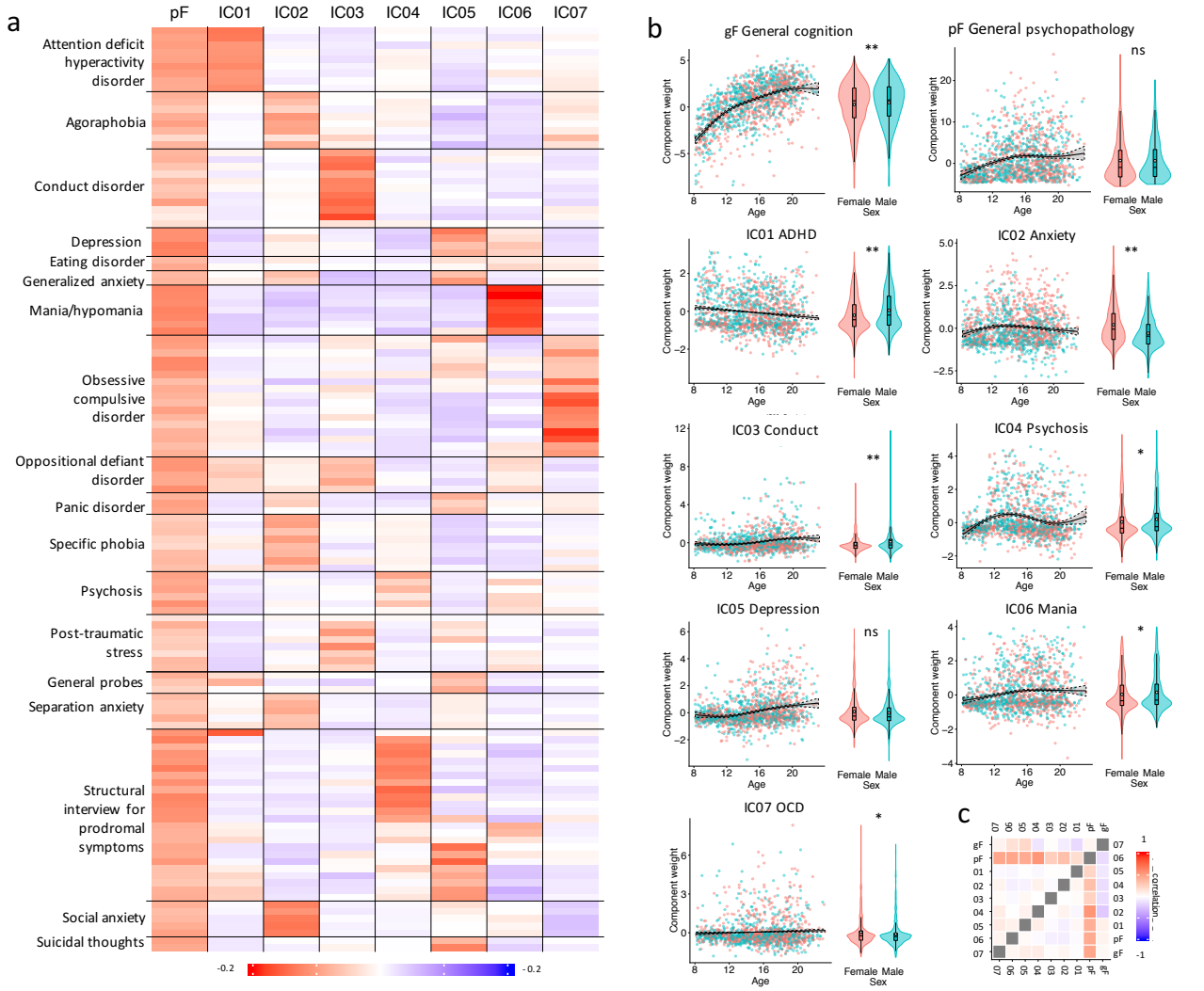

Figure 1: a: Loadings of 129 clinical items from 18 questionnaires on the general psychopathology factor (pF) and the seven clinical independent components (IC01-IC07). Clinical conditions targeted by each questionnaire are listed on the y-axis, while Supplementary Table 2 lists all 129 individual items; **b:** Effects of age and sex on cognitive/clinical scores (asterisks denote significant sex differences; * < .05, *** <.001); **c:** correlations between all cognitive/clinical scores before (upper triangle) and after (lower triangle) correcting for effects of age and sex.

