Linking Cerebellar Functional Gradients to Transdiagnostic Behavioral Dimensions of Psychopathology

Debo Dong^{1,2}, Xavier Guell^{3,4}, Sarah Genon^{2,5}, Yulin Wang^{6,7}, Ji Chen^{2,5}, Simon B. Eickhoff^{2,5}, Cheng Luo^{1*}, Dezhong Yao^{1,8}

¹The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, High-Field Magnetic Resonance Brain Imaging Key Laboratory of Sichuan Province, School of life Science and technology, University of Electronic Science and Technology of China, China

²Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7), Research Centre Jülich, Jülich, Germany

³McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, United States

⁴Massachusetts General Hospital and Harvard Medical School, Boston, United States

⁵Institute for Systems Neuroscience, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

⁶Faculty of Psychological and Educational Sciences, Department of Experimental and Applied Psychology, Vrije Universiteit Brussel, Belgium

⁷Faculty of Psychology and Educational Sciences, Department of Data Analysis, Ghent University, Belgium

⁸Research Unit of NeuroInformation, Chinese Academy of Medical Sciences, 2019RU035, Chengdu, China

***Corresponding to:** School of life science and technology, University of Electronic Science and Technology of China, Chengdu, China, Tel: +86-28-83201018, Fax: +86-(0)28-83206972; E-mail: chengluo@uestc.edu.cn (C. Luo).

Running title: Cerebellar gradients and dimensions of psychopathology

1   **Abstract**

2

3   High co-morbidity and substantial overlap across psychiatric disorders encourage a transition
4   in psychiatry research from categorical to dimensional approaches that integrate neuroscience
5   and psychopathology. Cerebellum is involved in a wide range of nonmotor cognitive
6   functions and mental disorders. An important question thus centers on the extent to which
7   cerebellar function can be linked to transdiagnostic dimensions of psychopathology. Here, this
8   question is investigated using partial least squares to identify latent dimensions linking
9   cerebellar connectome properties as assessed by macroscale spatial gradients of connectivity
10   to a large set of clinical and behavioral measures in 198 participants across diagnostic
11   categories. This analysis reveals significant correlated patterns of cerebellar connectivity
12   gradients and behavioral measures that could be represented into four latent dimensions:
13   general psychopathology, general lack of attention regulation, internalizing symptoms, and
14   dysfunctional memory. Each dimension is associated with a distinct spatial pattern of
15   cerebellar connectivity gradients. These findings highlight the relevance of cerebellar
16   connectivity as a necessity for the study and classification of transdiagnostic dimensions of
17   psychopathology .

18

19   **Introduction**

20

21   Our understanding of cerebellar contributions to neurological function has changed from a
22   traditional view focused on motor coordination, to a modern understanding that also
23   implicates the cerebellum in a broad range of high-level cognitive and affective processes.¹
24   An increasing body of evidence also supports cerebellar involvement in a wide range of
25   psychiatric disorders.^{2,3} Up to now, most psychiatric studies investigating the role of the
26   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 disorder²³ 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 However, previous studies investigating functional connectivity-informed dimensions of psychopathology often ignore the importance

1 of the cerebellum, e.g., by using a coarse delineation of the cerebellum with only a few
2 regions of interest to represent the whole cerebellar information.^{29,30} Recent developments in
3 cerebellar functional mapping indicate that cerebellar functional organization can be
4 characterized using macroscale spatial gradients of connectivity, a low dimensional
5 continuous space that reflects the overarching spatial patterns that underpin the observed
6 neural data.³¹ The principal connectivity gradient of cerebellar cortex captures a progression
7 from sensorimotor to cognitive processing areas,³¹ similar to the organization of the cerebral
8 cortex.^{32,33} This low-dimensional representation of the principal axis of cerebellar macroscale
9 functional organization thus provides a useful tool to characterize cerebellar function at the
10 single-subject level which can then be correlated with single-subject behavioral measures.
11 This approach offers an unprecedented opportunity to interrogate the relationship between
12 cerebellar functional organization and behavioral measures of clinical phenomena, cognitive
13 ability, and personality traits in mental health and disease.

14 In this study, we analyzed UCLA Consortium for Neuropsychiatric Phenomics open access
15 dataset, a large resting-state fMRI and behavioral dataset³⁴ using gradient-based and partial
16 least squares, a multivariate data-driven statistical techniques with the objective to discover
17 the latent dimensions that link cerebellar functional organization to behavioral measures
18 spanning clinical, cognitive, and personality trait domains (Table S1 and Table S2) across
19 healthy controls (HC, n=92) and patients with attention-deficit/hyperactivity disorder (ADHD,
20 n=35), bipolar disorder (BD, n=36) and schizophrenia (SZ, n=35). Table 1 shows a summary
21 of demographic and clinical information of each group. This approach yielded dimensions
22 that optimally linked co-varying cerebellar connectivity gradients and behavior in individuals
23 across traditional diagnostic categories, in accordance with a transdiagnostic dimensional
24 approach. Multiple control analyses were used to optimize the robustness of these latent
25 dimensions. Furthermore, we performed 10-fold cross-validation to assess the generalization
26 performance of latent dimensions to unseen test data. Importantly, cross-validation

1 approaches can help guard against overfitting that arises from high dimensional
2 neurobiological data.³⁵

3

4 **Results**

5 **Pattern of the principal functional connectivity gradient in cerebellum**

6

7 The principal gradient (or principal gradient) explains as much of the variance in the data as
8 possible (~30%, Figure 1), represents a well-understood motor-to-supramodal organizational
9 principle in the cerebellar connectivity. The principal connectivity gradient of cerebellar
10 cortex captured a progression from sensorimotor to cognitive processing areas. Specifically,
11 it extended bilaterally from lobules IV/V/VI and lobule VIII to posterior aspects of Crus I and
12 Crus II as well as medial regions of lobule IX. This observed spatial distribution was similar
13 to previous reports of the principal functional connectivity gradient of the cerebellar cortex in
14 healthy humans.³¹

A. The principal cerebellar gradient

B. Variance explained by gradient

15

16 Figure 1. (A) The principal cerebellar connectivity gradient. (B) Covariance explained by
17 each gradient. Red circles correspond to the gradients that explained at least a variance of 1%.

18 **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 S3, we only focused on the first four LVs (LV1: $r=0.62$, permuted $p=2.0 \times 10^{-2}$; LV2: $r=0.56$, permuted $p=2.0 \times 10^{-3}$; LV3: $r=0.61$, permuted $p=3.0 \times 10^{-2}$; LV4: $r=0.60$, permuted $p=1.2 \times 10^{-2}$; **Figures 2, 3, 4, 5A**). The variance explained by each LV was 19.5%, 13.7%, 8.8% and 6.0%, respectively (Figure S1). 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, $r=0.21$, $p=2.5 \times 10^{-3}$; LV2, $r=0.27$, $p=2.1 \times 10^{-3}$; LV3, $r=0.22$, $p=2.3 \times 10^{-3}$; LV4, $r=0.16$, $p=2.5 \times 10^{-3}$). 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 S4). We also found that age, sex, education, site, or FD were not associated with any LV (Table S5).

LV1: general psychopathology

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 2B) and psychotic symptoms (Table S6) 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 2C). Notably, both cerebellar gradient and behavioral composite scores were higher in all diagnostic groups when compared with HCs (Figure 2D; all differences were statistically significant except for ADHD). Exploratory analyses indicated that higher cerebellar gradient

1 and behavioral composite scores in LV1 were associated with greater medication load. There
2 was no significant association between LV1 composite scores and substance use (Table S5).
3 Our interpretation is that LV1 is associated mainly with general psychopathology and high-
4 order cognitive control deficits (see discussion).

5
6 Figure 2. Latent variable 1: general psychopathology. (A) Correlation between cerebellar
7 connectivity gradient and behavioral composite scores of participants. (B) Significant

1 behavioral features associated with LV1. The contribution of each behavior is measured by
 2 correlations between participants' behavioral scores and the corresponding behavioral
 3 composite scores. Error bars indicate bootstrapped standard deviations. (C) Significant
 4 gradient pattern associated with LV1. The contribution of each voxel is measured by
 5 correlation between participants' cerebellar gradient scores and the corresponding cerebellar
 6 gradient composite scores (FDR correction, $q < 0.05$). Gradient pattern displayed on cerebellar
 7 flat maps were generated using the SUIT toolbox
 8 (<http://www.diedrichsenlab.org/imaging/suit.htm>). (D) Group differences in cerebellar
 9 connectivity gradient and behavioral composite scores. Significant differences are indicated
 10 by asterisks (FDR correction, $q < 0.05$).

11 **LV2: general lack of attention regulation**

12 The main contributors of behavior to LV2 were mainly involved in a general lack of attention
 13 regulation, e.g., higher ADHD symptoms, attention impulsivity, depression, mood lability,
 14 interpersonal sensitivity, daydreaming and social anxiety, and lower control ability and
 15 persistence (Figure 3B). LV2 included positive weight in cerebellar Crus I, II and lobule IX
 16 and negative weight in lobules VI, VIIB and VIIIA (Figure 3C). Notably, patients with
 17 ADHD had the highest cerebellar gradient scores for LV2 (Figure 3D). Behavioral composite
 18 scores were significantly higher in patients with ADHD or BD than in HC and patients with
 19 SZ. There was no significant association between composite scores and medication load or
 20 substance use (Table S5). Our interpretation is that LV2 is associated mainly with inadequate
 21 attention regulation (see discussion).

1

2 Figure 3. Latent variable 2: general lack of attention regulation. (A) Correlation between
3 cerebellar connectivity gradient and behavioral composite scores of participants. (B)
4 Significant behavioral features associated with LV2. The contribution of each behavior is
5 measured by correlations between participants' behavioral scores and the corresponding
6 behavioral composite scores. Error bars indicate bootstrapped standard deviations. (C)
7 Significant gradient pattern associated with LV2. The contribution of each voxel is measured
8 by correlations between participants' cerebellar gradient scores and the corresponding

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

4 **LV3: internalizing symptoms**

5 The main contributors of behavior to LV3 were mainly correlated with behavioral measures
6 related to internalizing symptoms, e.g., higher harm avoidance, social anxiety, control,
7 anhedonia, and somatization, and less externalizing symptoms, e.g., functional and motor
8 impulsivity as well as novelty seeking (Figure 4B). LV3 included positive weight in
9 cerebellar anterior vermis (I-VI) and negative weight in left Crus I, II, as well as lobules
10 VIIIA and VIIIB (Figure 4C). Cerebellar gradient and behavioral composite scores were
11 significantly higher in patients with BD or SZ when compared with patients with ADHD
12 (Figure 4D). Higher cerebellar gradient and behavioral composite scores were associated with
13 greater medication load (Table S5). There was no significant association between LV3
14 composite scores and substance use (Table S5). Our interpretation is that LV3 is associated
15 mainly with higher internalizing symptoms and lower externalizing behavior (see discussion).

1
2 Figure 4. Latent variable 3: internalizing symptoms. (A) Correlation between cerebellar
3 connectivity gradient and behavioral composite scores of participants. (B) Significant
4 behavioral features associated with LV3. The contribution of each behavior is measured by
5 correlations between participants' behavioral scores and the corresponding behavioral
6 composite scores. Error bars indicate bootstrapped standard deviations. (C) Significant
7 gradient pattern associated with LV3. The contribution of each voxel is measured by

1 correlations between participants' cerebellar gradient scores and the corresponding cerebellar
2 gradient composite scores (FDR correction, $q < 0.05$). (D) Group differences in cerebellar
3 connectivity gradient and behavioral composite scores. Significant differences are indicated
4 by asterisks (FDR correction, $q < 0.05$).

5 **LV4: dysfunctional memory**

6 The main contributors of behavior to LV4 included worse performance in multiple memory
7 domains, as well as with less somatization, interpersonal sensitivity and depression (Figure
8 5B). LV4 included positive weight in Crus I, II and lobules IX and negative weight in lobule
9 VI (Figure 5C). There was no significant difference among diagnostic groups (Figure 5D).
10 There was no significant association between composite scores and medication load or
11 substance use (Table S5). Our interpretation is that LV4 is associated mainly with
12 dysfunctional memory (see discussion).

1
2 Figure 5. Latent variable 4: dysfunctional memory. (A) Correlation between cerebellar
3 connectivity gradient and behavioral composite scores of participants. (B) Significant
4 behavioral features associated with LV4. The contribution of each behavior is measured by
5 correlations between participants' behavioral scores and the corresponding behavioral
6 composite scores. Error bars indicate bootstrapped standard deviations. (C) Significant
7 gradient pattern associated with LV4. The contribution of each voxel is measured by

1 correlations between participants' cerebellar gradient scores and the corresponding cerebellar
2 gradient composite scores (FDR correction, $q < 0.05$). (D) Group differences in cerebellar
3 connectivity gradient and behavioral composite scores. There were no significant differences
4 among diagnostic groups in LV4 (FDR correction, $q < 0.05$).

5 **Control Analyses**

6 Additional control analyses ensured the robustness of the first four LVs to cerebellar gradients
7 based on cerebellar-cerebral FC, confounding variables, non-Gaussian distributions of the
8 behavioral data, diagnostic factors (HCs and patients separately), and site factors (each site
9 separately) (see Supporting Information and Table S3). Results of PLS using only control
10 individuals or only patients demonstrated moderate to high correlations with original saliences
11 for the first four LVs. However, correlations dropped to 0.14 and 0.22 for LV5 (Table S3);
12 hence we did not describe LV5.

13

14 **Discussion**

15

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

1 of psychopathology – and ultimately for the diagnosis, prognosis, treatment, and prevention of
2 mental illness.

