Supplementary Information: Brain network dynamics reflect psychiatric illness status and transdiagnostic symptom profiles across health and disease

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Supplementary Tables

Table S1. 110 behavioral, cognitive, and clinical measures used for symptom fingerprinting.

Measure name (full)	A priori labels	Cluster assignment	Factor loading (rel. %)
Positive and negative syndrome scale (negative subscale)	internalizing, thought disorder, global	internalizing	0.4
Positive and negative syndrome scale (positive subscale)	thought disorder, global	internalizing	0.5
Broad autism phenotype questionnaire (rigid subscale, avg.)	social, externalizing, global	internalizing	1.1
Broad autism phenotype questionnaire (aloof subscale, avg.)	social, externalizing, global	internalizing	1.1
Positive and negative syndrome scale (general subscale)	global, thought disorder	internalizing	1.1
Range of impaired functioning tool (total)	social, externalizing	internalizing	1.2
Barratt impulsiveness scale (subscale 1, self control)	externalizing, healthy functioning	internalizing	1.2
Barratt impulsiveness scale (subscale 2, non-planning)	externalizing, healthy functioning	internalizing	1.6
Broad autism phenotype questionnaire (pragmatic language, avg.)	social, externalizing, global	internalizing	1.6
Retrospective self-report of inhibition (social/school subscale)	internalizing, externalizing	internalizing	1.6
Profile of mood states (confusion subscale t-score)	internalizing, thought disorder	internalizing	2.0
Positive urgency measure (total, avg.)	externalizing	internalizing	2.0
Experiences in close relationships inventory (avoidance subscale)	social, externalizing	internalizing	2.0
Cognitive failures questionnaire (forgetfulness subscale)	global, thought disorder	internalizing	2.1
Behavioral inhibition/activation scale (inhibition subscale)	reward, internalizing	internalizing	2.1
Anxiety sensitivity index	internalizing	internalizing	2.1
Cognitive failures questionnaire (false triggering subscale)	global, thought disorder	internalizing	2.2
Cognitive emotion regulation questionnaire (rumination subscale)	internalizing	internalizing	2.2
Temperament and character inventory (temperaments, harm avoidance subscale)	internalizing	internalizing	2.3
NEO five-factor personality inventory (neuroticism factor)	healthy functioning	internalizing	2.3
Quick inventory of depressive symptomatology (total, sum)	internalizing	internalizing	2.5
Cognitive failures questionnaire (distractibility subscale)	global, thought disorder	internalizing	2.5
State-trait anxiety inventory (trait anxiety subscale)	internalizing	internalizing	2.5
Barratt impulsiveness scale (subscale 2, attentional)	externalizing	internalizing	2.5

Cognitive emotion regulation questionnaire (self blame subscale)	internalizing	internalizing	2.5
State-trait anxiety inventory (state anxiety subscale)	internalizing	internalizing	2.6
Barratt impulsiveness scale (subscale 1, attention)	externalizing	internalizing	2.7
Ruminative responsiveness scale (total, sum)	internalizing	internalizing	2.7
Retrospective self-report of inhibition (fear/illness subscale)	internalizing, externalizing	internalizing	2.7
Perceived stress scale (total)	internalizing	internalizing	2.7
Montgomery-Asberg depression rating scale (total)	internalizing	internalizing	2.8
Barratt impulsiveness scale (subscale 1, cognitive instability)	externalizing, thought disorder	internalizing	2.9
Profile of mood states (anger subscale t-score)	externalizing	internalizing	2.9
Experiences in close relationships inventory (reassurance subscale)	social, externalizing	internalizing	3.0
Depression anxiety stress scale (anxiety subscale)	internalizing	internalizing	3.0
Profile of mood states (tension subscale t-score)	internalizing	internalizing	3.1
Profile of mood states (depression subscale t-score)	internalizing	internalizing	3.1
Depression anxiety stress scale (depression subscale)	internalizing	internalizing	3.2
Profile of mood states (fatigue subscale t-score)	internalizing	internalizing	3.4
Cognitive emotion regulation questionnaire (catastrophizing subscale)	internalizing	internalizing	3.4
Experiences in close relationships inventory (pulling back subscale)	social, externalizing	internalizing	3.4
Clinical global impression (severity score)	global	internalizing	3.6
Depression anxiety stress scale (stress subscale)	internalizing	internalizing	3.8
Domain specific risk taking (risk perception, recreational subscale)	externalizing, risk, social, global	externalizing	1.2
Young mania rating scale (disruptive behavior subscale)	externalizing	externalizing	1.4
Domain specific risk taking (risk perception, health subscale)	externalizing, risk, social, global	externalizing	1.5
Domain specific risk taking (risk perception, ethical subscale)	externalizing, risk, social, global	externalizing	2.3
Temperament and character inventory (characters, cooperativeness subscale)	healthy functioning	externalizing	2.5
Young mania rating scale (sleep subscale)	thought disorder, somatic, internalizing	externalizing	2.7
Temperament and character inventory (temperaments, persistence subscale)	healthy functioning, internalizing	externalizing	2.9
NEO five-factor personality inventory (agreeableness factor)	healthy functioning	externalizing	3.0
Multidimensional scale for perceived social support (friend subscale)	social, global, externalizing	externalizing	3.2
Temperament and character inventory (temperaments, reward dependence subscale)	externalizing, reward	externalizing	3.5