Effects of age and sex on all cognitive and clinical summary scores are displayed in Figure 1b and Supplementary Results. In brief, general cognitive function (gF) showed the expected strong positive association with age, with slightly higher mean scores in males than in females. Mean levels of general psychopathology also increased over the sampled age span, but did not differ between males and females. 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[13,63,64], males scored higher on components reflecting ADHD, conduct problems, psychosis and mania, while females had higher scores on components reflecting various anxiety disorders and OCD. No significant sex differences were observed for the component reflecting depression.

MRI-based morphometry

Data-driven decomposition of cerebellar grey matter maps using a model order of 10 yielded a set of bilateral components (Figure 2a), which tended to split into unilateral components at higher model orders (see Supplementary Figures 1-3 for results using model orders of 5, 15 and 20). We consequently chose this 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 Fig.2a) showed distinct patterns of whole-brain functional connectivity (Fig 3b-c), which were associated with different functional terms in the neuroimaging literature (Fig 2d). In brief, the connectivity maps of four components (IC02, IC05, IC06 and IC09) were most closely associated with motor control, while the remaining connectivity networks showed stronger associations with various cognitive functions. See Supplementary Figures and Tables 4-7 for estimated effects of age, sex and eTIV for all cerebellar and cerebral anatomical features.

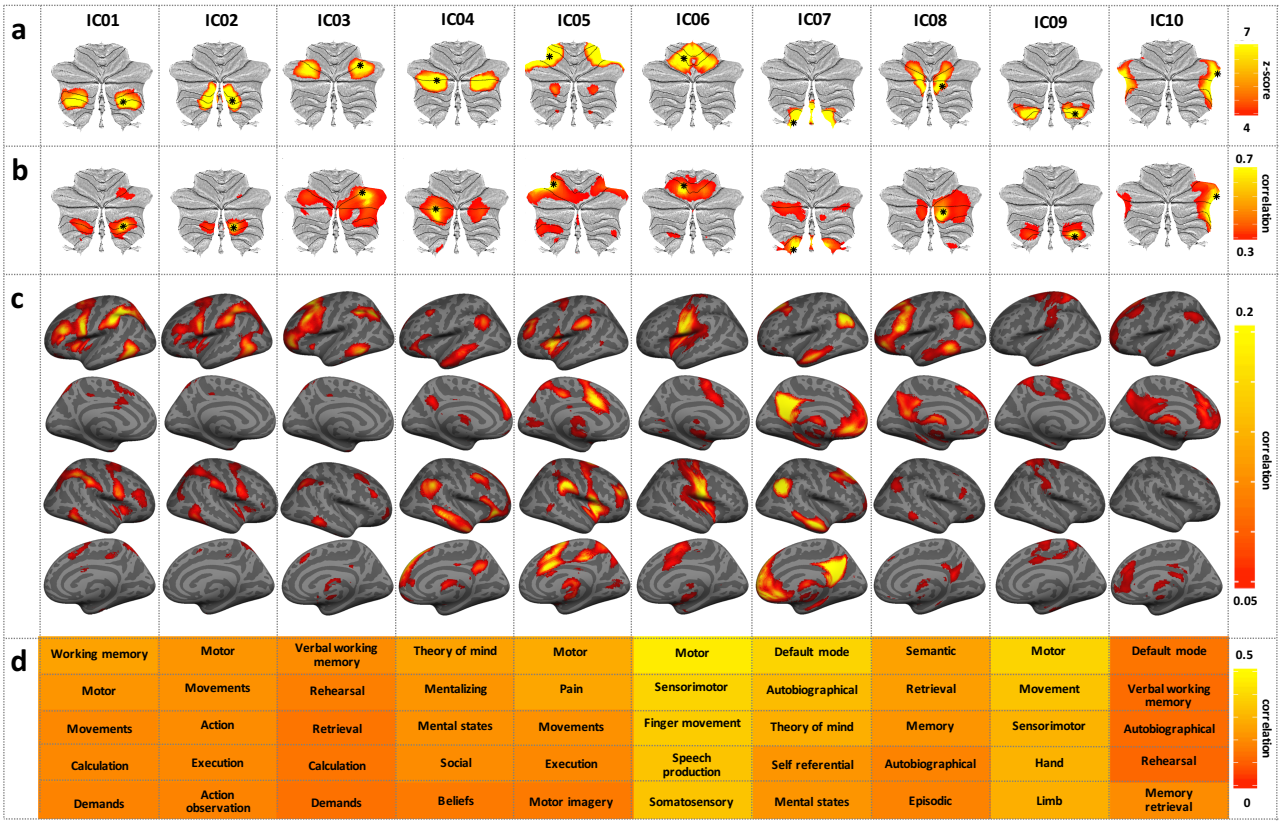

Figure 2: a: The ten independent components resulting from data-driven decomposition of cerebellar grey matter maps projected onto flat-maps of the cerebellar cortex[92]. Asterisks denote the peak voxel for each component. **b-c:** Cerebellar and cerebro-cortical functional connectivity maps (determined using NeuroSynth[44,93]) for each of the peak voxels shown in **a**. **d:** Top 5 functional terms associated with each of the full-brain cerebellar connectivity maps shown in **b** and **c**.

Structure-function associations

Results from the main structure-function analyses are presented in Figure 3.

