Linking cerebellar functional gradients to transdiagnostic behavioral dimensions of psychopathology

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Abstract

Objective: There is ample evidence for high co-morbidity and substantial overlap across psychiatric disorders, encouraging a transition in psychiatry research from categorical to dimensional approaches that integrate neuroscience and psychopathology. Converging evidence suggests that the cerebellum is involved in a wide range of cognitive functions and mental disorders. The authors examined the extent to which cerebellar function can be linked to transdiagnostic dimensions of psychopathology.

Methods: The authors used a multivariate data-driven statistical technique (partial least squares) to identify latent dimensions linking human cerebellar connectome as assessed by functional MRI to a large set of clinical, cognitive, and trait measures in a sample of 198 participants, including healthy controls (n=92) as well as patients diagnosed with attention-deficit/hyperactivity disorder (n=35), bipolar disorder (n=36), and schizophrenia (n=35). Macroscale spatial gradients of connectivity at voxel level were used to characterize cerebellar connectome properties, which provide a low-dimensional representation of cerebellar connectivity, i.e., a sensorimotor-supramodal hierarchical organization.

Results: This multivariate analysis revealed significant correlated patterns of cerebellar connectivity gradients and behavioral measures that could be represented into four latent dimensions. Each dimension was associated with a unique spatial pattern of cerebellar connectivity gradients across all participants, and linked to different clusters of behavioral measures including clinical, cognitive, and personality scores. Multiple control analyses and 10-fold cross-validation confirmed the robustness and generalizability of the yielded four

dimensions.

Conclusions: The robust associations between cerebellar functional gradients and multiple transdiagnostic behavioral dimensions of psychopathology highlight the importance of cerebellar function in transdiagnostic behavioral dimensions of psychopathology.

Introduction

Our understanding of cerebellar contributions to neurological function has changed from a traditional view focused on motor coordination, to a modern understanding that also implicates the cerebellum in a broad range of high-level cognitive and affective processes (1). An increasing body of evidence also supports cerebellar involvement in a wide range of psychiatric disorders (2, 3). Up to now, most psychiatric studies investigating the role of the cerebellum have been conducted based on categorical diagnostic criteria that view psychiatric disorders as independent entities (4). It is increasingly recognized that existing clinical diagnostic categories might be suboptimal, as there is substantial overlap in symptoms, cognitive dysfunction and genetic factors across multiple psychiatric disorders (4, 5). These overlaps can be reflected by shared neurobiological structure and function, and polymorphism abnormalities across psychiatric syndromes (6–9). The high rates of comorbidity between psychiatric disorders and heterogeneity within one diagnostic group further exacerbates this problem (10–12). This context has motivated transdiagnostic initiatives, such as the National Institute of Mental Health's Research Domain Criteria (13), which encourages a transition in psychiatry research from categorical to dimensional approaches that integrate neuroscience and psychopathology (13).

Recent clinical neuroscience studies have begun to adopt transdiagnostic approaches to highlight the importance of altered cerebellar structure in broad risk for psychopathology (14–16). Previous animal and human neuroimaging studies have provided converging evidence for the involvement of cerebellar function in a wide range of behaviors that are dependent on circuits connecting the cerebellum with multiple cerebral cortical regions (1, 17–19). Accumulating evidence supports dysfunctional cerebellar connectivity in many psychiatric disorders, such as schizophrenia (20),

bipolar disorder (21), major depression (22), attention-deficit/hyperactivity disorder (23) and autism (24). Moreover, study of clinical high-risk subjects demonstrate that dysconnectivity of cerebellar circuits can serve as a state-independent neural signature for psychosis prediction and characterization (25). Within this context, an understudied area of investigation is the extent to which cerebellar function can be linked to transdiagnostic dimensions of psychopathology.

Resting-state functional connectivity has been widely used to characterize disconnection mechanisms in many psychiatric disorders (26, 27), and is a promising tool for deepening our understanding of transdiagnostic dimensions (28–30). Recent developments in cerebellar functional mapping indicate that cerebellar functional organization can be characterized using macroscale spatial gradients of connectivity, a low dimensional continuous space that reflects the overarching spatial patterns that underpin the observed neural data (31). The principal connectivity gradient of cerebellar cortex captures a progression from sensorimotor to cognitive processing areas (31), similar to the organization of the cerebral cortex (32, 33). This low-dimensional representation of the principal axis of cerebellar macroscale functional organization thus provides a useful tool to characterize cerebellar function at the single-subject level which can then be correlated with single-subject behavioral measures. This approach offers an unprecedented opportunity to interrogate the relationship between cerebellar functional organization and behavioral measures of clinical phenomena, cognitive ability, and personality traits in mental health and disease.

Here we analyzed a large resting-state fMRI and behavioral dataset (34) using gradient-based and partial least squares, a multivariate data-driven statistical techniques with the objective to discover

the latent dimensions that link cerebellar functional organization to behavioral measures spanning clinical, cognitive, and personality trait domains across healthy controls (HC), patients with attention-deficit/hyperactivity disorder (ADHD), bipolar disorder (BD) and schizophrenia (SZ). This approach yielded dimensions that optimally linked co-varying cerebellar connectivity gradients and behavior in individuals across traditional diagnostic categories, in accordance with a transdiagnostic dimensional approach. Multiple control analyses were used to optimize the robustness of these latent dimensions. Furthermore, we performed 10-fold cross-validation to assess the generalization performance of latent dimensions to unseen test data. Importantly, cross-validation approaches can help guard against overfitting that arises from high dimensional neurobiological data (35).

Methods and materials

Participants

Data from the UCLA Consortium for Neuropsychiatric Phenomics (CNP) dataset (34) were downloaded from OpenNeuro (https://openneuro.org/datasets/ds000030/versions/00001). This dataset consists of neuroimaging and behavioral data from 272 right-handed participants, including both HC (n=130) and individuals with neuropsychiatric disorders including SZ (n=50), BD (n=49), and ADHD (n=43). Details about participant recruitment can be found in the original publication (34). Written informed consent was obtained from all participants and related procedures were approved by the Institutional Review Boards at UCLA and the Los Angeles County Department of Mental Health. Table 1 shows a summary of demographic and clinical information of the 198 participants who survived image preprocessing quality controls (see below).

Behavioral assessment

The CNP behavioral measures encompass an extensive set of clinical, personality traits, neurocognitive and neuropsychological scores (Table S1). Behavioral measures were excluded from the partial least squares (PLS) analysis when data was missing for at least 1 participant among the 198 participants. As a result, we included a set of 55 behavioral and self-report measures from 19 clinical, personality traits, neurocognitive and neuropsychological tests in the PLS analysis. Table S2 summarized the behavioral measures for each group. Excluded behavioral measures were considered in post-hoc analyses (Table S3).