Young mania rating scale (language, thought disorder subscale)	thought disorder, externalizing	externalizing	3.5
Panic disorder severity scale (panic frequency subscale)	internalizing	externalizing	3.7
Temporal experience of pleasure scale (anticipatory subscale)	reward, thought disorder	externalizing	3.8
Multidimensional scale for perceived social support (family subscale)	social, global, externalizing	externalizing	4.1
Behavioral inhibition/activation scale (activation, reward responsiveness subscale)	reward, internalizing	externalizing	4.2
Cognitive emotion regulation questionnaire (refocus/planning subscale)	healthy functioning, externalizing	externalizing	4.5
Multidimensional scale for perceived social support (significant other subscale)	social, global, externalizing	externalizing	4.6
Profile of mood states (vigor subscale t-score)	externalizing	externalizing	4.7
Temperament and character inventory (characters, self directedness subscale)	healthy functioning	externalizing	4.8
NEO five-factor personality inventory (extraversion factor)	healthy functioning	externalizing	4.8
NEO five-factor personality inventory (conscientiousness factor)	healthy functioning	externalizing	4.8
Cognitive emotion regulation questionnaire (positive reappraisal subscale)	healthy functioning	externalizing	5.6
Young mania rating scale (irritability subscale)	externalizing	externalizing	6.7
Snaith-Hamilton pleasure scale (total)	reward, externalizing, internalizing	externalizing	15.9
Young mania rating scale (speech subscale)	thought disorder, externalizing	cognition	0.0
Fagerstrom test for nicotine dependence (total)	externalizing	cognition	0.0
TestMyBrain (fast reaction test)	healthy functioning, cognitive	cognition	0.1
Domain specific risk taking (risk perception, financial subscale)	externalizing, risk, social, global	cognition	0.1
TestMyBrain (word sentence association paradigm)	healthy functioning, cognitive	cognition	0.1
Young mania rating scale (content subscale)	thought disorder	cognition	0.4
TestMyBrain (reading the mind in the eyes test)	healthy functioning, cognitive	cognition	0.5
TestMyBrain (matrix reasoning)	healthy functioning, cognitive	cognition	0.5
Experiences in close relationships inventory (anxiety subscale)	social, externalizing	cognition	0.5
TestMyBrain (continuous performance test)	healthy functioning, cognitive	cognition	0.7
Clinical global impression (global improvement score)	global	cognition	0.7
Young mania rating scale (sexual interest subscale)	thought disorder, externalizing	cognition	0.9
Domain specific risk taking (risk perception, social subscale)	externalizing, risk, social, global	cognition	1.0
TestMyBrain (fast choice test)	healthy functioning, cognitive	cognition	1.1
Shipley Institute of living scale (vocab subscale t-score)	healthy functioning, cognitive	cognition	1.4
Shipley Institute of living scale (IQ score)	healthy functioning, cognitive	cognition	1.4
NEO five-factor personality inventory (openness factor)	healthy functioning	cognition	1.4

