nature human behaviour

Supplementary information

https://doi.org/10.1038/s41562-025-02332-0

Spontaneous brain regional dynamics contribute to generalizable brain–behaviour associations

In the format provided by the authors and unedited

TABLE OF CONTENTS

SUPPLEMENTARY METHODS **2**

1. FINGERPRINTING ANALYSIS 2
2. BEHAVIORAL PHENOTYPES FOR GENERALIZATION IN THE *SUBSTANCE USE MODE* 2
3. BEHAVIORAL MEASURES FOR GENERALIZATION IN THE *COGNITION MODE* 5

SUPPLEMENTARY REFERENCE **7**

SUPPLEMENTARY FIGURES **8**

SUPPLEMENTARY FIG. 1 8
SUPPLEMENTARY FIG. 2 9
SUPPLEMENTARY FIG. 3 11
SUPPLEMENTARY FIG. 4 12
SUPPLEMENTARY FIG. 5 13
SUPPLEMENTARY FIG. 6 14
SUPPLEMENTARY FIG. 7 15
SUPPLEMENTARY FIG. 8 16
SUPPLEMENTARY FIG. 9 17

SUPPLEMENTARY TABLES **18**

SUPPLEMENTARY TABLE 1 18
SUPPLEMENTARY TABLE 2 18
SUPPLEMENTARY TABLE 3 18
SUPPLEMENTARY TABLE 4 19
SUPPLEMENTARY TABLE 5 24
SUPPLEMENTARY TABLE 6 25

Supplementary Methods

1. Fingerprinting analysis

Since RSRD and RSFC features differ in their physical interpretation (the former representing dynamic characteristics of individual regions, while the latter captures one of inter-regional coupling types), we controlled for variations in feature type, dimensionality, and selection proportion to ensure a fair comparison. Specifically, we first computed the ICC values for all 36,585 RSFC features across 271 brain regions within the same reference group (*Extended Data* **Fig. 3a**). To align with the feature selection strategy used for RSRD, we selected 44 brain regions with the highest region-level ICC values, creating region-wise refined RSFC features (*Extended Data* **Fig. 3c**). This approach ensured comparability in feature type and dimensionality, as the refined RSRD features were also based on the 44 regions with the highest ICC values across brain regions. Furthermore, to match the dimensionality, the RSFC feature vector length (44 regions × 270 connections) closely aligned with that of the refined RSRD features (44 features × 271 regions). Given that RSFC fingerprinting is often based on edge-level features, and that our refined RSRD features retained approximately 1% of the original feature set (44 out of 4,945 features), we applied a similar refinement to the RSFC features by selecting the top 1% of edges based on their ICC values (366 out of 36,585 edges; *Extended Data* **Fig. 3b** and **Fig. 3d**). This ensured that both modalities retained a comparable proportion of features.

In summary, we evaluated the complementary abilities of RSRD and RSFC features in capturing individual differences by applying fingerprinting analyses to five types of input features: refined RSRD (11,924 × 1), dense RSRD (1,340,495 × 1), region-wise refined RSFC (11,880 × 1), edge-wise refined RSFC (366 × 1), and dense RSFC (36,856 × 1). Specifically, for each evaluated feature type, we computed Pearson correlation coefficients by comparing each participant's features from REST1 (Day 1) with those of all participants from REST2 (Day 2). Correct identification was defined as a case where a participant's features from REST1 showed the highest correlation with their own features in REST2. Overall accuracy was determined by the proportion of correct identifications. Feature matrices were averaged from four scan sessions across two days, generating REST1 and REST2 matrices. Prior to assessing cross-day correlations, data for each day were separately normalized across participants and brain regions (for RSRD features) to ensure zero mean and unit variance. Fingerprinting analysis was conducted on an independent dataset of 898 HCP-YA participants, distinct from those used in feature selection. Sample sizes ranged from 100 to 800 participants, with each condition tested 100 times using randomly selected participant lists to minimize chance effects.

2. Behavioral phenotypes for Generalization in the *Substance Use Mode*

2.1 Substance use phenotypes

Substance use phenotypes in the HCP-D cohort. In the HCP-D cohort, substance use behaviors were assessed using the NIDA Substance Abuse and Alcohol Core survey, adapted from the PhenX Toolkit. This assessment focused on self-reported tobacco and alcohol use, and the corresponding behavioral

data were released under the *phenx_su01* data structure. However, among the 31 phenotypes related to smoking and alcohol use frequency, only three had more than 50 valid responses, and these variables exhibited left-skewed distributions (*Supplementary* **Fig. 8**), suggesting an absence of clear substance use tendencies in the HCP-D cohort.

Given the absence of direct measures of substance use behaviors, we additionally considered behavioral indicators empirically associated with substance use vulnerability during development. Specifically, we included the frequency of engagement with M-rated video games—rated "Mature" for individuals aged 17 and older due to violent, sexual, or substance-related content[1]. This phenotype was provided in the HCP-D release under the *screentime01* data structure, with the relevant variable labeled as *screentime13_y*. The use of this indicator as a proxy for substance use vulnerability is supported by both theoretical and empirical evidence. The DSM-5 criteria for Internet Gaming Disorder closely parallel those for substance use disorders[2], and problematic gaming has been shown to co-occur with substance use and share underlying neurobiological mechanisms[3]. Empirical findings further support this link: adolescents who frequently play M-rated games report higher levels of alcohol, tobacco, and cannabis use[4], and longitudinal evidence indicates that early exposure predicts increased substance use over time[5].

Substance use phenotypes in the UK Biobank cohort. We analyzed substance use phenotypes in the UK Biobank using data from the initial assessment visit. Variable selection closely followed prior large-scale neuroimaging and behavioral genetics studies. All measures were defined using UK Biobank Data-Field identifiers, accessible via the online data showcase (https://biobank.ndph.ox.ac.uk/). The following phenotypes were included:

- Weekly alcohol intake (Data Field IDs: 1568, 1578, 1588, 1598, 1608): Total weekly alcohol consumption was estimated by summing across five self-reported beverage-specific items that have been used in previous studies[6,7]. To mitigate the influence of excessive consumption, participants exceeding sex-specific thresholds for heavy drinking (>18 drinks/week for females and >24 drinks/week for males; as per Daviet et al[8]) were excluded. The distribution of weekly intake was positively skewed, and a log transformation was applied to facilitate downstream analyses.
- Lifetime cannabis use (Data Field ID: 20453): This is a four-level categorical variable indicating the frequency of lifetime cannabis use, previously used in studies[7,9].
- Ever smoking (Data Field IDs: 1249, 1239, 20116): A binary measure reflecting any lifetime history of smoking, derived from multiple items covering past use (1249), current use (1239), and overall smoking status (20116), previously used in studies[6,7]. Responses were harmonized to consistently reflect whether the participant had ever engaged in tobacco use.
- Ever addicted (Data Field ID: 20401): A binary variable capturing whether participants reported ever being addicted to any substance or behavior, previously used in studies[10].

Participants with missing values or responses such as "do not know" or "prefer not to answer" on any of the four substance use items were excluded, resulting in a final sample of 13,918 individuals with

complete phenotype and covariate data. To capture the shared variance across these behaviors, we performed principal component analysis (PCA), a method applied to derive composite indices of risky or externalizing behaviors[6,11]. The first principal component (PC1), which explained 35.5% of the total variance and showed positive loadings on all four phenotypes, was used as a composite index of general substance use for subsequent generalization analyses. The distributions of each phenotype and the extracted PC1 are presented in *Extended Data* **Fig. 7b**. Full PCA results, including variance explained and factor loadings, are provided in *Supplementary* **Fig. 7a**.

2.2 Externalizing problems phenotypes

Drawing on converging evidence that identifies substance use as a core component of the broader externalizing spectrum, we expanded the validation of this CCA mode beyond substance-specific behaviors to encompass the broader domain of externalizing problems. This broader scope is grounded in well-established dimensional models of psychopathology, particularly the Hierarchical Taxonomy of Psychopathology (HiTOP), which conceptualizes externalizing problems as a spectrum of interrelated behaviors—including substance use, rule-breaking, and antisocial traits—that reflect a shared liability structure[12]. Complementary findings from genetic and neurophysiological research further support substantial overlap in heritable risk and shared neural mechanisms across externalizing behaviors, particularly in domains related to inhibitory control and reward sensitivity[13]. Based on the available behavioral measures in the HCP-D and UK Biobank datasets, we selected externalizing problems phenotyeps as complementary validation targets.

Externalizing problems phenotypes in the HCP-D cohort. For the HCP-D generalization analysis, we selected phenotypes within the externalizing problems domain based on available measures from the Adult Self-Report (ASR) and the Child Behavior Checklist (CBCL). The ASR was administered to participants aged 18 to 22 as a self-report instrument, while the CBCL was completed by parents of participants aged 6 to 18. Four phenotypes were selected from each instrument, capturing key components of externalizing problems: ADHD problems, rule-breaking behavior, aggressive behavior, and total externalizing problems. The ASR-derived phenotypes were obtained from the NDA data structure *asr01*, including the following variables: *adh_total* (ADHD problems), *aggressive_behavior_total* (aggressive behavior), *rule_breaking_behavior_total* (rule-breaking behavior), and *externalizing_problems_total* (total externalizing problems). The CBCL-derived phenotypes were obtained from the NDA data structure *cbcl01*, including the following variables: *cbcl_adhd_raw* (ADHD problems), *cbcl_aggressive_raw* (aggressive behavior), *cbcl_rulebreak_raw* (rule-breaking behavior), and *cbcl_external_raw* (total externalizing problems).