Data Acquisition and Image Preprocessing

Resting-state functional and structural MRI data were collected on two 3T Siemens Trio scanners at UCLA using the same acquisition parameters. See supplementary methods for details.

Among the 272 participants, there were seven participants with missing T1 weighted scans, four participants were missing resting-state functional MRI data scans, and 1 participant had signal dropout in the cerebellum (36), thus only data from 260 participants were preprocessed. All preprocessing steps were consistent with our previous study (37, 38). In brief, the preprocessing steps included slice timing, realignment, normalization, wavelet despiking of head motion artifacts, regression of linear trend, Friston 24 head motion parameters, white matter and CSF signal, and filtering (0.01-0.1 Hz) (see supplementary methods for details). Because global signal may be an important neuroimaging feature in clinical populations (39), we did not conduct global signal regression (GSR) in our main analyses, but GSR was considered in control analysis. In addition, we excluded 42 participants due to head motion exceeding 1.5 mm or 1.5° rotation or with >10% images showing framewise displacements>0.5mm (40) or mean FD>0.20mm during MRI

acquisition. Further, we further excluded 20 participants because of incomplete coverage of the cerebellum. This process left 198 participants as a final sample for our study, among which there were 35 ADHD, 36 BD, 92 HC and 35 SZ participants.

Cerebellar connectivity gradient extraction

We used diffusion map embedding (41) to identify a low-dimensional embedding gradient from a high-dimensional intra-cerebellar cortex connectivity matrix. Diffusion embedding results in multiple, continuous maps ("gradients"), which capture the similarity of each voxel's functional connections along a continuous space. In other words, this data-driven analysis results in connectivity gradients that provide a description of the connectome where each voxel is located along a gradient according to its connectivity pattern. In order to maximize reliability, reproducibility, and interpretability, we only used the first gradient component in our analyses. The first gradient (or principal gradient) explains as much of the variance in the data as possible (~30%, Figure S1), represents a well-understood motor-to-supramodal organizational principle in the cerebellar and cerebro-cerebral connections, and has been shown to be reproducible at the single subject level (31). See supplementary methods for more details. We reported the intra-cerebellar FC gradient (6242 voxels) as the main result, but also included cerebellar-cerebral FC gradients in control analyses.

Partial Least Squares analysis

We applied PLS to investigate the relationship between cerebellar connectivity gradient and behavioral measures across diagnostic categories. PLS is a multivariate statistical technique that derives latent variables (LVs), by finding weighted patterns of variables from two given data sets that maximally covary with each other (42, 43). Each LV is comprised of a cerebellar connectivity

gradient pattern at voxel level ("gradient saliences") and a behavioral profile ("behavioral saliences"). Individual-specific cerebellar gradient and behavioral composite scores for each LV were obtained by linearly projecting the gradient and behavioral measures of each participant onto their respective saliences. See supplementary methods for mathematical details. Because mean framewise displacement (FD) was negatively correlated with several behavioral measures and there were significant differences in age, sex, education, site, and mean FD across groups (Table 1), we regressed out these confounding effects from both behavioral and cerebellar gradient data before PLS analysis.

In order to evaluate the significance of the top five LVs of interest, permutation tests were performed. The contribution of a given gradient voxel or behavior to a given LV was assessed by a bootstrapping procedure. To test the generalizability of each LV, a 10-fold cross-validation of the PLS analysis with 200 repetitions was performed. If a given LV was statistically significant, we tested the differences of composite scores of behavior or gradient between different diagnoses, which would help interpret the significant function of this LV. In addition, we tested whether the composite scores for significant LVs were correlated with confounding factors (age, sex, years of education, head motion, site, medication load and substance use). See supplementary methods and results for details. False discovery rate (FDR) correction ($q<0.05$) was applied to all analyses.

Control Analyses

We tested whether LVs were robust to global signal regression, total cerebellar grey matter volume regression, cerebellar gradients based on cerebellar-cerebral FC, adding confounding variables (age, sex, education, site, and head motion) into the behavioral data for the PLS analysis, non-Gaussian distributions of the behavioral data, diagnostic factors (HCs and patients separately),

and site factors (each site separately). To assess the robustness of each LV, we computed Pearson's correlations between cerebellar gradient (or behavioral) saliences obtained in each control analysis and cerebellar gradient (or behavioral) saliences from the original PLS analysis. Finally, to confirm that each diagnostic group contributed the same amount to the overall composite correlations, we used the Fisher r-to-z transformation to compare the pairwise r-values (44). See supplementary methods for details.

Results

Four Robust LVs Linking Cerebellar Gradients and Behavior

PLS correlation analysis revealed five significant latent variables (LVs) that reflect the direct covariant mapping between cerebellar connectivity gradients and behavioral measures. Since the fifth LV did not show robustness in control analyses as detailed in Table S4, we only focused on the first four LVs (LV1: r=0.62, permuted $p=2.0x10^{-2}$; LV2: r=0.56, permuted $p=2.0x10^{-3}$; LV3: r=0.61, permuted $p=3.0x10^{-2}$; LV4: r=0.60, permuted $p=1.2x10^{-2}$; Figures 1-4A). The variance explained by each LV was 19.5%, 13.7%, 8.8% and 6.0%, respectively (Figure S2). Importantly, 10-fold cross-validation confirmed generalizability (i.e. robustness of results in new data) of the first four LVs, as indicated by significant correlation between cerebellar gradient and behavioral composite scores in the test folds (LV1, r=0.21, $p=2.5x10^{-3}$; LV2, r=0.27, $p=2.1x10^{-3}$; LV3, r=0.22, $p=2.3x10^{-3}$; LV4, r=0.16, $p=2.5x10^{-3}$). Furthermore, the four LVs were robust to GSR and total cerebellar grey matter volume regression, as indicated by the high correlation (r>0.83) between saliences of original PLS and PLS with GSR or total cerebellar grey matter volume regression. In addition, each diagnostic group contributed similarly to the overall composite correlations of these four LVs (FDR q > 0.05 for all pairwise comparisons, see Table S5). We also found that age, sex,

education, site, or FD were not associated with any LV (Table S6).

LV 1

The main contributors of behavior to LV1 were overall associated with greater psychopathology, e.g., higher impulsiveness, mood lability, dysfunctional impulsivity, anxiety, depression, somatization, social/physical anhedonia (Figure 1B) and psychotic symptoms (Table S3) including mania, delusions and hallucinations; in addition to worse high-order cognitive control (e.g., working memory). LV1 included positive weight in cerebellar lobules V, VI, VIIIA and VIIIB and negative weight in Crus I and II (Figure 1C). Notably, both cerebellar gradient and behavioral composite scores were higher in all diagnostic groups when compared with HCs (Figure 1D; all differences were statistically significant except for ADHD). Exploratory analyses indicated that higher cerebellar gradient and behavioral composite scores in LV1 were associated with greater medication load. There was no significant association between LV1 composite scores and substance use (Table S6). Our interpretation is that LV1 is associated mainly with general psychopathology and high-order cognitive control deficits (see discussion).

