Title: Cerebellar grey matter volume is associated with cognitive function and psychopathology in adolescence

Running title: Cerebellar structure 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 (the Philadelphia Neurodevelopmental Cohort, N=1401, age-range: 8 - 23).

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-values < .0009). Analyses of specific symptom domains revealed significant associations with rates of norm-violating behavior (r = .17; p < .0009), as well as psychosis (r = .12; p < .0009) and anxiety (r = .09; p =.0117) symptoms. In contrast, we observed no associations with attention deficits, 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.

Introduction

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(5) and autism(6). However, while 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 already in adolescence, when initial symptoms typically first present(8, 12, 13), or only emerge later in the disease process. Moreover, whether individual differences in cerebellar structure in adolescents are indicative of non-specific 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.

Here, 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 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 grey matter maps into spatially independent components, before testing for structure-function 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). Further, 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. We finally 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 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 to 23.2) included in the publicly available Philadelphia Neurodevelopmental Cohort (PNC)(19, 20)(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(24), we included performance scores from the full PNC sample (n=6,487) on 12 computerized cognitive tests(20) and 129 questionnaire items from the PNCs GOASSESS computerized assessment battery(20), including adapted items from several different questionnaires, such as the World Health Organization Composite International Diagnostic Interview (CID; (33)), the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children (Kiddie-SADS, (28), the Structured Interview for Prodromal Syndromes (SIPS; (34)), and the PRIME Screen Revised (PRIME; (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 below 18 years of age, we relied on information from interviews with caregivers or legal guardians (20). See Supplementary Tables 1 and 2 for individual cognitive tests/clinical items. Using the full PNC sample (n=6,487), 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 also examine specific symptom domains, all clinical item scores (n=6,487) were submitted to independent component analysis (ICA) using ICASSO(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/clinical measures were tested using generalized additive models (GAMs) as implemented in the r-package "mgcv"(37), and a set of adjusted cognitive/clinical scores were computed by regressing out main effects of age and sex (see Supplementary Methods). All subsequent structure-function analyses were conducted using these age- and sex-adjusted scores.

Collection and processing of MRI data:

As previously described(19, 38, 39), all MPRAGE T1-weighted images were collected using the same scanner (Siemens Tim Trio 3 Tesla, Erlangen, Germany; 32 channel head coil), using the following parameters; TR 1810 ms, TE 3.51 ms, FOV 180x240 mm, matrix 256x192, 160 slices, TI 1100 ms, flip angle 9 degrees, effective voxel resolution of 0.9 x 0.9 x 1mm. All images were first processed using FreeSurfer version 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 regions-of-interest (ROIs) per hemisphere(42). Next, the bias-corrected images from the FreeSurfer pipeline were subjected to cerebellum-optimized voxel-based morphometry (VBM) using the SUIT-toolbox (v3.2(43, 44)), running on MATLAB 2014a. In the first step, SUIT isolates the cerebellum and brainstem, segments images into grey and white matter maps. In order to avoid voxels from the occipital cerebral cortex in the SUIT-generated cerebellar grey matter maps, we excluded all voxels that overlapped with the FreeSurfer-generated maps of cortical grey and white matter. In a second step, SUIT normalizes these (FreeSurfer-pruned) cerebellar grey matter maps to a cerebellar template using Dartel(45), ensuring superior cerebellar alignment compared with whole-brain procedures(44). 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(46), we used a data-driven approach in our primary analyses. Specifically, we subjected the modulated cerebellar grey 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.

In order to characterize the resulting cerebellar VBM-components, we used NeuroSynth(48) 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(48) database (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(49-51) and eTIV(52, 53) (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(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/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 the squared correlation-adjusted marginal co-relation (CAR) scores(55) for each iteration, yielding distributions of 10*10,000 CAR^2 estimates.

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 volumetric estimates of 28 cerebellar lobules as features as well as from 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(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 ROI based the Desikan-Killany atlas in FreeSurfer, respectively (See Supplementary Figure 2). We chose thickness as our cortical feature of interest, due 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, in order 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 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(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 Supplementary Table 2 for a list of all clinical items and Supplementary Figure 3 for item-specific numerical PCA and ICA weights. Effects of age and sex on all cognitive and clinical summary scores are displayed in Figure 1b and Supplementary Table 3. In brief, general cognitive function (gF) showed the expected strong positive association with age, with slightly higher mean scores in males than in females. 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(8, 58, 59), 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 depression. As shown in the lower triangle of Figure 1c and Supplementary Table 4, age 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 (pF; r ranging from .22 to .54). General cognitive function (gF) showed weak negative correlations with general psychopathology (pF), ADHD, Anxiety, Conduct and Psychosis (r-values ranging from -.1 to -.23).

MRI-based morphometry

Data-driven decomposition of cerebellar grey 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 split into unilateral components at higher model orders (see Supplementary Figures 4-6 for 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 Fig.2a) showed distinct patterns of whole-brain functional connectivity (Fig 2b-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 7-10 and Supplementary Tables 5-8 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: $r = .20$; $p < .0009$) and general psychopathology ($r = .12$, $p < .0009$). When using cerebellar features to predict clinical

components, we observed significant results for Conduct (r = .16; p < .0009), Psychosis (r = .12; p < .0009) and Anxiety (r = .09; p = 0.0117), but not for ADHD (r = .01; ns), Depression (r = -.02; ns), Mania (r = .03; ns) or 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 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, Conduct was negatively correlated with cerebellar IC01 and IC09, while 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 (see Supplementary Figure 12).

Results from the voxel-based analyses are given in Figure 3d and Supplementary Table 9. 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. 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 13-14 for CAR-scores). In brief, the subcortical model performed worse than the cerebellar model, with a notable exception for OCD (r = .08; p = .0423), where pallidum volume emerged as the most important feature. The cortical thickness model performed better than the cerebellar model for general cognitive function (r = .26; p < .0009) and yielded comparable results for Anxiety (r = .09; p = .0225), but performed worse than the cerebellar model in predicting general psychopathology, Conduct and Psychosis (all rs < .0.08; all ps => .072). Models using all anatomical features significantly predicted general cognitive function (r = .29; p < .0009), general psychopathology (r = .13; p < .0009), Anxiety (r =.10; p = .0153), Conduct (r =.14; p < .0009) and Psychosis (r =.10; p = .0162). Univariate analyses yielded similar results (see Supplementary Figures 15-16).

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, especially general psychopathology, Conduct and Psychosis.

Control analyses

See Supplementary Results and Supplementary Figure 17 for detailed results. In brief, the negative correlation between cerebellar IC03 and psychotic symptoms remained significant when controlling for general cognitive function, general psychopathology, MRI data quality, 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 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, the analyses of independent components based on clinical symptom scores revealed a pattern of diagnostic specificity, in that significant results were observed for psychosis symptoms 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. These patterns also showed 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 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, while 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. 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(17). Consistent with their results, across the seven clinical components we also observe 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(61-63), including white matter integrity and grey matter volume of the cerebellum(15).

The majority of existing structural MRI-studies on psychosis have focused on cerebral structures(64), 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 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, which has been strongly implicated in cognitive control processes(65). Indeed, previous functional MRI studies of working memory using the PNC sample found that activation of cerebellar Crus I was associated task performance (66), and that reduced activation in this region was associated with overall level of psychopathology (67). Structural alterations in this cerebellar region also emerged as one of the strongest predictors of transition to psychosis in a recent study of high-risk populations(68). 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 cerebello-cerebral connectivity in schizophrenia patients(69, 70) and high-risk groups(71, 72), while behavioral studies find impaired cerebellar learning in both patients with schizophrenia(73-75) and their first-degree relatives(76).

Of note, our findings differ in some respects from a previous study of structural brain alterations in a partially overlapping sample of psychosis spectrum youth[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(77) and the cerebrum(78). 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(79) and functional activation(80) 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 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(81), suggesting a direct or indirect genetic impact. Further, cerebellar volume, like hippocampal volume(82), has been shown to be very sensitive to stress hormone exposure. While this effect is especially strong during infancy(83) it has also been observed in adults with very high levels of circulating corticosteroids due to Cushing´s disease(84). 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(85).

Strikingly, associations with psychotic symptoms and norm-violating behavior were stronger for the cerebellum than for subcortical volumes or regional cortical thickness. Since this pattern was not observed across all examined phenotypes (e.g., cortical thickness was the best predictor of general cognitive function, while 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 fMRI-studies (86, 87), these results suggest that traditional cerebellar subdivisions do not optimally capture either the inter-subject 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(72) or conversion to frank psychosis(68). 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 cerebello-cerebral connectivity patterns are largely developed and similar to those seen in

adults by middle childhood (88), 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. While not surprising, given the multiple factors that influence the expression of psychiatric symptoms(85, 89, 90), 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.

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Disclosures

The authors declare no conflict of interest

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Figure legends

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, 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, while Supplementary Table 2 lists all 129 individual items and Supplementary Figure 3 gives numeric PCA and ICA weights for each item; **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.

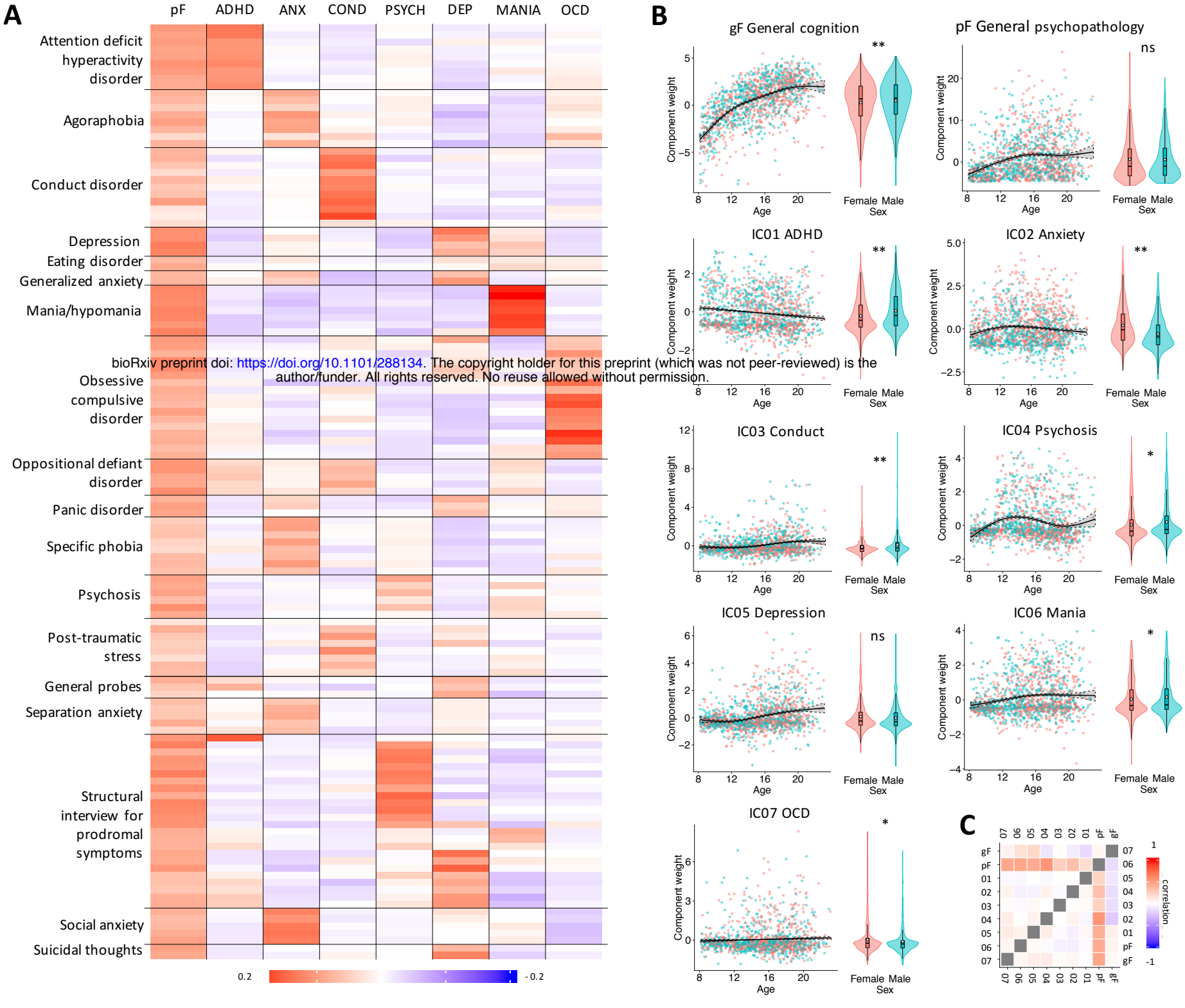
Figure 2: Cerebellar anatomical indices. a: The ten independent components resulting from data-driven decomposition of cerebellar grey matter maps projected onto flat-maps of the cerebellar cortex(91). Asterisks denote the peak voxel for each component. **b-c:** Cerebellar and cerebro-cortical functional connectivity maps (determined using NeuroSynth(46, 92)) 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**.

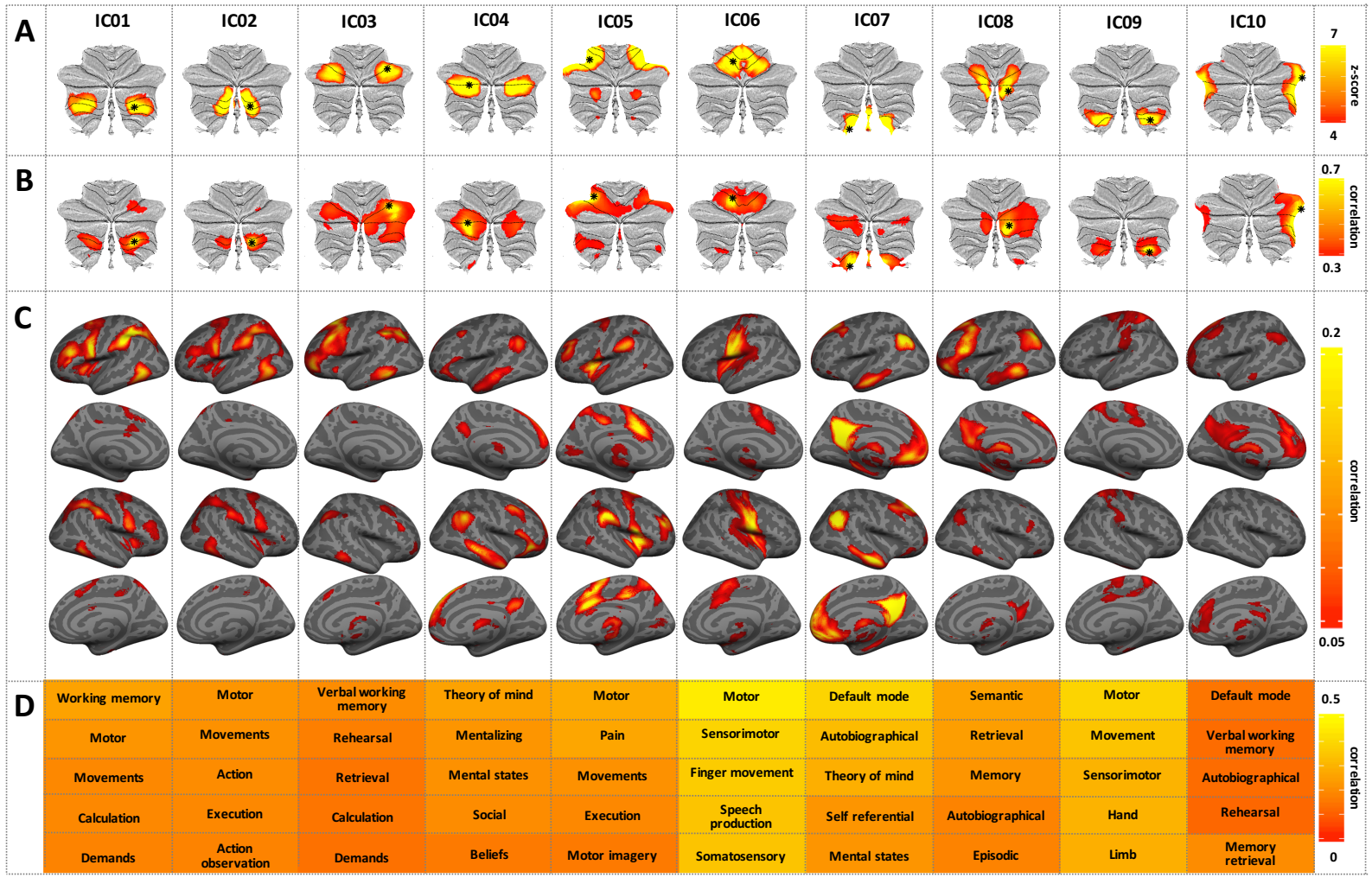
Figure 3: Cerebellar structure-function associations. a: Distributions of correlations between predicted and actual cognitive/clinical scores across 10,000 iterations of the 10-fold cross-validated model. White dots denote the mean, used as point estimates for comparison with each model's empirical null 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).