Young mania rating scale (elevated mood subscale)	thought disorder, internalizing	cognition	1.6
TestMyBrain (symbol matching test)	healthy functioning, cognitive	cognition	1.6
Young mania rating scale (increased motor subscale)	somatic, externalizing	cognition	1.7
Young mania rating scale (appearance subscale)	internalizing, thought disorder	cognition	2.5
Multnomah community ability scale (total)	social, global, externalizing	cognition	4.5
Domain specific risk taking (risk taking, social subscale)	externalizing, risk, social, global	cognition	5.2
Temporal experience of pleasure scale (consummatory subscale)	reward, thought disorder	cognition	5.5
Behavioral inhibition/activation scale (activation, drive subscale)	reward, internalizing	cognition	6.2
Behavioral inhibition/activation scale (activation, fun seeking subscale)	reward, internalizing	cognition	6.7
Experiences in close relationships inventory (frustrated subscale)	social, externalizing	cognition	8.9
Cognitive emotion regulation questionnaire (acceptance subscale)	healthy functioning, internalizing	cognition	11.0
Cognitive emotion regulation questionnaire (perspective subscale)	healthy functioning	cognition	14.4
Cognitive emotion regulation questionnaire (positive refocusing subscale)	healthy functioning, thought disorder	cognition	19.3
Temperament and character inventory (characters, self transcendence subscale)	thought disorder, internalizing, healthy functioning	social/reward	3.7
Alcohol tobacco caffeine use questionnaire (total)	externalizing	social/reward	4.6
Domain specific risk taking (risk taking, recreational subscale)	externalizing, risk, social, global	social/reward	4.7
Barratt impulsiveness scale (subscale 1, motor)	externalizing	social/reward	5.5
Barratt impulsiveness scale (subscale 1, cognitive complexity)	externalizing, thought disorder	social/reward	5.8
Barratt impulsiveness scale (subscale 1, perseverance)	externalizing, healthy functioning	social/reward	6.0
Cognitive emotion regulation questionnaire (blaming others subscale)	externalizing, internalizing	social/reward	6.6
Temperament and character inventory (temperaments, novelty seeking subscale)	externalizing, reward	social/reward	7.6
Barratt impulsiveness scale (subscale 2, motor)	externalizing	social/reward	7.7
Domain specific risk taking (risk taking, health subscale)	externalizing, risk, social, global	social/reward	9.4
Domain specific risk taking (risk taking, ethical subscale)	externalizing, risk, social, global	social/reward	12.1
Domain specific risk taking (risk taking, financial subscale)	externalizing, risk, social, global	social/reward	12.1
Experiences in close relationships inventory (avoid closeness subscale)	social, externalizing	social/reward	14.2

Table S1 legend. These measures (each row) correspond to the x- and y-axes on the individual-differences correlation matrix in main text **Fig. 3A**. A priori labels refer to a pre-mapping of each measure to potential dimensions of functioning based on the literature and consensus across the study team. This was implemented to reduce the possibility of researcher bias in naming clusters (3rd column) that resulted

from hierarchical agglomerative clustering of the matrix in **Fig. 3A**. Once the clustering solution was optimized (see **Methods**), PCA was performed on each cluster of measures, and based on the relative importance of each measure's factor loading onto the first PC (4th column), we used a priori labels to guide naming conventions for each cluster. Avg. = average. Note that measures within each cluster are sorted in ascending order of factor loading. See [1] for more detailed information about session acquisition, source references, versioning, and quality assurance analyses for the TCP dataset.