Externalizing problems phenotypes in the UK Biobank cohort. For the UK Biobank cohort, in addition to the four substance use behaviors described above, we included four additional phenotypes commonly used in UKB-based studies of externalizing problems:

- lifetime number of sexual partners (Field ID: 2149): A continuous variable reflecting lifetime number of sexual partners, previously used in studies[6,7,11]. A log transformation was applied to reduce skewness following standard preprocessing.
- Frequency of driving over the speed limit (Field ID: 1100): An ordinal variable with four levels indicating the frequency of speeding, previously used in studies[6,7,11].
- Risk-taking (Field ID: 2040): A binary (yes/no) measure assessing self-reported general risk-taking tendency, previously used in studies [6,7,11].
- Irregularity (Field ID: 20401): A binary (yes/no) measure reflecting general impulsivity, previously used in studies[7,14].

Consistent with the procedure used for substance use phenotypes, participants with missing responses or answers such as "do not know" or "prefer not to answer" on any of the eight externalizing items were excluded, resulting in a final sample of 13,357 individuals with complete phenotype and covariate data. As with the substance use phenotypes, we performed principal component analysis (PCA) on the eight externalizing phenotypes to derive a composite index. The first principal component (PC1), which explained 20.3% of the total variance and showed positive loadings on all items, was used as a general externalizing behavior index for subsequent generalization analyses. The distributions of each phenotype and the extracted PC1 are presented in *Extended Data* **Fig. 7b.** Full PCA results, including variance explained and factor loadings, are provided in *Supplementary* **Fig. 7b**.

3. Behavioral Measures for Generalization in the *Cognition Mode*

Cognition phenotypes in the HCP-D cohort. In the HCP-D cohort, cognitive phenotypes were selected to align with those used in the HCP-YA cohort, which primarily relied on measures from the NIH Toolbox. We selected overlapping cognitive measures and additionally included fluid intelligence, assessed using age-appropriate versions of the Wechsler Intelligence Scales (WAIS-IV or WISC-V, depending on age groups in the HCP-D). The selected cognitive phenotypes spanned multiple domains, including executive function, memory, processing speed, language, self-regulation, and composite cognition scores. The specific variables and their associated NDA data structures are as follows:

- Fluid Cognition Composite (*nih_fluidcogcomp_unadjusted*, NIH Toolbox; *cogcomp01*);
- Crystallized Cognition Composite (*nih_crycogcomp_unadjusted*, NIH Toolbox; *cogcomp01*);
- Total Cognition Composite (*nih_totalcogcomp_unadjusted*, NIH Toolbox; *cogcomp01*);
- Early Childhood Cognition Composite (*nih_eccogcomp_unadjusted*, NIH Toolbox; *cogcomp01*);
- Executive Function / Inhibitory Control (*nih_flanker_unadjusted*, Flanker Task; *flanker01*);
- Executive Function / Cognitive Flexibility (*nih_dccs_unadjusted*, Dimensional Change Card Sort Test; *dccs01*);
- Episodic Memory (*nih_picseq_unadjusted*, Picture Sequence Memory Task; *psm01*);
- Processing Speed (*nih_patterncomp_unadjusted*, Pattern Comparison; *pcps01*);
- Language / Reading Decoding (*tbx_reading_score*, Oral Reading Recognition; *orrt01*);
- Self-Regulation (*auc_40000*, Delay Discounting; *deldisk01*);
- Fluid Intelligence (*matrixreasoning*, Matrix Reasoning Task; *wais_iv_part101* or *wisc_v01*).

Cognition phenotypes in the UK Biobank cohort. In the UK Biobank, cognitive assessments were derived from task paradigms that differ substantially from those used in the HCP studies. To enable cross-cohort generalization and ensure consistency with previous UKB-based research, we selected five cognitive performance measures that have been widely adopted in prior studies[15-17]. All variables were coded such that higher scores reflect better cognitive performance. The selected cognitive phenotypes included:

- Fluid intelligence/reasoning (Field ID: 20016): Sum of correct answers across 13 reasoning questions;
- Numeric memory (Field ID: 4282): Maximum number of digits correctly recalled;
- Tower rearranging (Field ID: 21004): Number of tower puzzles solved correctly;
- Matrix pattern completion (Field ID: 6373): Number of matrix reasoning items answered correctly;
- Symbol digit substitution (Field ID: 23324): Number of correct symbol-digit matches;

We used cognitive assessments from the UK Biobank imaging visit (Instance 2.0). The distributions of investigated cognitive phenotypes are shown in *Extended Data* **Fig. 7c**. Analyses were based on all available valid observations for each phenotype.

Supplementary Reference

1 Thompson, K. M., Tepichin, K. & Haninger, K. Content and ratings of mature-rated video games. *Archives of Pediatrics & Adolescent Medicine* **160**, 402-410 (2006). https://doi.org:10.1001/archpedi.160.4.402

2 Smith, K. L., Hummer, T. A. & Hulvershorn, L. A. Pathological Video Gaming and Its Relationship to Substance Use Disorders. *Curr Addict Rep* **2**, 302-309 (2015). https://doi.org:10.1007/s40429-015-0075-6

3 Burleigh, T. L., Griffiths, M. D., Sumich, A., Stavropoulos, V. & Kuss, D. J. A Systematic Review of the Co-occurrence of Gaming Disorder and Other Potentially Addictive Behaviors. *Curr Addict Rep* **6**, 383-401 (2019). https://doi.org:10.1007/s40429-019-00279-7

4 Cranwell, J., Whittamore, K., Britton, J. & Leonardi-Bee, J. Alcohol and Tobacco Content in UK Video Games and Their Association with Alcohol and Tobacco Use Among Young People. *Cyberpsychology, Behavior, and Social Networking* **19**, 426-434 (2016). https://doi.org:10.1089/cyber.2016.0093

5 Hull, J. G., Brunelle, T. J., Prescott, A. T. & Sargent, J. D. A Longitudinal Study of Risk-Glorifying Video Games and Behavioral Deviance. *Journal of personality and social psychology* **107**, 300-325 (2014). https://doi.org:10.1037/a0036058

6 Aydogan, G. *et al.* Genetic underpinnings of risky behaviour relate to altered neuroanatomy. *Nature Human Behaviour* **5**, 787-794 (2021). https://doi.org:10.1038/s41562-020-01027-y

7 Baselmans, B. *et al.* The Genetic and Neural Substrates of Externalizing Behavior. *Biological Psychiatry Global Open Science* **2**, 389-399 (2022). https://doi.org:10.1016/j.bpsgos.2021.09.007

8 Daviet, R. *et al.* Associations between alcohol consumption and gray and white matter volumes in the UK Biobank. *Nature Communications* **13**, 1175 (2022). https://doi.org:10.1038/s41467-022-28735-5

9 Pasman, J. A. *et al.* GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal effect of schizophrenia liability. *Nature Neuroscience* **21**, 1161-1170 (2018). https://doi.org:10.1038/s41593-018-0206-1

10 Khan, A., Minbay, M., Attia, Z., Ay, A. A. & Ingram, K. K. Sex- and Substance-Specific Associations of Circadian-Related Genes with Addiction in the UK Biobank Cohort Implicate Neuroplasticity Pathways. *Brain Sci* **14**, 1282 (2024). https://doi.org:10.3390/brainsci14121282

11 Karlsson Linnér, R. *et al.* Multivariate analysis of 1.5 million people identifies genetic associations with traits related to self-regulation and addiction. *Nature Neuroscience* **24**, 1367-1376 (2021). https://doi.org:10.1038/s41593-021-00908-3

12 Krueger, R. F. *et al.* Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): II. Externalizing superspectrum. *World Psychiatry* **20**, 171-193 (2021). https://doi.org:10.1002/wps.20844

13 Krueger, R. F. *et al.* Etiologic connections among substance dependence, antisocial behavior and personality: Modeling the externalizing spectrum. *Journal of Abnormal Psychology* **111**, 411-424 (2002). https://doi.org:10.1037/0021-843X.111.3.411

14 Sudlow, C. *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* **12**, e1001779 (2015). https://doi.org:10.1371/journal.pmed.1001779

15 Li, Y. *et al.* The brain structure and genetic mechanisms underlying the nonlinear association between sleep duration, cognition and mental health. *Nature Aging* **2**, 425-437 (2022). https://doi.org:10.1038/s43587-022-00210-2

16 Liu, S., Abdellaoui, A., Verweij, K. J. H. & van Wingen, G. A. Replicable brain–phenotype associations require large-scale neuroimaging data. *Nature Human Behaviour* **7**, 1344-1356 (2023). https://doi.org:10.1038/s41562-023-01642-5