Figure 4: Predictive performance of cerebral models. 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: Relative feature importance across brain regions. 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 general anatomical classification of each feature, while error bars denote the 2.5th and 97.5th percentiles of these CAR-score distributions.




A
IC01
IC02
IC03
IC04
IC05
IC06
IC07
IC08
IC09
IC10
7
z-score
4
B
0.7
correlation
0.3
C
0.2
correlation
0.05
D
Working memory
Motor
Movements
Calculation
Demands
Motor
Movements
Action
Execution
Action observation
Verbal working memory
Rehearsal
Retrieval
Calculation
Demands
Theory of mind
Mentalizing
Mental states
Social
Beliefs
Motor
Pain
Movements
Execution
Motor imagery
Motor
Sensorimotor
Finger movement
Speech production
Somatosensory
Default mode
Autobiographical
Theory of mind
Self referential
Mental states
Semantic
Retrieval
Memory
Autobiographical
Episodic
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Movement
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Limb
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Rehearsal
Memory retrieval
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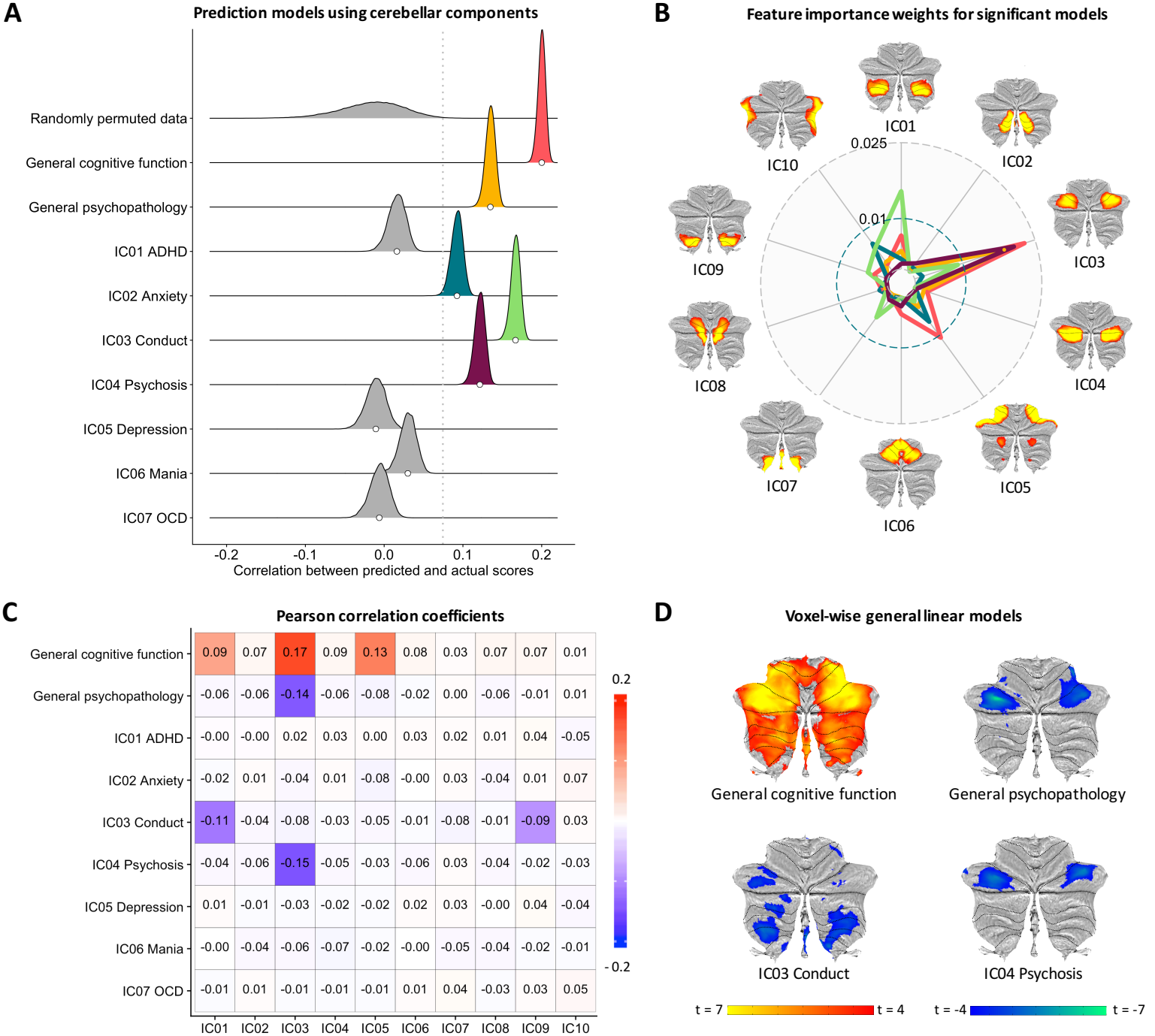
A
Prediction models using cerebellar components
Randomly permuted data
General cognitive function
General psychopathology
IC01 ADHD
IC02 Anxiety
IC03 Conduct
IC04 Psychosis
IC05 Depression
IC06 Mania
IC07 OCD
-0.2
-0.1
0.0
0.1
0.2
Correlation between predicted and actual scores
B
Feature importance weights for significant models
0.025
0.01
IC01
IC02
IC03
IC04
IC05
IC06
IC07
IC08
IC09
IC10
C
Pearson correlation coefficients
General cognitive function 0.09 0.07 0.17 0.09 0.13 0.08 0.03 0.07 0.07 0.01
General psychopathology -0.06 -0.06 -0.14 -0.06 -0.08 -0.02 0.00 -0.06 -0.01 0.01
IC01 ADHD -0.00 -0.00 0.02 0.03 0.00 0.03 0.02 0.01 0.04 -0.05
IC02 Anxiety -0.02 0.01 -0.04 0.01 -0.08 -0.00 0.03 -0.04 0.01 0.07
IC03 Conduct -0.11 -0.04 -0.08 -0.03 -0.05 -0.01 -0.08 -0.01 -0.09 0.03
IC04 Psychosis -0.04 -0.06 -0.15 -0.05 -0.03 -0.06 0.03 -0.04 -0.02 -0.03
IC05 Depression 0.01 -0.01 -0.03 -0.02 -0.02 0.02 0.03 -0.00 0.04 -0.04
IC06 Mania -0.00 -0.04 -0.06 -0.07 -0.02 -0.00 -0.05 -0.04 -0.02 -0.01
IC07 OCD -0.01 0.01 -0.01 -0.01 -0.01 0.01 0.04 -0.03 0.03 0.05
IC01 IC02 IC03 IC04 IC05 IC06 IC07 IC08 IC09 IC10
0.2
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D
Voxel-wise general linear models
General cognitive function
General psychopathology
IC03 Conduct
IC04 Psychosis
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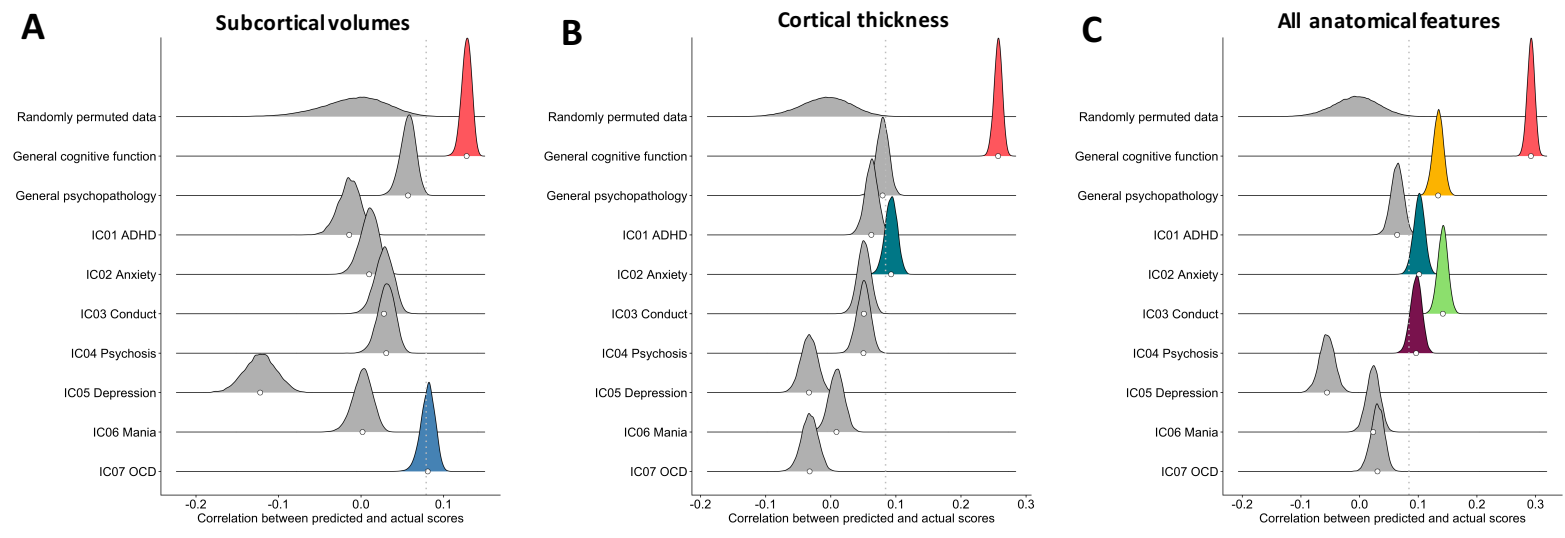
t = -4
t = -7


A
Subcortical volumes
B
Cortical thickness
C
All anatomical features
Randomly permuted data
General cognitive function
General psychopathology
IC01 ADHD
IC02 Anxiety
IC03 Conduct
IC04 Psychosis
IC05 Depression
IC06 Mania
IC07 OCD
-0.2
-0.1
0.0
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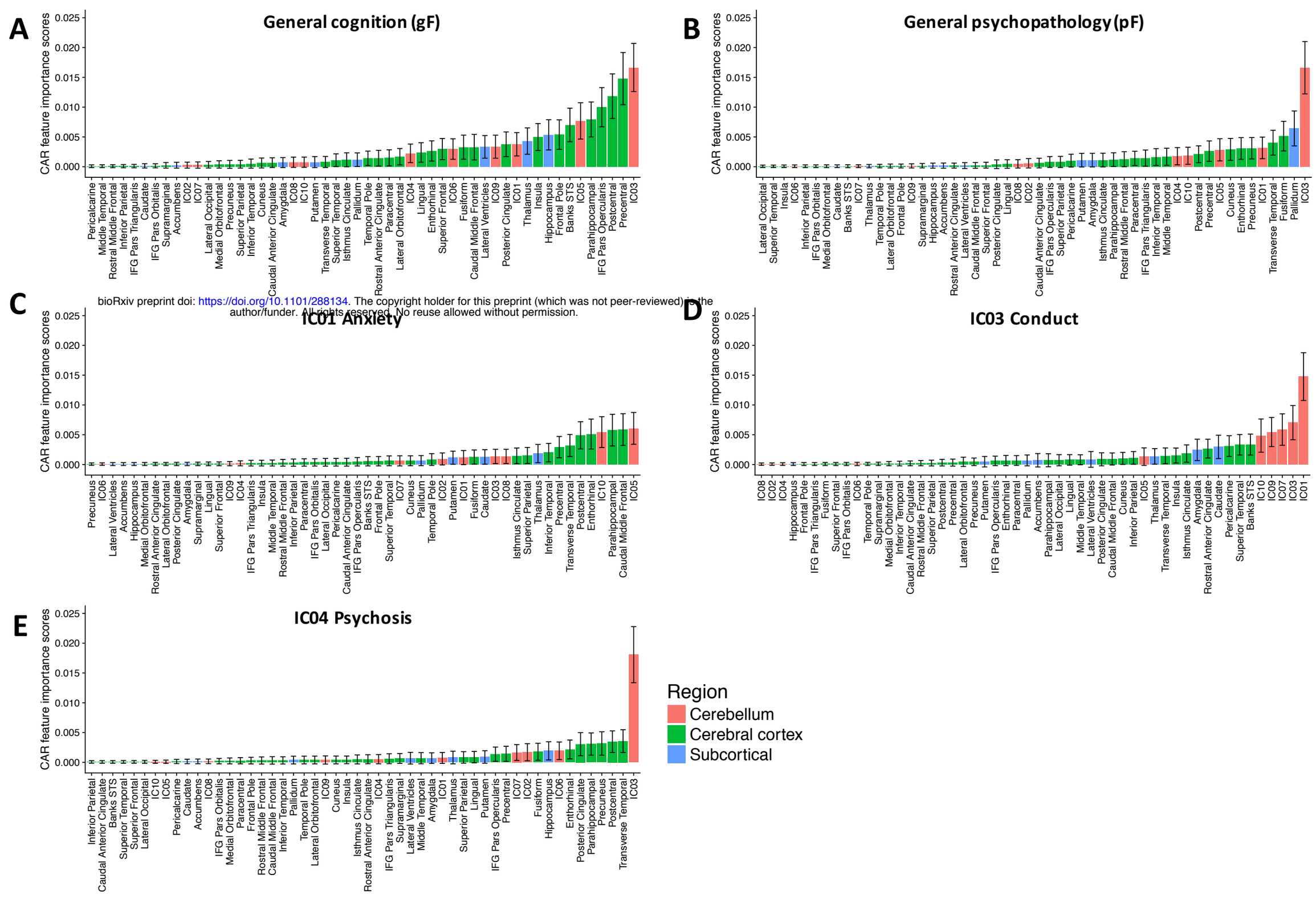
0.3
Correlation between predicted and actual scores



Supplementary information: Cerebellar grey matter volume is associated with cognitive function and psychopathology in adolescence

Supplementary Methods:

Participants, inclusion criteria and quality control procedures: Access to the PNC data was obtained with permission #8642 (project title: Neurodevelopmental brain networks: Integrating multimodal imaging, cognition and genetics). Phenotypic data were available from 6487 participants, while MRI data were available from 1601 participants. Data from four subjects suffered data corruption during download, while 76 participants with severe or major physical medical conditions requiring standing medications and monitoring (as assessed by trained personnel in the PNC study team(1, 2)) and 72 participants with missing data on medical status were removed from the sample prior to analyses. In addition, one participant with MRI data was excluded due to missing phenotypic data. For the remaining 1448 participants, we implemented a flagging procedure based on robust PCA(3) for detecting signal to noise-, and segmentation outliers based on the FreeSurfer output. Flagged datasets were carefully inspected, with minor edits performed when necessary. Scans from 47 participants were rejected due to poor MRI quality based on visual inspection. For an additional quantitative assessment of MRI quality, we calculated the Euler numbers (one for each hemisphere) for each dataset and computed the sum of these two Euler numbers as an index of overall MRI quality(4). Supplementary Figure 1 displays the distributions of these summed Euler numbers for included and excluded datasets, respectively. As expected, mean Euler number differed significantly between included and excluded datasets and the distributions showed only moderate overlap. We thus believe these quantitative results corroborate our original quality control procedure. Euler numbers for included datasets were also included as covariates in control analyses (see below), testing for potentially confounding effects of MRI data quality(4). The final sample (N= 1401) ranged between 8.2 and 23.2 years of age (mean age: 15.12, SD: 3.62), and was 52.8% female. Mean age was slightly higher (t=2.7, p=.006868 for females (15.4; SD: 3.6)) than males (14.8; SD: 3.62).

Computation of cognitive and clinical summary scores: Supplementary Table 1 provides an overview of all cognitive test scores used to compute the index of cognitive function (gF). The gF score was computed by submitting cognitive test score from 6487 participants to a principal component analysis and extracting subject weights on the first principal component (explaining 30.7% of the variance in the total sample). The first factor weights on each cognitive measure are given in Supplementary Table 1.

Supplementary Table 2 lists all 129 items used to compute both the general index of psychopathology (pF) and the clinical independent component scores. As described previously(5), 1,627 participants had missing values on one or several clinical items. For all but two participants which had missing values on all 129 clinical items, the missing values were replaced with the

nearest-neighbor value based on Euclidean distance. The percentage of missing values for the 129 items ranged from 0-7%.