3 A large body of literature has shown cerebellar functional abnormalities in mental disorders.^{2,3}
4 New trends in psychiatry focus on transdiagnostic dimensions of psychopathology.^{4,36} The
5 present study is the first to link both approaches. Adopting a transdiagnostic approach, three
6 influential studies analyzing brain structure showed that alterations in cerebellar structure is
7 associated with broad risk for psychopathology.^{14–16} However, these studies focused on
8 clinical symptoms or cognitive function. The broader set of behavioral phenotypes in the
9 present study allowed us to explore other dimensions of psychopathology, not constrained
10 within the limits of clinical symptoms commonly investigated in many transdiagnostic
11 studies.^{15,16,28,30,37–39} Prior cerebellar structure studies using factor analyses suggested the
12 presence of latent dimensions of psychopathology such as internalizing symptoms,
13 externalizing symptoms, and psychosis symptoms,⁴⁰ as well as a general psychopathology (or
14 p) factor.⁴¹ While these dimensions are reliable and reproducible, they are entirely derived
15 from clinical assessments, not informed by brain-based data such as fMRI functional
16 connectivity. More broadly, previous studies investigating functional connectivity-informed
17 dimensions of psychopathology often ignore the importance of the cerebellum, e.g., by using
18 a coarse delineation of the cerebellum with only a few regions of interest to represent the
19 whole cerebellar information.^{29,30} These limitations were overcome in the present
20 investigation. Further, compared to methods that focus on a single view (such as factor
21 analysis applied on clinical data), the present study derived behavioral dimensions from co-
22 varying individual differences in connectivity gradients and behavioral measures. This
23 approach resonates with the Research Domain Criteria research framework that encourages
24 the integration of many levels of information.³⁶

25 Our study indicates that individual variability in cerebellar functional connectivity gradient
26 organization captures variability along multiple behavioral dimensions across mental health

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

12 Functional gradient organizations in the brain have been proposed to reflect an architecture
 13 that optimizes the balance of externally and internally oriented functioning, which is critical
 14 for flexibility of human cognition.³³ In this gradient organization, association areas are located
 15 at maximal distance from regions of primary areas that are functionally specialized for
 16 perceiving and acting in the here and now, supporting cognition and behavior not constrained
 17 by the immediate environment.^{33,42–44} The intricate neuronal circuitry of the cerebellum has
 18 been hypothesized to function as a “forward controller,” creating internal models of how a
 19 given behavioral output will dynamically fit with contextual information,⁴⁵ which is critical
 20 for monitoring and coordinating information processing in the service of mental
 21 processes.^{1,46,47} Thus, information processing in cerebellar circuits associated with multiple
 22 transdiagnostic dimensions of psychopathology shown here may reflect impaired monitoring
 23 and coordination of information—including one’s own thoughts and emotions—necessary to
 24 guide behavior, reflecting an imbalance of externally and internally oriented functioning,
 25 which may serve as possible intermediate phenotypes across mental health and diseases.

1 The most significant finding of the present investigation is the demonstration of an association
2 between individual variations in cerebellar functional gradient values and multiple behavioral
3 measures across mental health and diseases. Most behavior indicators were related to more
4 than one dimension (Figure 2-5C). However, we noticed that the loadings of each behavior to
5 each dimension can vary greatly, which highlighted the unique and different clusters of
6 behavioral measures contributing to each dimension. As other brain-behavior association
7 studies using multivariate analysis based on machine learning,⁴⁸ while it is not possible to
8 provide a definitive characterization of the functional significance of each LV based on the
9 analyses presented here, we here present one possible line of interpretation.

10 In LV1, greater behavioral composite score was associated with greater behavioral measures
11 that we interpreted as general psychopathology and higher-cognitive control disabilities
12 (including impulsiveness, mood lability, dysfunctional impulsivity, anxiety, depression,
13 somatization, social/physical anhedonia and psychotic symptoms including mania, delusions
14 and hallucinations). In line with the interpretation of LV1 as general psychopathology, both
15 cerebellar gradient and behavioral composite scores were higher in all diagnostic groups when
16 compared with HCs. Factor-analytic studies of multiple symptoms and diagnoses suggest that
17 the structure of mental disorders can be summarized by three factors: internalizing,
18 externalizing, and thought disorders.⁴⁰ The empirical observation that even these three
19 transdiagnostic latent factors are positively correlated⁴⁹ has given rise to a more radical
20 hypothesis, which is that there is the general psychopathology (or p) factor,⁴¹ which is thought
21 to reflect individuals' susceptibility to develop "any and all forms of common
22 psychopathologies".⁵⁰ The p factor has been extended to index functional impairment,
23 negative affect, emotion dysregulation, and cognitive deficits (e.g., attention and memory
24 problems) (for a review see⁴). LV1 may thus reflect the p factor widely discussed in
25 transdiagnostic cohorts.⁴¹

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

8 In LV3, greater behavioral composite scores were dominantly correlated with greater
9 behavioral measures related to internalizing symptoms (including harm avoidance, social
10 anxiety, control, and anhedonia) and lower externalizing symptoms (including functional and
11 motor impulsivity, novelty seeking, and hypomanic personality). LV3 may thus reflect an
12 internalizing vs. externalizing factor.^{40,49}

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

19 Notably, Kebets and colleagues investigated RSFC-informed dimensions of psychopathology
20 in the CNP dataset,²⁹ focusing on connectivity within and between cerebral and subcortical
21 areas and derived a general psychopathology variable similar to LV1 in our study (other LVs
22 were different), indicating that cerebral and cerebellar analyses might offer complementary
23 information regarding the relationship between brain activity and behavioral measures. Future
24 studies analyzing both cerebral and cerebellar data might determine whether cerebellar data
25 offers similar or distinct information regarding the relationship between brain activity and
26 behavioral measures when compared to analyses of cerebral data.

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

12 In summary, our results support an association between cerebellar functional connectivity
 13 gradients and multiple behavioral dimensions of psychopathology (general psychopathology,
 14 general lack of attention regulation, internalizing symptoms and dysfunctional memory)
 15 across healthy subjects and patients diagnosed with a variety of mental disorders. These
 16 findings highlight the importance of cerebellar function in transdiagnostic behavioral
 17 dimensions of psychopathology, and contribute to the development of cerebellar neuroscience
 18 as a tool that may significantly contribute to the diagnosis, prognosis, treatment, and
 19 prevention of cognitive and affective illness.

20

21 **Methods**

22 **Participants**

23 Data from the UCLA Consortium for Neuropsychiatric Phenomics (CNP) dataset ³⁴ were
 24 downloaded from OpenNeuro (<https://openneuro.org/datasets/ds000030/versions/00001>). This
 25 dataset consists of neuroimaging and behavioral data from 272 right-handed participants,
 26 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 S6).

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. Resting-state functional MRI data were collected using a T2*-weighted echoplanar imaging sequence with the following scan parameters: TR/TE=2000ms/30 ms, flip angle = 90°, matrix 64 × 64, field of view (FOV) =192*192 mm², 34 interleaved slices, slice thickness =4 mm, and oblique slice orientation. The resting fMRI scan lasted 304 s for each participant, and 157 volumes were acquired. During scanning, all participants were instructed to keep relaxed and keep their eyes open. Additionally, T1-weighted high-resolution anatomical data were acquired for each participant using an MPRAGE sequence (scan parameters: TR/TE= 1900 ms/2.26 ms, matrix=256 × 256,

1 FOV=250*250 mm², sagittal plane, slice thickness =1 mm, 176 slices). The anatomical data
 2 were used to normalize functional data. See Supporting Information for details.
 3 Among the 272 participants, there were seven participants with missing T1 weighted scans,
 4 four participants were missing resting-state functional MRI data scans, and 1 participant had
 5 signal dropout in the cerebellum,⁵¹ thus only data from 260 participants were preprocessed.
 6 All preprocessing steps were consistent with our previous study.^{52,53} In brief, the
 7 preprocessing steps included slice timing, realignment, normalization, wavelet despiking of
 8 head motion artifacts, regression of linear trend, Friston 24 head motion parameters, white
 9 matter and CSF signal, and filtering (0.01-0.1 Hz) (see Supporting Information for details).
 10 Because global signal may be an important neuroimaging feature in clinical populations,⁵⁴ we
 11 did not conduct global signal regression (GSR) in our main analyses, but GSR was considered
 12 in control analysis. In addition, we excluded 42 participants due to head motion exceeding 1.5
 13 mm or 1.5° rotation or with >10% images showing framewise displacements>0.5mm⁵⁵ or
 14 mean FD>0.20mm during MRI acquisition. Further, we further excluded 20 participants
 15 because of incomplete coverage of the cerebellum. This process left 198 participants as a final
 16 sample for our study, among which there were 35 ADHD, 36 BD, 92 HC and 35 SZ
 17 participants.

18 **Cerebellar connectivity gradient extraction**

19 We used diffusion map embedding⁵⁶ to identify a low-dimensional embedding gradient from
 20 a high-dimensional intra-cerebellar cortex connectivity matrix. Diffusion embedding results in
 21 multiple, continuous maps (“gradients”), which capture the similarity of each voxel’s
 22 functional connections along a continuous space. In other words, this data-driven analysis
 23 results in connectivity gradients that provide a description of the connectome where each
 24 voxel is located along a gradient according to its connectivity pattern. In order to maximize
 25 reliability, reproducibility, and interpretability, we only used the first gradient component in
 26 our analyses. The first gradient (or principal gradient) explains as much of the variance in the

1 data as possible (~30%, Figure 1), represents a well-understood motor-to-supramodal
 2 organizational principle in the cerebellar and cerebro-cerebral connections, and has been
 3 shown to be reproducible at the single subject level.³¹ (Guell et al., 2018; note that gradient 2
 4 could not be reproduced as successfully as the principal gradient at the single-subject level)
 5 See Supporting Information for more details. We reported the intra-cerebellar FC gradient
 6 (6242 voxels) as the main result, but also included cerebellar-cerebral FC gradients in control
 7 analyses.

8 **Partial Least Squares analysis**

9 We applied PLS to investigate the relationship between cerebellar connectivity gradient and
 10 behavioral measures across diagnostic categories. PLS is a multivariate statistical technique
 11 that derives latent variables (LVs), by finding weighted patterns of variables from two given
 12 data sets that maximally covary with each other.^{57,58} Each LV is comprised of a cerebellar
 13 connectivity gradient pattern at voxel level (“gradient saliences”) and a behavioral profile
 14 (“behavioral saliences”). Individual-specific cerebellar gradient and behavioral composite
 15 scores for each LV were obtained by linearly projecting the gradient and behavioral measures
 16 of each participant onto their respective saliences. See Supporting Information for
 17 mathematical details. Because mean framewise displacement (FD) was negatively correlated
 18 with several behavioral measures and there were significant differences in age, sex, education,
 19 site, and mean FD across groups (Table 1), we regressed out these confounding effects from
 20 both behavioral and cerebellar gradient data before PLS analysis.

21 In order to evaluate the significance of the LVs, we applied permutation testing using 1000
 22 permutations to determine the null distribution of the singular values. Considering significant
 23 group differences in various behavioral measures (Table S2), the permutation procedure was
 24 performed within each primary diagnostic group. Our results of interest were the top five LVs
 25 which explained at least 5% of covariance between cerebellar gradients and behavioral

1 measures (see below). We applied a false discovery rate (FDR) correction of $q < 0.05$ on the
2 permuted p-values of the five LVs to control for multiple comparisons.

3 To assess the contribution of a given gradient voxel or behavior to a given LV, we computed
4 correlations between the original measure (gradient voxel or behavior) and the corresponding
5 composite scores^{59,60}. A large correlation (i.e., large weight, positive or negative) for a given
6 measure (behavioral or gradient voxel) for a given LV indicates greater contribution of the
7 behavior or gradient voxel to the LV. Then, the confidence intervals for these correlations
8 were determined a by bootstrapping procedure that generated 500 samples with replacement
9 from the original gradient and behavioral data. Considering significant diagnostic differences
10 in many behavioral measures (Table S2), we took diagnostic groups into account within each
11 bootstrap sample. To identify variables (gradient voxels or clinical measures) that make a
12 significant contribution to the overall pattern, we calculated Bootstrapped Z scores as the ratio
13 of each variable's correlation coefficient (i.e., weight) to its bootstrap-estimated standard error.
14 Then, we converted the Z scores to p values, which were FDR corrected ($q < 0.05$).

15 To test the generalizability of each LV, we used a 10-fold cross-validation of the PLS analysis
16 with 200 repetitions. Importantly, the cross-validation approach can help to guard against
17 overfitting that arises from high dimensional neurobiological data.³⁵ Specifically, first, we
18 assigned 90% of the participants (within each primary diagnostic group) to the training set
19 and the remaining 10% of participants (within each primary diagnostic group) to the test set.
20 For each training set, PLS was used to estimate gradient and behavioral saliences (i.e., U_{train}
21 and V_{train}). Next, the test data were projected onto the gradient and behavioral patterns derived
22 from the training set. This allowed us to estimate individual-specific gradient and behavior
23 composite scores and their correlation for the test sample (i.e. $\text{corr}(X_{\text{test}}U_{\text{train}}, Y_{\text{test}}V_{\text{train}})$) for
24 LVs 1-4. This procedure was repeated 200 times to make sure the results are not biased by the
25 initial split. Finally, we used a permutation test (behavioral data shuffled 1000 times within
26 each diagnostic group) to assess the significance of these correlation coefficients.

1 Considering significant group differences in many behavioral measures (Table S2), we took
2 diagnostic groups into account for the permutation procedure, bootstrapping procedure and
3 cross-validation in the main text. However, when ignoring diagnostic groups (regarding all
4 participants as one group), the results remained almost unchanged. See supplementary results
5 for details.