LV2

The main contributors of behavior to LV2 were mainly involved in a general lack of attention regulation, e.g., higher ADHD symptoms, attention impulsivity, depression, mood lability, interpersonal sensitivity, daydreaming and social anxiety, and lower control ability and persistence (Figure 2B). LV2 included positive weight in cerebellar Crus I, II and lobule IX and negative weight in lobules VI, VIIB and VIIIA (Figure 2C). Notably, patients with ADHD had the highest cerebellar gradient scores for LV2 (Figure 2D). Behavioral composite scores were significantly higher in patients with ADHD or BD than in HC and patients with SZ. There was no significant

association between composite scores and medication load or substance use (Table S6). Our interpretation is that LV2 is associated mainly with inadequate attention regulation (see discussion).

LV3

The main contributors of behavior to LV3 were mainly correlated with behavioral measures related to internalizing symptoms, e.g., higher harm avoidance, social anxiety, control, anhedonia, and somatization, and less externalizing symptoms, e.g., functional and motor impulsivity as well as novelty seeking (Figure 3B). LV3 included positive weight in cerebellar anterior vermis (I-VI) and negative weight in left Crus I, II, as well as lobules VIIIA and VIIIB (Figure 3C). Cerebellar gradient and behavioral composite scores were significantly higher in patients with BD or SZ when compared with patients with ADHD (Figure 3D). Higher cerebellar gradient and behavioral composite scores were associated with greater medication load (Table S6). There was no significant association between LV3 composite scores and substance use (Table S6). Our interpretation is that LV3 is associated mainly with higher internalizing symptoms and lower externalizing behavior (see discussion).

LV4

The main contributors of behavior to LV3 included worse performance in multiple memory domains, as well as with less somatization, interpersonal sensitivity and depression (Figure 4B). LV3 included positive weight in Crus I, II and lobules IX and negative weight in lobule VI (Figure 4C). There was no significant difference among diagnostic groups. There was no significant association between composite scores and medication load or substance use (Table S6). Our interpretation is that LV4 is associated mainly with dysfunctional memory (see discussion).

Control Analyses

Additional control analyses ensured the robustness of the first four LVs to cerebellar gradients based on cerebellar-cerebral FC, confounding variables, non-Gaussian distributions of the behavioral data, diagnostic factors (HCs and patients separately), and site factors (each site separately) (see supplemental results). Results of PLS using only control individuals or only patients demonstrated moderate to high correlations with original saliences for the first four LVs. However, correlations dropped to 0.14 and 0.22 for LV5; hence we did not describe LV5.

Discussion

Although the importance of cerebellar function in mental health and disease is increasingly recognized, the degree to which cerebellar connectivity is associated with transdiagnostic behavioral dimensions of psychopathology remains largely unknown. Leveraging a unique dataset including resting-state fMRI and behavioral assessments spanning clinical, cognitive, and personality traits, we found robust correlated patterns of cerebellar connectivity gradients and behavioral measures that could be represented in four transdiagnostic dimensions. Each dimension was associated with a unique spatial pattern of cerebellar connectivity gradients, and linked to different clusters of behavioral measures, supporting that individual variability in cerebellar functional connectivity can capture variability along multiple behavioral dimensions across psychiatric diagnoses. Our findings highlight the relevance of cerebellar neuroscience as a central piece for the study and classification of transdiagnostic dimensions of psychopathology – and ultimately for the diagnosis, prognosis, treatment, and prevention of mental illness.

Linking cerebellar functional gradients to transdiagnostic dimensions of psychopathology

A large body of literature has shown cerebellar functional abnormalities in mental disorders (2, 3). New trends in psychiatry focus on transdiagnostic dimensions of psychopathology (4, 45). The present study is the first to link both approaches.

Adopting a transdiagnostic approach, three influential studies analyzing brain structure showed that alterations in cerebellar structure is associated with broad risk for psychopathology (14–16). However, these studies focused on clinical symptoms or cognitive function. The broader set of behavioral phenotypes in the present study allowed us to explore other dimensions of psychopathology, not constrained within the limits of clinical symptoms commonly investigated in many transdiagnostic studies (15, 16, 28, 30, 46–48). Prior cerebellar structure studies using factor analyses suggested the presence of latent dimensions of psychopathology such as internalizing symptoms, externalizing symptoms, and psychosis symptoms (49), as well as a general psychopathology (or p) factor (50). While these dimensions are reliable and reproducible, they are entirely derived from clinical assessments, not informed by brain-based data such as fMRI functional connectivity. More broadly, previous studies investigating functional connectivity-informed dimensions of psychopathology often ignore the importance of the cerebellum, e.g., by using a coarse delineation of the cerebellum with only a few regions of interest to represent the whole cerebellar information (29, 30). These limitations were overcome in the present investigation. Further, compared to methods that focus on a single view (such as factor analysis applied on clinical data), the present study derived behavioral dimensions from co-varying individual differences in connectivity gradients and behavioral measures. This approach resonates with the Research Domain Criteria research framework that encourages the integration of many levels of information (45).

Our study indicates that individual variability in cerebellar functional connectivity gradient organization captures variability along multiple behavioral dimensions across mental health and disease. The associations with diverse dimensions of psychopathology were expected based on the consensus that the cerebellum is involved in virtually all aspects of behavior in health and disease (1). In 1998, Mesulam proposed that brain regions can be organized along a gradient ranging from sensory-motor to higher-order brain processes (33). In line with Mesulam, most of the variance of cerebellar RSFC resembles a gradient that spans from primary sensory-motor cortices to high–order transmodal regions of the default-mode network (31). This principal gradient may thus represent one fundamental principle driving a hierarchical organization of cerebellar motor, cognitive, and affective functions. Here we show for the first time that there is a link between this principal gradient of cerebellar organization and behavioral measures across individuals with and without diagnoses of cognitive or affective disease.

Functional gradients may in part reflect a balance between externally and internally oriented functioning (33). In this gradient organization, association areas are located at maximal distance from regions of primary areas that are functionally specialized for perceiving and acting in the here and now, supporting cognition and behavior not constrained by the immediate environment (33, 51–53). The intricate neuronal circuitry of the cerebellum has been hypothesized to function as a "forward controller," creating internal models of how a given behavioral output will dynamically fit with contextual information (54), which is critical for monitoring and coordinating information processing in the service of mental processes (1, 55, 56). Thus, information processing in cerebellar circuits associated with multiple transdiagnostic dimensions of psychopathology shown here may reflect impaired monitoring and coordination of

information—including one's own thoughts and emotions—necessary to guide behavior, reflecting an imbalance of externally and internally oriented functioning.