In brief, analogous to the notion of a positive manifold in the cognitive domain (frequently termed the g-factor), a general psychopathology factor (or p-factor) has been proposed as a parsimonious explanation for the considerable correlations between different symptoms of psychopathology, as well as the common comorbidity and genetic overlaps across psychiatric diagnostic categories (for a recent review, see(6)). Thus, the general psychopathology factor (pF) reflects the shared variance across symptom domains, while independent components (by definition) reflects independent sources of variance in the same dataset. By reporting results analyzed from two such alternative nosological perspectives, we believe that our reported findings will have the maximal future impact, regardless of whether "lumping" (general psychopathology) or "splitting" (independent components) will eventually turn out to be the most fruitful approach towards a deeper understanding of psychopathology.

The pF score was computed by submitting data from the full set of PNC participants (N = 6487) to a principal component analysis and extracting subject weights on the first principal component (explaining 12.9% of the variance). The first principal component weights on each clinical item are displayed in Figure 1, with numerical information given in Supplementary Figure 3. As described previously(5), the ICA model order for clinical score decomposition was chosen after testing several different model orders ranging from 3-15, for each of which 100 permutations were run, and based on the observed independence and reliability of the resulting components. The independent component weights on each clinical item are displayed in Figure 1, with numerical information given in Supplementary Figure 3. Note that all clinical items (traditionally associated with distinct diagnostic categories) had positive and relatively uniform weights on pF (range from .02 to .13). In contrast, weights on independent components were more specific to a smaller set of symptoms, and showed a wider range which also included negative weights on some symptoms (range from -.07 to .19).

Effects of gender and age on cognitive/clinical sores were tested by fitting generalized additive models (GAMs) to account for potentially non-linear effects of age. We used GAM as implemented in the R-package “mgcv”, with age modeled using cubic splines with 5 knots the level of smoothness automatically selected using the restricted maximum likelihood method (“REML”). For the full model, we report the percent variance explained, for parametric terms we report t- and p-values, while for smooth age-term, we report F-values and approximate p-values.

Age- and gender-adjusted cognitive/clinical scores were computed by reconstructing data from the intercept and residuals of these GAM-models (i.e., omitting the age- and gender-coefficients).

Independent component analysis (ICA) of cerebellar grey matter maps:
ICA of the modulated cerebellar grey matter maps was performed using FSL MELODIC with standard settings. A binary mask was constructed by thresholding the mean unmodulated cerebellar grey matter map at .01 and multiplying it with the probabilistic cerebellar grey matter map from the SUIT template (also thresholded at .01). We initially tested model orders ranging from 5 to 20 (in steps of 1), and decided on a model order of 10 for the main analyses, since this produced a concise set of largely bilateral components which tended to fuse in to larger bilateral components at lower model orders and fragment into unilateral components at higher model orders (See Supplementary Figures 4-6 for examples of ICA-decompositions using alternative model orders of 5, 15 and 20).

The 10 independent components together accounted for 60.03% of the total variance in the modulated grey matter maps used as input to the analysis, with each component explaining between between 4.07% and 7.65% of the total variance (and between 8.31% and 12.74 % of the explained variance). In comparison, the 5-, 15- and 20-component models accounted for respectively 48.00, 65.72 and 69.73% of the total variance. Correlations between the 10 cerebellar ICs before and after adjusting for effects of sex, age and estimated total intracranial volume are given in Supplementary Figure 11.

For functional characterization of the resulting cerebellar grey matter components, we used results from a large (N=1000) resting state fMRI functional connectivity study(7) (implemented in NeuroSynth(8)) to map the full-brain functional connectivity of the peak voxel of each component, and plotted both cerebellar maps (thresholded at r = .3) and cerebrocortical maps (thresholded at r = .05) for illustration (Figure 2B and C). We next 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(8) database. We report the top five functional terms (Fig 2D), i.e. a pruned version of Neurosynth output after exclusion of all terms related to brain anatomy, methodology, etc. Spatial correlations between whole-brain connectivity maps and the meta-analytic maps for the reported terms in Figure 2D ranged from .108 to .457.

ROI-wise adjustment for effects of age- gender and estimated total intracranial volume:
Before inclusion in multivariate or univariate models, all volumetric anatomical features were adjusted for main effects of gender and eTIV as described above for clinical scores, i.e., by fitting GAM-models and reconstructing data from model parameters and residuals. As for clinical sores, effects of age on anatomical features were estimated using cubic splines with 5 knots, with the level of smoothness automatically selected using the restricted maximum likelihood method ("REML"). For all volumetric features (but not for cortical thickness), we also used GAM (with the same input parameters as for age) to estimate potentially non-linear effects of eTIV(9, 10). For each GAM- model, we report total explained variance, t, F and p-values as described for cognitive/clinical data above.

Univariate analyses:

In a set of univariate analyses, we computed the Pearson correlation coefficients between all (sex-, age- and eTIV-corrected) anatomical features included in each prediction model and all predicted (sex- and age-corrected) cognitive/clinical components. Statistical significance (corrected for multiple comparisons across the set of features for each model) was determined by permutation testing. Specifically, we randomly permuted the cognitive/clinical subject weights 10.000 times, computed the resulting matrices of structure-function correlations and extracted the maximal and minimal correlation coefficients from each iteration to form empirically derived null-distributions. Structure-function associations were considered significant at a corrected alpha-level of .05 (two-tailed).

Voxel-wise analyses:

Statistical analyses testing voxel-wise associations between cerebellar volume and age- and gender-adjusted cognitive/clinical scores, while controlling for main effects of gender, age, and estimated total intracranial volume(eTIV), were performed using FSL Randomise. Sex was modelled as two binary variables, while age, eTIV and cognitive/clinical scores were z-transformed and modelled as three continuous variables. Statistical inference was based on permutation testing (using 10.000 permutations per contrast), with voxels considered significant at a corrected alpha-level of .05 (two-tailed).

Analyses controlling for potentially confounding factors:

Information on general cognitive function (i.e., the gF score) and general psychopathology (i.e., the pF score), as well as the mean Euler number (a quantitative index of MRI data quality(4)) were available for all 1401 subjects, while information on maternal and paternal education level was available for 1274 subjects. In order to control for these potentially confounding variables, which previously have been shown to be associated with both psychiatric symptoms(11) and brain morphology(12-15), we performed additional univariate after adjusting both clinical and anatomical features for main effects of the respective variable (in addition to sex and age, as well as estimated total intracranial volume for volumetric features).

In order to test whether the use of two different assessment strategies for participants below and above 18 years of age (collateral informants versus self report), we performed a control analysis including only the 1035 participants below 18 years. Information on substance abuse was available for 594 participants. In the control analyses examining this potentially confounding variable, we excluded all subjects who reported having experienced one or more negative psychological or physical effects of alcohol use, or having ever tried illicit substances (n=225), leaving 369 participants in this pruned subsample.

Supplementary Results:

Effects of age and sex on cognitive/clinical scores

The main results are displayed in Figure 1B, while the total percent variance explained by the models, t- and F-values for the gender and (smooth) age terms, as well as their respective p-values are given in Supplementary Table 3.

Relationships between cognitive/clinical scores

The main results are displayed in Figure 1C, with numerical values given in Supplementary Table 4. Briefly, correlations between individual scores on clinical independent components were very weak (range -.072 to .097), suggesting that these components indeed reflected largely independent sources of variance in the clinical data. Moreover, all clinical independent components showed weak to moderate positive correlations with the General Psychopathology factor (pF), ranging from .222 for ADHD to .538 for Psychosis. In line with previous reports in both an overlapping(16) and an independent sample(17), we also observed a weak negative correlation between General Psychopathology and General Cognition (r = -.147). Among the clinical independent components, ADHD, Anxiety, Conduct and Psychosis showed weak negative correlations with General Cognition (range: -.102 to -.230), while Depression, Mania and OCD showed very weak positive correlations with General Cognition (range: .033 to .080).

Effects of age, sex and estimated total cranial volume on brain features:

The GAM-estimated smooth functions for age and estimated total cranial volume (eTIV) are displayed (together with raw data and gender effects) in Supplementary Figures 7-10 and Supplementary Tables 4-7. Briefly, we observed significant effects of eTIV on all volumetric features, while age- and gender-effects were more variable. Specifically, with regards to the cerebellar components, we observed significant effects of age on subject weights for IC02, IC04, IC06 and IC10. When adjusting for eTIV, IC05, IC06 and IC09 showed significantly higher subject weights in males relative to females, while IC02, IC07, IC08 and IC10 showed the opposite pattern.

Prediction models and univariate analyses using cerebellar lobular volumes:

Results from the prediction models using cerebellar lobules as predictive features are presented in Supplementary Figure 12A. Significant results were observed for general cognitive function (gF; r = .19, p < 0.009), general psychopathology (pF; r =.12, p < 0.009), conduct disorder (IC03: r = .15, p < 0.009) and psychosis (IC04: r = .12, p < 0.009), while the nominally significant association with anxiety did not survive multiple comparisons correction (IC02: r = .06, ns). Cerebellar lobular volumes did not significantly predict subclinical symptoms of ADHD (IC01: r = .02, ns), depression (IC02: r = .01, ns), mania (IC02: r = .01, ns), or OCD (IC02: r = .05, ns). Feature importance indices (CAR-scores for significant prediction models are depicted in Supplementary Figure 12B-F.

Control analyses: Supplementary Figure 17A and B display all univariate associations between cerebellar and clinical IC scores, when adjusting both feature sets for general cognitive function and general level of psychopathology, respectively. As expected, given the existing evidence for associations between these factors and both clinical symptoms(5, 11) and brain structure(5, 13, 15), the structure-function associations observed in our main analyses were slightly reduced in these control analyses, but remained significant. Specifically, when adjusting both clinical and anatomical features for effects of general cognitive function, these analyses yielded correlation coefficients of -.11 ($p < .001$) between psychosis symptoms and cerebellar IC03, and -.10 ($p < .01$) between conduct disorder and cerebellar IC01. When similarly adjusting for effects of general psychopathology, we observed correlation coefficients of -.08 ($p < .05$) for the association between psychosis symptoms and cerebellar IC03, and -.10 ($p < .01$) for the association between conduct disorder and cerebellar IC01.

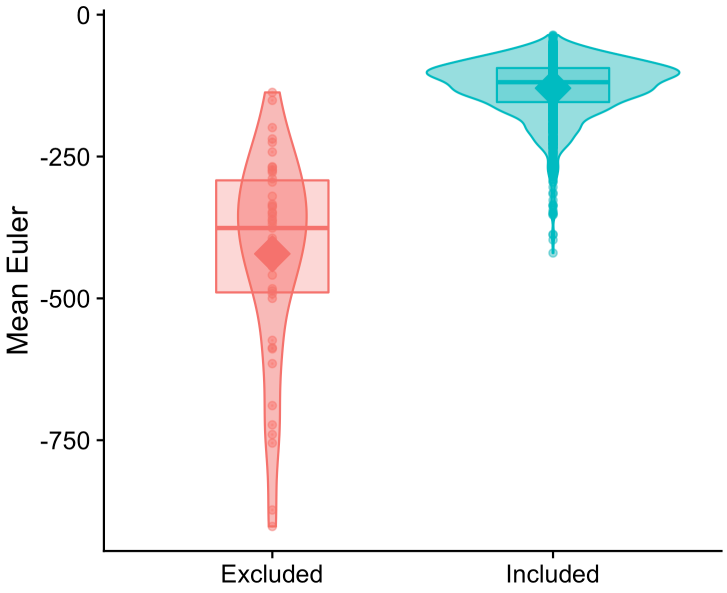
Results from the correlation analyses run after adjusting all anatomical features for effects of mean Euler number (a quantitative index of MRI data quality) are displayed in Supplementary Figure 17C. Both the association between cerebellar IC03 and psychosis symptoms (correlation coefficient: -.15, $p < .001$) and the association between IC01 and norm violating behavior (correlation coefficient: -.11, $p < .001$) remained significant.

Results from the correlation analyses run after adjusting all clinical and anatomical features for effects of maternal and paternal education levels are displayed in Supplementary Figure 17D. The association between cerebellar IC03 and psychosis symptoms remained significant (correlation coefficient: -.14, $p < .001$), but the association between IC01 and norm violating behavior did not (correlation coefficient: -.08, ns).

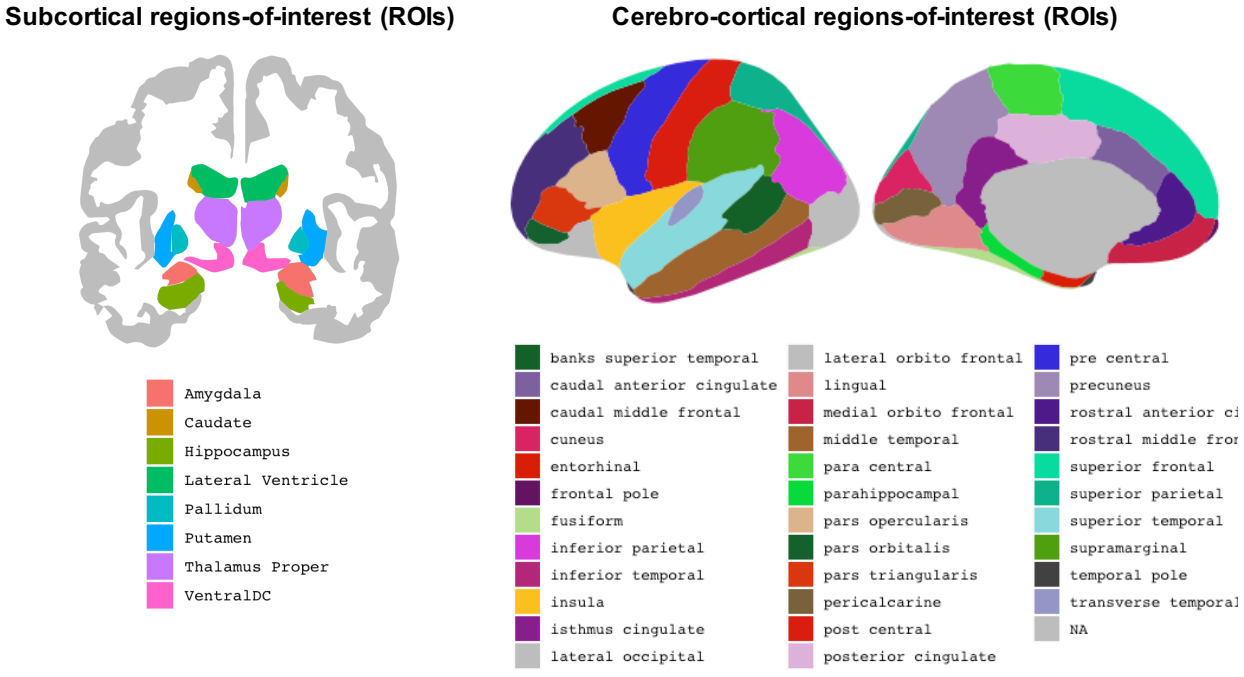
Results from correlation analyses in the pruned dataset containing only participants who reported no use of illicit substances and no negative experiences with alcohol (n=389) are displayed in Supplementary Figure 17E. Of note, the associations between psychosis symptoms and cerebellar IC03 remained significant in this pruned subsample (correlation coefficient: -.17, $p < .05$), while the association between cerebellar volumes and norm violating behavior did not (correlation coefficient: -.06, ns).

Results from correlation analyses in the pruned dataset containing only participants who with information provided from collateral informants (primary caregivers or legal guardians) (n=1035) are displayed in Supplementary Figure 17F. Both the association between cerebellar IC03 and psychosis symptoms (correlation coefficient: -.15, $p < .001$) and the association between IC01 and norm violating behavior (correlation coefficient: -.12, $p < .001$) remained significant.

Supplementary figures and tables:



Supplementary Figure 1: Mean Euler numbers for included and excluded datasets. Violin plots represent the distributions, small circles individual data points, and the large diamonds group means, while boxplots show medians end interquartile ranges. Mean Euler numbers differed significantly between included and excluded datasets ($p = 2^{-e4}$, based on 10.000 permutations).

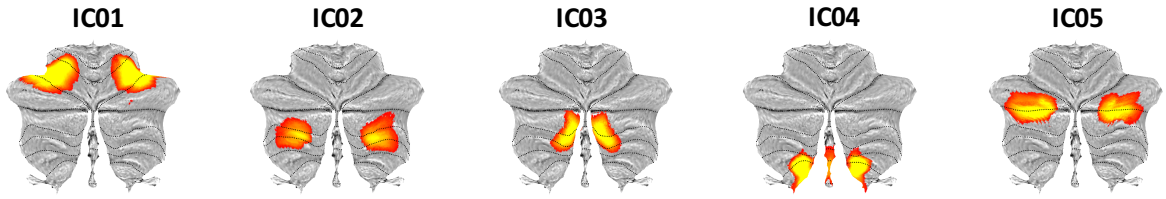


Supplementary Figure 2: The subcortical and cerebro-cortical regions-of-interest used in the current study. Figures have been produced using the R-package "ggseg"(18).