6 If a given LV was statistically significant, we performed one-way ANOVA to test whether
7 cerebellar gradient and behavioral composite scores of this LV were different among different
8 diagnoses, if significant, least significant difference (LSD, in SPSS) post hoc tests were
9 performed, which would help interpret the significant function of this LV. In addition, we
10 furthermore tested whether the composite scores for significant LVs were correlated with
11 confounding factors including age, sex, years of education, head motion, acquisition site,
12 medication load (number of medications current use) and substance use (number of substances
13 use, including nicotine, alcohol, cannabis and other psychotropic substances). T tests were
14 performed for categorical variables, and Pearson's correlations were performed for continuous
15 measures. Given the exploratory nature of medication and substance use effect analysis in our
16 study, we only consider the number of medications or substance current use, it should keep
17 caution when interpreting these results. For binary measures, we used T tests, and for
18 continuous measures, we used Pearson's correlations.

19 False discovery rate (FDR) correction ($q < 0.05$) was applied to all analyses.

20 **Control Analyses**

21 We tested whether LVs were robust to global signal regression, total cerebellar grey matter
22 volume regression, cerebellar gradients based on cerebellar-cerebral FC, adding confounding
23 variables (age, sex, education, site, and head motion) into the behavioral data for the PLS
24 analysis, non-Gaussian distributions of the behavioral data, diagnostic factors (HCs and
25 patients separately), and site factors (each site separately). To assess the robustness of each
26 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.⁶¹ See Supporting Information for details.

Data and code availability

All data are freely provided by from the UCLA Consortium for Neuropsychiatric Phenomics (CNP)³⁴ available from OpenNeuro (<https://openneuro.org/datasets/ds000030/versions/00001>). Cerebellar connectivity gradients were constructed by BrainSpace toolbox (<https://github.com/MICA-MNI/BrainSpace>).⁶² We used the Matlab code from <https://github.com/danizoeller/myPLS>⁶³ and https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/disorder_subtypes/KebedeTs2019_TransdiagnosticComponents,²⁹ based on Krishnan et al. (2011)⁵⁸ to implement the PLS calculating.

Acknowledgements

This work was supported by the grant from National Key R&D Program of China (2018YFA0701400, C Luo), The grants from the National Nature Science Foundation of China (grant number: 61933003, D Yao, 81771822, C Luo and 81471634, C Luo), The Project of Science and Technology Department of Sichuan Province (2019YJ0179, C Luo), and the CAMS Innovation Fund for Medical Sciences (CIFMS) (No.2019-I2M-5-039, D Yao). We thank Dr Valeria Kebets, National University of Singapore for helpful comments and methodological discussion. We also thank the CNP investigators for making their data available for public access. All authors have agreed to this submission. A preprint of the present manuscript has been archived on the biorxiv.org preprint server (<https://doi.org/10.1101/2020.06.15.153254>).

Conflict of Interest

The authors declare no conflict of interest.

References

1. Schmahmann JD, Guell X, Stoodley CJ, Halko MA. The Theory and Neuroscience of Cerebellar Cognition. *Annu Rev Neurosci.* 2019;42(1):337-364. doi:10.1146/annurev-neuro-070918-050258
2. Sathyanesan A, Zhou J, Scafidi J, Heck DH, Sillitoe R V., Gallo V. Emerging connections between cerebellar development, behaviour and complex brain disorders. *Nat Rev Neurosci.* 2019;20(5):298-313. doi:10.1038/s41583-019-0152-2
3. Stoodley CJ. The Cerebellum and Neurodevelopmental Disorders. *Cerebellum.* 2016;15(1):34-37. doi:10.1007/s12311-015-0715-3
4. Caspi A, Moffitt TE. All for one and one for all: Mental disorders in one dimension. *Am J Psychiatry.* 2018;175(9):831-844. doi:10.1176/appi.ajp.2018.17121383
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(4):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(2):172-179. doi:10.1001/jamapsychiatry.2019.3351
7. Goodkind M, Eickhoff SB, Oathes DJ, et al. Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry.* 2015;72(4):305-315. doi:10.1001/jamapsychiatry.2014.2206
8. McTeague LM, Huemer J, Carreon DM, Jiang Y, Eickhoff SB, Etkin A. Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *Am J Psychiatry.* 2017;174(7):676-685. doi:10.1176/appi.ajp.2017.16040400
9. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet.* 2013;45(9):984-994. doi:10.1038/ng.2711

- 1   10.   Jacobi F, Wittchen HU, Höltin C, et al. Prevalence, co-morbidity and correlates of
2   mental disorders in the general population: Results from the German Health Interview
3   and Examination Survey (GHS). *Psychol Med.* 2004;34(4):597-611.
4   doi:10.1017/S0033291703001399
- 5   11.   Feczko E, Miranda-Dominguez O, Marr M, Graham AM, Nigg JT, Fair DA. The
6   Heterogeneity Problem: Approaches to Identify Psychiatric Subtypes. *Trends Cogn Sci.*
7   2019;23(7):584-601.
- 8   12.   Chen J, Patil KR, Weis S, et al. Neurobiological Divergence of the Positive and
9   Negative Schizophrenia Subtypes Identified on a New Factor Structure of
10   Psychopathology Using Non-negative Factorization: An International Machine
11   Learning Study. *Biol Psychiatry.* 2020;87(3):282-293.
12   doi:10.1016/j.biopsych.2019.08.031
- 13   13.   Cuthbert BN. The RDoC framework: Facilitating transition from ICD/DSM to
14   dimensional approaches that integrate neuroscience and psychopathology. *World*
15   *Psychiatry.* 2014;13(1):28-35. doi:10.1002/wps.20087
- 16   14.   Moberget T, Alnæs D, Kaufmann T, et al. Cerebellar Gray Matter Volume Is
17   Associated With Cognitive Function and Psychopathology in Adolescence. *Biol*
18   *Psychiatry.* 2019;86(1):65-75. doi:10.1016/j.biopsych.2019.01.019
- 19   15.   Romer AL, Knodt AR, Houts R, et al. Structural alterations within cerebellar circuitry
20   are associated with general liability for common mental disorders. *Mol Psychiatry.*
21   2017;(February 2017):1084-1090. doi:10.1038/mp.2017.57
- 22   16.   Romer AL, Knodt AR, Sison ML, et al. Replicability of structural brain alterations
23   associated with general psychopathology: evidence from a population-representative
24   birth cohort. *Mol Psychiatry.* 2019;86(1):65-75. doi:10.1038/s41380-019-0621-z

- 1 17. Caligiore D, Pezzulo G, Baldassarre G, et al. Consensus Paper: Towards a Systems-
2 Level View of Cerebellar Function: the Interplay Between Cerebellum, Basal Ganglia,
3 and Cortex. *Cerebellum*. 2017;16(1):203-229. doi:10.1007/s12311-016-0763-3
- 4 18. Bostan AC, Dum RP, Strick PL. Cerebellar networks with the cerebral cortex and basal
5 ganglia. *Trends Cogn Sci*. 2013;17(5):241-254.
- 6 19. Kelly RM, Strick PL. Cerebellar Loops with Motor Cortex and Prefrontal Cortex of a
7 Nonhuman Primate. *J Neurosci*. 2003;23(23):8432-8444. doi:10.1523/jneurosci.23-23-
8 08432.2003
- 9 20. Brady RO, Gonsalvez I, Lee I, et al. Cerebellar-Prefrontal Network Connectivity and
10 Negative Symptoms in Schizophrenia. *Am J Psychiatry*. 2019;176(7):512-520.
11 doi:10.1176/appi.ajp.2018.18040429
- 12 21. Shinn AK, Roh YS, Ravichandran CT, Baker JT, Öngür D, Cohen BM. Aberrant
13 Cerebellar Connectivity in Bipolar Disorder With Psychosis. *Biol Psychiatry Cogn
14 Neurosci Neuroimaging*. 2017;2(5):438-448.
- 15 22. Jiang Y, Duan M, Chen X, et al. Aberrant Prefrontal-Thalamic-Cerebellar Circuit in
16 Schizophrenia and Depression: Evidence from a Possible Causal Connectivity. *Int J
17 Neural Syst*. 2019;29(5):1850032. doi:10.1142/S0129065718500326
- 18 23. Kucyi A, Hove MJ, Biederman J, Van Dijk KRA, Valera EM. Disrupted functional
19 connectivity of cerebellar default network areas in attention-deficit/hyperactivity
20 disorder. *Hum Brain Mapp*. 2015;36(9):3373-3386. doi:10.1002/hbm.22850
- 21 24. Stoodley CJ, D'Mello AM, Ellegood J, et al. Altered Cerebellar connectivity in
22 autism spectrum disorders and rescue of autism related behaviors in mice. *Nat Neurosci*.
23 2017;47(3):549-562. doi:10.1097/CCM.0b013e31823da96d.Hydrogen
- 24 25. Cao H, Chén OY, Chung Y, et al. Cerebello-thalamo-cortical hyperconnectivity as a
25 state-independent functional neural signature for psychosis prediction and
26 characterization. *Nat Commun*. 2018;9(1):1-9. doi:10.1038/s41467-018-06350-7

- 1 26. Sha Z, Wager TD, Mechelli A, He Y. Common dysfunction of large-scale
2 neurocognitive networks across psychiatric disorders. *Biol Psychiatry*. 2019;85(5):379-
3 388.
- 4 27. Buckholtz JW, Meyer-Lindenberg A. Psychopathology and the Human Connectome:
5 Toward a Transdiagnostic Model of Risk For Mental Illness. *Neuron*. 2012;74(6):990-
6 1004. doi:10.1016/j.neuron.2012.06.002
- 7 28. Elliott ML, Romer A, Knodt AR, Hariri AR. A Connectome-wide Functional Signature
8 of Transdiagnostic Risk for Mental Illness. *Biol Psychiatry*. 2018;84(6):452-459.
9 doi:10.1016/j.biopsych.2018.03.012
- 10 29. Kebets V, Holmes AJ, Orban C, et al. Somatosensory-Motor Dysconnectivity Spans
11 Multiple Transdiagnostic Dimensions of Psychopathology. *Biol Psychiatry*.
12 2019;86(10):779-791. doi:10.1016/j.biopsych.2019.06.013
- 13 30. Xia CH, Ma Z, Ciric R, et al. Linked dimensions of psychopathology and connectivity
14 in functional brain networks. *Nat Commun*. 2018;9(1):1-14. doi:10.1038/s41467-018-
15 05317-y
- 16 31. Guell X, Schmahmann JD, Gabrieli J DE, Ghosh SS. Functional gradients of the
17 cerebellum. *Elife*. 2018;7:1-22. doi:10.7554/elife.36652
- 18 32. Margulies DS, Ghosh SS, Goulas A, et al. Situating the default-mode network along a
19 principal gradient of macroscale cortical organization. *Proc Natl Acad Sci*.
20 2016;113(44):12574-12579. doi:10.1073/pnas.1608282113
- 21 33. Mesulam M-M. From sensation to cognition. *Brain*. 1998;121(6):1013-1052.
- 22 34. Poldrack RA, Congdon E, Triplett W, et al. A phenome-wide examination of neural
23 and cognitive function. *Sci Data*. 2016;3:1-12. doi:10.1038/sdata.2016.110
- 24 35. Yarkoni T, Westfall J. Choosing Prediction Over Explanation in Psychology: Lessons
25 From Machine Learning. *Perspect Psychol Sci*. 2017;12(6):1100-1122.
26 doi:10.1177/1745691617693393

- 1 36. Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): Toward a
2 New Classification Framework for Research on Mental Disorders. *Am J Psychiatry*.
3 2010;(July):748-751. doi:10.1176/appi.ajp.2010.09091379
- 4 37. Kaczkurkin A, Park SS, Sotiras A, et al. Evidence for Dissociable Linkage of
5 Dimensions of Psychopathology to Brain Structure in Youths. *Am J Psychiatry*.
6 2019;176(12):1000-1009. doi:10.1016/j.biopsych.2019.03.763
- 7 38. Kaczkurkin AN, Moore TM, Calkins ME, et al. Common and dissociable regional
8 cerebral blood flow differences associate with dimensions of psychopathology across
9 categorical diagnoses. *Mol Psychiatry*. 2018;23(10):1981-1989.
10 doi:10.1038/mp.2017.174
- 11 39. Shanmugan S, Wolf DH, Calkins ME, et al. Common and dissociable mechanisms of
12 executive system dysfunction across psychiatric disorders in youth. *Am J Psychiatry*.
13 2016;173(5):517-526. doi:10.1176/appi.ajp.2015.15060725
- 14 40. Lahey BB, Krueger RF, Rathouz PJ, Waldman ID, Zald DH. A hierarchical causal
15 taxonomy of psychopathology across the life span. *Psychol Bull*. 2017;143(2):142-186.
- 16 41. Lahey BB, Applegate B, Hakes JK, Zald DH, Hariri AR, Rathouz PJ. Is there a general
17 factor of prevalent psychopathology during adulthood? *J Abnorm Psychol*.
18 2012;121(4):971-977.
- 19 42. Wang P, Kong R, Kong X, et al. Inversion of a large-scale circuit model reveals a
20 cortical hierarchy in the dynamic resting human brain. *Sci Adv*. 2019;5(1):1-12.
21 doi:10.1126/sciadv.aat7854
- 22 43. Murphy C, Wang H-T, Konu D, et al. Modes of operation: A topographic neural
23 gradient supporting stimulus dependent and independent cognition. *Neuroimage*.
24 2019;186(1):487-496.
- 25 44. Murphy C, Jefferies E, Rueschemeyer SA, et al. Distant from input: Evidence of
26 regions within the default mode network supporting perceptually-decoupled and