Interpreting the functional significance of each latent variable

The most significant finding of the present investigation is the demonstration of an association between individual variations in cerebellar functional gradient values and multiple behavioral measures across mental health and diseases. While it is not possible to provide a definitive characterization of the functional significance of each LV based on the analyses presented here, we here present one possible line of interpretation.

In LV1, greater behavioral composite score was associated with greater behavioral measures that we interpreted as general psychopathology and higher-cognitive control disabilities (including impulsiveness, mood lability, dysfunctional impulsivity, anxiety, depression, somatization, social/physical anhedonia and psychotic symptoms including mania, delusions and hallucinations). In line with the interpretation of LV1 as general psychopathology, both cerebellar gradient and behavioral composite scores were higher in all diagnostic groups when compared with HCs. Factor-analytic studies of multiple symptoms and diagnoses suggest that the structure of mental disorders can be summarized by three factors: internalizing, externalizing, and thought disorders (e.g., Lahey et al., 2017). The empirical observation that even these three transdiagnostic latent factors are positively correlated (57) has given rise to a more radical hypothesis, which is that there is the general psychopathology (or p) factor (50), which is thought to reflect individuals' susceptibility to develop "any and all forms of common psychopathologies" (58). The p factor has been extended to index functional impairment, negative affect, emotion dysregulation, and cognitive deficits (e.g., attention and memory problems) (for a review see Caspi and Moffitt,

2018). LV1 may thus reflect the p factor widely discussed in transdiagnostic cohorts (50).

In LV2, greater behavioral composite scores were predominantly correlated with greater scores in areas related to a general lack of attention regulation including ADHD symptoms and attention impulsivity. Importantly, patients with ADHD had the highest gradient composite scores. LV2 might thus capture inattention and impulsivity/hyperactivity symptoms which characterize ADHD. However, other dimensions such as depression and schizoid personality were also included in LV2, arguing against a purely inattention-related nature of LV2.

In LV3, greater behavioral composite scores were dominantly correlated with greater behavioral measures related to internalizing symptoms (including harm avoidance, social anxiety, control, and anhedonia) and lower externalizing symptoms (including functional and motor impulsivity, novelty seeking, and hypomanic personality). LV3 may thus reflect an internalizing vs. externalizing factor (49, 57).

LV4 was predominantly associated with negative correlations with behavioral measures, most strongly in the memory domain (long delay free recall, short delay cued recall, long delay cued recall, short delay free recall, and visual reproduction delayed recall). LV4 might thus dominantly reflect dysfunctional memory, although other behavioral domains also played a significant role in the behavioral composition of LV4 including restlessness, somatization, and persistence.

Notably, Kebets and colleagues investigated RSFC-informed dimensions of psychopathology in the CNP dataset (29), focusing on connectivity within and between cerebral and subcortical areas and derived a general psychopathology variable similar to LV1 in our study (other LVs were different), indicating that cerebral and cerebellar analyses might offer complementary information regarding the relationship between brain activity and behavioral measures. Future studies

analyzing both cerebral and cerebellar data might determine whether cerebellar data offers similar or distinct information regarding the relationship between brain activity and behavioral measures when compared to analyses of cerebral data.

Limitations

While providing novel evidence for associations between cerebellar hierarchical organization shown by fMRI and different dimensions of psychopathology, our analyses can provide only correlational – not causal – inferences between cerebellar function and behavior; future interventional experiments such as brain stimulation studies may be able to demonstrate not only an association but also a causal link between cerebellar function as indexed by functional gradients and behavioral measures. Another limitation that can be addressed in future research includes the relatively limited range of diagnostic categories in the patient population (ADHD, SZ, and BD); future research may extend our analyses to include additional patient populations. The analyses on the impact of medication and substance use were exploratory in our study; future studies with higher statistical power might adopt stronger statistical thresholds to study medication and substance use effects.

Conclusions

Our results support an association between cerebellar functional connectivity gradients and multiple behavioral dimensions across healthy subjects and patients diagnosed with a variety of mental disorders. These findings highlight the importance of cerebellar function in transdiagnostic behavioral dimensions of psychopathology, and contribute to the development of cerebellar neuroscience as a tool that may significantly contribute to the diagnosis, prognosis, treatment, and prevention of cognitive and affective illness.

References

1. Schmahmann JD, Guell X, Stoodley CJ, et al.: The Theory and Neuroscience of Cerebellar Cognition. Annu Rev Neurosci 2019; 42
2. Sathyanesan A, Zhou J, Scafidi J, et al.: Emerging connections between cerebellar development, behaviour and complex brain disorders [Internet]. Nat Rev Neurosci 2019; 20:298–313Available from: http://dx.doi.org/10.1038/s41583-019-0152-2
3. Stoodley CJ: The Cerebellum and Neurodevelopmental Disorders. Cerebellum 2016; 15:34–37
4. Caspi A, Moffitt TE: All for one and one for all: Mental disorders in one dimension. Am J Psychiatry 2018; 175:831–844
5. Kotov R, Krueger, Robert F. Watson D, Achenbach, Thomas M. Althoff RR, et al.: The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. J Abnorm Psychol 2017; 126:454–477
6. Janiri D, Moser DA, Doucet GE, et al.: Shared Neural Phenotypes for Mood and Anxiety Disorders: A Meta-analysis of 226 Task-Related Functional Imaging Studies. JAMA Psychiatry 2020; 77:172–179
7. Goodkind M, Eickhoff SB, Oathes DJ, et al.: Identification of a common neurobiological substrate for mental Illness. JAMA Psychiatry 2015; 72:305–315
8. McTeague LM, Huemer J, Carreon DM, et al.: Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. Am J Psychiatry 2017; 174:676–685
9. Lee SH, Ripke S, Neale BM, et al.: Genetic relationship between five psychiatric

disorders estimated from genome-wide SNPs. Nat Genet 2013; 45:984–994

10. Jacobi F, Wittchen HU, Hölting C, et al.: Prevalence, co-morbidity and correlates of mental disorders in the general population: Results from the German Health Interview and Examination Survey (GHS). Psychol Med 2004; 34:597–611

11. Feczko E, Miranda-Dominguez O, Marr M, et al.: The Heterogeneity Problem: Approaches to Identify Psychiatric Subtypes. Trends Cogn Sci 2019; 23:584–601

12. Chen J, Patil KR, Weis S, et al.: Neurobiological Divergence of the Positive and Negative Schizophrenia Subtypes Identified on a New Factor Structure of Psychopathology Using Non-negative Factorization: An International Machine Learning Study. Biol Psychiatry 2020; 87:282–293

13. Cuthbert BN: The RDoC framework: Facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry 2014; 13:28–35

14. Moberget T, Alnæs D, Kaufmann T, et al.: Cerebellar Gray Matter Volume Is Associated With Cognitive Function and Psychopathology in Adolescence. Biol Psychiatry 2019; i