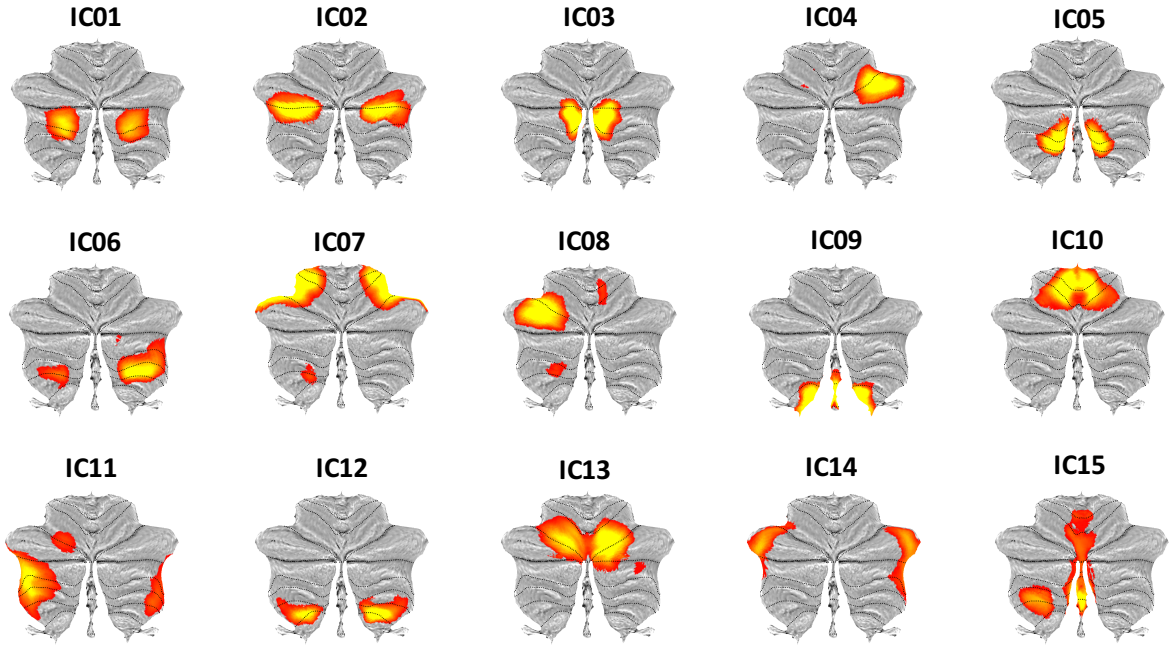
	pF	ADHD	ANX	COND	PSYCH	DEP	MANIA	OCD
001	0.11	0.14	0	−0.03	0.01	−0.02	−0.01	0
002	0.1	0.13	−0.02	−0.02	0	−0.01	−0.02	0.01
003	0.1	0.11	−0.01	−0.02	−0.03	0.02	0.02	0
004	0.09	0.11	0.01	−0.02	0.01	−0.02	0	−0.01
005	0.1	0.11	−0.01	−0.03	0.02	−0.01	−0.01	0.01
006	0.11	0.12	0	−0.01	0.01	−0.03	0	0.01
007	0.1	0.11	−0.01	−0.02	0	−0.04	0.02	0.01
008	0.09	0.11	−0.02	0	0	−0.03	−0.01	0.02
009	0.09	0.12	0	−0.01	0.01	−0.04	0	0.02
010	0.08	0.01	0.09	0	0	−0.01	−0.02	0.02
011	0.07	0.01	0.07	0	0.02	0	−0.04	0.02
012	0.06	0	0.05	−0.01	0.02	−0.04	−0.02	0.03
013	0.08	−0.01	0.11	0.02	0.01	−0.06	−0.03	0.02
014	0.1	0	0.09	0	0.02	−0.04	−0.03	0
015	0.08	0	0.1	0.01	0	−0.03	−0.03	0.02
016	0.04	0	0.03	0.05	−0.02	−0.02	−0.04	0.07
017	0.08	−0.01	0.09	0.02	0	−0.06	−0.03	0.03
018	0.08	0.01	0	0.1	−0.01	−0.01	0.02	−0.02
019	0.08	−0.03	0	0.14	−0.04	0.02	0	−0.03
020	0.06	0.01	−0.01	0.15	0	−0.02	−0.01	−0.02
021	0.04	−0.02	0	0.1	−0.02	−0.01	−0.02	0
022	0.07	0.02	0.01	0.13	0	−0.02	−0.01	−0.02
023	0.06	0	0	0.12	0.01	−0.01	−0.01	−0.03
024	0.06	−0.02	0.01	0.14	−0.01	0	−0.03	−0.02
025	0.1	−0.01	0	0.15	−0.01	−0.01	0	−0.03
026	0.03	−0.02	0	0.14	−0.01	−0.03	−0.02	0.02
027	0.02	−0.02	0	0.17	−0.02	−0.04	−0.03	0.01
028	0.03	−0.01	0	0.03	0.01	0	0	−0.01
029	0.11	−0.03	0	−0.02	−0.04	0.13	0.02	−0.03
030	0.11	−0.04	0.03	−0.01	−0.05	0.11	0.03	−0.03
031	0.13	−0.02	0.01	0.01	−0.04	0.06	0.06	−0.03
032	0.13	−0.03	0.01	−0.01	−0.02	0.08	0.05	−0.03
033	0.07	−0.02	0.02	−0.01	−0.02	0.03	0.02	0.02
034	0.09	0	0	0	0	0.01	0.04	0.02
035	0.07	0	0.07	−0.06	−0.04	0.06	−0.02	0
036	0.08	0.02	0.05	−0.05	−0.04	0.11	−0.02	0.01
037	0.12	−0.02	−0.03	−0.03	−0.04	−0.04	0.19	−0.01
038	0.12	−0.02	−0.05	−0.03	−0.03	−0.05	0.2	−0.02
039	0.12	−0.03	−0.06	−0.02	−0.02	−0.03	0.18	−0.02
040	0.13	−0.02	−0.04	−0.04	−0.03	−0.03	0.17	0
041	0.12	−0.04	−0.03	−0.03	−0.03	−0.02	0.18	−0.02
042	0.11	−0.04	−0.04	−0.01	−0.02	−0.04	0.18	−0.01
043	0.13	−0.04	−0.01	0	−0.05	0.02	0.14	−0.02
044	0.1	−0.02	−0.03	0.03	0.01	0.09	−0.05	0.06
045	0.1	−0.01	−0.01	0.02	0.02	0.02	−0.03	0.06
046	0.08	0	0	0	−0.04	0.02	−0.02	0.11
047	0.12	−0.02	−0.01	0.01	−0.02	0.03	0.02	0.07
048	0.12	−0.02	−0.01	−0.01	−0.02	0.06	0.01	0.06
049	0.1	−0.01	−0.01	0.02	0.02	0.05	−0.03	0.06
050	0.07	0.01	−0.05	−0.03	−0.04	0.01	0.02	0.14
051	0.09	−0.02	0.01	0.04	−0.01	0.01	0	0.08
052	0.08	0.01	−0.02	0.01	−0.03	−0.04	−0.04	0.16
053	0.07	0.02	−0.03	0	−0.04	−0.04	−0.02	0.17
054	0.1	0	−0.01	0	−0.03	−0.05	0	0.13
055	0.08	0.01	−0.02	0.03	−0.01	−0.05	−0.03	0.12
056	0.06	0.02	−0.02	0	−0.01	−0.04	−0.05	0.11
057	0.08	0.02	−0.05	−0.03	−0.02	−0.03	0	0.19
058	0.08	0.02	−0.03	0.02	−0.03	−0.05	−0.01	0.17
059	0.07	0.01	−0.01	−0.02	−0.03	−0.01	0.03	0.09
060	0.08	−0.01	0	−0.01	−0.03	−0.01	0.02	0.11
061	0.11	0.04	0.02	0.06	−0.03	−0.02	0.04	−0.02
062	0.11	0.05	0.01	0.07	−0.02	−0.02	0.04	−0.04
063	0.09	0.06	0.01	0.07	0	−0.01	0.02	−0.01
064	0.09	0.04	0.01	0.09	0	−0.03	0.02	−0.02
065	0.12	0.04	0.03	0.05	−0.02	−0.01	0.04	−0.02

	pF	ADHD	ANX	COND	PSYCH	DEP	MANIA	OCD
066	0.08	−0.02	0.04	−0.02	−0.04	0.08	−0.01	0.02
067	0.1	−0.03	0.05	−0.02	−0.02	0.05	0.01	0.02
068	0.09	−0.02	0	−0.01	−0.01	0.06	0	0.02
069	0.05	−0.01	0.09	−0.01	0.01	−0.04	−0.01	−0.02
070	0.06	−0.02	0.1	0.01	0.01	−0.04	−0.02	−0.01
071	0.06	−0.01	0.06	0	0.01	−0.03	0	−0.01
072	0.05	0.01	0.1	−0.01	0.02	−0.04	−0.04	0
073	0.04	0.02	0.07	−0.03	0.01	−0.03	−0.01	−0.01
074	0.07	−0.01	0.08	−0.01	0.01	−0.03	−0.03	0.02
075	0.07	−0.01	0.1	0.02	0.01	−0.04	−0.03	−0.01
076	0.07	0.02	0.06	−0.03	0.01	−0.01	−0.03	0.03
077	0.1	−0.01	−0.01	−0.02	0.09	−0.02	0	0.01
078	0.09	−0.03	0.01	−0.01	0.05	−0.02	0.05	−0.01
079	0.1	−0.01	−0.01	0	0.07	−0.01	0	0.01
080	0.07	−0.02	−0.01	0	0.03	−0.02	0.04	0
081	0.11	−0.03	0.01	−0.01	0.06	−0.03	0.05	0
082	0.09	−0.03	0	0	0.01	−0.01	0.03	0.02
083	0.03	0	0.01	0.01	0.01	−0.01	0	0
084	0.08	−0.03	−0.01	0.06	−0.01	0.04	−0.01	−0.01
085	0.06	−0.03	0	0.11	−0.02	0.02	0	−0.03
086	0.05	−0.02	0.02	0.05	−0.03	0.06	−0.03	0
087	0.05	−0.03	−0.02	0.12	−0.01	0	0	−0.01
088	0.03	−0.03	0.01	0.05	−0.02	−0.01	0.02	0
089	0.07	−0.04	0	0.08	−0.01	−0.01	0.02	0
090	0.07	−0.04	0.02	0.05	−0.01	−0.02	0.04	−0.02
091	0.08	0.04	0.01	0	−0.01	0.08	−0.02	−0.02
092	0.06	0.08	−0.02	−0.04	0	0.06	−0.01	0
093	0.05	0	0	0.01	−0.01	0.09	−0.05	−0.02
094	0.07	0	0.06	−0.01	−0.02	0.02	−0.01	−0.02
095	0.06	0.01	0.08	−0.01	−0.03	0.02	−0.01	−0.01
096	0.06	0.02	0.09	0	−0.02	0.02	−0.02	0
097	0.09	−0.01	0.06	−0.01	−0.02	0.01	0	−0.02
098	0.04	0.03	0.07	−0.03	−0.02	0.02	−0.01	0.01
099	0.11	0.16	−0.01	−0.03	0.01	0	−0.02	0.01
100	0.13	−0.02	−0.01	−0.02	0.11	0.02	0	−0.03
101	0.08	0	−0.01	−0.01	0.13	−0.03	−0.04	−0.01
102	0.11	−0.01	−0.02	0	0.13	0.01	−0.05	−0.02
103	0.11	−0.02	−0.02	0	0.12	−0.03	−0.02	0
104	0.13	−0.02	0	−0.02	0.13	−0.01	−0.02	−0.03
105	0.09	−0.01	−0.02	−0.01	0.13	−0.04	−0.03	0
106	0.11	−0.03	−0.01	0.02	0.1	0	−0.04	−0.01
107	0.09	0	−0.01	−0.01	0.15	−0.05	−0.03	−0.02
108	0.13	−0.02	−0.03	−0.02	0.13	0.02	−0.02	−0.01
109	0.12	−0.01	−0.02	−0.03	0.14	−0.03	0	0
110	0.11	−0.02	−0.01	0.01	0.11	−0.03	−0.02	−0.01
111	0.11	−0.01	−0.04	−0.03	0.1	0.06	−0.05	0.02
112	0.08	0.01	0	−0.02	0.02	−0.01	0.08	−0.01
113	0.08	0.02	−0.01	−0.02	0.02	0	0.07	−0.01
114	0.08	0.04	−0.01	−0.02	0.05	0.01	0.03	−0.01
115	0.09	−0.02	−0.04	−0.03	−0.01	0.14	0	0
116	0.09	−0.02	−0.03	0.03	0	0.09	0.02	0.01
117	0.11	−0.01	−0.05	0.01	0.01	0.15	−0.01	0.01
118	0.07	0.02	0	0	0.05	0.07	−0.05	−0.02
119	0.06	0.04	−0.02	−0.05	0.01	0.09	−0.05	−0.03
120	0.06	0.03	−0.03	−0.03	0	0.07	−0.04	−0.02
121	0.08	0.05	−0.03	−0.03	0.01	0.11	−0.07	−0.02
122	0.09	0.05	−0.02	0	0.03	0.11	−0.05	−0.01
123	0.08	0	0.13	−0.01	−0.01	0.03	0	−0.04
124	0.07	−0.01	0.11	−0.02	−0.01	0.02	0	−0.04
125	0.07	−0.02	0.13	0	−0.01	0	0.02	−0.05
126	0.09	−0.02	0.14	−0.01	−0.01	0	0.01	−0.05
127	0.1	−0.02	0.13	−0.01	−0.01	0	0.02	−0.05
128	0.1	−0.02	0	0	0	0.07	−0.02	0
129	0.09	−0.02	−0.01	0.01	0	0.13	−0.04	−0.02

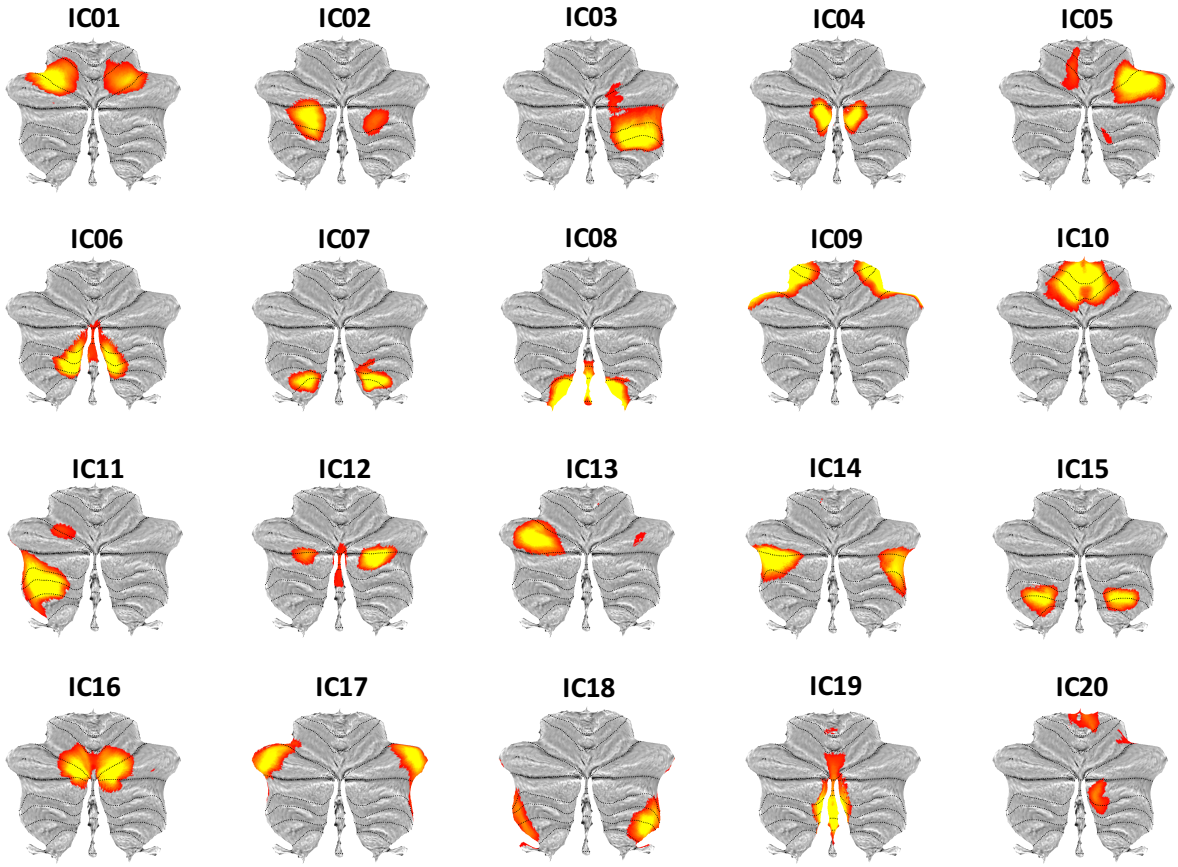
Supplementary Figure 3: Principal component (pF) and independent component weights for each clinical item. pF: General psychopathology; ADHD: Attention Deficit Disorder; ANX: Anxiety; COND: Conduct disorder; PSYC: Psychosis; DEP: Depression; MANIA: Mania; OCD: Obsessive-compulsive disorder.