- 1 conceptually-guided cognition. *Neuroimage*. 2018;171(June 2017):393-401.
- 2 doi:10.1016/j.neuroimage.2018.01.017
- 3 45. Ito M. Control of mental activities by internal models in the cerebellum. *Nat Rev*
- 4 *Neurosci*. 2008;9(4):304-313.
- 5 46. Andreasen NC, Paradiso S, O’Leary DS. “Cognitive dysmetria” as an integrative
- 6 theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry?
- 7 *Schizophr Bull*. 1998;24(2):203–218.
- 8 <http://www.psycontent.com/index/LW167M3316708832.pdf%0Ahttp://schizophreniab>
- 9 <ulletin.oxfordjournals.org/content/24/2/203.full.pdf>.
- 10 47. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain*.
- 11 1998;121(4):561-579. doi:10.1093/brain/121.4.561
- 12 48. Kohoutová L, Heo J, Cha S, et al. Toward a unified framework for interpreting
- 13 machine-learning models in neuroimaging. *Nat Protoc*. 2020;15:1399–1435.
- 14 doi:10.1038/s41596-019-0289-5
- 15 49. Wright AGC, Krueger RF, Hobbs MJ, Markon KE, Eaton NR, Slade T. The structure
- 16 of psychopathology: Toward an expanded quantitative empirical model. *J Abnorm*
- 17 *Psychol*. 2013;122(1):281-294.
- 18 50. Caspi A, Houts RM, Belsky DW, et al. The p Factor: One General Psychopathology
- 19 Factor in the Structure of Psychiatric Disorders? *Clin Psychol Sci*. 2014;2(2):119-137.
- 20 51. Gorgolewski KJ, Durnez J, Poldrack RA. Preprocessed Consortium for
- 21 Neuropsychiatric Phenomics dataset. *FI000Research*. 2017;6:1262.
- 22 52. Dong D, Duan M, Wang Y, et al. Reconfiguration of Dynamic Functional Connectivity
- 23 in Sensory and Perceptual System in Schizophrenia. *Cereb Cortex*. 2018:1-13.
- 24 doi:10.1093/cercor/bhy232
- 25 53. Dong D, Luo C, Guell X, et al. Compression of Cerebellar Functional Gradients in
- 26 Schizophrenia Debo. *Schizophr Bull*. 2020:1-14. doi:10.1093/schbul/sbaa016

- 1 54. Hahamy A, Calhoun V, Pearlson G, et al. Save the Global: Global Signal Connectivity
2 as a Tool for Studying Clinical Populations with Functional Magnetic Resonance
3 Imaging. *Brain Connect.* 2014;4(6):395-403. doi:10.1089/brain.2014.0244
- 4 55. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but
5 systematic correlations in functional connectivity MRI networks arise from subject
6 motion. *Neuroimage.* 2012;59(3):2142-2154. doi:10.1016/j.neuroimage.2011.10.018
- 7 56. Coifman RR, Lafon S, Lee AB, et al. Geometric diffusions as a tool for harmonic
8 analysis and structure definition of data: Multiscale methods. *Proc Natl Acad Sci U S A.*
9 2005;102(21):7432-7437.
- 10 57. McIntosh AR, Mišić B. Multivariate Statistical Analyses for Neuroimaging Data. *Annu*
11 *Rev Psychol.* 2013;64:499-525.
- 12 58. Krishnan A, Williams LJ, McIntosh AR, Abdi H. Partial Least Squares (PLS) methods
13 for neuroimaging: A tutorial and review. *Neuroimage.* 2011;56(2):455-475.
14 doi:10.1016/j.neuroimage.2010.07.034
- 15 59. Courville T, Thompson B. Use of Structure Coefficients in Published Multiple
16 Regression Articles: β is not Enough. *Educ Psychol Meas.* 2001;61(2):229-248.
17 doi:10.1177/0013164401612006
- 18 60. Sherry A, Henson RK. Conducting and Interpreting Canonical Correlation Analysis in
19 Personality Research: A User-Friendly Primer. *J Pers Assess.* 2005;84(1):37-48.
20 doi:10.1207/s15327752jpa8401
- 21 61. Diedenhofen B, Musch J. Cocor: A comprehensive solution for the statistical
22 comparison of correlations. *PLoS One.* 2015;10(4):1-12.
23 doi:10.1371/journal.pone.0121945
- 24 62. Wael RV de, Benkarim O, Paquola C, et al. BrainSpace: a toolbox for the analysis of
25 macroscale gradients in neuroimaging and connectomics datasets. *Commun Biol.*
26 2020;3:1-10.

- 1 63. Zöller D, Schaer M, Scariati E, Padula MC, Eliez S, Van De Ville D. Disentangling
2 resting-state BOLD variability and PCC functional connectivity in 22q11.2 deletion
3 syndrome. *Neuroimage*. 2017;149:85-97. doi:10.1016/j.neuroimage.2017.01.064
4

1 Table 1. Demographic characteristics of the each diagnostic group

Variables	ADHD	BD	HC	SZ	F or X^2	P value
Sample size	35	36	92	35		
Age (years, mean(SD))	31.40(10.50)	34.44(8.91)	30.50(8.50)	35.54(8.97)	3.51	1.6×10^{-2}
Male sex, n(%)	18(51.4)	19(52.8)	51(55.4)	27(77.1)	6.54	8.8×10^{-2}
Education (years, mean(SD))	14.43(1.79)	14.64(1.94)	15.26(1.62)	12.71(1.64)	18.75	1.0×10^{-10}
Site 1, n(%)	17(48.6)	18(50)	73(79.3)	14(40)	23.72	2.9×10^{-5}
Head motion, mean FD, mean(SD)	0.069(0.04)	0.083(0.05)	0.066(0.03)	0.096(0.04)	6.16	5.1×10^{-4}
Number of current medication use (mean(SD))	0.57(1.14)	2.50(1.93)	0(0)	2.20(1.57)	57.19	1.6×10^{-26}
Number of substance use (mean(SD))	1.31(1.68)	2.58(2.09)	0.62(1.10)	2.46(2.23)	17.89	2.7×10^{-10}

2 Notes: Group differences were determined by either one-way ANOVA for continuous variables or chi-
3 square tests for categorical variables. FD, framewise displacement; Number of substances use,
4 including nicotine, alcohol, cannabis and other psychotropic substances

Supporting Information

Linking Cerebellar Functional Gradients to Transdiagnostic Behavioral

Dimensions of Psychopathology

Debo Dong, Xavier Guell, Sarah Genon, Yulin Wang, Ji Chen, Simon B. Eickhoff, Cheng Luo*, Dezhong Yao

Supplemental Methods

Data acquisition and image preprocessing

MRI data were acquired two 3T Siemens Trio scanners, located at the Ahmanson-Lovelace Brain Mapping Center (Siemens version syngo MR B15) and the Staglin Center for Cognitive Neuroscience (Siemens version syngo MR B17) at UCLA. Resting-state functional MRI data were collected using a T2*-weighted echoplanar imaging (EPI) sequence with the following parameters: TR/TE=2000ms/30 ms, flip angle = 90°, matrix 64×64 , field of view = 192×192 mm², 34 interleaved slices, slice thickness = 4 mm, and oblique slice orientation. The resting fMRI scan lasted 304 s for each participant, and 157 volumes were acquired. Participants were asked to remain relaxed and keep their eyes open; they were not presented any stimuli or asked to respond during the scan. Additionally, T1-weighted high-resolution anatomical data were acquired for each participant using an MPRAGE sequence (scan parameters: TR/TE= 1900 ms/2.26 ms, matrix= 256×256 , FOV= 250×250 mm², sagittal plane, slice thickness = 1 mm, 176 slices). The anatomical data were used to normalize functional data.

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,^[1] thus only data from 260 participants were preprocessed. All preprocessing steps were carried out using the Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI v4.1^[2]) and Matlab scripts. Consistent with our previous study,^[3,4] functional images were (1) discarded in the first five volumes, (2) slice-time corrected, (3) realigned, (4) co-registered to the high-resolution 3D anatomic volume, (5) warped into

1 MNI152 standard space (resampling the voxel size into $3 \times 3 \times 3 \text{ mm}^3$), (6) underwent wavelet
 2 despiking of head motion artifacts^[5]), (7) underwent regression of motion and non-relevant
 3 signals, including linear trend, Friston 24 head motion parameters,^[6,7] white matter (CompCor,
 4 5 principal components), and CSF signal (CompCor, 5 principal components^[8]), and (8) were
 5 filtered using a band-pass filter (0.01-0.1 Hz). Because global signal may be an important
 6 neuroimaging feature in clinical populations,^[9] and global signal regression has been shown to
 7 induce anticorrelations in resting-state data,^[10] we did not conduct global signal regression in
 8 our main analyses. Because the topic of global signal regression (GSR) is still controversial,
 9 we considered GSR in a separate control analysis. In addition, we excluded 48 participants
 10 due to head motion exceeding 1.5 mm or 1.5° rotation or with >10% frame-to-frame motion
 11 quantified by framewise displacements ($\text{FD} > 0.5 \text{ mm}$,^[11]) or mean $\text{FD} > 0.20 \text{ mm}$ during MRI
 12 acquisition. Further, we excluded 20 participants because of not full coverage of cerebellum.
 13 This process left 198 participants as a final sample of our study.

14 **Connectivity gradient analyses**

15 In detail, the voxel-level connectivity matrix within cerebellar cortex for each subject was
 16 computed using Fisher Z-transformed Pearson correlations. Based on previous studies,^[12–15]
 17 we thresholded the rsFC matrix with the top 10% of connections per row retained, whereas all
 18 others were zeroed. The negative connections were zeroed as well. Then, we used cosine
 19 distance to generate a similarity matrix that reflected the similarity of connectivity profiles
 20 between each pair of voxels.

21

22 Then, we used diffusion map embedding^[16] to identify a low-dimensional embedding from a
 23 high-dimensional connectivity matrix. This methodological strategy has been able to
 24 successfully identify relevant aspects of functional organization in cerebral cortex and
 25 cerebellum in previous studies.^[12,14] Similar to Principal Component Analysis (PCA),
 26 diffusion map embedding can identify principal gradient components accounting for the

1 variance in descending order. If we applied PCA to the connectivity matrix, each voxel in
2 cerebellar cortex would be assigned to a particular network with discrete borders. In contrast,
3 diffusion map embedding allowed us to identify gradients of connectivity patterns from the
4 similarity matrix. In this way, the result of diffusion embedding is not one single mosaic of
5 discrete networks, but multiple, continuous maps (gradients), which capture the similarity of
6 each voxel's functional connections along a continuous space. In other words, this data-driven
7 analysis results in connectivity gradients that provide a description of the connectome where
8 each voxel is located along a gradient according to its connectivity pattern. Voxels with
9 similar connectivity patterns are located close to one another along a given connectivity
10 gradient. All gradients are orthogonal to each other and capture a portion of data variability in
11 descending order.

12
13 There is a single parameter α to control how the density of sampling points affects the
14 underlying manifold ($\alpha = 0$, the maximal influence of sampling density; $\alpha = 1$, no influence of
15 sampling density) in the diffusion map embedding algorithm. Following previous studies,^{[12–}
16 ^{14]} we set $\alpha = 0.5$, which can help retain the global relations between data points in the
17 embedded space. Then, we used an average connectivity matrix calculated from all
18 participants to produce a group-level gradient component template. We then performed
19 Procrustes rotation to align the gradients of each participant to this template, following the
20 strategy of previous analyses.^[17] In order to maximize reliability, reproducibility, and
21 interpretability, we only used the first gradient component in our analyses. The first gradient
22 (or principal gradient) explains as much of the variance in the data as possible (~30%, Figure
23 1), represents a well-understood motor-to-supramodal organizational principle in the
24 cerebellar and cerebro-cerebral connections^[14] and has been shown to be reproducible at the
25 single subject level in the cerebellum (Guell et al., 2018; note that gradient 2 could not be
26 reproduced as successfully as the principal gradient at the single-subject level). The explained

1 variance of principle gradient (30%) was similar to recent reports using diffusion map
2 embedding analyses in functional connectivity.^[12–14,18]

3

4 We reported the intra-cerebellar FC gradient (6242 voxels) as the main results, but also we
5 included the cerebellar-cerebral FC gradients in control analyses. The same calculation
6 procedures used in intra-cerebellar functional connectivity gradient analysis were performed
7 for cerebellar-cerebral cortical gradient analysis (cerebellar-cerebral cortical FC matrix).

8 **Partial least squares analysis**

9 PLS is a multivariate procedure that seeks maximal correlations between two matrices by
10 deriving LVs, which are optimal linear combinations of the original matrices.^[19,20] We applied
11 PLS to the cerebellar gradient and behavioral measures across diagnostic categories. Given
12 two matrices, $X_{n \times p}$ and $Y_{n \times q}$, where n is the number of observations (e.g., participants, here
13 $n=198$), p and q are the number of variables (e.g., cerebellar gradient ($p=6242$) and behavioral
14 features ($q=55$), respectively), after z-scoring X and Y (across participants), we calculated the
15 covariance matrix $R=Y^T X$. Then, singular value decomposition (SVD) of $R=USV^T$ produced
16 in three low-dimensional latent variables: U and V are the singular vectors (called behavioral
17 and cerebellar gradient saliences, similar to loadings in principal components analysis), while
18 S is a diagonal matrix containing the singular values. After that, by linearly projecting the
19 cerebellar gradient and behavioral measures of each participant onto their respective saliences,
20 we obtained individual-specific cerebellar gradient and behavioral composite scores for each
21 LV, which reflect the participants' individual cerebellar gradient and behavioral contribution
22 to each LV (similar to factor scores in principal components analysis). PLS seeks to find
23 saliences that maximize the covariance between cerebellar gradient and behavioral composite
24 scores. The covariance explained by each LV is estimated by dividing the squared singular
25 value by the sum of all squared singular values. Because FD was negatively correlated with
26 several behavioral measures mainly involving memory function (false discovery rate (FDR),

1 $q < 0.05$, including long delay free recall, visual reproduction immediate recall, delayed recall
2 and recognition, matrix reasoning, and letter fluency) and there were significant differences in
3 age, sex, education, site, and head motion (mean FD) across groups (Table 1), we regressed
4 them out from both the behavioral and cerebellar gradient data before PLS analysis.