15. Romer AL, Knodt AR, Houts R, et al.: Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. Mol Psychiatry 2017; 1084–1090

16. Romer AL, Knodt AR, Sison ML, et al.: Replicability of structural brain alterations associated with general psychopathology: evidence from a population-representative birth cohort. Mol Psychiatry 2019;

17. Caligiore D, Pezzulo G, Baldassarre G, et al.: Consensus Paper: Towards a Systems-Level View of Cerebellar Function: the Interplay Between Cerebellum, Basal Ganglia, and Cortex [Internet]. Cerebellum 2017; 16:203–229Available from: http://dx.doi.org/10.1007/s12311-016-0763-3

18. Bostan AC, Dum RP, Strick PL: Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci 2013; 17:241–254

19. Kelly RM, Strick PL: Cerebellar Loops with Motor Cortex and Prefrontal Cortex of a Nonhuman Primate. J Neurosci 2003; 23:8432–8444

20. Brady RO, Gonsalvez I, Lee I, et al.: Cerebellar-Prefrontal Network Connectivity and Negative Symptoms in Schizophrenia. Am J Psychiatry 2019; appi.ajp.2018.1

21. Shinn AK, Roh YS, Ravichandran CT, et al.: Aberrant Cerebellar Connectivity in Bipolar Disorder With Psychosis. Biol Psychiatry Cogn Neurosci Neuroimaging 2017; 2:438–448

22. Jiang Y, Duan M, Chen X, et al.: Aberrant Prefrontal-Thalamic-Cerebellar Circuit in Schizophrenia and Depression: Evidence from a Possible Causal Connectivity. Int J Neural Syst 2019; 29

23. Kucyi A, Hove MJ, Biederman J, et al.: Disrupted functional connectivity of cerebellar default network areas in attention-deficit/hyperactivity disorder. Hum Brain Mapp 2015; 36:3373–3386

24. Stoodley CJ, D'Mello1 AM, Ellegood J, et al.: Altered Cerebellar connectivity in autism spectrum disorders and rescue of autism related behaviors in mice. Nat Neurosci 2017; 47:549–562

25. Cao H, Chén OY, Chung Y, et al.: Cerebello-thalamo-cortical hyperconnectivity as a state-independent functional neural signature for psychosis prediction and characterization [Internet]. Nat Commun 2018; 9Available from: http://dx.doi.org/10.1038/s41467-018-06350-7

26. Sha Z, Wager TD, Mechelli A, et al.: Common dysfunction of large-scale neurocognitive networks across psychiatric disorders. Biol Psychiatry 2019; 85:379–388

27. Buckholtz JW, Meyer-Lindenberg A: Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness [Internet]. Neuron 2012; 74:990–1004Available from: http://dx.doi.org/10.1016/j.neuron.2012.06.002

28. Elliott ML, Romer A, Knodt AR, et al.: A Connectome-wide Functional Signature of Transdiagnostic Risk for Mental Illness [Internet]. Biol Psychiatry 2018; 84:452–459Available from: https://doi.org/10.1016/j.biopsych.2018.03.012

29. Kebets V, Holmes AJ, Orban C, et al.: Somatosensory-Motor Dysconnectivity Spans Multiple Transdiagnostic Dimensions of Psychopathology [Internet]. Biol Psychiatry 2019; 86:779–791Available from: https://doi.org/10.1016/j.biopsych.2019.06.013

30. Xia CH, Ma Z, Ciric R, et al.: Linked dimensions of psychopathology and connectivity in functional brain networks [Internet]. Nat Commun 2018; 9:1–14Available from: http://dx.doi.org/10.1038/s41467-018-05317-y

31. Guell X, Schmahmann JD, Gabrieli J DE, et al.: Functional gradients of the cerebellum. Elife 2018; 7:1–22

32. Margulies DS, Ghosh SS, Goulas A, et al.: Situating the default-mode network along a

principal gradient of macroscale cortical organization. Proc Natl Acad Sci 2016; 113:12574–12579

33. Mesulam M-M: From sensation to cognition. Brain 1998; 121:1013–1052

34. Poldrack RA, Congdon E, Triplett W, et al.: A phenome-wide examination of neural and cognitive function. Sci Data 2016; 3:1–12

35. Yarkoni T, Westfall J: Choosing Prediction Over Explanation in Psychology: Lessons From Machine Learning. Perspect Psychol Sci 2017; 12:1100–1122

36. Gorgolewski KJ, Durnez J, Poldrack RA: Preprocessed Consortium for Neuropsychiatric Phenomics dataset. F1000Research 2017; 6:1262

37. Dong D, Duan M, Wang Y, et al.: Reconfiguration of Dynamic Functional Connectivity in Sensory and Perceptual System in Schizophrenia [Internet]. Cereb Cortex 2018; 1–13Available from: https://academic.oup.com/cercor/advance-article/doi/10.1093/cercor/bhy232/5112936

38. Dong D, Luo C, Guell X, et al.: Compression of Cerebellar Functional Gradients in Schizophrenia Debo. Schizophr Bull 2020; 1–14

39. Hahamy A, Calhoun V, Pearlson G, et al.: Save the Global: Global Signal Connectivity as a Tool for Studying Clinical Populations with Functional Magnetic Resonance Imaging. Brain Connect 2014; 4:395–403

40. Power JD, Barnes KA, Snyder AZ, et al.: Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion [Internet]. Neuroimage 2012; 59:2142–2154Available from: http://dx.doi.org/10.1016/j.neuroimage.2011.10.018

41. Coifman RR, Lafon S, Lee AB, et al.: Geometric diffusions as a tool for harmonic analysis and structure definition of data: Multiscale methods. Proc Natl Acad Sci U S A 2005; 102:7432–7437

42. McIntosh AR, Mišić B: Multivariate Statistical Analyses for Neuroimaging Data. Annu Rev Psychol 2013; 64:499–525

43. Krishnan A, Williams LJ, McIntosh AR, et al.: Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review [Internet]. Neuroimage 2011; 56:455–475Available from: http://dx.doi.org/10.1016/j.neuroimage.2010.07.034

44. Diedenhofen B, Musch J: Cocor: A comprehensive solution for the statistical comparison of correlations. PLoS One 2015; 10:1–12

45. Insel T, Cuthbert B, Garvey M, et al.: Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on M ental Disorders. Am J Psychiatry 2010; 748–751

46. Kaczkurkin A, Park SS, Sotiras A, et al.: Evidence for Dissociable Linkage of Dimensions of Psychopathology to Brain Structure in Youths. Am J Psychiatry 2019; 176:1000–1009