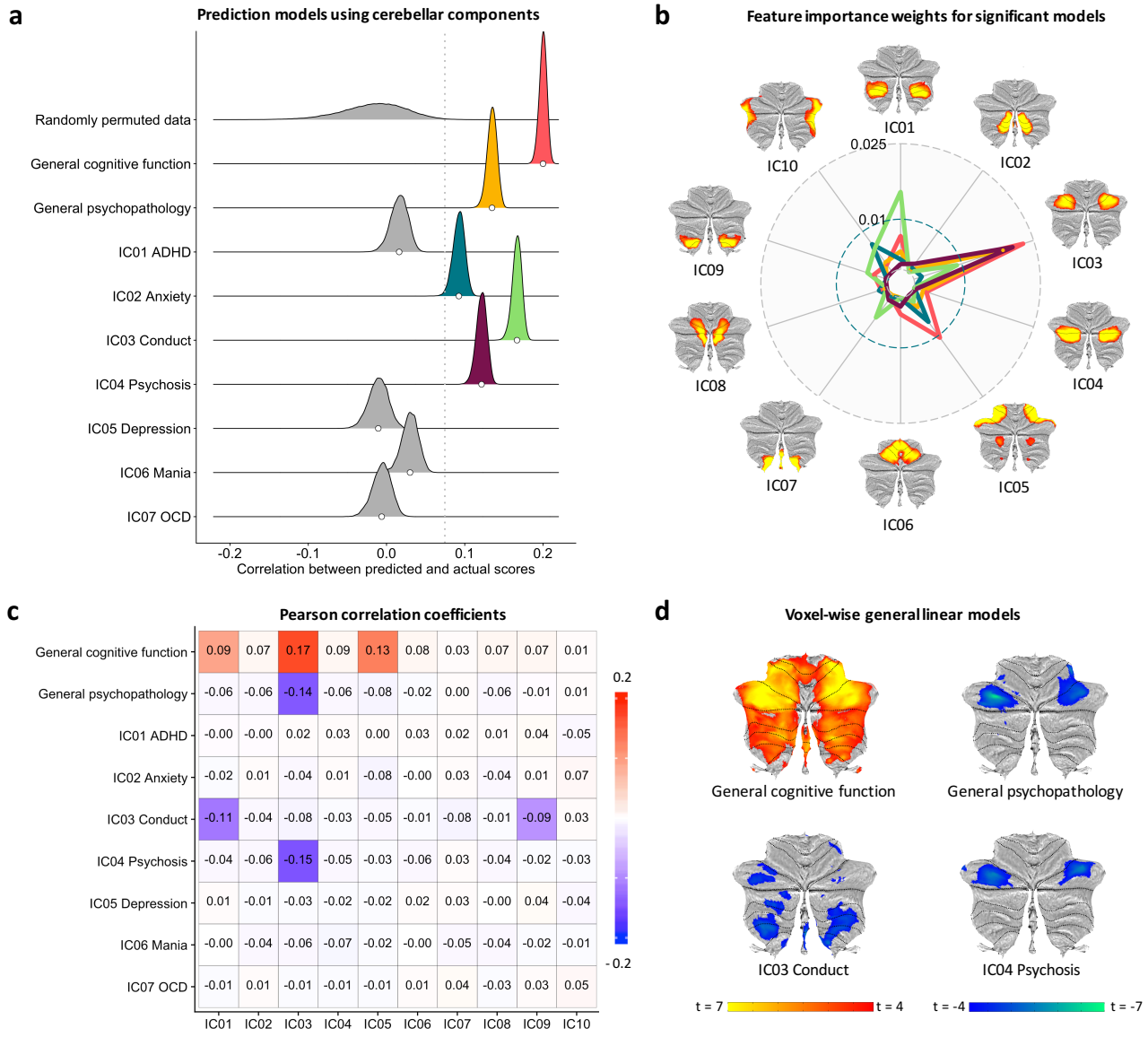

Figure 3: a: Distributions of correlations between predicted and actual cognitive/clinical scores across 10,000 iterations of the 10-fold cross-validated model. White dots denote the mean, used as point estimates for comparison with each model's empirical null distribution (computed by fitting the predictive models to randomly permuted cognitive/clinical data, across 10,000 iterations). For illustrative purposes we here plot the empirical null-distribution summed across all prediction models. The dotted grey line represents the one-tailed .05 threshold, Bonferroni-adjusted for 9 tests. **b:** Feature importance weights (CAR-scores) for the five significant models (color code as in a); **c:** Univariate correlations between cerebellar ICs and cognitive/clinical scores. Colored tiles mark significant associations (corrected for multiple comparisons across the matrix); **d:** T-statistics from the voxel-wise general linear models, thresholded at $p < .05$, two-tailed (based on 10.000 permutations).

As hypothesized, cerebellar morphological features predicted both general cognitive function (mean correlation between observed and predicted scores: $r = .20$; $p < .0009$) and general psychopathology ($r = .12$, $p < .0009$). When using cerebellar features to predict

clinical components, we observed significant results for IC03 Conduct (r = .16; p < .0009), IC04 Psychosis (r = .12; p < .0009) and IC02 Anxiety (r = .09; p = 0.0117), but not for IC01 ADHD (r = .01; ns), IC05 Depression (r = -.02; ns), IC06 Mania (r = .03; ns) or IC07 OCD (r = -.01; ns). 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 (gF), general psychopathology (pF) and prodromal 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 (gF) was positively correlated with subject weights on IC01, IC03, and IC05, while overall psychopathology (pF) was negatively correlated with subject weights on IC03. Of the seven clinical ICs, IC03 Conduct was negatively correlated with cerebellar IC01 and IC09, while IC04 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 (Supplementary Figure 8).