5

6 **Control Analyses**

7 **Global signal regression**

8

9 Given global signal regression is still the controversial issue in the rsfMRI field, in control
10 analysis, we conducted global signal regression in the rsfMRI preprocessing to check whether
11 the GSR significantly affects the four LVs.

12

13 **Regressing out cerebellar grey matter volume**

14

15 To test whether the total cerebellar grey matter volume significantly affect the robustness of
16 the four LVs, we re-computed PLS after regressing out total cerebellar grey matter volume
17 from gradient features. We used the SUI to calculate the total cerebellar grey matter
18 volume.^[24] Briefly, SUI isolates the cerebellum and brainstem, then segments images into
19 grey matter maps and normalizes these maps to a cerebellar template, ensuring superior
20 cerebellar alignment across subjects. Normalized cerebellar grey matter maps were modulated
21 by the Jacobian of the transformation matrix to preserve absolute grey matter volume. We
22 extracted the summed modulated grey matter value (i.e., a measure of regional volume) for 28
23 cerebellar lobules defined in the probabilistic SUI Atlas, and regarded resulting value as
24 total cerebellar grey matter volume.^[25]

25

26 **Cerebellar gradient based on cerebellar-cerebral FC**

1

2 Given the cerebellar functional gradients can be similarly constructed based on intra-
3 cerebellar FC or cerebellar-cerebral FC in the literature, we also tested cerebellar gradient
4 based on cerebellar-cerebral FC. Intra-cerebellar connectivity gradient analysis focuses on
5 exploring the intrinsic organization of the cerebellum without involving its connectivity
6 profiles with the cerebral hemispheres or other brain structures. The cerebellar-cerebral
7 cortical gradients emphasize the communication between cerebellar and cerebral cortex ^[14].

8

9 **Including confounds**

10

11 Instead of regressing age, sex, education, site, and head motion (mean FD) out from the data
12 prior to PLS analysis, we added them to the behavioral data for the new PLS analysis.

13

14 **Quantile normalization**

15

16 Because many behavioral measures included in the PLS analysis were non-Gaussian
17 distribution, to exclude the potential effect on the robustness of LVs, we used quantile
18 normalization to improve the Gaussian distributions of the behavioral data and re-computed
19 PLS between the normalized behavioral and cerebellar gradient data.

20

21 **Patients and sites factor**

22

23 Furthermore, to ensure that our results were not separately driven by the HCs or by patients,
24 we recomputed PLS using only control individuals or only patients. Finally, to ensure that
25 results were not mainly driven by a single site, we recomputed PLS using data of each site
26 separately.

1

2 **Contribution of each diagnostic group to the overall composite correlations**

3

4 To confirm each diagnostic group contributes the same amount to the overall composite
5 correlations, we used the Fisher r-to-z transformation to compare the pairwise r-values, i.e.,
6 correlation value between behavioral and gradient composite scores within each diagnostic
7 group.^[26]

8

Supplemental Results

9 When ignoring diagnostic groups, i.e., regarding all participants as one group, the results
10 remained almost unchanged. Specifically, the first four LVs were still significant (LV1:
11 $r=0.62$, permuted $p=0.008$; LV2: $r=0.56$, permuted $p=0.005$; LV3: $r=0.61$, permuted $p=0.038$;
12 LV4: $r=0.60$, permuted $p=0.01$). The significant behavioral and cerebral connectivity gradient
13 features associated with each LV remained almost unchanged, see figure S2-S5. The 10-fold
14 cross-validation for the first four LVs was still successful as indicated by significant
15 correlation between cerebellar gradient and behavioral composite scores in the test folds (LV1,
16 $r=0.12$, $p=0.0029$; LV2, $r=0.16$, $p=0.0027$; LV3, $r=0.11$, $p=0.0029$; LV4, $r=0.07$, $p=0.0032$).

17 **Control Analyses**

18 **Global signal regression**

19

20 Results were similar to the original PLS. Correlations between the saliences of the new and
21 the original PLS analysis for the first four LVs ranged from 0.87 to 0.96 (Table S3),
22 suggesting high correlation.

23

24 **Regressing out total cerebellar grey matter volume**

25

1 Results were similar to the original PLS. Correlations between the saliences of the new and
2 the original PLS analysis for the first four LVs ranged from 0.97 to 1 (Table S3), suggesting
3 high correlation.

4 5 **Cerebellar gradient based on cerebellar-cerebral FC**

6
7 When using cerebellar gradient based on cerebellar-cerebral FC, results were similar to the
8 original PLS using the cerebellar gradient based on intra-cerebellar FC. Correlations between
9 the saliences of the new and the original PLS analysis for the first four LVs ranged from 0.77
10 to 0.99, suggesting high correlation (Table S3).

11 12 **Including confounds**

13
14 Results were similar to the original PLS, with moderate to high correlations between the
15 saliences of the new and the original PLS analysis ranging from 0.61 to 0.93 for LVs 1-4
16 (Table S3).

17 18 **Quantile normalization**

19
20 Results were similar to the original PLS, with high correlations between the saliences of the
21 new and the original PLS analysis ranging from 0.95 to 0.99 for LVs 1-4 (Table S3).

22 23 **Patients and sites factor**

24
25 When using healthy participants separately in the new PLS analysis, correlations between the
26 saliences of the new and the original PLS analysis ranged between 0.46-0.83 for the first four

1 LVs, suggesting moderate to high correlation. However, correlations dropped to 0.14 and 0.22
2 for LV5; hence we did not describe LV5 further. When considering only patients, correlations
3 between the saliences of the new and the original PLS analysis ranged between 0.55-0.93 for
4 the first four LVs, suggesting moderate to high correlation (Table S3).

5

6 When using only participants from site 1 in the new PLS analysis, correlations between the
7 saliences of the new and the original PLS analysis ranged between 0.66-0.96 for the first four
8 LVs, suggesting high correlation. When considering only participants from site 2, correlations
9 between the saliences of the new and the original PLS analysis ranged between 0.49-0.97 for
10 the first four LVs, suggesting moderate to high correlation (Table S3).

11

12 **Contribution of each diagnostic group to the overall composite correlations**

13

14 There was no significant difference between pairs of correlation coefficients (Table S4, FDR
15 $q > 0.05$ for all pairwise comparisons), suggesting that each diagnostic group contributed
16 similarly to the overall composite correlations of these four LVs.

17

References in this supplement materials

- [1] K. J. Gorgolewski, J. Durnez, R. A. Poldrack, *F1000Research* **2017**, 6, 1262.
- [2] C. G. Yan, X. Di Wang, X. N. Zuo, Y. F. Zang, *Neuroinformatics* **2016**, 14, 339.
- [3] D. Dong, M. Duan, Y. Wang, X. Zhang, X. Jia, Y. Li, F. Xin, D. Yao, C. Luo, *Cereb. Cortex* **2018**, 1.
- [4] D. Dong, C. Luo, X. Guell, Y. Wang, H. He, M. Duan, S. B. Eickhoff, *Schizophr. Bull.* **2020**, 1.
- [5] A. X. Patel, P. Kundu, M. Rubinov, P. S. Jones, P. E. Vértes, K. D. Ersche, J. Suckling, E. T. Bullmore, *Neuroimage* **2014**, 95, 287.
- [6] K. J. Friston, S. Williams, R. Howard, R. S. J. Frackowiak, *Magn. Reson. Med.* **1996**, 3, 346.
- [7] T. D. Satterthwaite, M. A. Elliott, R. T. Gerraty, K. Ruparel, J. Loughhead, M. E. Calkins, S. B. Eickhoff, H. Hakonarson, R. C. Gur, R. E. Gur, D. H. Wolf, *Neuroimage* **2013**, 64, 240.
- [8] Y. Behzadi, K. Restom, J. Liau, T. T. Liu, *Neuroimage* **2007**, 37, 90.
- [9] A. Hahamy, V. Calhoun, G. Pearlson, M. Harel, N. Stern, F. Attar, R. Malach, R. Salomon, *Brain Connect.* **2014**, 4, 395.
- [10] K. Murphy, R. M. Birn, D. A. Handwerker, T. B. Jones, P. A. Bandettini, *Neuroimage* **2009**, 44, 893.
- [11] J. D. Power, K. A. Barnes, A. Z. Snyder, B. L. Schlaggar, S. E. Petersen, *Neuroimage* **2012**, 59, 2142.
- [12] D. S. Margulies, S. S. Ghosh, A. Goulas, M. Falkiewicz, J. M. Huntenburg, G. Langs, G. Bezgin, S. B. Eickhoff, F. X. Castellanos, M. Petrides, E. Jefferies, J. Smallwood, *Proc. Natl. Acad. Sci.* **2016**, 113, 12574.
- [13] S. J. Hong, R. V. de Wael, R. A. I. Bethlehem, S. Larivière, C. Paquola, S. L. Valk, M. P. Milham, A. Di Martino, D. S. Margulies, J. Smallwood, B. C. Bernhardt, *Nat. Commun.* **2019**, 10, 1.
- [14] X. Guell, J. D. Schmahmann, J. DE Gabrieli, S. S. Ghosh, *Elife* **2018**, 7, 1.
- [15] R. Vos De Wael, S. Larivière, B. Caldairou, S. J. Hong, D. S. Margulies, E. Jefferies, A. Bernasconi, J. Smallwood, N. Bernasconi, B. C. Bernhardt, *Proc. Natl. Acad. Sci. U. S. A.* **2018**, 115, 10154.

- 1 [16] R. R. Coifman, S. Lafon, A. B. Lee, M. Maggioni, B. Nadler, F. Warner, S. W. Zucker, *Proc.*
2 *Natl. Acad. Sci. U. S. A.* **2005**, *102*, 7432.
- 3 [17] G. Langs, P. Golland, S. S. Ghosh, *Med Image Comput Comput Assist Interv.* **2015**, 313.
- 4 [18] Ş. Bayrak, A. A. Khalil, K. Villringer, J. B. Fiebach, D. S. Margulies, S. Ovadia-Caro,
5 *NeuroImage Clin.* **2018**, *24*.
- 6 [19] A. R. McIntosh, B. Mišić, *Annu. Rev. Psychol.* **2013**, *64*, 499.
- 7 [20] A. Krishnan, L. J. Williams, A. R. McIntosh, H. Abdi, *Neuroimage* **2011**, *56*, 455.
- 8 [21] T. Courville, B. Thompson, *Educ. Psychol. Meas.* **2001**, *61*, 229.
- 9 [22] A. Sherry, R. K. Henson, *J. Pers. Assess.* **2005**, *84*, 37.
- 10 [23] T. Yarkoni, J. Westfall, *Perspect. Psychol. Sci.* **2017**, *12*, 1100.
- 11 [24] J. Diedrichsen, *Neuroimage* **2006**, *33*, 127.
- 12 [25] T. Moberget, N. T. Doan, D. Alnæs, T. Kaufmann, A. Córdova-Palomera, T. V. Lagerberg, J.
13 Diedrichsen, E. Schwarz, M. Zink, S. Eisenacher, P. Kirsch, E. G. Jönsson, H. Fatouros-
14 Bergman, L. Flyckt, G. Pergola, T. Quarto, A. Bertolino, D. Barch, A. Meyer-Lindenberg, I.
15 Agartz, O. A. Andreassen, L. T. Westlye, *Mol. Psychiatry* **2018**, *23*, 1512.
- 16 [26] B. Diedenhofen, J. Musch, *PLoS One* **2015**, *10*, 1.
- 17

1 **Table S1. Behavior measures used in the present study**

Scale	Subscale	Number of subjects available
Young Mania Rating Scale-C	Total score	106
Hamilton Psychiatric Rating Scale for Depression	Total score (items 1-17)	106
Scale for the Assessment of Positive Symptoms	Delusions	72
	Hallucinations	72
	Bizarre behavior	72
	Positive formal thought disorder	71
Scale for the Assessment of Negative Symptoms	Alogia	72
	Anhedonia	72
	Attention	72
	Avolition	72
	Blunt affect	72
Brief Psychiatric Rating Scale	Positive symptoms	106
	Negative symptoms	106
	Mania/disorganization	106
	Depression/anxiety	106
Hopkins Symptom Checklist	Anxiety	198*
	Depression	198*
	Obsessive compulsiveness	198*
	Somatization	198*
	Interpersonal sensitivity	198*
Adult ADHD clinical diagnosis scale	Inattention	106
	Hyperactivity	106
Adult Self-Report Scale v.1.1 Screener	ADHD symptoms (total score)	198*
Chapman Psychosis-Prone Scales	Perceptual aberrations	198*
	Social anhedonia	198*
	Physical anhedonia	198*
	Infrequency	198*
Scale for Traits that Increase Risk for Bipolar II Disorder	Mood lability	198*
	Daydreaming	198*
	Energy/activity	198*
	Social anxiety	198*
Golden & Meehl's Seven MMPI Items Selected by Taxonomic Method	Schizoid-type personality	198*
Eckblad and Chapman's Hypomanic Personality Scale	Hypomanic personality	198*
Temperament and Character Inventory	Reward dependence	198*
	Persistence	198*
	Novelty seeking	198*