17 Marek, S. *et al.* Reproducible brain-wide association studies require thousands of individuals. *Nature* **603**, 654-660 (2022). https://doi.org:10.1038/s41586-022-04492-9

Supplementary Figures

Supplementary Fig. 1

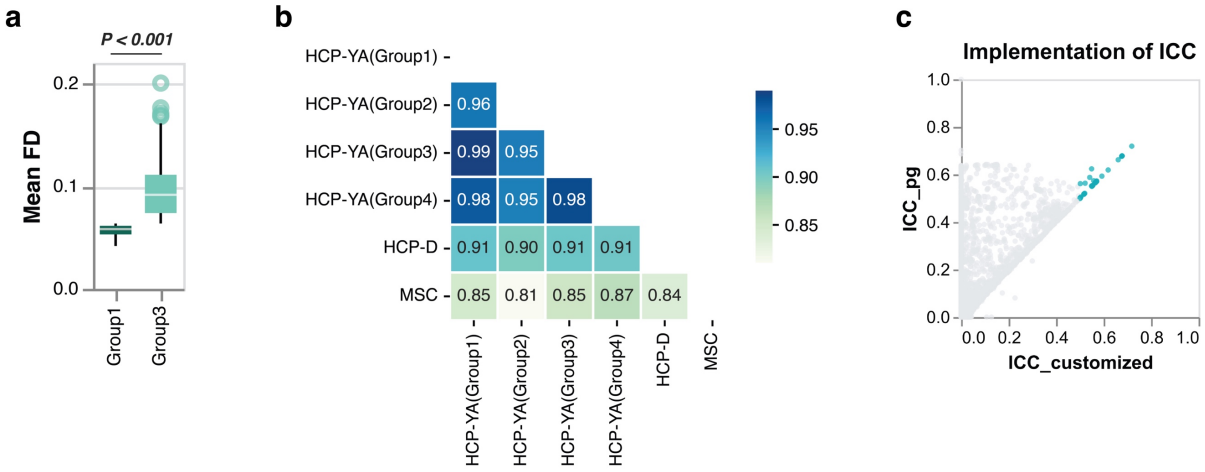

Fig. S1. ICC consistency analysis. **(a)** difference in mean framewise displacement (FD) between HCP-YA Group 1 and Group 3 in the RSRD reliability validation analysis (two-sided *t*-test, $t = 13.90$, $P < 0.001$). **(b)** Correlation matrix displaying Spearman correlations between feature-level ICCs computed across different groups or cohorts: HCP-YA (Groups 1–4), HCP-D, and MSC datasets, consistent with the data presented in **Fig. 2d–e** of the main text. **(c)** ICC values for HCP-YA Group 1 (primary analysis) were recalculated using the *intraclass_corr* function from the Pingouin package to examine approximation effects. The 44 features selected in the primary analysis are highlighted in blue, showing consistent results across both calculation methods. ICC values calculated with the *intraclass_corr* function for all analyzed groups are provided in *Supplementary* **Table 2**.

Supplementary Fig. 2

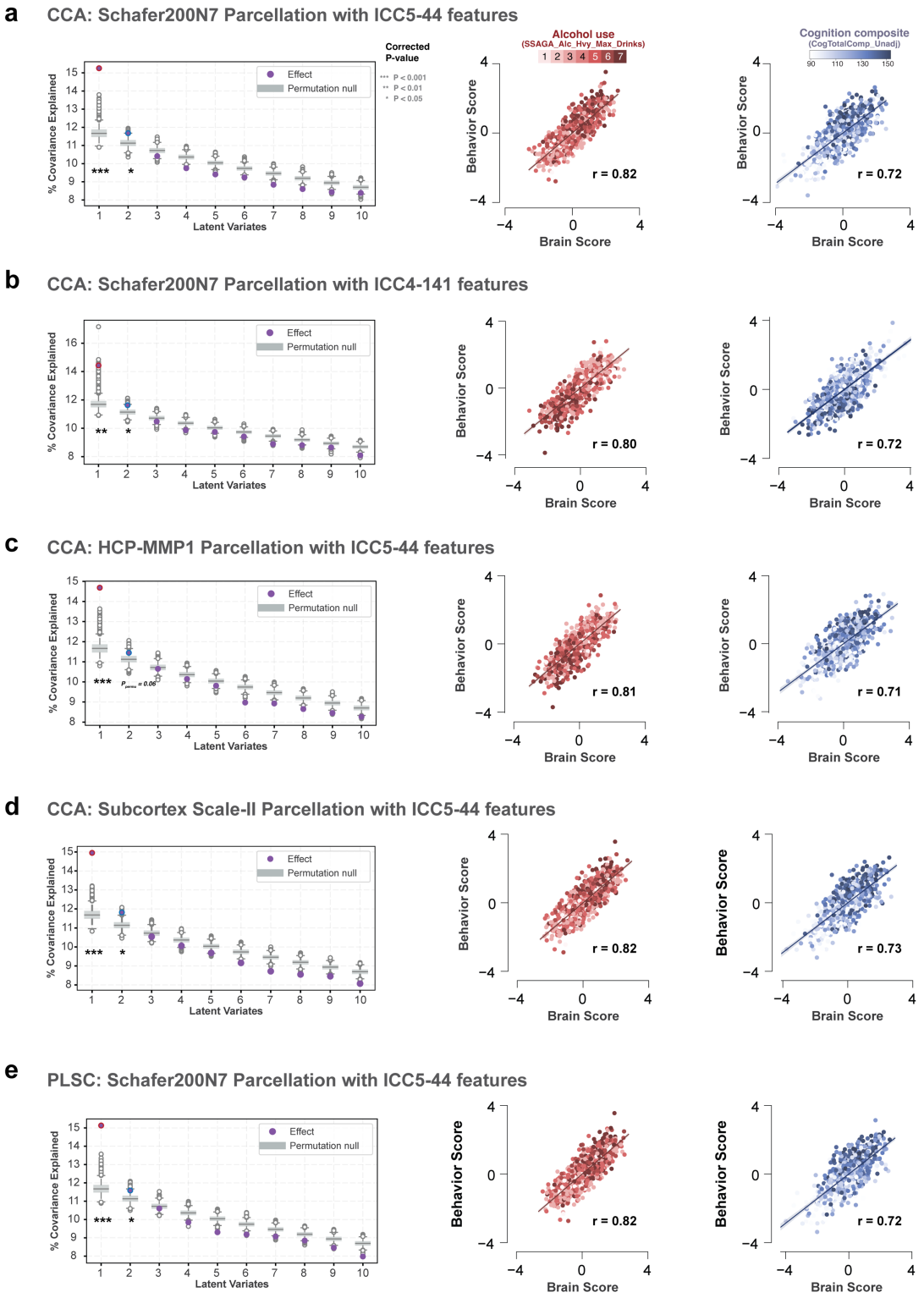

Fig. S2. Robustness of brain–behavior associations to methodological variations. Covariance explained and brain-behavior association patterns are shown for latent variates derived from five different methodological approaches: **(a)** Primary analysis (as reported in the main text); **(b)** Using 141 time-series features with feature-level ICC > 0.4 as brain inputs to the CCA pipeline; **(c)** Using an alternative cortical parcellation (HCP-MMP atlas with 360 cortical regions); **(d)** Using an alternative

subcortical parcellation (32-parcel version of the Melbourne subcortex atlas); **(e)** Applying Partial Least Squares Canonical (PLSC) as an alternative multivariate analysis method.For each approach, the left panel shows the covariance explained by successive latent variates. Statistical significance was assessed using one-sided permutation testing (10,000 permutations), in which participants' behavioral data were randomly shuffled while preserving family structure (see Methods). Purple dots indicate the observed covariance explained by each variate; grey boxes represent the null distribution. Significance levels from one-sided permutation testing are denoted as***$P < 0.001$, **$P < 0.01$, and *$P < 0.05$. The right scatter plots illustrate correlation patterns for the first two latent variates. Colored dots highlight key behavioral variables loading onto the *Substance Use* and *Cognition* Modes.