Supplementary Figures

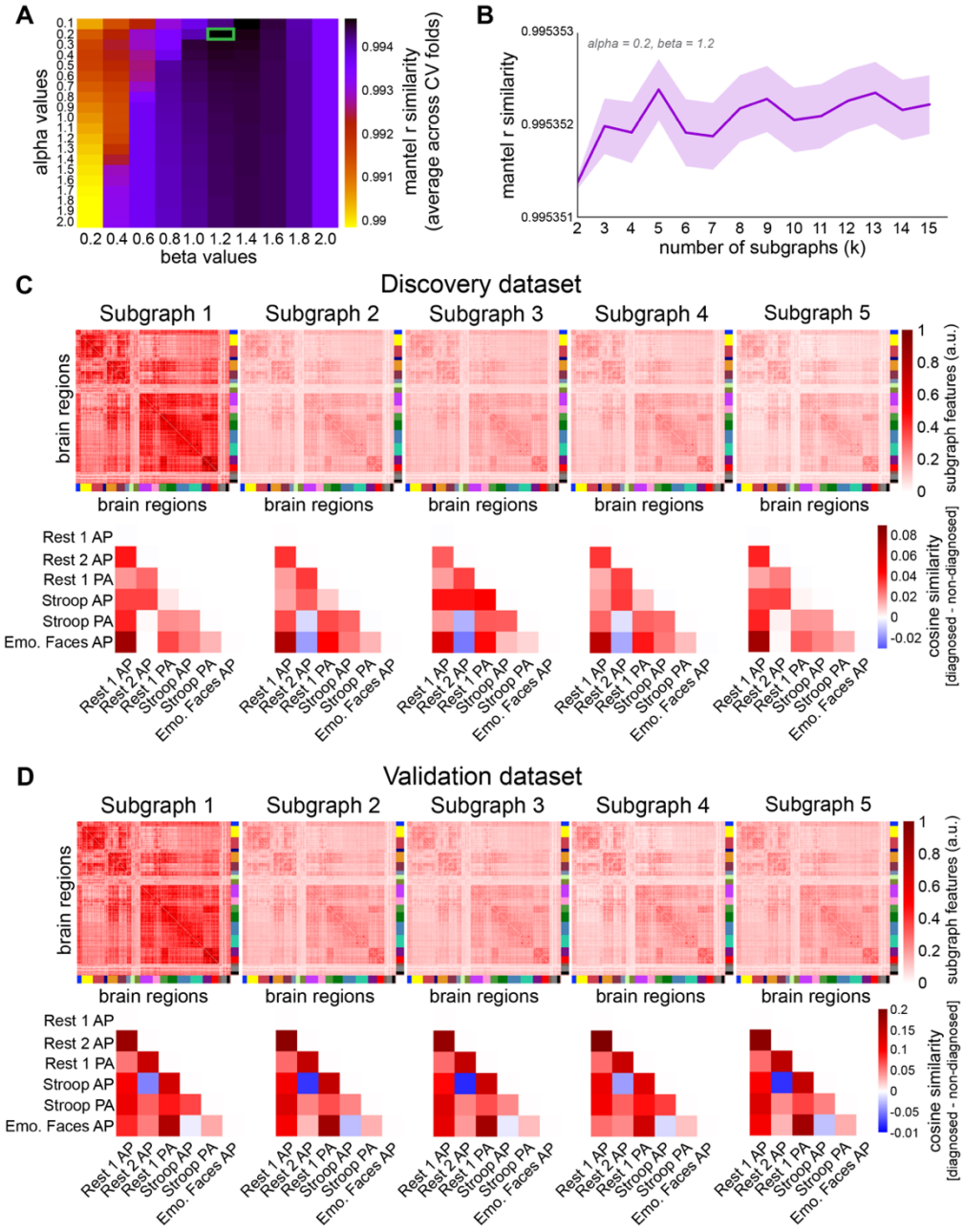

Figure S1. Validation and optimization of non-negative matrix factorization (NMF) for uncovering brain network dynamics. (**A**) Cross validation (100 folds) results for tuning NMF parameters alpha and beta. Mantel *r* estimates a nonparametric correlation between the original FC input and the NMF-reconstructed FC. The optimal parameter pair is highlighted in green. (**B**) Same as A, but for the number of subgraphs (*k*), while holding alpha and beta at the optimal levels in A. Cross-validation accuracy was stable for 5-10 subgraphs, and we chose a solution of *k*=5 for consistency with prior literature[2-5].(**C**) *Top*: NMF subgraph features, reformatted into region-by-region networks. *Bottom*: main-text **Fig. 2F**, including all subgraphs. (**D**) Same as C (discovery dataset), except for the validation dataset.