Barratt Impulsiveness Scale (BIS-11)	Harm avoidance	198*
	Attentional impulsivity	198*
Dickman Functional and Dysfunctional Impulsivity Scale	Motor impulsivity	198*
	Nonplanning	198*
	Functional impulsivity	198*
Impulsiveness, Venturesomeness and Empathy Scale	Dysfunctional impulsivity	198*
	Impulsiveness	198*
Multidimensional Personality Questionnaire (MPQ)—Control subscale	Venturesomeness	198*
	Empathy	198*
	Control	198*
Delay Discounting Task	Small rewards	196
	Medium rewards	196
	Large rewards	196
	Total	196
Balloon Analog Risk Task	Total pumps	189
California Verbal Learning Test (CVLT-II)	Short delay free recall	198*
	Short delay cued recall	198*
	Long delay free recall	198*
	Long delay cued recall	198*
	Long delay recognition	198*
Scene Recognition Task	Encoding accuracy	196
	Encoding RT	196
	Recall accuracy	196
	Recall RT	196
Remember-Know Task	Remember words accuracy	168
	Remember colors accuracy	168
	Remember forced recognition 1 feature	168
	Remember forced recognition 2 features	168
	Remember mean RT	165
	Know words accuracy	168
	Know colors accuracy	168
	Know forced recognition 1 feature	168
	Know forced recognition 2 features	168
	Know mean RT	161
Wechsler Memory Scale (WMS-IV)	Symbol span	198*
	Visual reproduction immediate recall	198*
	Visual reproduction delayed	198*

	recall	
	Visual reproduction	198*
	recognition	
	Digit span forward	198*
	Digit span backward	198*
	Digit span sequencing	198*
Spatial Maintenance and Manipulation Task	Maintenance mean accuracy	190
	Maintenance median RT	190
	Manipulation mean accuracy	190
	Manipulation median RT	190
Verbal Maintenance and Manipulation Task	Maintenance mean accuracy	189
	Maintenance median RT	189
	Manipulation mean accuracy	189
	Manipulation median RT	189
Spatial Capacity Task	Load 1 accuracy	197
	Load 1 mean RT	197
	Load 3 accuracy	197
	Load 3 mean RT	197
	Load 5 accuracy	197
	Load 5 mean RT	197
	Load 7 accuracy	197
	Load 7 mean RT	197
	Maximum capacity	197
Verbal Capacity Task	Load 3 accuracy	197
	Load 3 mean RT	197
	Load 5 accuracy	197
	Load 5 mean RT	197
	Load 7 accuracy	197
	Load 7 mean RT	197
	Load 9 accuracy	197
	Load 9 mean RT	197
	Maximum capacity	197
Wechsler Adult Intelligence Scale (WAIS-IV)	Matrix reasoning	198*
	Letter/number sequencing	198*
	Vocabulary	198*
Delis-Kaplan Executive Function System	English verbal fluency	198*
	Spanish verbal fluency	68
Stroop Color Word Task	Interference accuracy	198*
	Interference RT	198*
Color Trails Test	Interference index	198*
Stop Signal Task	Quantile RT	196
Task Switching Task	Accuracy	198*
	Interference	198*
	Switching cost	198*
	Residual switching cost	198*
Attention Network Task	Interference RT	197
Continuous Performance	Hit rate	198*

Go/No Go Task

Hits median RT 198*

False alarm rate 198*

- 1 Notes: This table lists both behavior measures used in the PLS analysis and measures only
- 2 considered in posthoc analyses (Table S3). Behavior measures used in the PLS analysis were
- 3 marked with *.

Table S2. Group differences among the Fifty-five Behavioral measures in the PLS analysis

Scale	Variables	ADHD	BD	HC	SZ	F	P value
Adult Self Report Scale	ADHD symptoms	15.51(3.86)	13.11(4.98)	8.89(2.81)	9.34(4.36)	32.54	4.41E-17
Hopkins Symptom Checklist	Depression	0.67(0.48)	0.91(0.63)	0.39(0.37)	0.72(0.59)	11.47	5.89E-7
	Obsessive compulsiveness	1.21(0.74)	1.10(0.75)	0.52(0.44)	0.95(0.61)	15.93	2.68E-9
	Anxiety	0.47(0.41)	0.71(0.62)	0.22(0.30)	0.71(0.65)	15.21	6.28E-9
	Somatization	0.35(0.28)	0.63(0.65)	0.22(0.24)	0.57(0.48)	12.75	1.22E-7
	Interpersonal sensitivity	0.76(0.55)	1.00(0.71)	0.40(0.37)	0.85(0.61)	14.32	1.83E-8
Chapman Psychosis-Proneness Scales	Infrequency (Careless response)	0.74(0.95)	0.89(1.21)	0.67(1.12)	1.57(1.50)	5.04	0.002
	Perceptual aberrations	4.11(3.81)	5.08(4.75)	2.16(2.67)	9.51(8.23)	21.30	5.70E-12
	Social anhedonia	14.09(8.87)	15.53(7.63)	10.15(7.15)	15.37(6.24)	7.27	1.21E-4
	Physical anhedonia	13.03(7.94)	15.47(9.66)	11.54(6.63)	15.71(6.72)	3.90	0.01
Scale for Traits that Increase Risk for Bipolar II Disorder	Mood lability	3.66(2.45)	5.14(2.97)	2.13(1.71)	3.97(2.66)	16.98	7.84E-10
	Energy(Restless)	3.74(2.06)	3.86(2.58)	3.05(2.15)	4.11(2.14)	2.60	0.05
	Daydreaming	3.91(1.42)	3.47(1.87)	3.14(1.82)	3.11(2.07)	1.78	0.15
	Social anxiety	3.09(1.63)	3.56(1.99)	3.01(1.90)	3.77(1.73)	1.87	0.14
Barratt Impulsiveness Scale	Attention impulsivity	22.00(3.91)	19.06(5.52)	14.59(3.33)	17.00(4.63)	30.31	4.08E-16
	Motor impulsivity	26.91(4.01)	24.61(5.51)	21.98(3.74)	22.71(4.43)	12.53	1.61E-7
	Nonplanning	28.60(4.39)	28.33(5.58)	23.05(4.38)	26.74(5.40)	17.68	3.46E-10
Multidimensional Personality Questionnaire	MPQ control	10.74(4.97)	11.72(7.30)	18.04(5.06)	16.23(5.09)	20.88	9.12E-12
Golden & Meehl's Seven MMPI	Schizoid personality	3.00(1.37)	3.83(1.63)	2.42(1.28)	3.43(1.63)	10.06	3.40E-6
Eckblad and Chapman's Hypomanic Personality Scale	Hypomanic personality	24.71(6.85)	23.25(11.58)	16.14(7.76)	19.80(8.73)	11.25	7.76E-7
Dickman Functional and Dysfunctional Impulsivity Scale	Functional impulsivity	7.03(2.93)	5.50(3.21)	6.60(2.72)	5.66(2.80)	2.61	0.05
	dysfunctional impulsivity	4.83(2.82)	5.36(4.28)	1.91(2.43)	4.06(3.46)	14.95	8.59E-9
Impulsiveness,	Eysenck	9.11(3.22)	9.08(4.54)	6.24(3.01)	9.23(3.49)	11.6	4.95E-7

Venturesomenes and Empathy Scale	impulsiveness					1	
	Eysenck	9.51(1.90)	7.78(2.61)	8.76(2.46)	8.29(2.67)	3.32	0.02
	venturesomeness						
	Eysenck empathy	11.17(2.77)	11.14(3.50)	10.63(3.13)	11.17(2.63)	0.49	0.69
Temperament and Character Inventory	Persistence	21.97(7.81)	19.11(9.37)	23.57(7.21)	22.14(6.28)	2.98	0.03
	Harm avoidance	11.97(6.41)	18.06(9.18)	11.91(6.50)	15.23(7.50)	7.44	9.66E-5
Harm	Reward dependence	14.86(4.88)	14.25(5.11)	15.96(4.44)	14.69(3.86)	1.58	0.20
	Novelty seeking	25.37(4.90)	22.64(7.81)	19.09(5.94)	18.60(5.56)	11.5	5.16E-7
California Verbal Learning Test	Short delay free recall	11.60(2.81)	10.69(3.58)	12.86(2.32)	8.95(3.56)	16.6	1.13E-9
	Short delay cued recall	12.29(2.23)	11.81(3.23)	13.33(2.10)	10.26(2.73)	13.5	4.65E-8
	Long delay free recall	12.20(2.42)	11.11(3.50)	13.27(2.32)	9.57(3.10)	17.2	5.81E-10
	Long delay cued recall	12.71(2.22)	12.11(3.47)	13.28(2.13)	10.23(3.15)	14.1	2.20E-8
	Long delay recognition	3.29(0.65)	3.32(0.86)	3.37(0.80)	2.61(0.95)	7.75	6.48E-5
Wechsler Memory Scale	Visual reproduction immediate recall	37.80(5.37)	35.72(4.96)	38.40(4.55)	32.74(8.27)	9.51	6.88E-6
	Visual reproduction delayed recall	30.57(8.79)	26.81(10.80)	32.95(8.46)	23.54(11.00)	9.79	4.83E-6
	Visual reproduction recognition	6.54(0.85)	6.11(1.24)	6.51(0.75)	5.46(1.75)	8.83	1.62E-5
	Symbol span	23.09(6.84)	21.31(6.47)	25.63(6.05)	17.26(6.88)	15.3	5.63E-9
	Digit span forward	11.09(1.92)	10.56(2.24)	11.11(2.34)	8.74(2.15)	10.3	2.39E-6
	Digit span backward	9.11(2.26)	8.92(2.39)	9.72(2.41)	7.26(2.23)	9.32	8.70E-6
	Digit span sequencing	9.03(1.95)	8.61(2.77)	9.78(2.39)	7.29(1.90)	10.2	2.74E-6
Wechsler Adult Intelligence Scale	Letter/Number sequencing	19.97(2.79)	19.75(2.71)	21.14(2.89)	17.83(3.49)	10.8	1.21E-6
	Vocabulary	42.97(9.18)	42.69(10.38)	43.58(8.59)	31.29(9.91)	16.0	2.27E-9
	Matrix reasoning	20.71(3.88)	19.28(4.74)	20.87(3.83)	15.69(4.98)	13.6	4.25E-8
Color Trails Test	ColorTrail interference	1.08(0.65)	1.10(0.59)	1.10(0.55)	1.09(0.62)	0.13	0.99
English Verbal fluency	Letter Fluency	41.03(10.44)	40.03(13.80)	41.79(12.02)	30.37(8.14)	8.75	1.81E-5
Task Switching	Taskswitch total accuracy	0.96(0.027)	0.96(0.0350)	0.97(0.027)	0.94(0.074)	5.49	0.001
	Taskswitch interference	57.77(88.49)	68.13(74.78)	42.76(63.76)	57.76(147.76)	0.77	0.52

Continuous Performance Go/NoGo Task	Taskswitch switch cost	274.16(120.28)	259.64(137.10)	262.40(145.15)	278.56(202.63)	0.15	0.93
	Taskswitch residual switch cost	79.01(121.13)	54.58(108.74)	54.69(105.19)	126.77(164.35)	3.30	0.02
	Total go hit	321.17(6.59)	319.44(8.61)	322.88(1.64)	317.91(12.20)	5.14	0.002
	Total false alarms	13.91(8.20)	12.78(7.21)	12.78(6.71)	13.29(6.54)	0.25	0.86
	Hits median RT	360.36(54.74)	387.50(60.31)	350.75(43.18)	386.59(51.09)	7.15	1.40E-4
Stroop Color Word Task		-	-0.020(0.041)	-	-	1.89	0.13
	Conflict effect	0.042(0.064)		0.035(0.056)	0.051(0.062)		
	Conflict effect RT	141.20(69.90)	128.87(60.23)	122.97(70.67)	122.55(75.54)	0.64	0.59

1 Notes: Mean (standard deviation) values are shown for each group. RT=reaction time.

Table S3. Absolute correlations between cerebellar gradient (or behavioral) saliences obtained in control analyses and cerebellar gradient (or behavioral) saliences from the original PLS analysis.