Supplementary Fig. 3

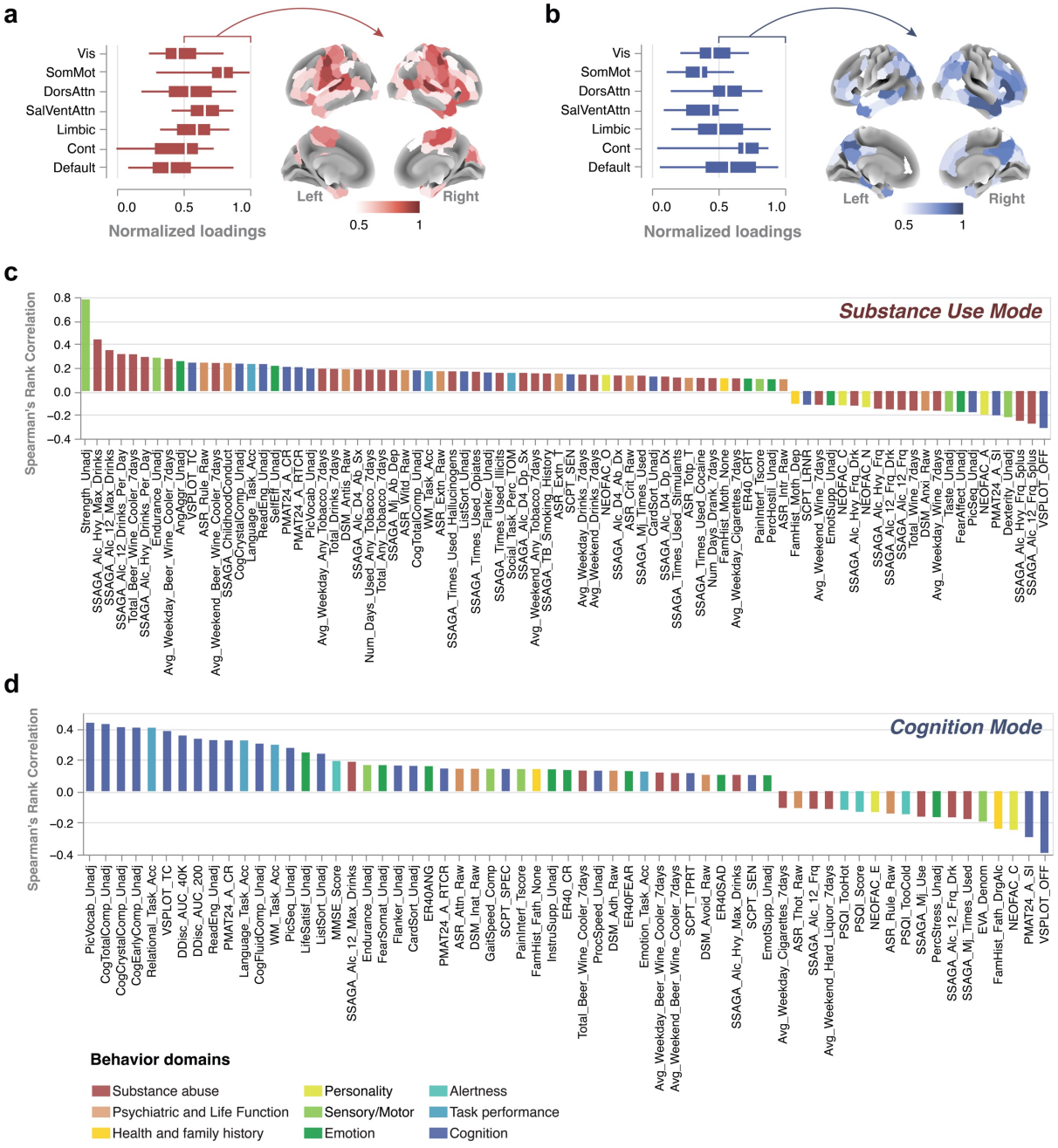

Fig. S3. Supplementary visualization of brain-behavior association patterns. **(a–b)** display the cortical loadings for the *Substance Use Mode* **(a)** and *Cognition Mode* **(b)**, respectively, providing further clarity to the spatial patterns shown in **Fig. 3** of the main text. The left panels show boxplots of regional loadings derived from the cortical brain maps displayed in **Figs. 3b** and **3f**, grouped according to the Yeo 7-network functional parcellation. Functional network abbreviations: Vis (Visual), SomMot (Somatomotor), DorsAttn (Dorsal Attention), SalVentAttn (Salience/Ventral Attention), Limbic (Limbic), Cont (Control), Default (Default Mode). The right panels present complementary surface visualizations of regions with relatively high loadings (normalized loading > 0.5). **(c–d)** Bar plot versions of the scatter plots shown in **Figs. 3i** and **3j** of the main text.

Supplementary Fig. 4

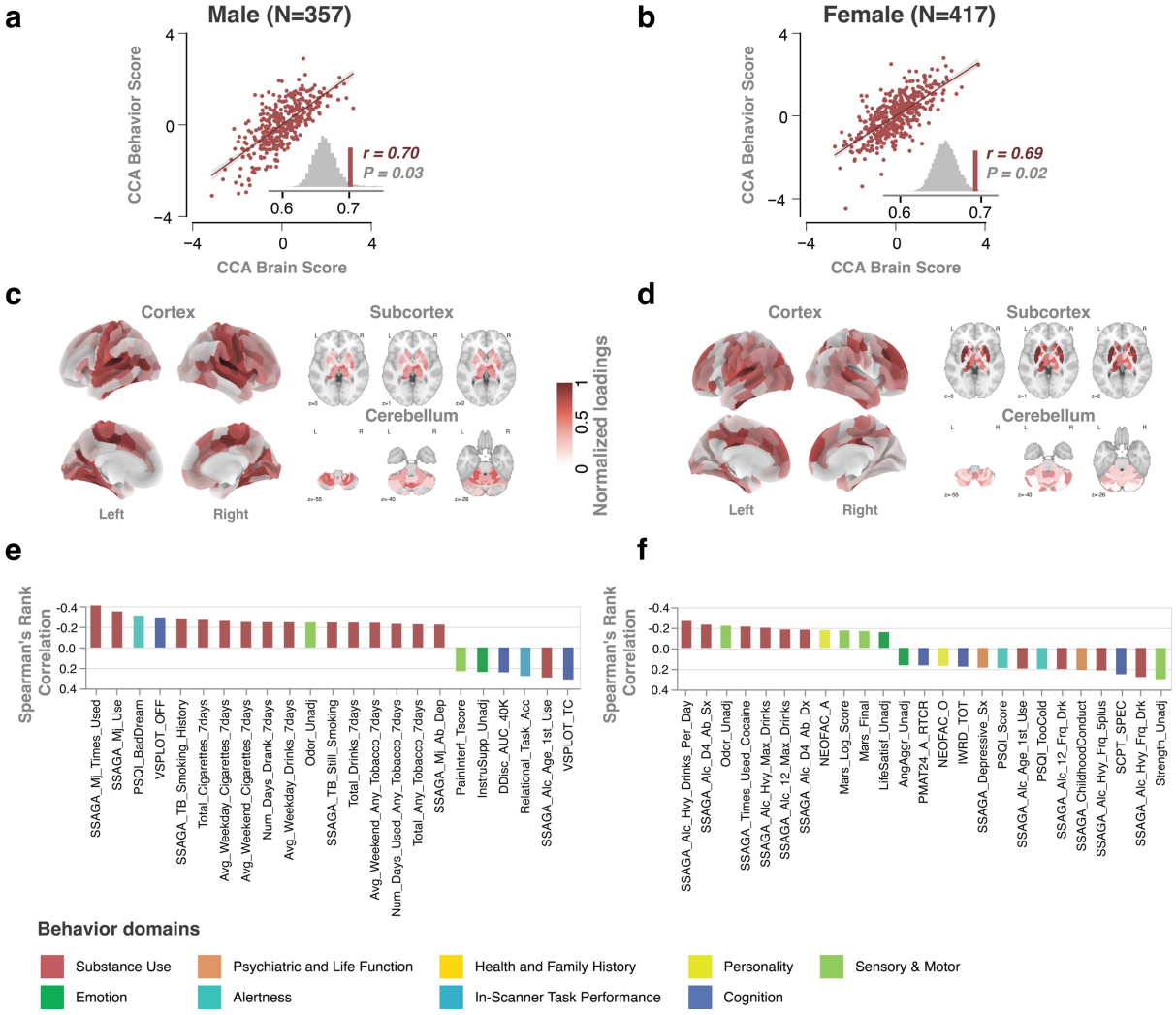

Fig. S4. ***Substance Use Mode*** **derived separately in HCP-YA male and female participants. (a–b)** CCA variates for the first brain-behavior mode derived from male and female participants, respectively. The inset in the bottom-right corner of each plot shows the null distribution of canonical correlations obtained from the permutation test (gray) and the corresponding empirical correlation (vertical line). **(c–d)** Spatial patterns of regional loadings (RSRD features) identified in males (c) and females (d), respectively, including contributions from cortical, subcortical, and cerebellar regions. **(e–f)** Behavioral phenotypes with absolute Spearman correlations greater than 0.2, ranked by strength of their contribution for males (e) and females (f), respectively. Bar height indicates correlation strength, and bars are color-coded by behavioral domain. The y-axis is reversed to highlight the strongest contributing phenotypes.