47. Kaczkurkin AN, Moore TM, Calkins ME, et al.: Common and dissociable regional cerebral blood flow differences associate with dimensions of psychopathology across categorical diagnoses [Internet]. Mol Psychiatry 2018; 23:1981–1989Available from: http://dx.doi.org/10.1038/mp.2017.174

48. Shanmugan S, Wolf DH, Calkins ME, et al.: Common and dissociable mechanisms of executive system dysfunction across psychiatricdisorders in youth. Am J Psychiatry

2016; 173:517–526

49. Lahey BB, Krueger RF, Rathouz PJ, et al.: A hierarchical causal taxonomy of psychopathology across the life span. Psychol Bull 2017; 143:142–186

50. Lahey BB, Applegate B, Hakes JK, et al.: Is there a general factor of prevalent psychopathology during adulthood? J Abnorm Psychol 2012; 121:971–977

51. Wang P, Kong R, Kong X, et al.: Inversion of a large-scale circuit model reveals a cortical hierarchy in the dynamic resting human brain. Trop Subtrop Agroecosystems 2019; 21

52. Murphy C, Wang H-T, Konu D, et al.: Modes of operation: A topographic neural gradient supporting stimulus dependent and independent cognition. Neuroimage 2019; 186:487–496

53. Murphy C, Jefferies E, Rueschemeyer SA, et al.: Distant from input: Evidence of regions within the default mode network supporting perceptually-decoupled and conceptually-guided cognition [Internet]. Neuroimage 2018; 171:393–401Available from: https://doi.org/10.1016/j.neuroimage.2018.01.017

54. Ito M: Control of mental activities by internal models in the cerebellum. Nat Rev Neurosci 2008; 9:304–313

55. Andreasen NC, Paradiso S, O'Leary DS: "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? [Internet]. Schizophr Bull 1998; 24:203–218Available from: http://www.psycontent.com/index/LW167M3316708832.pdf%0Ahttp://schizophreniabulletin.oxfordjournals.org/content/24/2/203.full.pdf

56. Schmahmann JD, Sherman JC: The cerebellar cognitive affective syndrome. Brain 1998; 121:561–579

57. Wright AGC, Krueger RF, Hobbs MJ, et al.: The structure of psychopathology: Toward an expanded quantitative empirical model. J Abnorm Psychol 2013; 122:281–294

58. Caspi A, Houts RM, Belsky DW, et al.: The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? Clin Psychol Sci 2014; 2:119–137

Figures

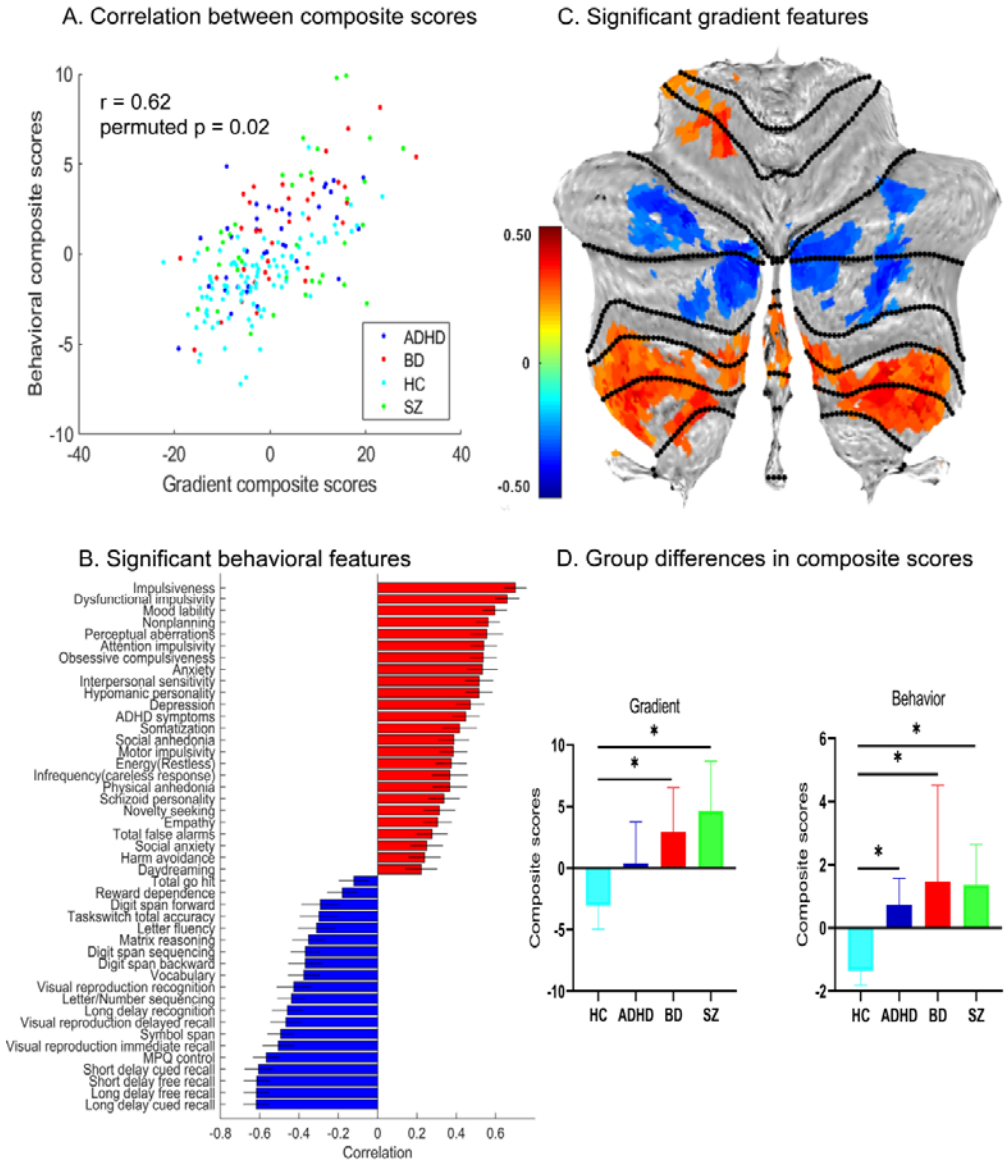

Figure 1. Latent variable 1. (A) Correlation between cerebellar connectivity gradient and behavioral composite scores of participants. (B) Significant behavioral features associated with LV1. The contribution of each behavior is measured by correlations between participants' behavioral scores and the corresponding behavioral composite scores. Error bars indicate bootstrapped standard deviations. (C) Significant gradient pattern associated with LV1. The contribution of each voxel is measured by correlation between participants' cerebellar gradient

scores and the corresponding cerebellar gradient composite scores (FDR correction, $q<0.05$). Gradient pattern displayed on cerebellar flat maps were generated using the SUIT toolbox (http://www.diedrichsenlab.org/imaging/suit.htm). (D) Group differences in cerebellar connectivity gradient and behavioral composite scores. Significant differences are indicated by asterisks (FDR correction, $q < 0.05$)..