	Latent dimension	GS R	Regressing out cerebellar grey matter volume	Cerebellar r-cerebral Gradient	Confounds included	Behavior normalized	Controls Only	Patients only	Site #1	Site #2
Correlations with original gradient saliences	LV #1	0.91	1	0.83	0.77	0.99	0.46	0.61	0.76	0.68
	LV #2	0.92	0.97	0.85	0.85	0.98	0.70	0.55	0.79	0.76
	LV #3	0.87	0.98	0.77	0.89	0.97	0.66	0.77	0.75	0.49
	LV #4	0.91	0.99	0.81	0.62	0.97	0.57	0.67	0.66	0.69
	LV #5	0.83	1	0.82	0.58	0.95	0.14	0.55	0.52	0.45
Correlations with original behavioral saliences	LV #1	0.98	1	0.99	0.93	1	0.83	0.82	0.96	0.97
	LV #2	0.95	0.98	0.96	0.84	0.97	0.80	0.59	0.90	0.89
	LV #3	0.96	0.99	0.93	0.93	0.97	0.87	0.93	0.89	0.70
	LV #4	0.94	0.99	0.92	0.61	0.95	0.71	0.64	0.74	0.76
	LV #5	0.87	1	0.94	0.63	0.95	0.22	0.69	0.63	0.61

1 **Table S4. Comparisons between pairs of correlation coefficients between**
2 **gradient composite scores and behavioral composite scores**

LV1(separated group-1)	LV2(separated group-1)	LV3(separated group-1)	LV4(separated group-1)
r_hc=0.6099; r_patients=0.5696 z = 0.4272, p = 0.6692	r_hc=0.5415;r_patients=0.5943 z = -0.5390, p = 0.5899	r_hc=0.5548;r_patients =0.6571 z = -1.1222, p = 0.2618	r_hc=0.5466;r_patients=0.6667 z = -1.3216, p = 0.1863
LV1(separated group-2)	LV2(separated group-2)	LV3(separated group-2)	LV4(separated group-2)

r_hc=0.6099;
r_sz=0.4539
r_bd=0.7114;
r_adhd=0.5740
hc-sz: z = 1.0633, p =
0.2877;
hc-bd: z = -0.8893, p =
0.3738
hc-adhd: z = 0.2683, p =
0.7885
sz-bd: z = -1.6139, p =
0.1065
sz-adhd: z = -0.6555, p =
0.5122
bd-adhd: z = 0.9534, p =
0.3404
	r_hc=0.5415; r_sz=0.7511
	r_bd=0.5103; r_adhd=0.6037
	hc-sz: z = -1.7912, p = 0.0733
	hc-bd: z = 0.2117, p = 0.8324
	hc-adhd: z = -0.4496, p =
	0.6530
	sz-bd: z = 1.6620, p = 0.0965
	sz-adhd: z = 1.1061, p =
	0.2687
	bd-adhd: z = -0.5474, p =
	0.5841
		r_hc=0.5548;
		r_sz=0.6782
		r_bd=0.7275;
		r_adhd=0.4116
		hc-sz: z = -0.9727, p =
		0.3307
		hc-bd: z = -1.4627, p =
		0.1436
		hc-adhd: z = 0.9109, p =
		0.3624
		sz-bd: z = -0.3935, p =
		0.6940
		sz-adhd: z = 1.5529, p =
		0.1204
		bd-adhd: z = 1.9583, p =
		0.0502
			r_hc=0.5466; r_sz=0.5607
			r_bd=0.8036; r_adhd=0.4845
			hc-sz: z = -0.0986, p = 0.9214
			hc-bd: z = -2.4296, p = 0.0151
			hc-adhd: z = 0.4108, p =
			0.6812
			sz-bd: z = -1.9139, p = 0.0556
			sz-adhd: z = 0.4200, p =
			0.6745
			bd-adhd: z = 2.3372, p =
			0.0194

4 Notes: There was no significant difference between pairs of correlation coefficients (FDR q >
5 0.05 for all pairwise comparisons)

6

1 **Table S5. Associations between cerebellar gradient or behavior composite scores and**
2 **confounding factors**

	LV1				LV2				LV3				LV4			
	Gradient composite scores		Behavioral composite scores		Gradient composite scores		Behavioral composite scores		Gradient composite scores		Behavioral composite scores		Gradient composite scores		Behavioral composite scores	
	r/t	p	r/t	p	r/t	p	r/t	p	r/t	p	r/t	p	r/t	p	r/t	p
Age	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
Sex	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
Education	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
Site	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
Motion	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
Total brain volume	-0.04	0.59	-0.08	0.26	-0.03	0.63	0.05	0.48	-0.05	0.44	-0.07	0.31	0.02	0.80	0.04	0.62
Cerebellar volume	-0.10	0.20	-0.04	0.55	0.15	0.03	0.17	0.02	-0.06	0.38	-0.10	0.18	0.07	0.32	0.02	0.73
Medication load	0.35	4.7E-7	0.39	1.2E-8	-0.09	0.19	0.07	0.30	0.18	0.01	0.28	6.2E-5	-0.07	0.30	0.06	0.43
Substance use	0.12	0.08	0.10	0.16	0.07	0.35	0.15	0.03	-0.13	0.06	-0.10	0.15	-0.03	0.65	-0.07	0.35

3 Notes: T tests were performed for binary measures, and Pearson's correlations were
4 performed for continuous measures. Bold refers to significant associations that survived FDR
5 correction ($q < 0.05$).

1 **Table S6. Correlations between subjects' behavioral measures and their**
2 **behavioral composite scores**

LV#1			LV#2		
	r	SD		r	SD
Eysenck impulsiveness	0.70	0.04	ADHD symptoms	0.60	0.04
Dysfunctional impulsivity	0.66	0.04	Attention impulsivity	0.57	0.05
Mood lability	0.60	0.04	Depression	0.55	0.05
Nonplanning	0.56	0.04	Mood lability	0.53	0.05
Perceptual aberrations	0.56	0.06	Interpersonal sensitivity	0.53	0.05
Attention impulsivity	0.54	0.05	Attention severity*	0.52	0.09
Obsessive compulsiveness	0.54	0.05	Obsessive compulsiveness	0.52	0.05
Anxiety	0.53	0.06	Daydreaming	0.52	0.05
Interpersonal sensitivity	0.52	0.05	Vocabulary	0.49	0.05
Hypomanic peronality	0.52	0.05	Schizoid personality	0.47	0.05
Depression	0.47	0.05	Harm avoidance	0.47	0.05
ADHD symptoms	0.45	0.05	Motor impulsivity	0.47	0.05
Somatization	0.42	0.07	Social anxiety	0.46	0.06
Social anhedonia	0.39	0.06	Dysfunctional impulsivity	0.46	0.05
Motor impulsivity	0.39	0.05	Nonplanning	0.45	0.05
Energy(Restless)	0.37	0.06	Anxiety	0.43	0.06
Infrequency(careless response)	0.37	0.07	HAMD_depression*	0.42	0.09
Physical anhedonia	0.37	0.07	Hyperactivity severity*	0.39	0.09
YMRC_mania*	0.36	0.10	Matrix reasoning	0.39	0.07
Depression/anxiety*	0.35	0.10	Letter fluency	0.39	0.06
Schizoid personality	0.34	0.06	Digit span backward	0.38	0.06
HAMD_depression*	0.33	0.10	Somatization	0.37	0.07
Delusions*	0.32	0.13	Depression/anxiety*	0.36	0.09
			Remember words		
Novelty seeking	0.31	0.06	accuracy*	0.36	0.07
Eysenck empathy	0.30	0.05	Long delay recognition	0.36	0.07
Total false alarms	0.28	0.06	Digit span forward	0.34	0.06
Mania/disorganization*	0.27	0.10	Eysenck impulsiveness	0.34	0.05
Positive formal thought*	0.25	0.13	Novelty seeking	0.33	0.06
Social anxiety	0.25	0.06	Social anhedonia	0.32	0.06
Positive symptoms*	0.25	0.10	Long delay cued recall	0.32	0.07
			Visual reproduction		
Hallucinations*	0.24	0.13	immediate recall	0.31	0.07
Harm avoidance	0.24	0.06	Digit span sequencing	0.31	0.05
			Verbal manipulation		
Attention*	0.24	0.12	accuracy*	0.29	0.06
Daydreaming	0.22	0.06	Symbol span	0.28	0.05
Attention severity*	0.18	0.10	Hypomanic peronality	0.28	0.06
Anhedonia*	0.17	0.12	Mania/disorganization*	0.27	0.10
Hyperactivity severity*	0.17	0.10	Short delay cued recall	0.27	0.08
Avolition*	0.16	0.12	Long delay free recall	0.26	0.07
			Visual reproduction		
Spatial capacity load 3			recognition	0.25	0.08
RT*	0.14	0.07	Taskswitch total accuracy	0.24	0.07
Bizarre behavior*	0.12	0.12			

ANT_Interference RT*	0.10	0.07	Visual reproduction		
Verbal capacity load 5 RT*	0.09	0.07	delayed recall	0.24	0.08
			Short delay free recall	0.23	0.07
Vpatial capacity load 3 RT*	0.09	0.06	Know forced recognition 2		
Delay discounting medium rewards*	0.09	0.07	features*	0.23	0.07
Taskswitch interference	0.09	0.07	Scene recognition encoding		
Delay discounting small rewards*	0.09	0.07	accuracy*	0.23	0.06
Alogia*	0.08	0.12	Letter/Number sequencing	0.22	0.06
Delay discounting total rewards*	0.08	0.07	Scene recognition recall		
			accuracy*	0.22	0.06
Spatial maintenance RT*	0.08	0.07	BART_total pumps*	0.21	0.07
Scene recognition encoding RT*	0.08	0.07	Verbal maintenance		
Delay discounting large rewards*	0.07	0.07	accuracy*	0.21	0.06
			Remember forced		
Blunt affect*	0.07	0.12	recognition 2 features*	0.20	0.07
Know forced recognition 1 feature*	0.07	0.07	Spatial capacity load 7		
Negative symptoms*	0.07	0.10	accuracy*	0.20	0.06
Taskswitch residSwitchCost	0.07	0.08	YMRC_mania*		
				0.19	0.10
			Spatial maintenance		
ColorTrail interference	0.06	0.07	accuracy*	0.19	0.07
Spatial capacity load 1 RT*	0.05	0.07	Know words accuracy*		
				0.19	0.07
Spatial capacity load 5 RT*	0.05	0.07	Eysenck empathy	0.18	0.06
Scene recognition recall RT*	0.04	0.07	Physical anhedonia	0.15	0.08
Spatial capacity load 7 RT*	0.02	0.07	Verbal capacity load 7		
Verbal maintenance RT*	0.02	0.07	accuracy*	0.15	0.07
			Know colors accuracy*	0.14	0.07
Stop signal quantile RT*	0.01	0.07	Verbal maximum		
Verbal manipulation RT*	0.01	0.07	capacity*	0.13	0.06
Functional impulsivity	0.01	0.07	Spatial maximum		
Remember forced recognition 1 feature*	0.00	0.07	capacity*	0.13	0.07
			Verbal capacity load 9 RT*	0.12	0.07
Remember mean RT*	0.00	0.07	Perceptual aberrations	0.12	0.06
Spatial manipulation RT*	-0.02	0.06	Verbal capacity load 3		
Eysenck venturesomeness	-0.02	0.07	accuracy*	0.12	0.07
Know colors accuracy*	-0.03	0.07	Go hit median RT	0.11	0.08
			Remember mean RT*	0.11	0.07
Verbal capacity load 7 RT*	-0.03	0.07	Remember colors accuracy*		
Taskswitch switch cost	-0.05	0.07		0.10	0.07
			Spatial capacity load 3		
Conflict effect RT	-0.07	0.06	accuracy*	0.10	0.07
			Bizarre behavior*	0.10	0.10
			Taskswitch interference	0.10	0.07
			Conflict effect RT	0.10	0.07
			Spatial manipulation		
			accuracy*	0.09	0.06
			Anhedonia*	0.09	0.11
			Know forced recognition 1		
			feature*	0.09	0.07

			Verbal capacity load 9		
Persistence	-0.08	0.07	accuracy*	0.08	0.07
Go hit median RT	-0.09	0.07	Delusions*	0.08	0.09
Know mean RT*	-0.10	0.08	Verbal capacity load 7 RT*	0.08	0.06
Remember forced recognition 2 features*	-0.12	0.06	Spatial capacity load 1		
			accuracy*	0.04	0.07
Total go hit	-0.12	0.06	Remember forced recognition 1 feature*	0.04	0.07
			Spatial capacity load 5		
Conflict effect	-0.13	0.09	accuracy*	0.03	0.07
Know words accuracy*	-0.13	0.07	Vpatial capacity load 3 RT*	0.03	0.06
Verbal capacity load 9 RT*	-0.13	0.07	Spatial manipulation RT*		
				0.03	0.07
BART_total pumps*	-0.13	0.06	Verbal capacity load 5		
			accuracy*	0.03	0.07
Spatial manipulation accuracy*	-0.16	0.06	Conflict effect		
				0.01	0.06
Reward dependence	-0.18	0.06	ColorTrail interference	-0.01	0.08
Spatial capacity load 7 accuracy*	-0.18	0.06	Verbal manipulation RT*		
				-0.02	0.07
Remember colors accuracy*	-0.23	0.07	Verbal capacity load 5 RT*		
				-0.02	0.07
Verbal capacity load 3 accuracy*	-0.24	0.07	ANT_Interference RT*		
				-0.02	0.06
Verbal capacity load 7 accuracy*	-0.25	0.07	Hallucinations*		
				-0.03	0.10
Verbal capacity load 9 accuracy*	-0.26	0.06	Positive symptoms*		
				-0.03	0.08
Scene recognition encoding accuracy*	-0.26	0.09	Taskswitch residSwitchCost		
				-0.03	0.07
Spatial maximum capacity*	-0.27	0.06	Energy(Restless)		
				-0.03	0.06
Spatial capacity load 1 accuracy*	-0.28	0.07	Scene recognition recall RT*		
				-0.04	0.07
Digit span forward	-0.29	0.08	Scene recognition encoding RT*		
				-0.04	0.07
Remember words accuracy*	-0.29	0.07	Delay discounting small rewards*		
				-0.04	0.06
Spatial maintenance accuracy*	-0.30	0.07	Taskswitch switch cost		
				-0.05	0.06
Taskswitch total accuracy	-0.30	0.08	Spatial maintenance RT*		
				-0.05	0.07
Verbal maximum capacity*	-0.31	0.07	Stop signal quantile RT*		
				-0.06	0.07
Letter fluency	-0.31	0.07	Know mean RT*		
				-0.06	0.07
Know forced recognition 2 features*	-0.32	0.07	Spatial capacity load 3 RT*		
				-0.08	0.07
Verbal capacity load 5 accuracy*	-0.32	0.07	Delay discounting medium rewards*		
				-0.08	0.07
Spatial capacity load 5 accuracy*	-0.34	0.06	Positive formal thought*		
				-0.08	0.11