Supplementary Fig. 5

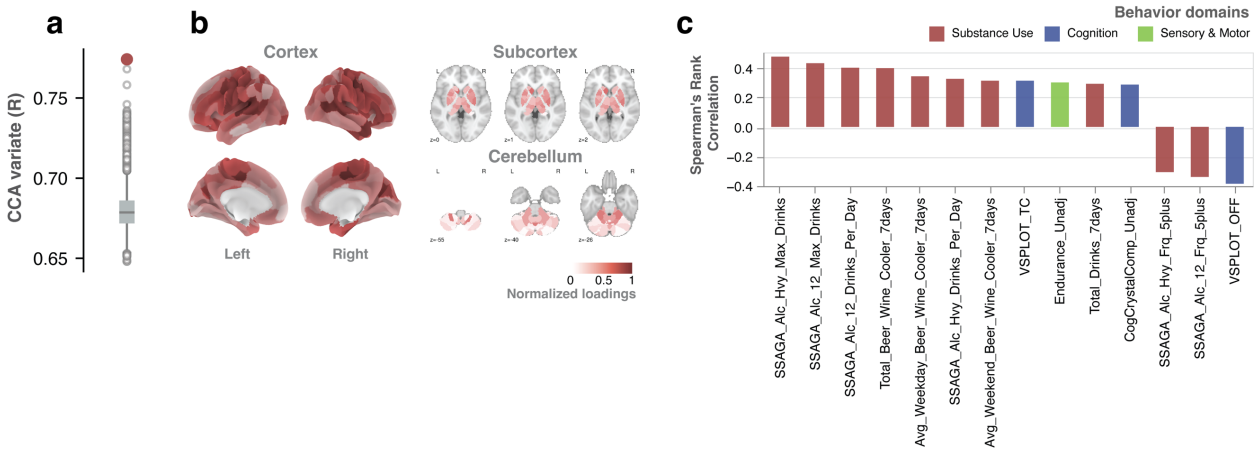

Fig. S5. Evaluating the impact of grip strength on *Substance Use Mode*. This analysis used the same dataset and preprocessing pipeline as the main CCA, but excluded grip strength from input behavior data. **(a)** CCA variates for the first canonical mode, with colored points representing empirical correlations and gray boxes showing null distributions from 10,000 family-preserving permutations. Panels **(b)** brain loading patterns across the cortex, subcortex, and cerebellum. **(c)** Behavioral relevance patterns shown as bar plots, ranked by their strength of association with the CCA behavior score. Bars are color-coded by behavioral domain, and bar height indicates correlation strength.

Supplementary Fig. 6

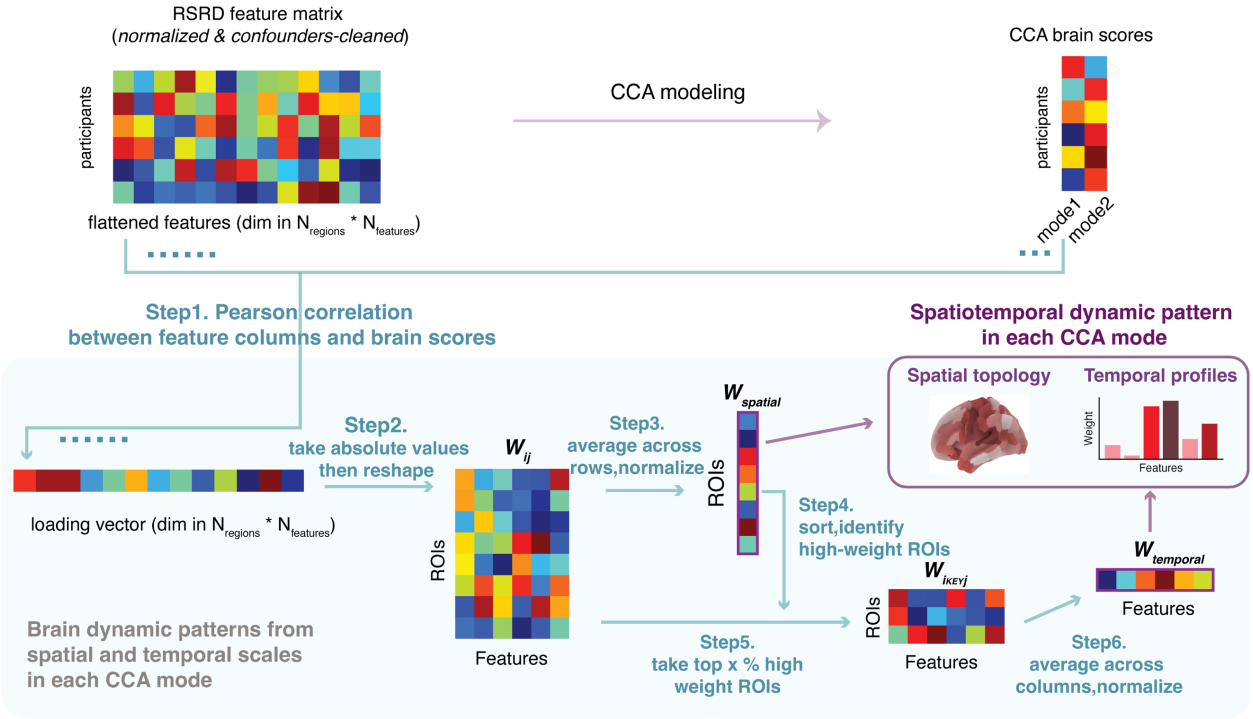

Fig. S6. Procedure for identifying brain spatiotemporal patterns in CCA modes. The flow of the analysis is indicated by blue arrows, with each step labeled in numerical order. See Methods for details.

Supplementary Fig. 7

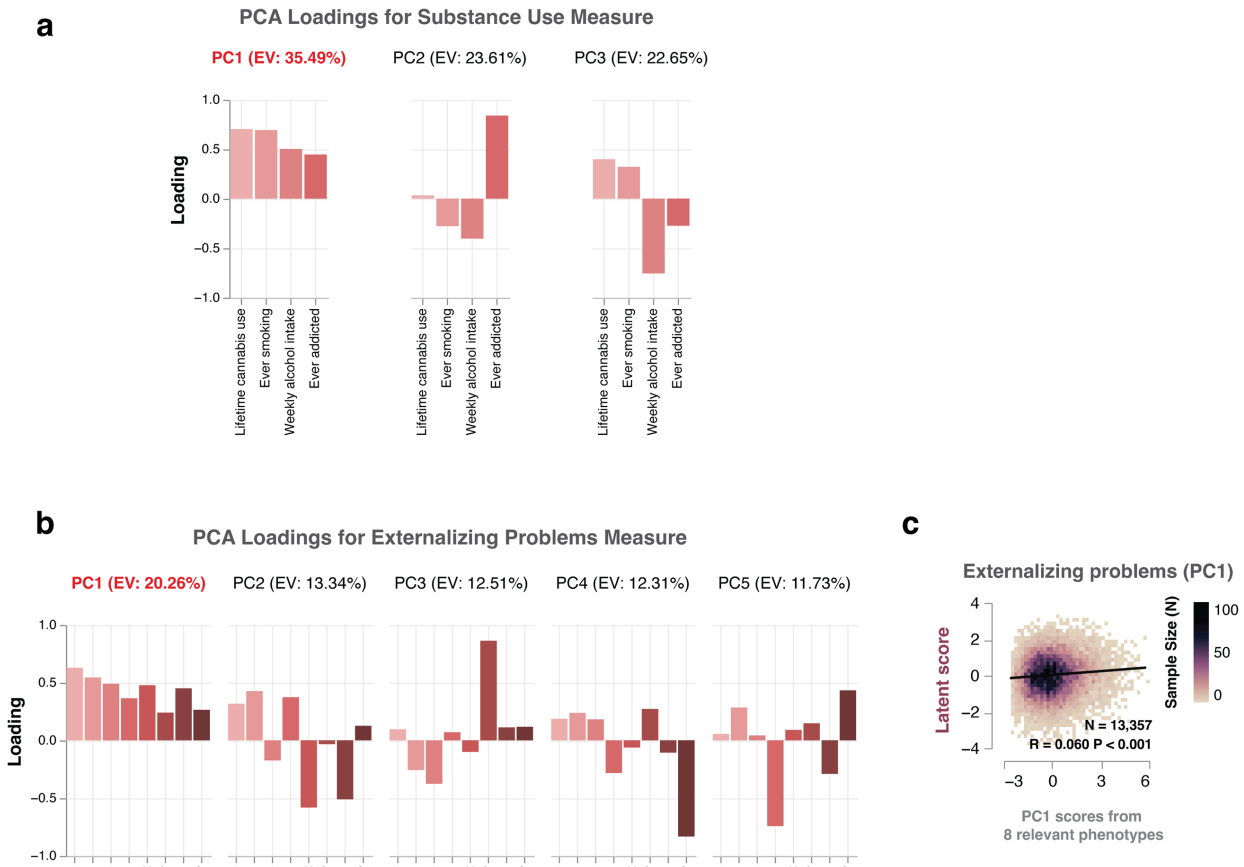

Fig. S7. PCA loadings for substance-related and externalizing measures, and generalization results of the *Substance Use Mode* in the UK Biobank. **(a)** Principal component loadings for the Substance Use measure, derived from four items: weekly alcohol intake, lifetime cannabis use, smoking status, and ever addicted. The first principal component (PC1), which explained 35.49% of the total variance (EV; highlighted in red), and showed positive loadings across all items, was used in the generalization analysis (see *Supplementary* Methods). **(b)** Principal component loadings for the Externalizing Problems measure, based on an expanded item set comprising the four substance-use items plus number of sexual partners, frequency of speeding, risk-taking tendency, and impulsivity. PC1, which explained 20.26% of the total variance (EV; highlighted in red), and exhibited positive loadings across all items, was applied in the complementary generalization analysis (see *Supplementary* Methods). **(c)** Association between the Externalizing Problems PC1 scores and the latent scores of the *Substance Use Mode*. Partial Spearman correlation coefficient (R), P-value (P), and sample size (N) are shown in the bottom right corner.