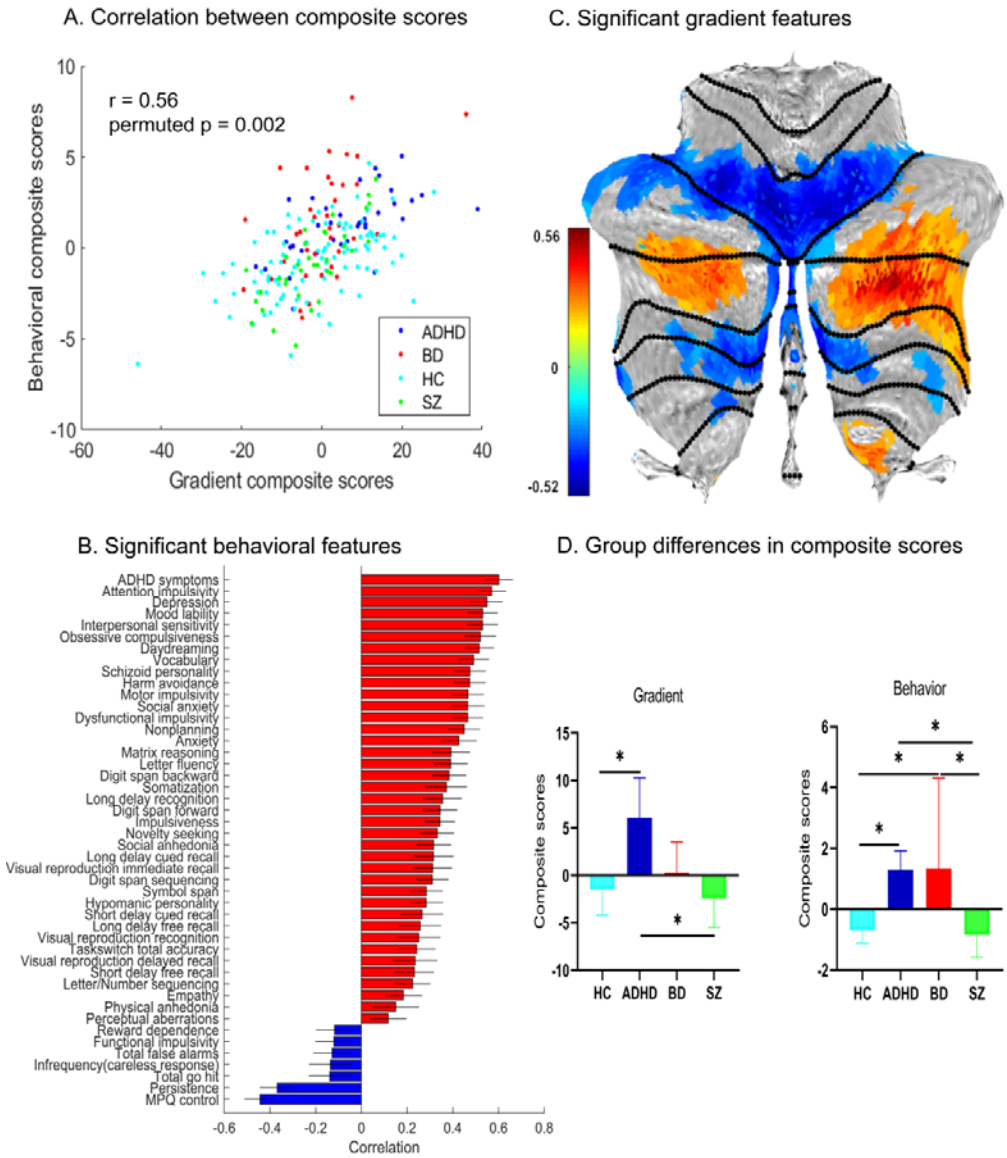

Figure 2. Latent variable 2. (A) Correlation between cerebellar connectivity gradient and behavioral composite scores of participants. (B) Significant behavioral features associated with LV2. The contribution of each behavior is measured by correlations between participants' behavioral scores and the corresponding behavioral composite scores. Error bars indicate bootstrapped standard deviations. (C) Significant gradient pattern associated with LV2. The contribution of each voxel is measured by correlations between participants' cerebellar gradient

scores and the corresponding cerebellar gradient composite scores (FDR correction, $q<0.05$). (D) Group differences in cerebellar connectivity gradient and behavioral composite scores. Significant differences are indicated by asterisks (FDR correction, $q < 0.05$).