Verbal manipulation accuracy*	-0.34	0.06	Attention*	-0.08	0.11
Spatial capacity load 3 accuracy*	-0.35	0.07	Avolition*	-0.10	0.10
Matrix reasoning	-0.35	0.06	Delay discounting total rewards*	-0.11	0.06
Digit span sequencing	-0.37	0.06	Spatial capacity load 1 RT*	-0.11	0.07
Digit span backward	-0.37	0.07	Reward dependence	-0.12	0.06
Vocabulary	-0.38	0.06	Functional impulsivity	-0.12	0.06
Verbal maintenance accuracy*	-0.41	0.07	Eysenck venturesomeness	-0.12	0.08
Visual reproduction recognition	-0.43	0.07	Negative symptoms*	-0.13	0.09
Letter/Number sequencing	-0.44	0.05	Total false alarms	-0.13	0.07
Long delay recognition	-0.46	0.06	Verbal maintenance RT*	-0.13	0.07
Visual reproduction delayed recall	-0.47	0.06	Infrequency(careless response)	-0.14	0.08
Symbol span	-0.49	0.05	Total go hit	-0.14	0.08
Scene recognition recall accuracy*	-0.49	0.07	Spatial capacity load 5 RT*	-0.14	0.07
Visual reproduction immediate recall	-0.51	0.06	Delay discounting large rewards*	-0.15	0.06
MPQ control	-0.57	0.05	Spatial capacity load 7 RT*	-0.17	0.07
Short delay cued recall	-0.61	0.05	Alogia*	-0.18	0.10
Short delay free recall	-0.61	0.05	Blunt affect*	-0.21	0.10
Long delay free recall	-0.62	0.05	Persistence	-0.37	0.06
Long delay cued recall	-0.62	0.05	MPQ control	-0.44	0.05

LV #3			LV#4		
	r	SD		r	SD
Harm avoidance	0.68	0.04	Total false alarms	0.28	0.07
Social anxiety	0.56	0.04	Nonplanning	0.20	0.07
Negative symptoms*	0.49	0.09	ColorTrail interference	0.17	0.06
MPQ control	0.45	0.06	Spatial capacity load 3 RT*	0.13	0.07
Alogia*	0.41	0.10	ANT_Interference RT*	0.13	0.07
Physical anhedonia	0.39	0.06	Total go hit	0.12	0.09
Blunt affect*	0.39	0.11	Scene recognition recall RT*	0.12	0.07
Social anhedonia	0.39	0.06	Taskswitch interference	0.11	0.07
Anhedonia*	0.38	0.12	Spatial maintenance RT*	0.11	0.07
Positive symptoms*	0.33	0.08	Spatial manipulation RT*	0.11	0.07
Somatization	0.33	0.06	Attention*	0.11	0.11
Depression/anxiety*	0.31	0.09	Spatial capacity load 5 RT*	0.10	0.07
Avolition*	0.30	0.11	Spatial capacity load 1 RT*	0.10	0.07
Attention*	0.25	0.11	Taskswitch residSwitchCost	0.10	0.06
Hallucinations*	0.25	0.11	Delay discounting medium	0.10	0.07

			rewards*		
Anxiety	0.23	0.08	Spatial capacity load 7 RT*	0.08	0.07
Depression	0.23	0.08	Know mean RT*	0.08	0.08
Schizoid personality			Delay discounting small		
	0.21	0.06	rewards*	0.07	0.07
HAMD_depression*	0.21	0.09	Verbal capacity load 5 RT*	0.07	0.08
Interpersonal sensitivity	0.19	0.09	Taskswitch switch cost	0.07	0.06
Mood lability			Delay discounting total		
	0.18	0.07	rewards*	0.07	0.07
Perceptual aberrations			Scene recognition encoding		
	0.18	0.07	RT*	0.07	0.07
Obsessive compulsiveness	0.17	0.08	Verbal maintenance RT*	0.06	0.07
Delusions*			Delay discounting large		
	0.16	0.11	rewards*	0.06	0.07
Go hit median RT			Remember colors		
	0.14	0.07	accuracy*	0.06	0.07
Scene recognition encoding RT*	0.14	0.07	Vpatial capacity load 3 RT*	0.05	0.07
Infrequency(careless response)			Daydreaming		
	0.11	0.08		0.05	0.07
Know mean RT*	0.09	0.07	Digit span forward	0.03	0.07
Stop signal quantile RT*	0.08	0.07	Avolition*	0.03	0.12
Scene recognition recall RT*	0.08	0.07	Verbal manipulation RT*	0.03	0.07
Remember mean RT*	0.07	0.07	Verbal capacity load 9 RT*	0.02	0.07
Vpatial capacity load 3 RT*	0.07	0.07	Verbal capacity load 7 RT*	0.02	0.07
Spatial maintenance RT*	0.07	0.07	Conflict effect	0.01	0.06
Spatial manipulation RT*	0.07	0.07	Eysenck venturesomeness	0.01	0.09
Spatial capacity load 1 RT*	0.07	0.07	Blunt affect*	0.00	0.11
Verbal capacity load 9 RT*			Know forced recognition 2		
	0.06	0.07	features*	0.00	0.08
Spatial capacity load 3 RT*	0.05	0.07	Alogia*	0.00	0.11
Verbal capacity load 5 RT*	0.05	0.07	Stop signal quantile RT*	0.00	0.07
BART_total pumps*	0.04	0.07	Conflict effect RT	0.00	0.07
Delay discounting large rewards*			MPQ control		
	0.04	0.06		-0.01	0.07
Spatial capacity load 5 RT*	0.04	0.06	Attention impulsivity	-0.01	0.07
Daydreaming	0.04	0.06	BART_total pumps*	-0.01	0.07
Spatial capacity load 7 RT*	0.03	0.07	Know colors accuracy*	-0.01	0.08
Eysenck empathy			Verbal capacity load 9		
	0.03	0.06	accuracy*	-0.02	0.07
Taskswitch residSwitchCost			Verbal maintenance		
	0.03	0.07	accuracy*	-0.02	0.07
Verbal maintenance RT*			Remember forced		
	0.02	0.07	recognition 2 features*	-0.02	0.08
Remember forced recognition 1 feature*			Know forced recognition 1		
	0.02	0.08	feature*	-0.03	0.08
Verbal capacity load 7 RT*	0.02	0.07	Vocabulary	-0.03	0.06
ANT_Interference RT*	0.02	0.07	Motor impulsivity	-0.03	0.08
Delay discounting total	0.02	0.07	Verbal capacity load 5	-0.03	0.07

rewards*			accuracy*		
Know forced recognition 1 feature*	0.02	0.07	Hyperactivity severity*	-0.03	0.10
Delay discounting medium rewards*	0.01	0.06	Digit span backward	-0.04	0.07
Long delay cued recall	0.00	0.07	Attention severity*	-0.04	0.10
Remember words accuracy*	0.00	0.07	Harm avoidance	-0.04	0.07
Long delay free recall	0.00	0.07	Remember forced recognition 1 feature*	-0.04	0.08
Short delay cued recall	0.00	0.07	Letter fluency	-0.05	0.07
Bizarre behavior*	-0.01	0.11	Hallucinations*	-0.05	0.10
Long delay recognition	-0.02	0.06	Spatial manipulation accuracy*	-0.05	0.07
Total go hit	-0.03	0.07	Know words accuracy*	-0.06	0.08
Know forced recognition 2 features*	-0.03	0.07	ADHD symptoms	-0.06	0.07
Taskswitch interference	-0.03	0.08	Remember words accuracy*	-0.07	0.08
Delay discounting small rewards*	-0.03	0.07	Novelty seeking	-0.07	0.08
Short delay free recall	-0.04	0.08	Verbal maximum capacity*	-0.08	0.07
Remember colors accuracy*	-0.05	0.07	Spatial capacity load 1 accuracy*	-0.09	0.07
Visual reproduction delayed recall	-0.07	0.07	Dysfunctional impulsivity	-0.09	0.06
Nonplanning	-0.07	0.07	Social anhedonia	-0.10	0.07
Verbal manipulation RT*	-0.07	0.07	Positive formal thought*	-0.10	0.11
ADHD symptoms	-0.07	0.07	Verbal manipulation accuracy*	-0.11	0.07
Attention impulsivity	-0.08	0.07	Spatial capacity load 5 accuracy*	-0.11	0.07
Taskswitch switch cost	-0.09	0.08	Scene recognition recall accuracy*	-0.12	0.07
YMRC_mania*	-0.10	0.10	Reward dependence	-0.12	0.08
Spatial maintenance accuracy*	-0.10	0.07	Infrequency(careless response)	-0.13	0.07
Know words accuracy*	-0.10	0.08	Letter/Number sequencing	-0.13	0.07
Scene recognition encoding accuracy*	-0.11	0.07	Delusions*	-0.13	0.10
Conflict effect RT	-0.11	0.06	Spatial maintenance accuracy*	-0.13	0.07
Spatial capacity load 1 accuracy*	-0.11	0.07	Remember mean RT*	-0.14	0.07
Visual reproduction immediate recall	-0.12	0.07	Verbal capacity load 7 accuracy*	-0.14	0.07
Vocabulary	-0.12	0.06	Physical anhedonia	-0.15	0.08
Taskswitch total accuracy	-0.12	0.07	Scene recognition encoding accuracy*	-0.15	0.07
Total false alarms	-0.12	0.07	Negative symptoms*	-0.15	0.10
Know colors accuracy*	-0.13	0.07	Eysenck impulsiveness	-0.17	0.07

Verbal maximum capacity*	-0.13	0.07	Mania/disorganization*	-0.17	0.10
Scene recognition recall accuracy*	-0.14	0.07	Perceptual aberrations	-0.18	0.06
Verbal capacity load 5 accuracy*	-0.14	0.07	Social anxiety	-0.18	0.07
ColorTrail interference	-0.16	0.07	Spatial maximum capacity*	-0.19	0.07
Remember forced recognition 2 features*	-0.16	0.07	Verbal capacity load 3 accuracy*	-0.19	0.07
Conflict effect	-0.16	0.07	Spatial capacity load 7 accuracy*	-0.20	0.07
Spatial capacity load 3 accuracy*	-0.16	0.07	Spatial capacity load 3 accuracy*	-0.20	0.07
Spatial capacity load 7 accuracy*	-0.16	0.07	Symbol span	-0.21	0.06
Verbal capacity load 7 accuracy*	-0.17	0.07	Mood lability	-0.22	0.07
Spatial maximum capacity*	-0.17	0.07	Positive symptoms*	-0.23	0.09
Verbal capacity load 9 accuracy*	-0.17	0.07	Anhedonia*	-0.24	0.12
Spatial capacity load 5 accuracy*	-0.18	0.07	Schizoid personality	-0.24	0.08
Eysenck impulsiveness	-0.18	0.06	Eysenck empathy	-0.24	0.07
Verbal maintenance accuracy*	-0.18	0.06	Taskswitch total accuracy	-0.25	0.07
Verbal capacity load 3 accuracy*	-0.19	0.07	Functional impulsivity	-0.25	0.07
Positive formal thought*	-0.19	0.12	YMRC_mania*	-0.27	0.11
Symbol span	-0.21	0.07	Obsessive compulsiveness	-0.27	0.06
Spatial manipulation accuracy*	-0.22	0.07	Digit span sequencing	-0.27	0.08
Digit span backward	-0.23	0.07	Go hit median RT	-0.28	0.07
Dysfunctional impulsivity	-0.23	0.07	Visual reproduction recognition	-0.29	0.07
Verbal manipulation accuracy*	-0.23	0.07	Depression/anxiety*	-0.30	0.10
Reward dependence	-0.24	0.06	Matrix reasoning	-0.31	0.06
Visual reproduction recognition	-0.26	0.06	Anxiety	-0.32	0.07
Letter/Number sequencing	-0.26	0.06	HAMD_depression*	-0.33	0.10
Letter fluency	-0.27	0.07	Bizarre behavior*	-0.33	0.12
Digit span forward	-0.27	0.06	Hypomanic peronality	-0.34	0.06
Matrix reasoning	-0.29	0.06	Long delay recognition	-0.34	0.06
Mania/disorganization*	-0.29	0.09	Visual reproduction immediate recall	-0.35	0.05
Digit span sequencing	-0.29	0.06	Interpersonal sensitivity	-0.36	0.06
Attention severity*	-0.30	0.09	Depression	-0.37	0.06
Eysenck venturesomeness	-0.35	0.06	Persistence	-0.37	0.07
Hyperactivity severity*	-0.43	0.09	Somatization	-0.39	0.06
Motor impulsivity	-0.45	0.06	Energy(Restless)	-0.40	0.05

Energy(Restless)			Visual reproduction		
	-0.49	0.05	delayed recall	-0.42	0.06
Hypomanic peronality	-0.50	0.05	Short delay free recall	-0.44	0.05
Persistence	-0.50	0.05	Long delay cued recall	-0.48	0.05
Novelty seeking	-0.62	0.05	Short delay cued recall	-0.49	0.05
Functional impulsivity	-0.71	0.03	Long delay free recall	-0.49	0.05

Notes: The contribution of each behavioral measure to LV 1-4 (correlation values) was shown as decreasing order, along with their bootstrap-estimated standard deviations (SD). This table lists both behavior measures that included in the PLS analysis and behavior measures that were considered in post hoc analyses due to missing data (*). Correlations with significant bootstrapped Z scores that survived FDR correction ($q < 0.05$) are shown in bold.

Figure S1. The amount of covariance explained by each LV. Five LVs survived after applying FDR correction ($q < 0.05$) to the p-values derived from permutation tests.

1
2 Figure S2. Significant behavioral and cerebral connectivity gradient features associated with
3 LV1.
4

1
2 Figure S3. Significant behavioral and cerebral connectivity gradient features associated with
3 LV2.
4

1
2 Figure S4. Significant behavioral and cerebral connectivity gradient features associated with
3 LV3.
4

1
2 Figure S5. Significant behavioral and cerebral connectivity gradient features associated with
3 LV4.