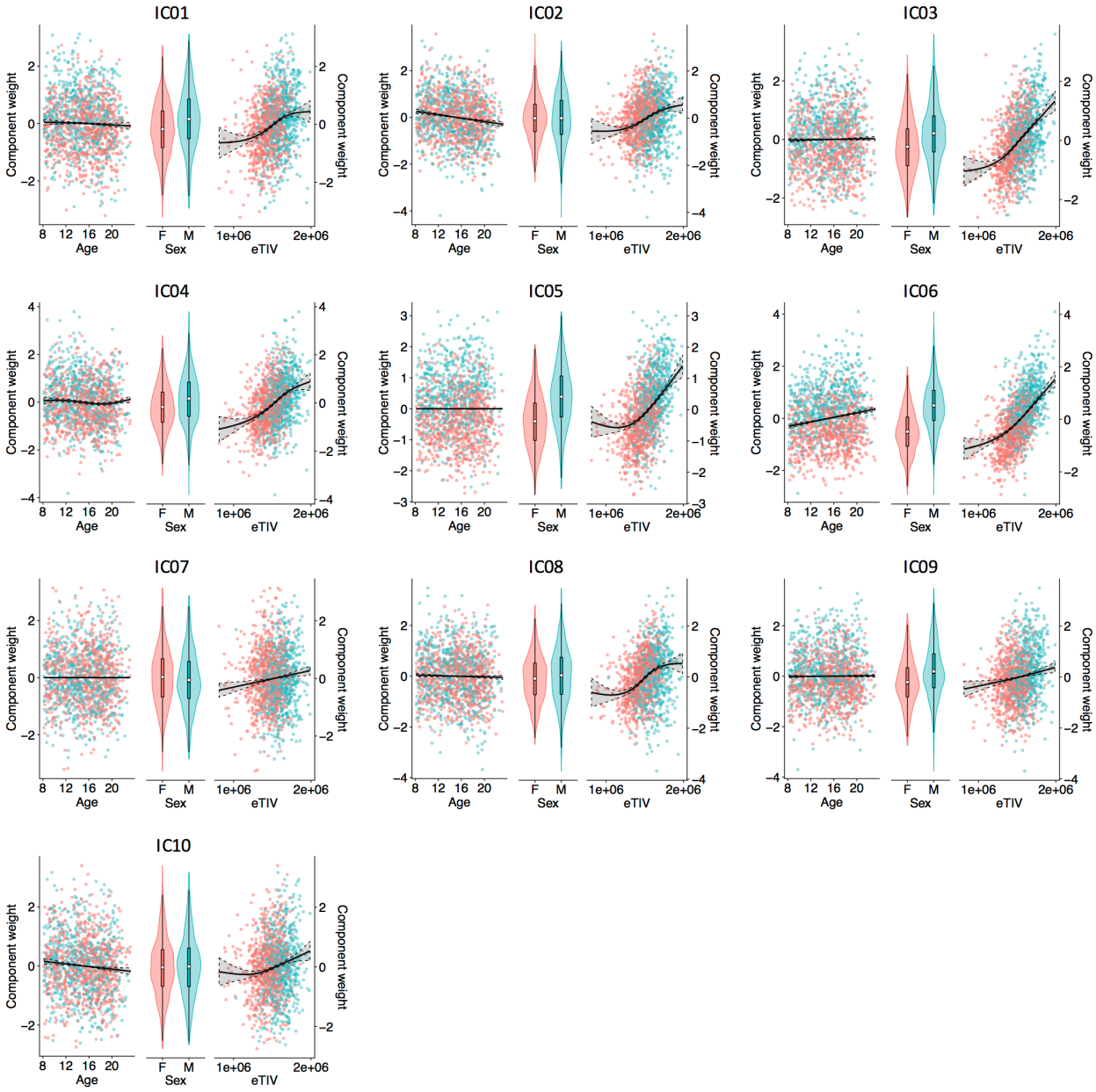
Supplementary Figure 4: ICA-decompositions of cerebellar grey matter maps using a model order of 5. Note IC01, which fuses regions assigned to cerebellar components IC03 and IC06 in the 10 component solution.



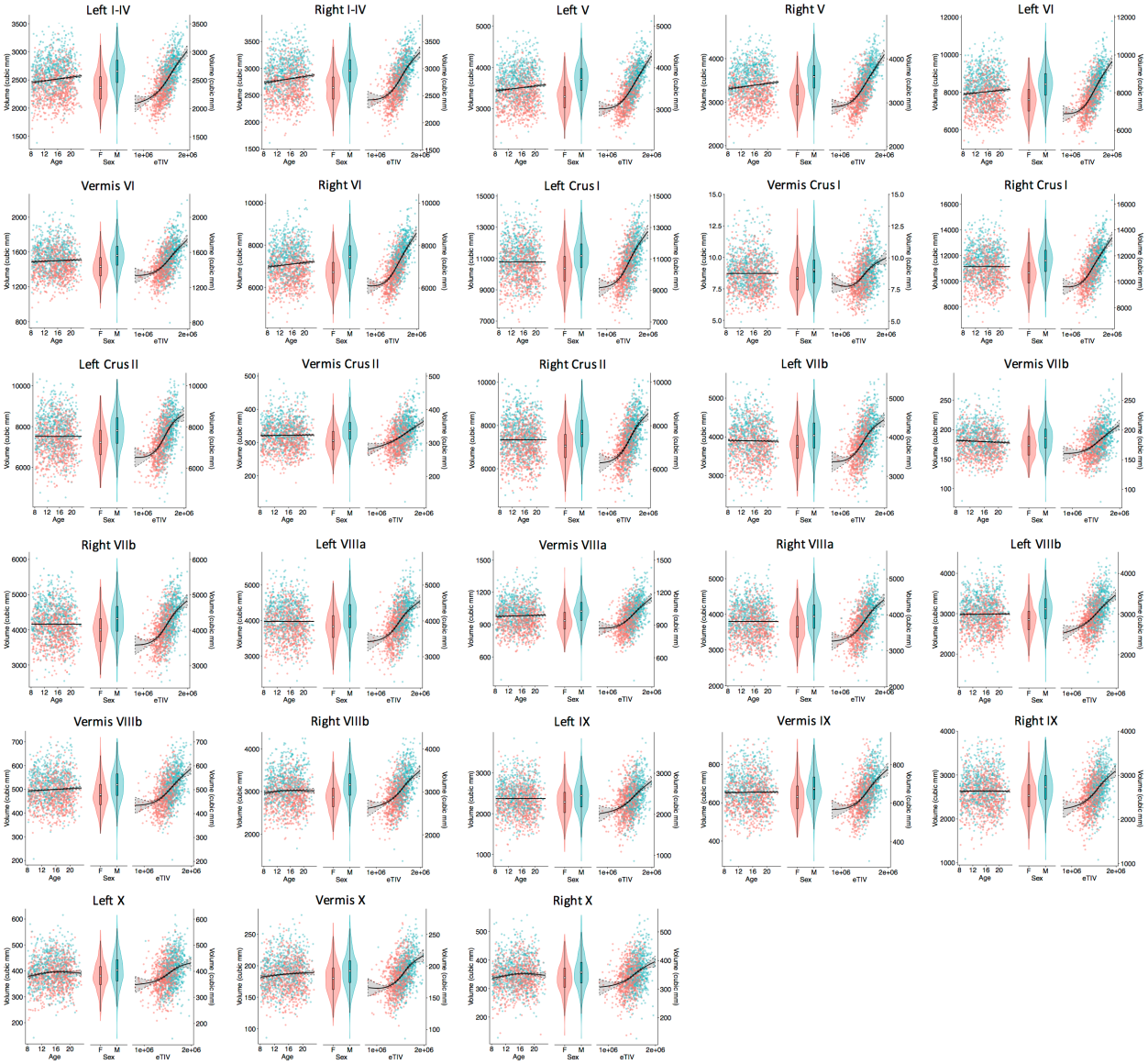
Supplementary Figure 5: ICA-decompositions of cerebellar grey matter maps using a model order of 15. Note IC04 and IC08, which largely correspond to the left and right aspect of the bilateral IC03 in the 10 component solution.



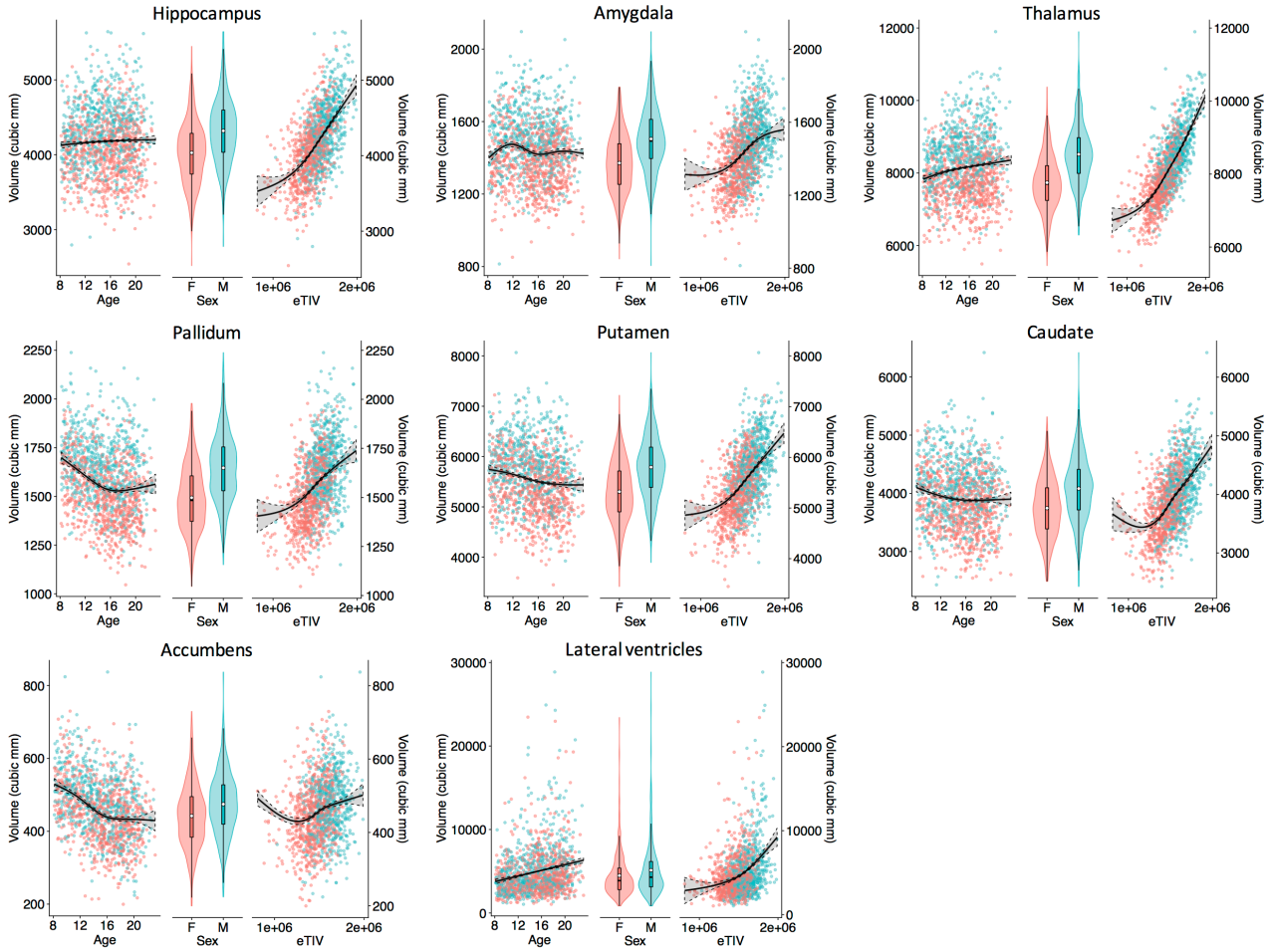
Supplementary Figure 6: ICA-decompositions of cerebellar grey matter maps using a model order of 20. Note IC05 and IC13, which largely correspond to the left and right aspect of the bilateral IC03 in the 10 component solution, and IC03 and IC11, which largely correspond to the left and right aspect of the bilateral IC03 in the 10 component solution.



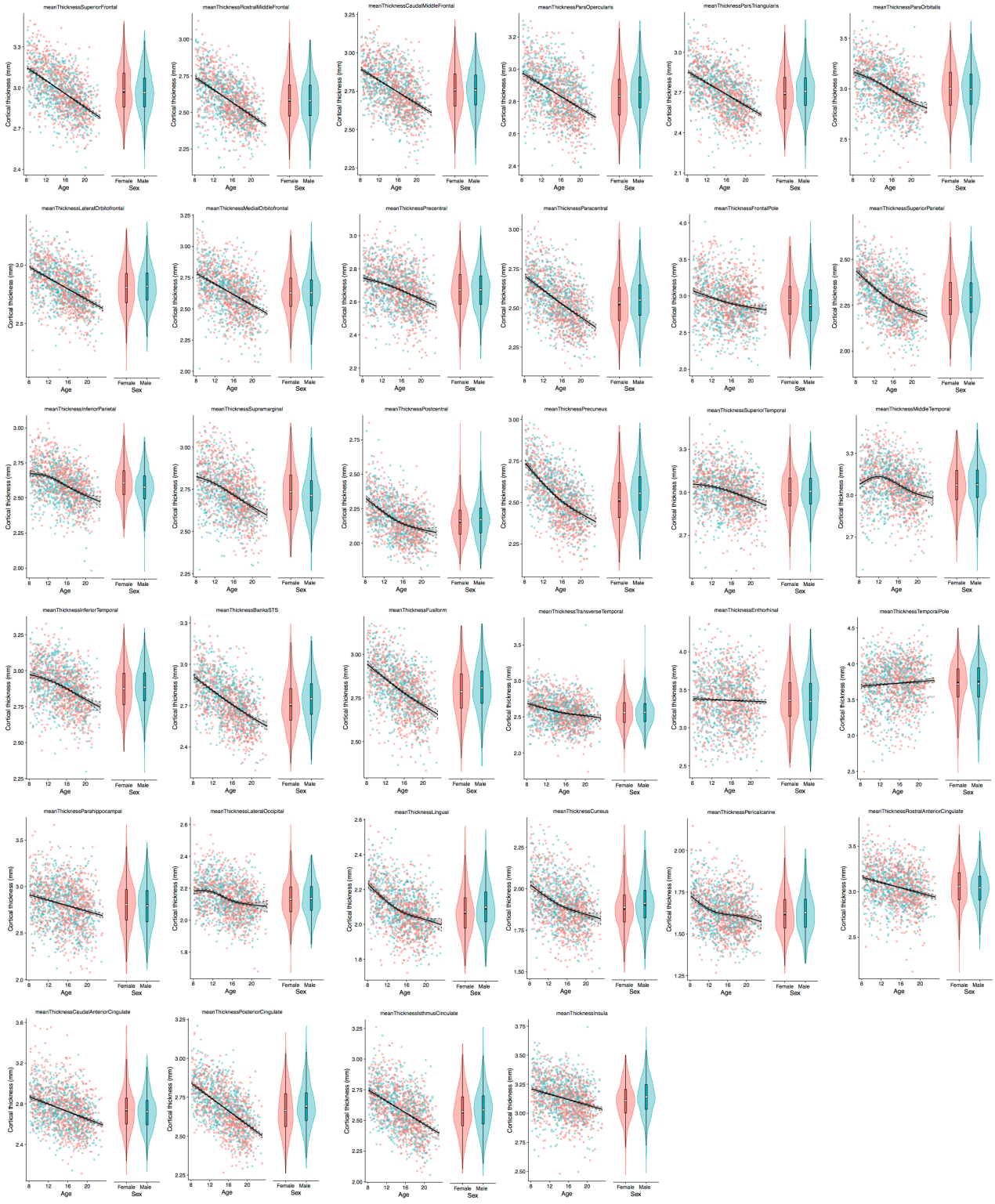
Supplementary Figure 7: Effects of age, gender and estimated total intracranial volume on subject weights for the 10 cerebellar components. Solid lines in the scatter plots depict the GAM-estimated smooth function, while shaded regions represent +/- 2 SEM. Distributions for each gender are represented in combined violin and box-plots, with the white dot indicating the group mean. For statistics, see Supplementary Table 4.