Supplementary Fig. 8

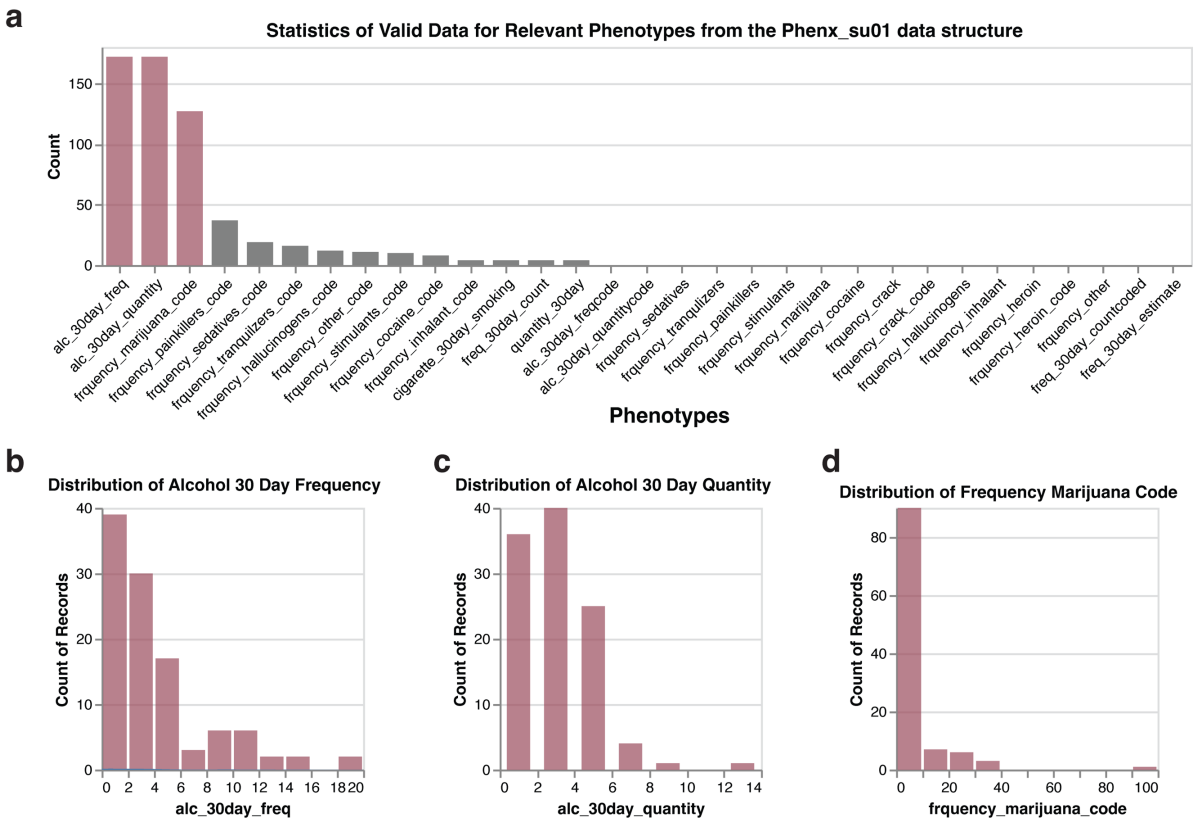

Fig. S8. Distribution of substance use phenotypes in HCP-D cohort. **(a)** Valid sample sizes (i.e., the number of non-missing and non-negative responses) for substance use assessments provided in the *PhenX01* data structure are shown, with items exceeding 50 valid responses highlighted in pink. Sample sizes for all other items were either below 50 or not available. **(b–d)** Distributions of the three substance use items with the largest number of valid responses identified in panel a: **(b)** alc_30day_freq, corresponding to the question: "During the past 30 days, on how many days did you drink one or more drinks of an alcoholic beverage?" Valid response range: 0–30. **(c)** alc_30day_quantity, corresponding to the question: "On the days that you drank during the past 30 days, how many drinks did you usually have each day? Count as a drink a can or bottle of beer; a wine cooler or a glass of wine, champagne, or sherry; a shot of liquor or a mixed drink or cocktail." Valid response range: 0–90. **(d)** frequency_marijuana_code, corresponding to the question: "During the past 30 days, on how many days did you use marijuana or hashish?" Valid response range: 0–30. Responses coded as 99 indicate "Don't know" across all items. Detailed descriptions of the assessments are available at https://nda.nih.gov/data-structure/phenx_su01. The distributions of these items were highly skewed, with most participants reporting minimal or no use, and the limited variability across participants indicated that the substance use dimension was unsuitable for generalization analyses in the HCP-D.

Supplementary Fig. 9

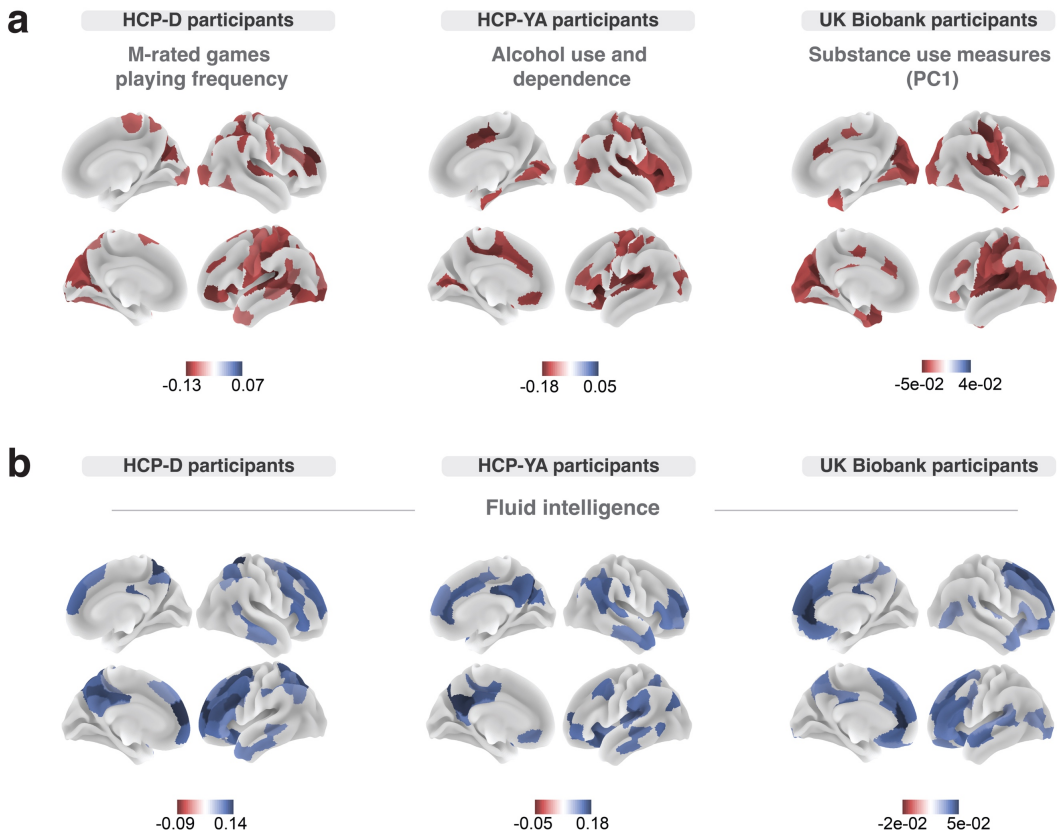

Fig. S9. Top 25% contributing brain regions for the CCA mode spatiotemporal patterns. Brain regions were selected based on the top 25% of region-wise correlations, either positive or negative depending on the dominant direction of association. These regions represent the strongest contributors to the spatial patterns shown in *Extended Data* **Fig. 9a** and **9b**. **(a)** Spatial distribution of contributing regions for the *Substance Use Mode*. **(b)** Spatial distribution of contributing regions for the *Cognition Mode*.

Supplementary Tables

Supplementary Table 1

Table S1. 100 unrelated HCP-YA participants with minimal head motion for high-reliability feature selection.

This table lists 100 participants (IDs marked in purple) with minimal head motion, selected from 400 unrelated individuals in the HCP-YA cohort for high-reliability ICC feature selection. Head motion was quantified as mean framewise displacement (FD) across four rs-fMRI scans, with FD values obtained from the HCP S1200 physiologic data summary (available at https://github.com/ThomasYeoLab/CBIG/blob/b69b822a15e2a94f1e439606552fc44b6858cf3c/stable_projects/preprocessing/Orban2020_tod/data_release/HCP_S1200_physio_data_summary_2020_02_11.csv).

(See separate file sheet *Table S1*).

Supplementary Table 2

Table S2. Definitions, hctsa keywords, and feature-level ICC values for 4,945 RSRD features.

This table lists the definitions, associated hctsa toolbox keywords, and feature-level ICC for each feature. It also includes ICC results computed across all groups, as presented in **Fig. 2d–e**. The 44 high-ICC RSRD features selected for the primary analysis are highlighted in blue.