Results from the voxel-based analyses are given in Figure 3d and Supplementary Table 8. In line with the main findings, we observed anatomically widespread positive associations with general cognitive function, while general psychopathology scores were associated with a more restricted pattern of cerebellar grey matter volume reduction, encompassing bilateral lobule VI and Crus I. Prodromal psychotic symptoms were associated with a largely overlapping pattern, while 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 voxel-wise results.

Prediction models using cerebral anatomical features

Figures 4 a-c present the performance of prediction models using volumetric estimates of 8 bilateral subcortical structures, cortical thickness estimates from 34 bilateral cerebral ROIs and scaled versions of all anatomical measures, respectively (see Supplementary Figures 9-10 for CAR-scores). In brief, the subcortical model performed worse than the cerebellar model, with a notable exception for IC07 OCD (r = .08; p = .0423), where pallidum volume emerged as the most predictive feature. The cortical thickness model performed better than the cerebellar model for general cognitive function (r = .26; p <

.0009) and yielded comparable results for IC02 Anxiety (r = .09; p = .0225), but performed worse than the cerebellar model in predicting general psychopathology, IC03 Conduct and IC04 Psychosis (all *r*s < .0.08; all *p*s => .072). Models using all anatomical features significantly predicted general cognitive function (gF: *r* = .29; *p* < .0009), general psychopathology (pF: *r* = .13; *p* < .0009), IC02 Anxiety (*r* =.10; *p* = .0153), IC03 Conduct (*r* =.14; *p* < .0009) and IC04 Psychosis (*r* =.10; *p* = .0162).