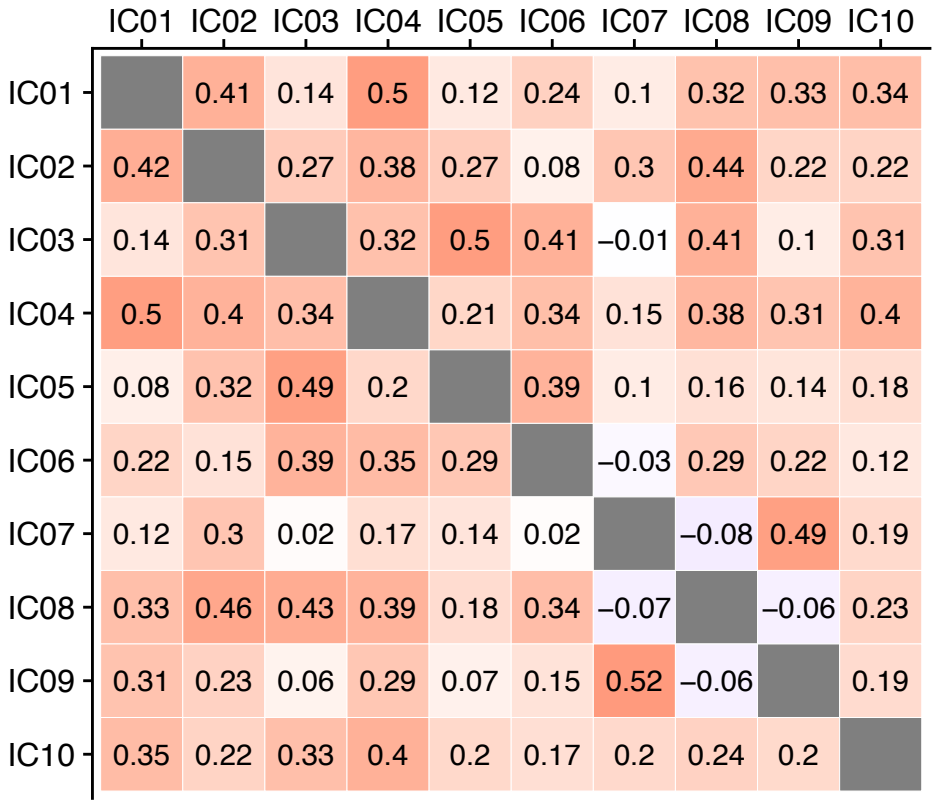
Supplementary Figure 8: Effects of age, gender and estimated total intracranial volume on volumes of the 28 cerebellar lobules. Solid lines in the scatter plots depict the GAM-estimated smooth function, while shaded regions represent +/- 2 SEM. Distributions for each gender are represented in combined violin and box-plots, with the white dot indicating the group mean. For statistics, see Supplementary Table 5.



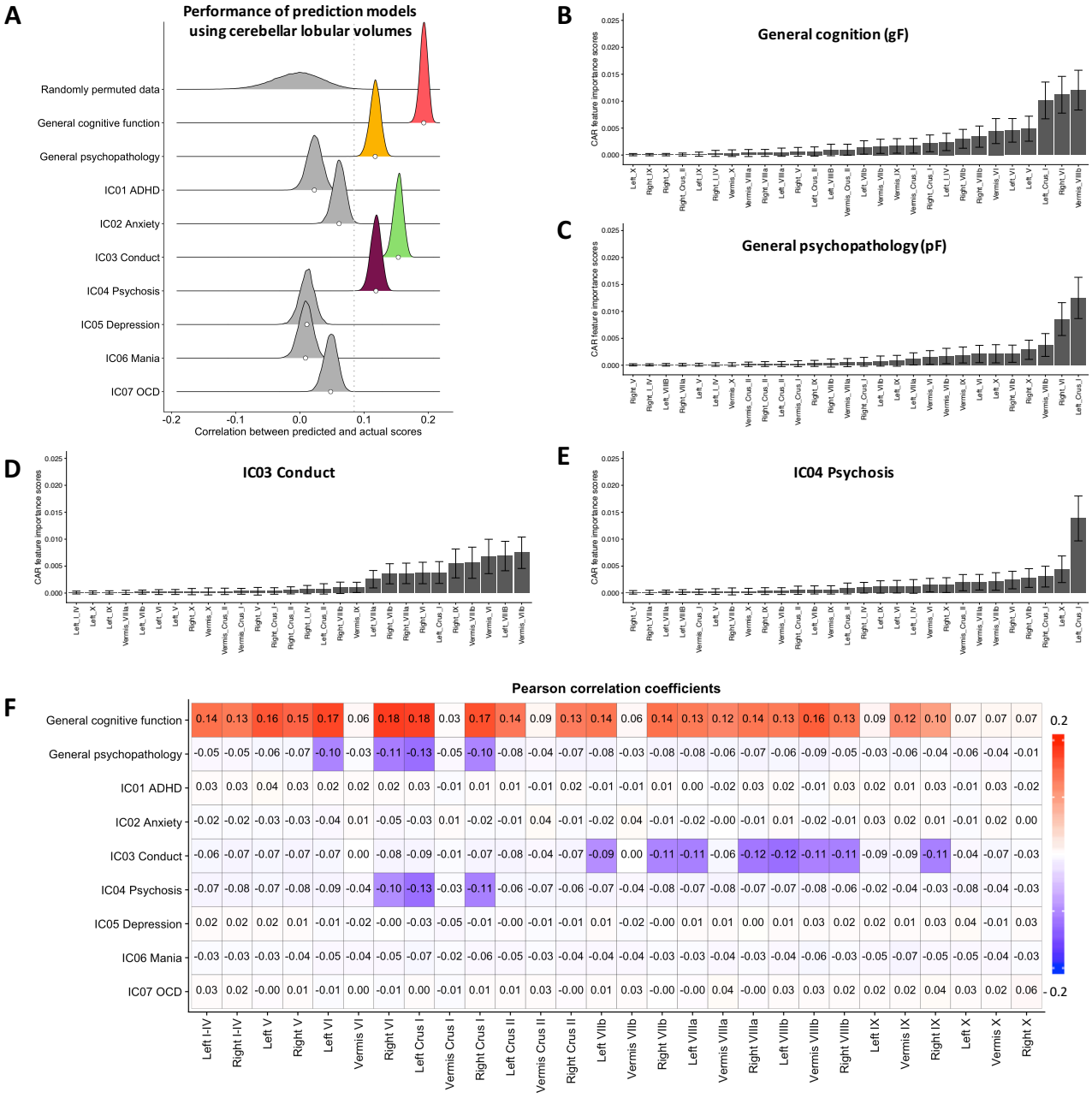
Supplementary Figure 9: Effects of age, gender and estimated total intracranial volume on volumes of the 8 (bilateral) subcortical structures. Solid lines in the scatter plots depict the GAM-estimated smooth function, while shaded regions represent +/- 2 SEM. Distributions for each gender are represented in combined violin and box-plots, with the white dot indicating the group mean. For statistics, see Supplementary Table 6.



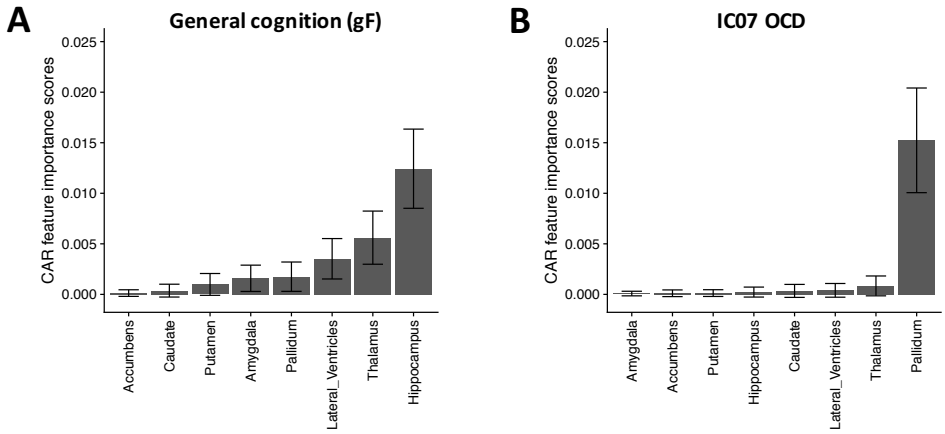
Supplementary Figure 10: Effects of age and gender on cortical thickness estimates for the 34 (bilateral) cerebro-cortical ROIs. Solid lines in the scatter plots depict the GAM-estimated smooth function, while shaded regions represent +/- 2 SEM. Distributions for each gender are represented in combined violin and box-plots, with the white dot indicating the group mean. For statistics, see Supplementary Table 7.



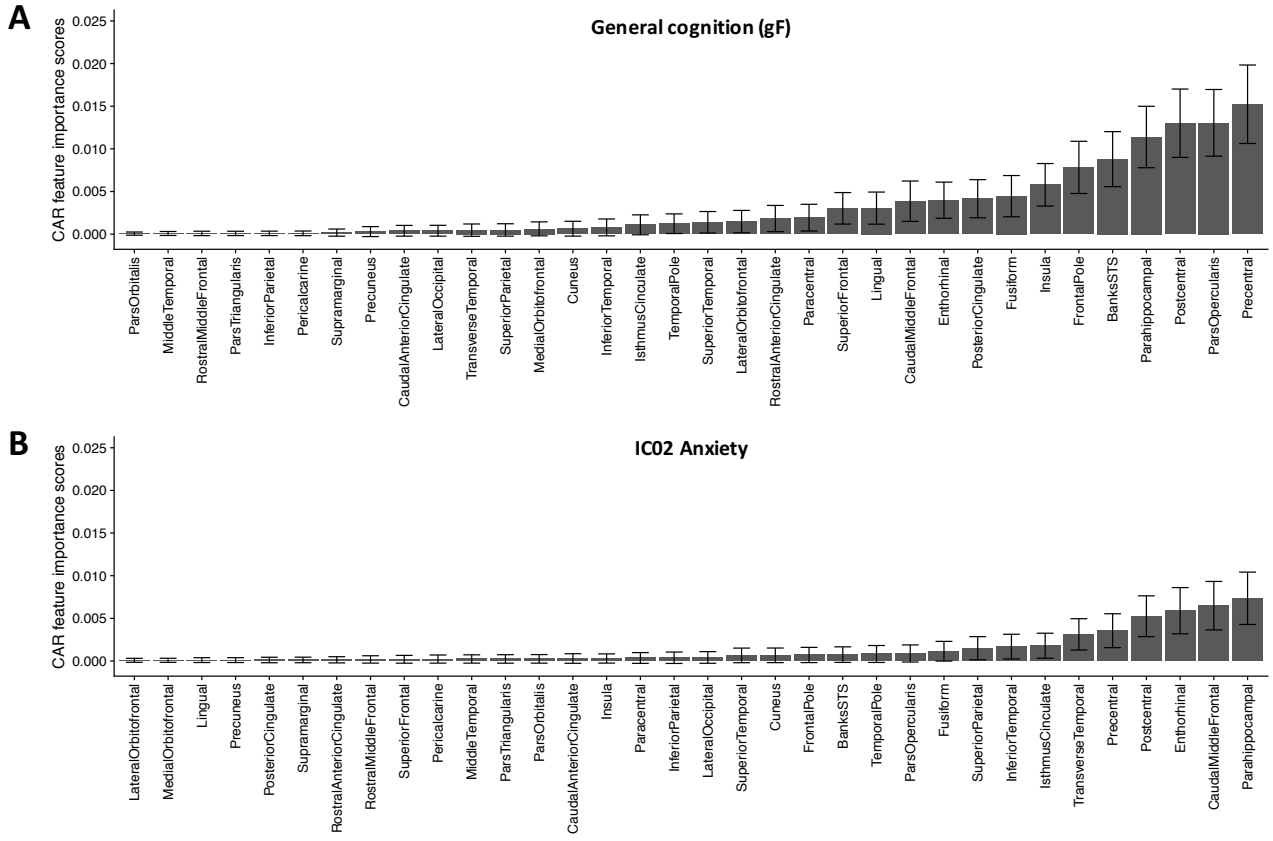
Supplementary Figure 11: Correlations between the 10 cerebellar components using raw components weights (above the diagonal) and component weights adjusted for effects of sex, age and total estimated intracranial volume (below the diagonal).



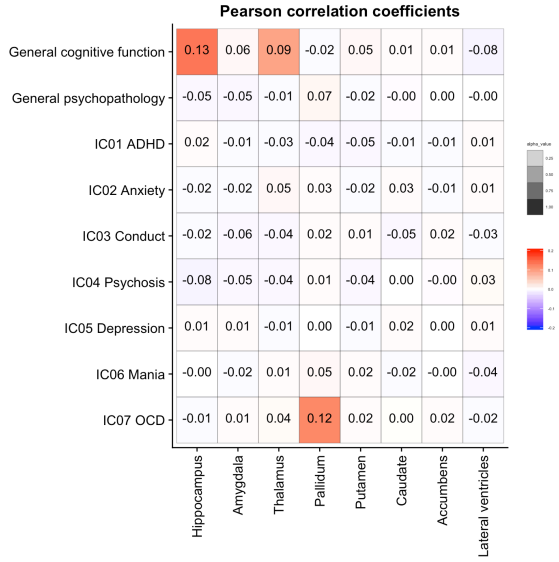
Supplementary Figure 12: Results from prediction models using cerebellar lobules **(A).** Feature importance weights (CAR-scores) for the four significant prediction models using the volumes of 28 cerebellar lobular ROIs **(B-E)**. CAR-scores were computed for each of 10,000 iterations of the model on randomly 10-fold partitioned data, yielding 100,000 estimates for each model. Error bars denote the 2.5th and 97.5th percentiles of these CAR-score distributions. Results from univariate correlation analyses **(F)**. Colored tiles mark significant associations ($p < .05$, based on 10,000 permutations and corrected for multiple comparisons across the matrix).



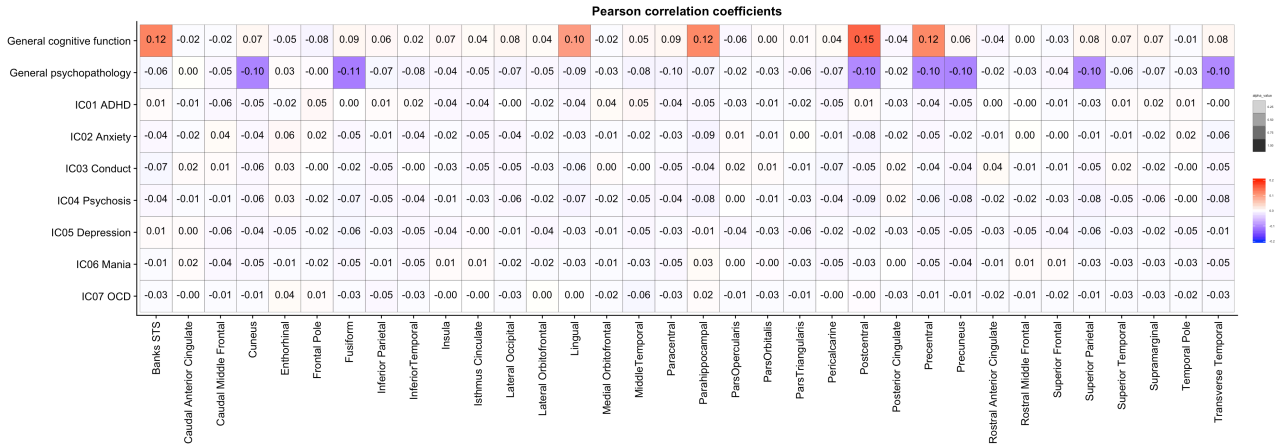
Supplementary Figure 13: Feature importance weights (CAR-scores) for the two significant prediction models using subcortical volumes. CAR-scores were computed for each of 10,000 iterations of the model on randomly 10-fold partitioned data, yielding 100,000 estimates for each model. Error bars denote the 2.5th and 97.5th percentiles of these CAR-score distributions.