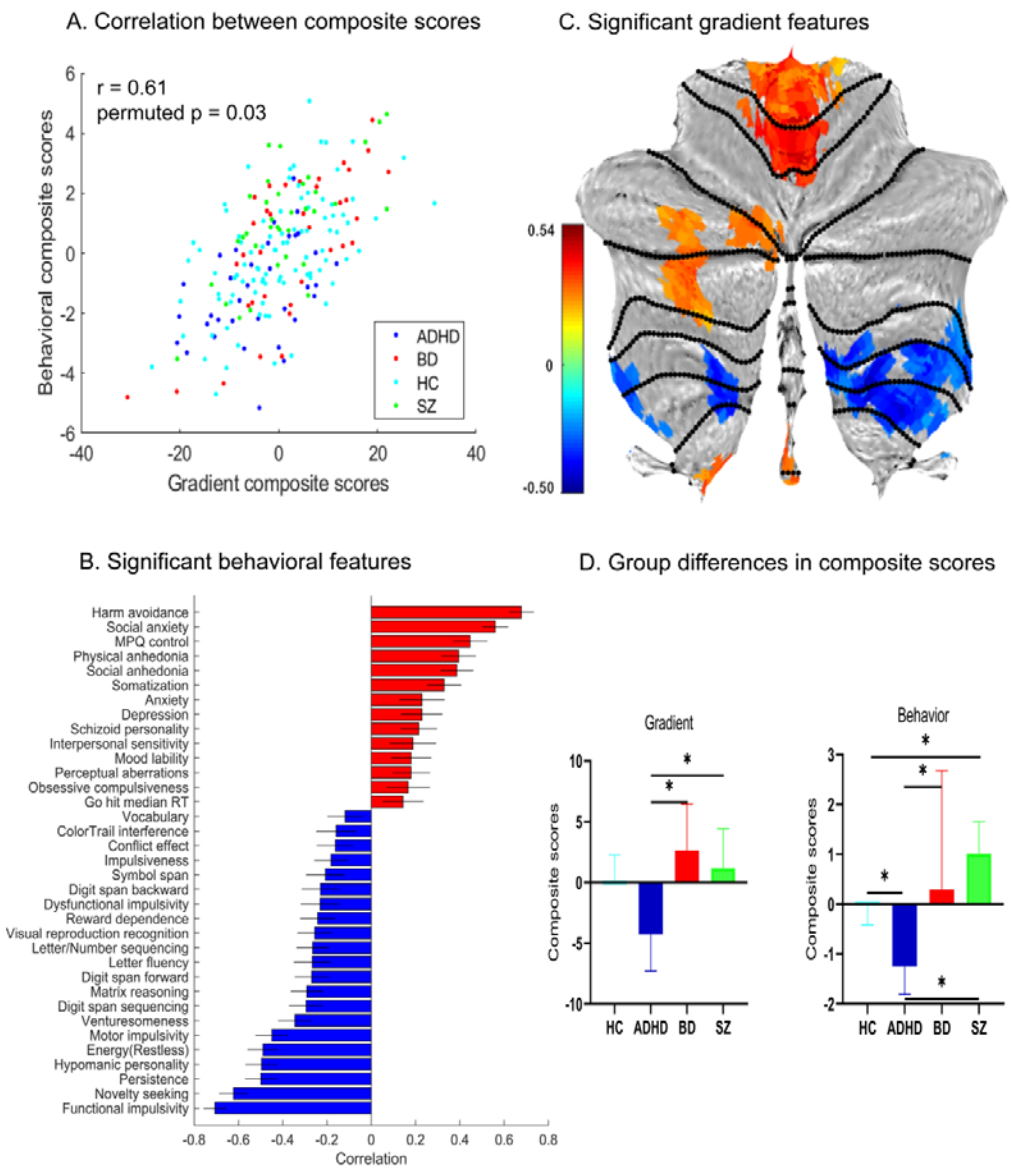

Figure 3. Latent variable 3. (A) Correlation between cerebellar connectivity gradient and behavioral composite scores of participants. (B) Significant behavioral features associated with LV3. The contribution of each behavior is measured by correlations between participants' behavioral scores and the corresponding behavioral composite scores. Error bars indicate bootstrapped standard deviations. (C) Significant gradient pattern associated with LV3. The contribution of each voxel is measured by correlations between participants' cerebellar gradient scores and the corresponding cerebellar gradient composite scores (FDR correction, q<0.05). (D)

Group differences in cerebellar connectivity gradient and behavioral composite scores. Significant differences are indicated by asterisks (FDR correction, $q < 0.05$).

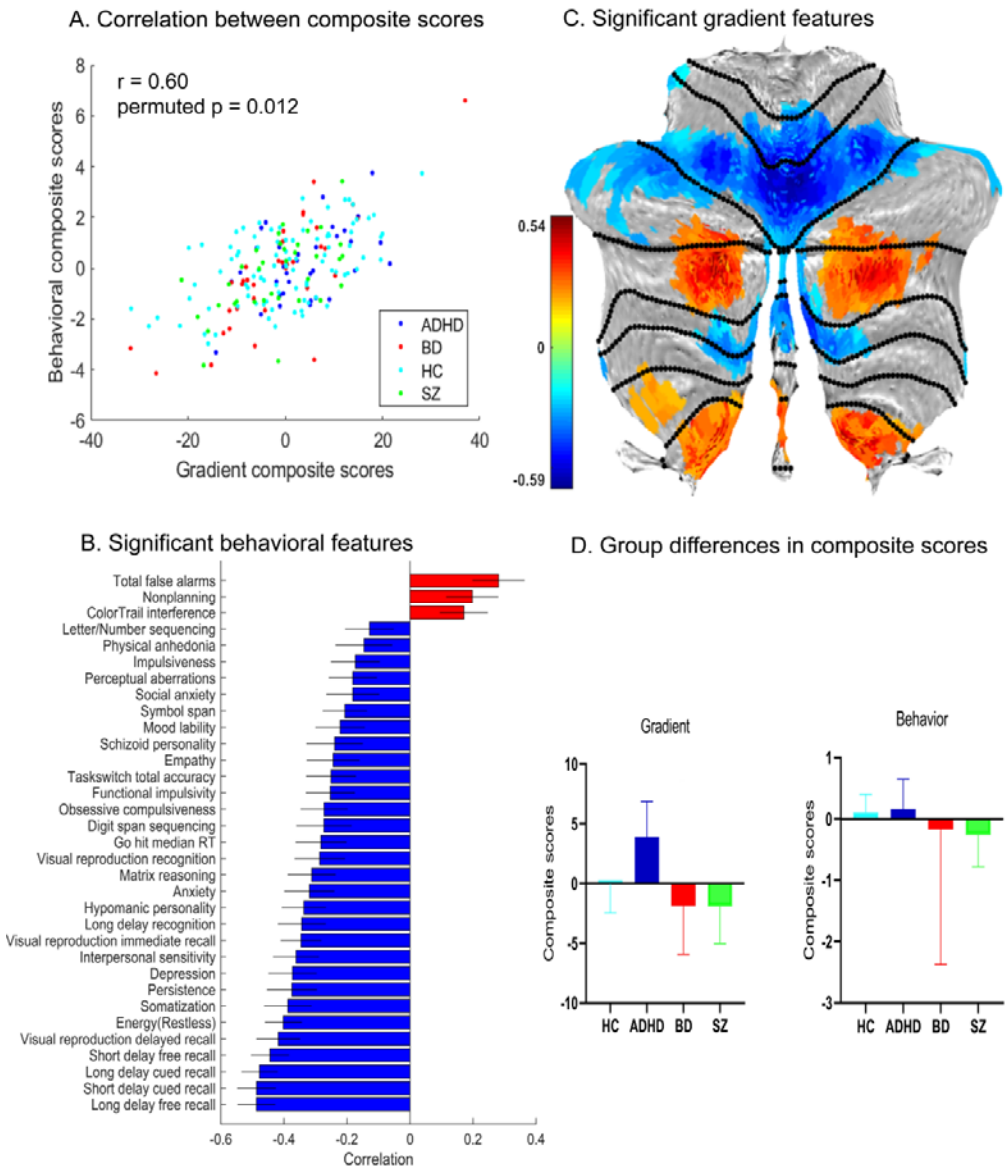

Figure 4. Latent variable 4. (A) Correlation between cerebellar connectivity gradient and behavioral composite scores of participants. (B) Significant behavioral features associated with LV4. The contribution of each behavior is measured by correlations between participants' behavioral scores and the corresponding behavioral composite scores. Error bars indicate bootstrapped standard deviations. (C) Significant gradient pattern associated with LV4. The contribution of each voxel is measured by correlations between participants' cerebellar gradient scores and the corresponding cerebellar gradient composite scores (FDR correction, q<0.05). (D)

Group differences in cerebellar connectivity gradient and behavioral composite scores. There were no significant differences among diagnostic groups in LV4 (FDR correction, $q<0.05$).