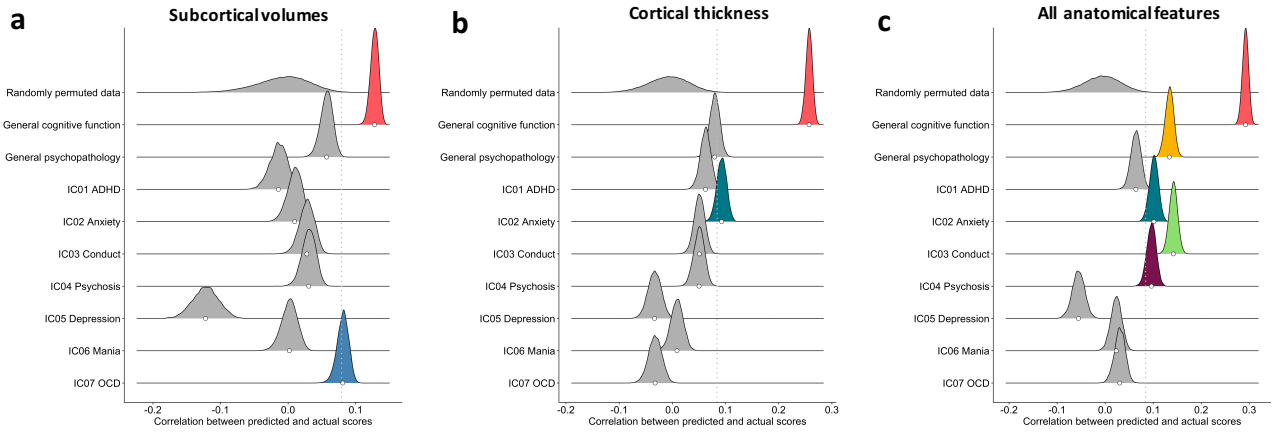

Figure 4: a: Predictive performance of machine learning models using **a:** Subcortical volumes; **b:** Mean thickness for 34 bilateral cerebrocortical ROIs; and **c:** Z-normalized versions of all anatomical features.

Figure 5 gives 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 (Fig 5 b-f), especially general psychopathology (pF), IC03 Conduct and IC04 Psychosis.