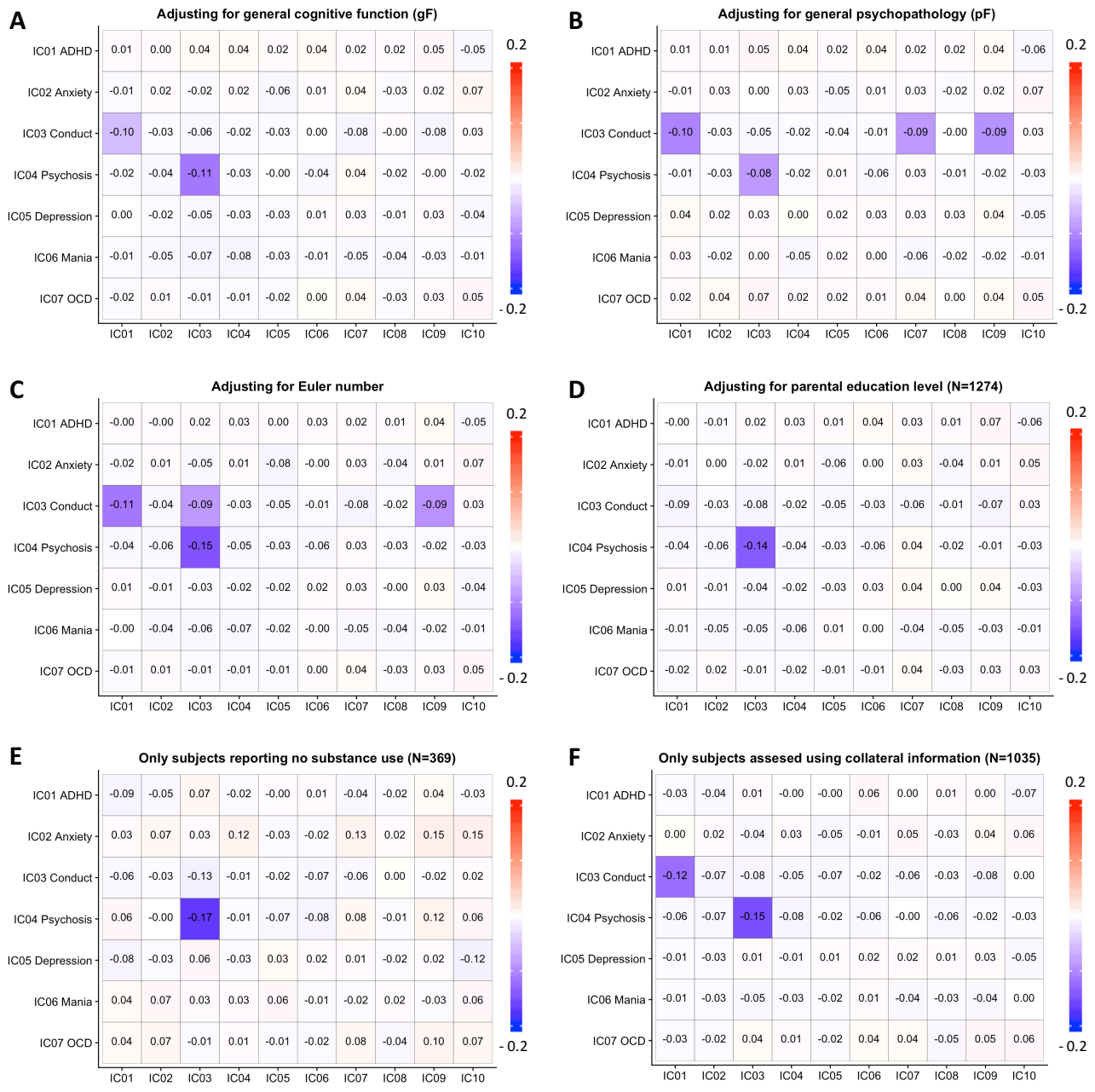
Supplementary Figure 14: Feature importance weights (CAR-scores) for the two significant prediction models using mean cortical thickness from 34 bilateral ROIs. CAR-scores were computed for each of 10,000 iterations of the model on randomly 10-fold partitioned data, yielding 100,000 estimates for each model. Error bars denote the 2.5th and 97.5th percentiles of these CAR-score distributions.



Supplementary Figure 15: Results from univariate correlation analyses using subcortical volumes. Colored tiles mark significant associations ($p < .05$, based on 10,000 permutations and corrected for multiple comparisons across the matrix)



Supplementary Figure 16: Results from univariate correlation analyses using mean cortical thickness from 34 bilateral ROIs. Colored tiles mark significant associations ($p < .05$, based on 10,000 permutations and corrected for multiple comparisons across the matrix)



Supplementary Figure 17: Results from univariate control analyses using cerebellar independent components. Colored tiles mark significant associations ($p < .05$, corrected for multiple comparisons across the matrix).

Supplementary Table 1: 17 cognitive test scores included in the principal component analysis (PCA) and their factor loadings on the first principal component.

Cognitive test	**Included outcome measure**	**gF-weight**
The Penn Age Differentiation Test	Percent correct responses	0.2845
The Penn Face Memory Test	Total correct responses	0.1953
Penn Emotion Identification Test	Total Correct Responses for All Test Trials, by genus	0.1593
Penn Word Memory Test	Total Correct Responses for All Test Trials	0.1367
Penn Verbal Reasoning Test	Total Correct Responses for All Test Trials, by genus	0.2770
Penn Emotion Differentiation Test	Percent of Correct Responses for All Test Trials, by genus	0.2344
Penn Motor Praxis task	Median Response Time for Correct Mouse Click Responses	-0.1565
Penn Matrix Reasoning Test	Percent of Correct Responses for All Test Trials, by genus	0.2613
Finger Tapping Test	Sum of Mean of Tap Responses for Dominant Hand Trials and Mean of Tap Responses of Non-Dominant Hand Trials	0.2210
Visual Object Learning Test	Total Correct Responses for All Test Trial	0.1505
Letter N-Back Test	Number of Correct Responses to for 1-Back and2-Back Trials	0.2939
Penn Conditional Exclusion Test	Number of Categories Achieved	0.1683
Penn Conditional Exclusion Test	Calculated Accuracy Measure	0.1183
Penn Continuous Performance Test	Total of Correct Responses to Number Trials (TP) and Letter Trials (TP)	0.1873
Penn Continuous Performance Test	Median Response Time for Correct Responses to Number Trials (TP) and Letter Trials (TP)	-0.1901
Penn Line Orientation Test	Percent Correct Responses for All Test Trials, by genus	0.5059
Wide Range Assessment Test(Reading/IQ)	WRAT: Wide Range Assessment Test 4 Total Raw Score	0.2917

Supplementary Table 2: The 129 clinical items included in PCA and ICA decompositions.

#	Questionnaire/Item
	Attention deficit Hyperactivity Disorder
1	Did you often have trouble paying attention or keeping your mind on your school, work, chores, or other activities that you were doing?
2	Did you often have problems following instructions and often fail to finish school, work, or other things you meant to get done?
3	Did you often dislike, avoid, or put off school or homework (or any other activity requiring concentration)?
4	Did you often lose things you needed for school or projects at home (assignments or books) or make careless mistakes in school work or other activities?
5	Did you often have trouble making plans, doing things that had to be done in a certain kind of order, or that had a lot of different steps?
6	Did you often have people tell you that you did not seem to be listening when they spoke to you or that you were daydreaming?
7	Did you often have difficulty sitting still for more than a few minutes at a time, even after being asked to stay seated, or did you often fidget with your hands or feet or wiggle in your seat or were you "always on the go"?
8	Did you often blurt out answers to other people's questions before they finished speaking or interrupt people abruptly?
9	Did you often join other people's conversations or have trouble waiting your turn (e.g., waiting in line, waiting for a teacher to call on you in class)?
	Agoraphobia
10	Have you ever been very nervous or afraid of: being in crowds (for example, a classroom, cafeteria, restaurant, or movie theater)?
11	Have you ever been very nervous or afraid of: going to public places (such as a store or shopping mall)?
12	Have you ever been very nervous or afraid of: being in an open field?
13	Have you ever been very nervous or afraid of: going over bridges or through tunnels?
14	Have you ever been very nervous or afraid of: traveling by yourself?
15	Have you ever been very nervous or afraid of: traveling away from home?
16	Have you ever been very nervous or afraid of: traveling in a car?
17	Have you ever been very nervous or afraid of: using public transportation like a bus or SEPTA?
	Conduct disorder
18	Was there ever a time when you often did things that got you into trouble with adults like lying or stealing (something worth more than $5, from family, others, or stores)?
19	Did you ever skip school, stay out at night later than you were supposed to (more than 2 hours), or run away from home overnight?
20	Did you ever set fires, break into cars, or destroy someone else's property on purpose?
21	Do you have a probation officer or have you ever been on probation?
22	Did you often bully others (hitting, threatening or scaring someone who was younger or smaller), threaten or frighten someone on purpose, or often start physical fights with others?
23	Have you ever been physically cruel to an animal or person (on purpose)?
24	Did you ever: try to hurt someone with a weapon (a bat, brick, broken bottle, knife, or gun)?
25	Did you ever: threaten someone?
26	Conduct Disorder: Did you ever: hold someone up?
27	Conduct Disorder: Did you ever: attack someone to steal from them?
28	Did you ever: trick or threaten someone into having sex with you, or did anyone ever accuse you of making them do something sexual?
	Depression
29	Has there ever been a time when you felt sad or depressed most of the time?
30	Has there ever been a time when you cried a lot, or felt like crying?
31	Has there ever been a time when you felt grouchy, irritable or in a bad mood most of the time; even little things would make you mad?
32	Has there ever been a time when nothing was fun for you and you just weren't interested in anything?
	Eating Disorder
33	Was there ever a time when you felt really fat or heavy, but other people said that you were too thin?
34	Has there been a time when your eating was out of control - you'd eat a large amount of food in a short period of time and could not stop yourself?
	Generalized Anxiety
35	Have you ever been a worrier?
36	Did you worry a lot more than most children/people your age?
	Mania/Hypomania

37	Have there been times when you were much more active, excited or energetic than usual, had problems sitting still, or needed to move around a lot?
38	Has there ever been a time when you felt so full of energy that you couldn't stop doing things and didn't get tired?
39	Has there ever been a time when you felt like you hardly needed sleep?
40	Have there been times when you kept talking a lot, couldn't stop talking, talked faster than usual, had thoughts faster than usual, or had so many ideas in your head that you could hardly keep track of them?
41	Have you ever had a time when you felt much more happy or excited than you usually do when there was nothing special going on?
42	Have you ever had a time when you felt like you could do almost anything?
43	Has there ever been a time when you felt unusually grouchy, cranky, or irritable; when the smallest things would make you really mad?
	Obsessive Compulsive Disorder
44	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as concern with harming others/self?
45	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as pictures of violent things?
46	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as thoughts about contamination/germs/illness?
47	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as fear that you would do something/say something bad without intending to?
48	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as feelings that bad things that happened were your fault?
49	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as forbidden/bad thoughts?
50	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as need for symmetry/exactness?
51	Have you ever been bothered by thoughts that don't make sense to you, that come over and over again and won't go away, such as religious thoughts?
52	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: cleaning or washing (for example, your hands, house)?
53	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: counting?
54	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: checking (for example, doors, locks, ovens)?
55	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: getting dressed over and over again?
56	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: going in and out a door over and over again?
57	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: ordering or arranging things?
58	Have you ever had to do something over and over again - that would have made you feel really nervous if you couldn't do it, like: doing things over and over again at bedtime, like arranging the pillows, sheets, or other things?
59	Have you ever saved up so many things that people complained or they got in the way
60	Do you feel the need to do things just right (like they have to be perfect)?
	Oppositional Defiant Disorder
61	Was there a time when you often did things that got you into trouble with adults such as losing your temper, arguing with or talking back to adults, or being grouchy or irritable with them?
62	Was there a time when you often got into trouble with adults for refusing to do what they told you to do or for breaking rules at home/school?
63	Did you often annoy other people on purpose or blame other people for your mistakes (excluding siblings)?
64	Did you ever get into trouble for getting even with other people by doing things to hurt them, telling lies about them, or messing up their things?

65	Were you often irritable or grouchy, or did you often get angry because you thought that things were unfair?
	Panic Disorder
66	Have you ever had an attack like this?
67	Has there ever been a time when all of a sudden you felt very, very scared or uncomfortable - and your chest hurt, you couldn't catch your breath, your heart beat very fast, you felt very shaky, and sweaty/tingly/numb in your hands or feet?
68	Has there ever been a time when all of a sudden, you felt that you were losing control, something terrible was going to happen, that you were going crazy, or going to die?
	Specific phobia
69	Have you ever been very nervous or afraid of animals or bugs, like dogs, snakes, or spiders?
70	Have you ever been very nervous or afraid of being in really high places, like a roof or tall building?
71	Have you ever been very nervous or afraid of water or situations involving water, such as a swimming pool, lake, or ocean?
72	Have you ever been very nervous or afraid of storms, thunder, or lightning?
73	Have you ever been very nervous or afraid of doctors, needles, or blood?
74	Have you ever been very nervous or afraid of closed spaces, like elevators or closets?
75	Have you ever been very nervous or afraid of flying or airplanes?
76	Have you ever been very nervous or afraid of any other things or situations?
	Psychosis
77	Have you ever heard voices when no one was there?
78	Has there ever been anything unusual about the way things smelled or felt or looked?
79	Have you ever seen visions or seen things which other people could not see?
80	Have you ever smelled strange odors other people could not smell?
81	Have you ever had strange feelings in your body like things were crawling on you or someone touching you and nothing or no one was there?
82	Have you ever believed in things and later found out they weren't true, like people being out to get you, or talking about you behind your back, or controlling what you do or think?
	Post-traumatic Stress Disorder
83	Have you ever been in a flood or a tornado or an earthquake or a hurricane or some other natural disaster where you thought you were going to die or be seriously hurt?
84	Have you ever been in a situation where you thought you or someone close to you was going to be killed or be hurt very badly (e.g. family violence)?
85	Have you ever been attacked by somebody or badly beaten?
86	Have you ever been very upset by someone forcing you to do something sexual?
87	Have you ever been threatened with a weapon?
88	Have you ever been in a bad accident?
89	Other than television or at the movies, have you ever seen or heard somebody get killed or get hurt very badly or die?
90	Have you ever been very upset by seeing a dead body or by seeing pictures of the dead body of somebody you knew well?
	General Probes
91	Have you ever talked to a counselor, psychologist, social worker, psychiatrist or some other professional about your feelings or problems with your mood or behaviors?
92	Are you currently taking medication because of your emotions and/or behaviors?
93	Have you ever had to go to a hospital and stay overnight because of problems with your mood, feelings, or how you were acting?
	Separation Anxiety
94	Since you were 5 years old, has there ever been a time when you had a lot of worries about your (attachment figures) and were very upset or got sick (for example, felt sick to your stomach, headaches, thrown-up) when you were away from him/her?
95	Has there ever been a time when you wanted to stay home from school or not go to other places (for example, sleep-overs) without your (attachment figures)?
96	When you knew that you were going to be away from home or (attachment figure(s)), did you get very upset and worry (e.g., when you learned (attachment figure(s)) were going on an upcoming trip or night out)?
97	Did you ever worry/have bad dreams about something terrible happening to you or your (attachment figures) so that you would not see them again?
98	Were you scared to be alone in your room (or any place in your house) or did you need your (attachment figure(s)) to stay with

	you while you fell asleep?
	Structural Interview for Prodromal Symptoms (Upper case items denote assessment by clinicians)
99	TROUBLE WITH FOCUS AND ATTENTION: Severity Scale
100	I think that I have felt that there are odd or unusual things going on that I can't explain.
101	I think that I might be able to predict the future.
102	I may have felt that there could possibly be something interrupting or controlling my thoughts, feelings, or actions.
103	I have had the experience of doing something differently because of my superstitions.
104	I think I may get confused at times whether something I experience or perceive may be real or may be just part of my imagination or dreams.
105	I have thought that it might be possible that other people can read my mind, or that I can read others' minds
106	I wonder if people may be planning to hurt me or even may be about to hurt me.
107	I believe that I have special natural or supernatural gifts beyond my talents and natural strengths.
108	I think I might feel like my mind is "playing tricks" on me.
109	I have had the experience of hearing faint or clear sounds of people or a person mumbling or talking when there is no one near me.
110	I think that I may hear my own thoughts being said out loud.
111	I have been concerned that I might be "going crazy."
112	Do people ever tell you that they can't understand you?
113	Do people ever seem to have difficulty understanding you?
114	CHANGES IN SPEECH, DISORGANIZED COMMUNICATION, TANGENTIAL SPEECH: Severity Scale
115	Do you ever feel a loss of sense of self or feel disconnected from yourself or your life?
116	Has anyone pointed out to you that you are less emotional or connected to people than you used to be?
117	CHANGES IN PERCEPTION OF SELF, OTHERS, OR THE WORLD IN GENERAL: Severity Scale
118	EXPRESSION OF EMOTION: Severity Scale
119	Within the past 6 months, are you having a harder time getting your work or schoolwork done?
120	Within the past 6 months, are you having a harder time getting normal activities done?
121	OCCUPATIONAL FUNCTIONING: Severity Scale
122	AVOLITION: Severity Scale
	Social Phobia
123	Was there ever a time in your life when you felt afraid or uncomfortable or really, really shy with people, like meeting new people, going to parties, or eating or drinking, writing or doing homework in front of others?
124	Was there ever a time in your life when you felt afraid or uncomfortable talking on the telephone or with people your own age who you don't know very well?
125	Was there ever a time in your life when you felt afraid or uncomfortable when you had to do something in front of a group of people, like speaking in class?
126	Was there ever a time in your life when you felt afraid or uncomfortable acting, performing, giving a talk/speech, playing a sport or doing a musical performance, or taking an important test or exam (even though you studied enough)?
127	Was there ever a time in your life when you felt afraid or uncomfortable because you were the center of attention and were concerned something embarrassing might happen and you felt very afraid or felt uncomfortable?
	Suicidal Thoughts
128	Have you ever thought a lot about death or dying?
129	Have you ever thought about killing yourself?