(See separate file sheet *Table S2*).

Supplementary Table 3

Table S3. Information on 44 high-ICC features defining the refined RSRD profiles.

This table lists the dynamic dimension, hctsa-assigned keywords, corresponding code file, and a concise description of each feature's dynamic characteristics.

(See separate file sheet *Table S3*).

Supplementary Table 4

Table S4. 159 behavioral phenotypes for CCA analysis in HCP-YA cohort. Dimension indicates the broad behavioral domain associated with each phenotype. Phenotypes refer to specific behavioral measures selected for CCA analysis. Assessment denotes the corresponding instrument or questionnaire from which each phenotype was derived. Detailed descriptions of the assessments and behavioral dimensions are available on the official HCP wiki (https://wiki.humanconnectome.org/).

Dimension	Phenotypes	Assessment
Alertness	PSQI_Pain	Sleep (Pittsburgh Sleep Questionnaire)
	PSQI_TooCold	Sleep (Pittsburgh Sleep Questionnaire)
	PSQI_TooHot	Sleep (Pittsburgh Sleep Questionnaire)
	PSQI_BadDream	Sleep (Pittsburgh Sleep Questionnaire)
	PSQI_Score	Sleep (Pittsburgh Sleep Questionnaire)
	MMSE_Score	Cognitive Status (Mini Mental Status Exam)
Cognition	CogCrystalComp_Unadj	NIH Toolbox Cognition Crystallized Composite
	CogEarlyComp_Unadj	NIH Toolbox Cognition Early Childhood Composite
	CogFluidComp_Unadj	NIH Toolbox Cognition Fluid Composite
	CogTotalComp_Unadj	NIH Toolbox Cognition Total Composite Score
	PicSeq_Unadj	Episodic Memory (NIH Toolbox Picture Sequence Memory Test)
	CardSort_Unadj	Executive Function/Cognitive Flexibility (NIH Toolbox Dimensional Change Card Sort)
	Flanker_Unadj	Executive Function/Inhibition (NIH Toolbox Flanker Inhibitory Control and Attention)
	PMAT24_A_RTCR	Fluid Intelligence (Penn Progressive Matrices)
	PMAT24_A_SI	Fluid Intelligence (Penn Progressive Matrices)
	PMAT24_A_CR	Fluid Intelligence (Penn Progressive Matrices)
	ReadEng_Unadj	Language/Reading Decoding (NIH Toolbox Oral Recognition Test)
	PicVocab_Unadj	Language/Vocabulary Comprehension (NIH Toolbox Picture Vocabulary Test)
	ProcSpeed_Unadj	Processing Speed (NIH Toolbox Pattern Comparison Processing Speed Test)
	DDisc_AUC_40K	Self-regulation/Impulsivity (Delay Discounting)
	DDisc_AUC_200	Self-regulation/Impulsivity (Delay Discounting)
	VSPLOT_CRTE	Spatial Orientation (Variable Short Penn Line Orientation Test)
	VSPLOT_OFF	Spatial Orientation (Variable Short Penn Line Orientation Test)
	VSPLOT_TC	Spatial Orientation (Variable Short Penn Line Orientation Test)
	SCPT_SEN	Sustained Attention (Short Penn Continuous Performance Test)
	SCPT_TPRT	Sustained Attention (Short Penn Continuous Performance Test)

	SCPT_LRNR	Sustained Attention (Short Penn Continuous Performance Test)
	SCPT_SPEC	Sustained Attention (Short Penn Continuous Performance Test)
	IWRD_TOT	Verbal Episodic Memory (Penn Word Memory Test)
	IWRD_RTC	Verbal Episodic Memory (Penn Word Memory Test)
	ListSort_Unadj	Working Memory (NIH Toolbox List Sorting Working Memory Test)
Emotion	ER40ANG	Emotion Recognition (Penn Emotion Recognition Test)
	ER40HAP	Emotion Recognition (Penn Emotion Recognition Test)
	ER40_CRT	Emotion Recognition (Penn Emotion Recognition Test)
	ER40NOE	Emotion Recognition (Penn Emotion Recognition Test)
	ER40_CR	Emotion Recognition (Penn Emotion Recognition Test)
	ER40FEAR	Emotion Recognition (Penn Emotion Recognition Test)
	ER40SAD	Emotion Recognition (Penn Emotion Recognition Test)
	AngHostil_Unadj	NIH Toolbox Anger-Hostility Survey
	FearAffect_Unadj	NIH Toolbox Fear-Affect Survey
	FearSomat_Unadj	NIH Toolbox Fear-Somatic Arousal Survey
	Sadness_Unadj	NIH Toolbox Sadness Survey
	AngAggr_Unadj	NIH Toolbox Anger-Physical Aggression Survey
	AngAffect_Unadj	NIH Toolbox Anger-Affect Survey
	MeanPurp_Unadj	NIH Toolbox Meaning and Purpose Survey
	LifeSatisf_Unadj	NIH Toolbox General Life Satisfaction Survey
	PosAffect_Unadj	NIH Toolbox Positive Affect Survey
	EmotSupp_Unadj	NIH Toolbox Emotional Support Survey
	Friendship_Unadj	NIH Toolbox Friendship Survey
	PercHostil_Unadj	NIH Toolbox Perceived Hostility Survey
	InstruSupp_Unadj	NIH Toolbox Instrumental Support Survey
	Loneliness_Unadj	NIH Toolbox Loneliness Survey
	PercReject_Unadj	NIH Toolbox Perceived Rejection Survey
	PercStress_Unadj	NIH Toolbox Perceived Stress Survey
	SelfEff_Unadj	NIH Toolbox Self-Efficacy Survey
Health and Family History	FamHist_Fath_None	Family History of Psychiatric and Neurologic Disorders
	FamHist_Fath_DrgAlc	Family History of Psychiatric and Neurologic Disorders
	FamHist_Fath_Dep	Family History of Psychiatric and Neurologic Disorders
	FamHist_Moth_None	Family History of Psychiatric and Neurologic Disorders
	FamHist_Moth_Dep	Family History of Psychiatric and Neurologic Disorders
In-Scanner Task Performance	WM_Task_Acc	Working Memory
	Gambling_Task_Perc_Larger	Gambling
	Emotion_Task_Acc	Emotion
	Social_Task_Perc_TOM	Social
	Language_Task_Acc	Language

	Gambling_Task_Perc_Smaller	Gambling
	Relational_Task_Acc	Relational
Motor	Endurance_Unadj	Endurance (2 minute walk test)
	Strength_Unadj	Strength (Grip Strength Dynamometry)
	Dexterity_Unadj	Dexterity (9-hole Pegboard)
	GaitSpeed_Comp	Locomotion (4-meter walk test)
Personality	NEOFAC_N	Five Factor Model (NEO-FFI)
	NEOFAC_A	Five Factor Model (NEO-FFI)
	NEOFAC_E	Five Factor Model (NEO-FFI)
	NEOFAC_C	Five Factor Model (NEO-FFI)
	NEOFAC_O	Five Factor Model (NEO-FFI)
Psychiatric and Life Function	ASR_Intn_T	Achenbach ASR-DSM Scales
	ASR_Anxd_Raw	Achenbach ASR-DSM Scales
	ASR_TAO_Sum	Achenbach ASR-DSM Scales
	DSM_Anxi_Raw	Achenbach ASR-DSM Scales
	DSM_Hype_Raw	Achenbach ASR-DSM Scales
	ASR_Soma_Raw	Achenbach ASR-DSM Scales
	ASR_Attn_Raw	Achenbach ASR-DSM Scales
	DSM_Inat_Raw	Achenbach ASR-DSM Scales
	ASR_Intr_Raw	Achenbach ASR-DSM Scales
	ASR_Intn_Raw	Achenbach ASR-DSM Scales
	ASR_Totp_Raw	Achenbach ASR-DSM Scales
	ASR_Oth_Raw	Achenbach ASR-DSM Scales
	DSM_Depr_Raw	Achenbach ASR-DSM Scales
	ASR_Aggr_Raw	Achenbach ASR-DSM Scales
	ASR_Rule_Raw	Achenbach ASR-DSM Scales
	ASR_Totp_T	Achenbach ASR-DSM Scales
	DSM_Antis_Raw	Achenbach ASR-DSM Scales
	DSM_Somp_Raw	Achenbach ASR-DSM Scales
	ASR_Extn_T	Achenbach ASR-DSM Scales
	ASR_Extn_Raw	Achenbach ASR-DSM Scales
	DSM_Avoid_Raw	Achenbach ASR-DSM Scales
	ASR_Crit_Raw	Achenbach ASR-DSM Scales
	ASR_Witd_Raw	Achenbach ASR-DSM Scales
	DSM_Adh_Raw	Achenbach ASR-DSM Scales
	ASR_Thot_Raw	Achenbach ASR-DSM Scales
	SSAGA_Depressive_Sx	Psychiatric History
	SSAGA_Depressive_Ep	Psychiatric History
	SSAGA_PanicDisorder	Psychiatric History
	SSAGA_ChildhoodConduct	Psychiatric History
	SSAGA_Agoraphobia	Psychiatric History