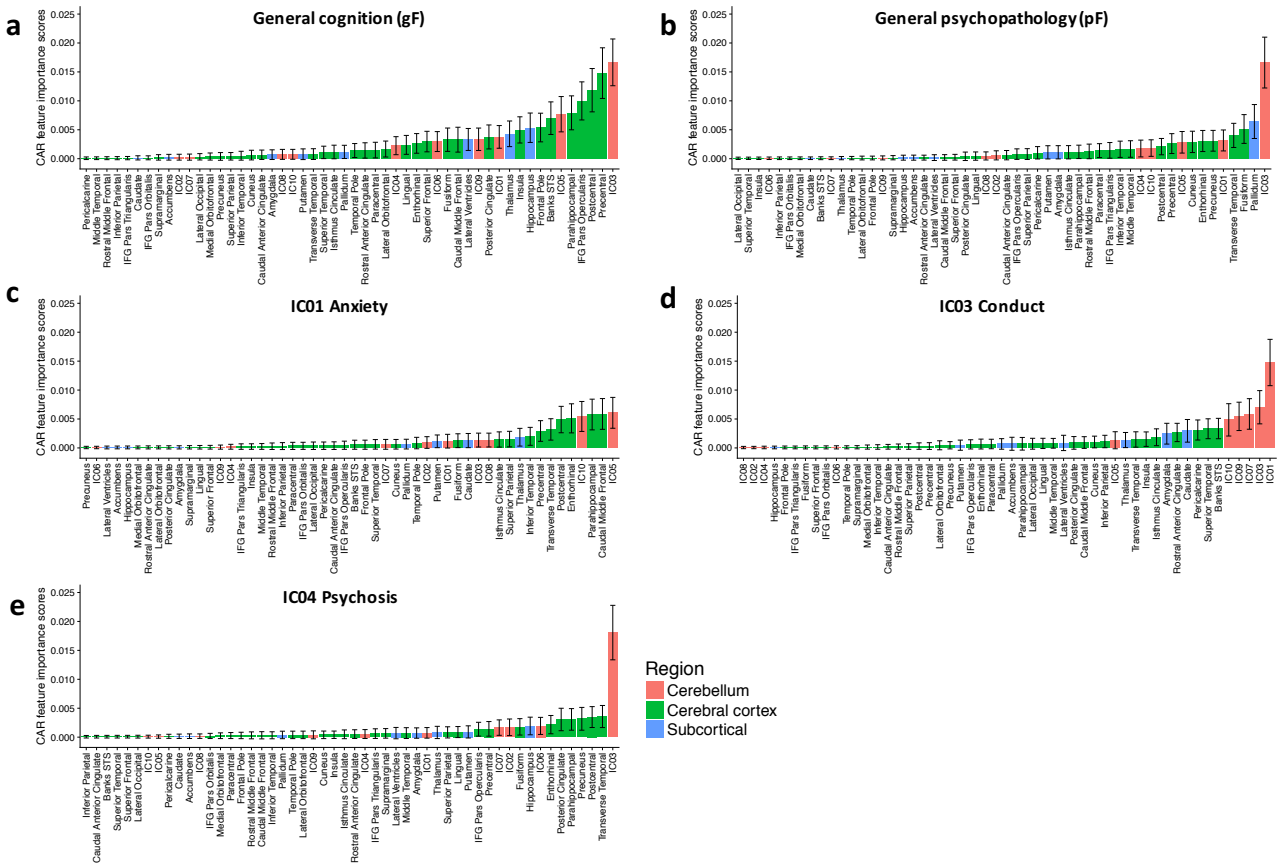

Figure 5: Feature importance weights (CAR-scores) for the five significant prediction models using all anatomical features. CAR-scores were computed for each of 10,000 iterations of the model on randomly 10-fold partitioned data, yielding 100,000 estimates for each model. Colors indicate the location of each feature, while error bars denote 2 standard deviations from the mean of these CAR-score distributions.

Control analyses

See Supplementary Results for details. In brief, the negative correlation between cerebellar IC03 and prodromal psychotic symptoms remained significant when controlling for general cognitive function, general psychopathology, parental education level, as well as in the subset of participants with no evidence of substance abuse (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 utilizing 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, structure-symptom associations showed diagnostic specificity, in that significant results were observed for sub-clinical symptoms of psychosis and 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. We also observed a pattern of cerebellar anatomical specificity, with volume reductions in bilateral lobules VI/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 prodromal psychotic symptoms and norm-violating behavior were stronger for the cerebellum than for subcortical volumes or regional cortical thickness. Together, these findings provide evidence for the cerebellum as a key brain structure underlying the development of core phenotypes of severe mental illness.

The associations with general cognitive function and general psychopathology were expected based on previous research in adults[26,30,31], and add to the growing database supporting a cerebellar role in cognition and affect[65]. Although the majority of structural MRI-studies on psychosis have focused on cerebral structures[66], our findings on sub-clinical psychotic symptoms are in general agreement with an emerging body of research. For instance, we have recently shown that cerebellar volume reductions is one of the strongest and most consistent morphological alterations in a large multi-site sample of schizophrenia patients (N = 983) and healthy controls (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, a cerebellar region that also emerged as one of the strongest predictors of transition to psychosis in a recent study of high-risk populations[67]. Moreover, functional neuroimaging studies consistently report reduced cerebello-cerebral connectivity in schizophrenia patients[68-71] and high-risk groups[72,73], while behavioral studies find impaired cerebellar learning in both patients with schizophrenia[74-76] and their first-degree relatives[77].

Our findings differ in some respects from a previous study of structural brain alterations in a partially overlapping sample of psychosis spectrum youth[34], 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[78] and the cerebrum[79]. Second, whereas the previous study employed an extreme group design[34], 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[80] and functional activation[81] in conduct disorder. However, since our control analyses

suggested that these associations might 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 underlying neurobiological processes, we observe that cerebellar volume - like hippocampal volume[82] - has previously been shown to be very sensitive to stress hormone exposure, especially during infancy[83,84] but also in adults with very high levels due to Cushing´s disease[85-87]. This may provide a potential link, to be tested in future research, between our findings and the well-documented role of stressful life events in the development of psychopathology[88].

A notable strength of the current study is the use of internal cross-validation, which should reduce the risk of overfitting, and thus ensure more generalizable effect estimates[89]. Its main limitation is the cross-sectional design, which prevents tests of causal relationships. Further, although the reported structure-function associations were robust and highly significant, cerebellar morphology explains only a limited part of the variance in clinical scores. While not surprising, given the multiple factors that influence the expression of psychiatric symptoms[88,90,91], this caveat must be kept in mind when interpreting the results.

Conclusions

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

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