Supplementary Table 3: Results from GAM-models of cognitive/clinical scores.

Model	Adjusted r^2	Deviance explained	Sex		Age	
			t-value	p-value	F-value	p-value
gF Cognition	0.409	41.1 %	***4.019***	***6.15e-05***	***241***	***< 2e-16***
pF Psychopathology	0.0705	7.32 %	0.297	0.767	***26.77***	***< 2e-16***
IC01 ADHD	0.0358	3.72 %	***4.616***	***4.27e-06***	***6.994***	***< 8.56e-08***
IC02 Anxiety	0.0653	6.75 %	***-8.910***	***< 2e-16***	***4.96***	***< 2.06e-05***
IC03 Conduct	0.059	6.17 %	***4.497***	***7.48e-06***	***18.49***	***< 2e-16***
IC04 Psychosis	0.0604	6.35 %	***2.481***	***0.0132***	***20.93***	***< 2e-16***
IC05 Depression	0.0781	8.09 %	-0.751	0.45302	***29.26***	***< 2e-16***
IC06 Mania	0.0339	3.64 %	***2.489***	***0.0129***	***11.49***	***1.53e-11***
IC07 OCD	0.00667	0.797 %	***-2.285***	***0.02243***	***1.127***	***0.0191***

Supplementary Table 4: Correlations between raw (upper triangle) and age and sex-adjusted (lower triangle) cognitive/clinical scores.

	gF	pF	IC01	IC02	IC03	IC04	IC05	IC06	IC07
gF Cognition		0.055	-0.163	-0.078	0.010	-0.111	0.204	0.160	0.062
pF Psychopathology	-0.147		0.175	0.329	0.257	0.540	0.437	0.459	0.456
IC01 ADD	-0.102	0.222		0.011	0.01	-0.034	-0.003	-0.038	-0.030
IC02 Anxiety	-0.142	0.329	0.049		-0.025	0.073	-0.056	-0.069	0.062
IC03 Conduct	-0.146	0.238	0.022	0.003		-0.000	0.037	-0.029	0.023
IC04 Psychosis	-0.230	0.538	-0.036	0.063	0.009		0.066	0.004	0.094
IC05 Depression	0.080	0.418	0.039	-0.066	-0.024	0.088		0.067	0.106
IC06 Mania	0.063	0.435	-0.023	-0.072	-0.066	-0.020	0.032		0.057
IC07 OCD	0.033	0.459	-0.013	0.046	0.019	0.097	0.092	0.052	

Supplementary Table 5: Results from GAM-models on cerebellar independent components.

Model	Adjusted r^2	Deviance explained	Sex		Age		eTIV	
			t-value	p-value	F-value	p-value	F-value	p-value
IC01	0.089	9.21 %	1.026	0.305	0.613	0.0812	***21.544***	***< 2e-16***
IC02	0.0759	7.91 %	***-5.08***	***4.18e-07***	***6.674***	***1.57e-07***	***21.587***	***< 2e-16***
IC03	0.205	20.8 %	-0.538	0.590	0.186	0.186	***67.826***	***< 2e-16***
IC04	0.153	15.7 %	-1.648	0.0995	***1.823***	***0.0124***	***49.569***	***< 2e-16***
IC05	0.2772	27.4 %	***6.739***	***2.33e-11***	0.002	0.317	***57.457***	***< 2e-16***
IC06	0.441	44.3 %	***10.835***	***< 2e-16***	***15.33***	***5.25e-15***	***105,94***	***< 2e-16***
IC07	0.0103	1.16 %	***-3.442***	***0.000595***	0	0.808544	***2.872***	***0.000424***
IC08	0.0985	10.4 %	***-4.174***	***3.18e-05***	0.29	0.142	***36.49***	***< 2e-16***
IC09	0.057	5.87 %	***4.792***	***1.83e-06***	0.076	0.253	***4.791***	***7.12e-06***
IC10	0.028	3.09 %	***-2.569***	***0.0103***	***2.494***	***0.000913***	***7.814***	***1.47e-08***

Supplementary Table 6: Results from GAM-models on cerebellar lobules.

Model	Adjusted r^2	Deviance explained	Sex		Age		eTIV	
			t-value	p-value	F-value	p-value	F-value	p-value
Left I to IV	0.436	43.8%	***6.495***	***1.15e-10***	***5.114***	***3.89e-06***	***142.936***	***< 2e-16***
Right I to IV	0.445	44.7%	***7.209***	***9.19e-13***	***6.425***	***2.7e-07***	***142.316***	***< 2e-16***
Left V	0.507	50.9%	***7.847***	***8.42e-15***	***4.768***	***7.96e-06***	***187.116***	***< 2e-16***
Right V	0.507	50.8%	***8.563***	***<2e-16***	***6.116***	***5.03e-07***	***179.262***	***< 2e-16***
Left VI	0.478	48%	***4.937***	***8.87e-07***	***2.948***	***0.000363***	***188.797***	***< 2e-16***
Vermis VI	0.3	30.3%	***3.853***	***0.000122***	***0.758***	***0.0449***	***86.209***	***< 2e-16***
Right VI	0.476	47.8%	***4.86***	***1.31e-06***	***3.674***	***7.74e-05***	***188.113***	***< 2e-16***
Left Crus I	0.365	36.7%	0.037	0.97	0.000	0.919	***144.9***	***< 2e-16***
Vermis Crus I	0.16	16.3%	0.49	0.625	0.000	0.899	***46.61***	***< 2e-16***
Right Crus I	0.389	39.1%	1.439	0.15	0.004	0.457	***150.879***	***< 2e-16***
Left Crus II	0.306	30.9%	0.59	0.555	0.001	0.588	***108.442***	***< 2e-16***
Vermis Crus II	0.199	20.1%	***5.774***	***9.55e-09***	0.158	0.203	***36.614***	***< 2e-16***
Right Crus II	0.323	32.5%	0.825	0.41	0.0	0.659	***115.8***	***< 2e-16***
Left VIIb	0.272	27.4%	0.454	0.65	0.137	0.219	***91.916***	***< 2e-16***
Vermis VIIb	0.192	19.5%	1.739	0.0823	***0.855***	***0.0355***	***51.753***	***< 2e-16***
Right VIIb	0.298	30%	0.724	0.469	0.003	0.464	***103.367***	***< 2e-16***
Left VIIIa	0.261	26.3%	0.917	0.359	0.002	0.545	***84.861***	***< 2e-16***
Vermis VIIIa	0.266	26.8%	***3.714***	***0.000212***	0.438	0.0976	***71.707***	***< 2e-16***
Right VIIIa	0.284	28.6%	1.059	0.29	0.001	0.591	***94.416***	***< 2e-16***
Left VIIIb	0.252	25.5%	***3.812***	***0.000144***	0.081	0.256	***65.826***	***< 2e-16***
Vermis VIIIb	0.251	25.4%	***2.303***	***0.0214***	***1.061***	***0.0221***	***73.072***	***< 2e-16***
Right VIIIb	0.285	28.7%	***4.992***	***6.73e-07***	***1.272***	***0.0299***	***71.249***	***< 2e-16***
Left IX	0.152	15.4%	-0.553	0.581	0.00	1	***47.44***	***< 2e-16***
Vermis IX	0.233	23.6%	-0.498	0.618	0.086	0.255	***79.439***	***< 2e-16***
Right IX	0.191	19.3%	0.615	0.539	0.103	0.276	***57.121***	***< 2e-16***
Left X	0.116	12%	0.961	0.337	***3.147***	***0.00049***	***28.428***	***< 2e-16***
Vermis X	0.214	21.7%	-0.812	0.417	***2.535***	***0.00102***	***70.884***	***< 2e-16***
Right X	0.12	12.4%	-0.019	0.984	***3.186***	***0.000427***	***32.475***	***< 2e-16***

Supplementary Table 7: Results from GAM-models on subcortical volumes.

Model	Adjusted r^2	Deviance explained	Sex		Age		eTIV	
			t-value	p-value	F-value	p-value	F-value	p-value
Hippocampus	0.366	36.8 %	0.957	0.339	***1.353***	***0.0154***	***139.471***	***< 2e-16***
Amygdala	0.26	26.3 %	***6.464***	***1.41e-10***	***5.684***	***2.1e-05***	***48.137***	***< 2e-16***
Thalamus	0.592	59.4 %	***4.596***	***4.7e-06***	***17.8***	***< 2e-16***	***309.2***	***< 2e-16***
Pallidum	0.351	35.4 %	***8.112***	***1.08e-15***	***40.12***	***< 2e-16***	***54.17***	***< 2e-16***
Putamen	0.352	35.5 %	***4.193***	***2.93e-05***	***13.43***	***1.31e-13***	***97.56***	***< 2e-16***
Caudate	0.323	32.7 %	0.44	0.66	***6.678***	***3.62e-07***	***113.156***	***< 2e-16***
Accumbens	0.204	20.8 %	1.858	0.0633	***58.84***	***< 2e-16***	***15.80***	***5.3e-15***
Lat. ventricles	0.155	15.7 %	***-2.172***	***0.03***	***17.24***	***< 2e-16***	***40.27***	***< 2e-16***

Supplementary Table 8: Results from GAM-models of ROI mean cortical thickness.

Model	Adjusted r^2	Deviance explained	Sex		Age	
			t-value	p-value	F-value	p-value
Superior Frontal	0.29	29.1%	***-3.97***	***7.56e-05***	***141.9***	***< 2e-16***
Rostral Middle Frontal	0.27	27.1%	***-2.443***	***0.0147***	***129.7***	***< 2e-16***
Caudal Middle Frontal	0.22	21.9 %	-1.88	0.0604	***97.88***	***< 2e-16***
IFG Pars Opercularis	0.20	19.6	***2.089***	***0.0369***	***82.12***	***< 2e-16***
IFG Pars Triangularis	0.22	22.6 %	0.328	0.743	***100.8***	***< 2e-16***
IFG Pars Orbitalis	0.18	18.4 %	-1.875	0.061	***78.29***	***< 2e-16***
Lateral Orbitofrontal	0.23	23.3 %	-0.115	0.908	***104.1***	***< 2e-16***
Medial Orbitofrontal	0.20	20 %	-1.191	0.234	***87.37***	***< 2e-16***
Precentral	0.10	10.4 %	-0.748	0.455	***40.08***	***< 2e-16***
Paracentral	0.28	28 %	0.731	0.465	**133.9**	***< 2e-16***
Frontal Pole	0.06	6.57 %	***-5.567***	***3.1e-08***	***17.88***	***< 2e-16***
Superior Parietal	0.26	26.1 %	-0.278	0.781	***122.2***	***< 2e-16***
Inferior Parietal	0.18	18.5 %	***-5.906***	***4.41e-09***	***73.31***	***< 2e-16***
Supramarginal	0.17	17.3 %	***-4.278***	***2.02e-05***	***70.23***	***< 2e-16***
Postcentral	0.22	22.1 %	-0.099	0.921	***97.91***	***< 2e-16***
Precuneus	0.36	36.6 %	***3.698***	***0.000226***	***192.4***	***< 2e-16***
Superior Temporal	0.07	6.9 %	0.194	0.846	***25.13***	***< 2e-16***
Middle Temporal	0.08	8.71 %	-0.369	0.712	***32.36***	***< 2e-16***
Inferior Temporal	0.15	14.8 %	0.122	0.903	***59.66***	***< 2e-16***
Banks STS	0.29	29.3 %	***3.607***	***0.000321***	***137.1***	***< 2e-16***
Fusiform	0.26	25.6 %	1.712	0.0872	***117.2***	***< 2e-16***
Transverse Temporal	0.06	6.33 %	-0.513	0.608	***23.07***	***< 2e-16***
Entorhinal	0.001	0.23 %	-0.947	0.344	0.469	0.0902
Temporal Pole	0.004	0.52 %	0.525	0.6	***1.589***	***0.00677***
Parahippocampal	0.05	5.17 %	-1.642	0.101	***18.56***	***< 2e-16***
Lateral Occipital	0.09	9.13 %	-0.383	0.702	***34.18***	***< 2e-16***
Lingual	0.21	20.9 %	***3.066***	***0.00221***	***86.61***	***< 2e-16***
Cuneus	0.14	14.3 %	***2.229***	***0.026***	***54.98***	***< 2e-16***
Pericalcarine	0.07	7.54 %	-0.282	0.778	***27.7***	***< 2e-16***
Rostral Anterior Cingulate	0.06	6.22 %	***-2.021***	***0.0435***	***22.48***	***< 2e-16***
Caudal Anterior Cingulate	0.12	12.2 %	***-3.235***	***0.00125***	***46.89***	***< 2e-16***
Posterior Cingulate	0.324	32.5	**2.424**	**0.0155**	***163.6***	***< 2e-16***
Isthmus Cingulate	0.23	23.1 %	0.229	0.819	***104***	***< 2e-16***
Insula	0.08	8.11 %	***3.29***	***0.00103***	***26.52***	***< 2e-16***

Supplementary Table 9: Significant results from the voxel-wise general linear models

Contrast	Cluster extent (voxels)	Peak coordinates x	y	z	*t*	*p*	Anatomical labels
gF positive	92614	36	-41	-28	8.29	<.0001	Widespread
	41	-20	-32	-38	5.62	<.0001	Left lobule X
pF negative	5727	39	-37	-32	5.72	<.0001	Right Crus I, Right VI, Right Crus II
	5220	-42	-71	-24	6.83	<.0001	Left Crus I, Left Crus II, Left lobule VI
	80	-37	-50	-23	4.80	.002	Left lobule VI
	64	-23	-74	-20	4.59	.006	Left lobule VI
	8	-34	-59	-21	4.28	.017	Left lobule VI
	7	-27	-72	-44	4.30	.016	Left Crus II
	3	-32	-64	-58	4.24	.021	Left Lobule VIIb
IC02 Anxiety negative	11	-31	-34	-35	4.26	.018	Left lobule VI
IC03 Conduct negative	6583	2	-60	-48	5.81	<.0001	Right Lobule VIII, Right Lobule IX, Right Lobule VIIb, Left Lobule IX, Vermis IX, Vermis VIIIa, Vermis VIIIb, Right Crus II
	2732	-26	-49	-57	5.40	<.0001	Left Lobule VIIIa, Left Lobule VIIb, Left Lobule IX
	975	-29	-69	-46	5.10	.001	Left Lobule VIIb, Left Crus II, Left VIIIa, Left Lobule VIIIb
	950	-43	-61	-37	4.93	.001	Left Crus I, Left Crus II
	491	-25	-83	-37	4.91	.002	Left Crus II
	360	-27	-63	-34	4.73	.003	Left Crus I, Left Lobule VI
	193	36	-40	-28	4.57	.006	Right Lobule VI, Right Lobule V
	38	32	-82	-25	4.29	.016	Right Crus I
	31	20	-87	-35	4.30	.016	Right Crus II
	23	33	-76	-31	4.27	.018	Right Crus I
	19	28	-63	-35	4.25	.019	Right Crus I
	14	38	-76	-26	4.22	.021	Right Crus I
	11	4	-40	-18	4.47	.009	Right Lobule I to IV
	9	32	-68	-20	4.31	.016	Right Lobule VI
	3	21	-57	-29	4.21	.021	Right Lobule VI
IC04 Psychosis negative	4182	-39	-71	-26	5.63	<.0001	Left Crus I, Left Crus II, Left Lobule VI
	3795	47	-62	-26	5.67	<.0001	Right Crus I, Right Lobule VI
	39	-42	-41	-35	4.99	.002	Left Crus I
	1	-22	-74	-21	4.22	0.021	Left Lobule VI

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