Sensory	EVA_Denom	Vision (EVA Scores and Farnsworth Test)
	PainInterf_Tscore	Pain (Pain Intensity and Interference Surveys)
	Mars_Final	Contrast Sensitivity (Mars Contrast Sensitivity)
	Odor_Unadj	Olfaction (Odor Identification Test)
	EVA_Correction	Vision (EVA Scores and Farnsworth Test)
	Mars_Log_Score	Contrast Sensitivity (Mars Contrast Sensitivity)
	Taste_Unadj	Taste (Taste Intensity Test)
Substance Use	Total_Drinks_7days	Alcohol Use 7-Day Retrospective
	Total_Beer_Wine_Cooler_7 days	Alcohol Use 7-Day Retrospective
	Num_Days_Drank_7days	Alcohol Use 7-Day Retrospective
	Total_Wine_7days	Alcohol Use 7-Day Retrospective
	Avg_Weekday_Drinks_7da ys	Alcohol Use 7-Day Retrospective
	Avg_Weekday_Wine_7day s	Alcohol Use 7-Day Retrospective
	Total_Hard_Liquor_7days	Alcohol Use 7-Day Retrospective
	Avg_Weekend_Hard_Liquo r_7days	Alcohol Use 7-Day Retrospective
	Avg_Weekend_Wine_7day s	Alcohol Use 7-Day Retrospective
	Avg_Weekend_Beer_Wine _Cooler_7days	Alcohol Use 7-Day Retrospective
	Avg_Weekday_Beer_Wine _Cooler_7days	Alcohol Use 7-Day Retrospective
	Avg_Weekend_Drinks_7da ys	Alcohol Use 7-Day Retrospective
	SSAGA_Alc_D4_Ab_Sx	Alcohol Use and Dependence
	SSAGA_Alc_12_Drinks_Pe r_Day	Alcohol Use and Dependence
	SSAGA_Alc_Hvy_Max_Dr inks	Alcohol Use and Dependence
	SSAGA_Alc_D4_Dp_Dx	Alcohol Use and Dependence
	SSAGA_Alc_12_Frq	Alcohol Use and Dependence
	SSAGA_Alc_Hvy_Frq_5pl us	Alcohol Use and Dependence
	SSAGA_Alc_12_Frq_Drk	Alcohol Use and Dependence
	SSAGA_Alc_Hvy_Drinks_ Per_Day	Alcohol Use and Dependence
	SSAGA_Alc_D4_Dp_Sx	Alcohol Use and Dependence
	SSAGA_Alc_12_Frq_5plus	Alcohol Use and Dependence
	SSAGA_Alc_Age_1st_Use	Alcohol Use and Dependence
	SSAGA_Alc_Hvy_Frq	Alcohol Use and Dependence
	SSAGA_Alc_Hvy_Frq_Drk	Alcohol Use and Dependence

	SSAGA_Alc_12_Max_Drinks	Alcohol Use and Dependence
	SSAGA_Alc_D4_Ab_Dx	Alcohol Use and Dependence
	SSAGA_Times_Used_Stimulants	Illicit Drug Use
	SSAGA_Times_Used_Opiates	Illicit Drug Use
	SSAGA_Times_Used_Hallucinogens	Illicit Drug Use
	SSAGA_Times_Used_Illicits	Illicit Drug Use
	SSAGA_Times_Used_Sedatives	Illicit Drug Use
	SSAGA_Times_Used_Cocaine	Illicit Drug Use
	SSAGA_Mj_Ab_Dep	Marijuana Use and Dependence
	SSAGA_Mj_Times_Used	Marijuana Use and Dependence
	SSAGA_Mj_Use	Marijuana Use and Dependence
	Avg_Weekday_Any_Tobacco_7days	Tobacco Use 7-Day Retrospective
	Times_Used_Any_Tobacco_Today	Tobacco Use 7-Day Retrospective
	Total_Cigarettes_7days	Tobacco Use 7-Day Retrospective
	Avg_Weekend_Cigarettes_7days	Tobacco Use 7-Day Retrospective
	Avg_Weekday_Cigarettes_7days	Tobacco Use 7-Day Retrospective
	Num_Days_Used_Any_Tobacco_7days	Tobacco Use 7-Day Retrospective
	Avg_Weekend_Any_Tobacco_7days	Tobacco Use 7-Day Retrospective
	Total_Any_Tobacco_7days	Tobacco Use 7-Day Retrospective
	SSAGA_TB_Smoking_History	Tobacco Use and Dependence
	SSAGA_TB_Still_Smoking	Tobacco Use and Dependence

Supplementary Table 5

Table S5. Generalization of the *Substance Use* and *Cognition Modes* in the HCP-D cohort.

(a) Generalization of the *Substance Use Mode*

Phenotypes	**R**	**P-val**	**P-bonferroni**	**Sample(N)**
Frequency of playing M-rated games	0.182	5.75E-06	**5.18E-05**	617
ASR:AD/H Problems	0.226	6.27E-03	**5.64E-02**	147
ASR:Externalizing Problems	0.171	3.97E-02	3.57E-01	147
ASR:Rule Breaking Behavior	0.154	6.39E-02	5.75E-01	147
CBCL:Aggressive Behavior	-0.04	3.82E-01	1.00E+00	472
ASR:Aggressive Behavior	0.065	4.40E-01	1.00E+00	147
CBCL:AD/H Problems	-0.027	5.61E-01	1.00E+00	472
CBCL:Externalizing Problems	-0.022	6.35E-01	1.00E+00	472
CBCL:Rule Breaking Behavior	0.018	7.04E-01	1.00E+00	472

(b) Generalization of the *Cognition Mode*

Phenotypes	**R**	**P-val**	**P-bonferroni**	**Sample(N)**
Fluid Intelligence	0.183	5.71E-06	**6.28E-05**	611
Self-regulation	0.152	1.64E-04	**1.80E-03**	612
Early Childhood Cognition Composite	0.147	2.01E-03	**2.21E-02**	445
Total Cognition Composite	0.141	3.04E-03	**3.34E-02**	445
Crystallized Cognition Composite	0.136	4.35E-03	**4.79E-02**	444
Executive Function/Cognitive Flexibility	0.116	1.49E-02	1.64E-01	446
Oral Reading Recognition	0.090	5.80E-02	6.38E-01	446
Executive Function/Inhibition	0.076	1.09E-01	1.00E+00	445
Pattern Comparison Processing Speed	0.031	5.13E-01	1.00E+00	446
Fluid Cognition Composite	0.016	7.42E-01	1.00E+00	454
Picture Sequence Memory	0.003	9.41E-01	1.00E+00	456

R = partial Spearman correlation coefficient; P-val = nominal P value; P-bonferroni = P value after Bonferroni correction; N = sample size. P-values are reported in scientific notation. Significant or trend-level associations after Bonferroni correction are highlighted in bold.

Supplementary Table 6

Table S6. Generalization of the *Substance Use* and *Cognition Modes* in the UK Biobank cohort

(a) Generalization of the *Substance Use Mode*

Phenotypes	**full sample (ages 45-85)**			**group1 (ages 45-60)**			**group2 (ages 60-82)**		
	R	P-val	Sample(N)	R	P-val	Sample(N)	R	P-val	Sample(N)
UKB Substance Use (PC1)	0.035	4.19E-05	13918	0.036	1.54E-02	4497	0.032	1.86E-03	9421
UKB Externalizing Problem (PC1)	0.060	3.55E-12	13557	0.059	9.60E-05	4397	0.059	1.88E-08	9160

(b) Generalization of the *Cognition Mode*

Phenotypes	**full sample (ages 45-85)**				**group1 (ages 45-60)**				**group2 (ages 60-82)**			
	R	P-val	P-bonferroni	Sample(N)	R	P-val	P-bonferroni	Sample(N)	R	P-val	P-bonferroni	Sample(N)
Fluid intelligence/reasoning	0.043	5.41E-12	**2.71E-11**	26392	0.046	1.20E-05	**5.98E-05**	9033	0.040	9.56E-08	**4.78E-07**	17359
Numeric memory	0.039	4.41E-09	**2.21E-08**	22275	0.039	8.79E-04	**4.39E-03**	7306	0.039	2.36E-06	**1.18E-05**	14969
Tower rearranging	0.029	7.67E-04	**3.83E-03**	21828	0.018	1.20E-01	6.01E-01	7176	0.026	1.51E-03	**7.55E-03**	14712
Matrix pattern completion	0.020	3.90E-03	**1.95E-02**	21891	0.006	6.10E-01	1.00E+00	7179	0.024	3.59E-03	**1.80E-02**	14652
Symbol digit substitution	-0.002	8.08E-01	1.00E+00	21895	-0.001	4.55E-01	1.00E+00	7181	0.002	8.28E-01	1.00E+00	14714

R = partial Spearman correlation coefficient; P-val = nominal P value; P-bonferroni = P value after Bonferroni correction; N = sample size. P-values are reported in scientific notation. Significant associations after Bonferroni correction are highlighted in bold. Multiple comparison correction was not applied to (a) as PC scores were used as composite variables.