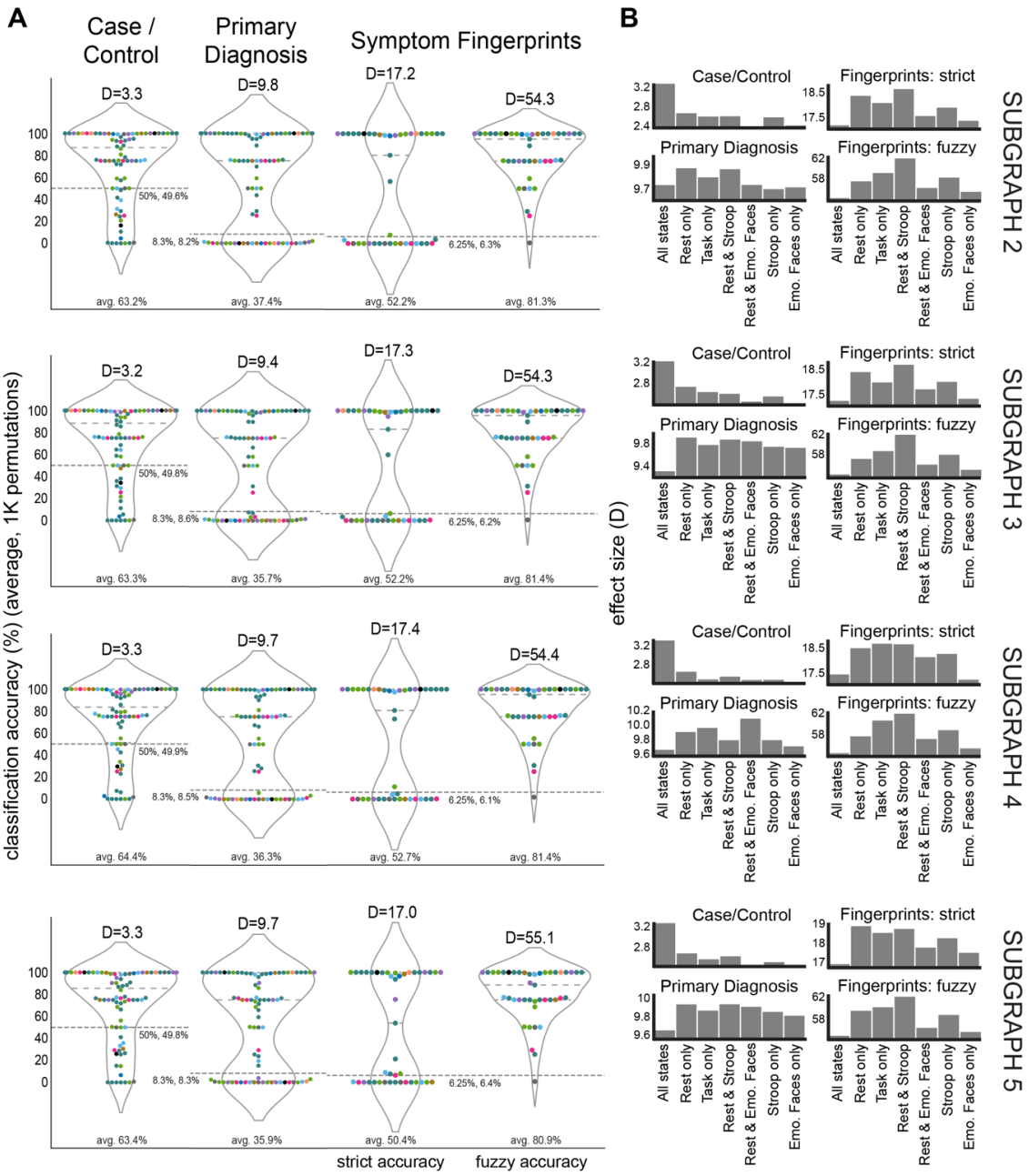

Figure S2. Brain network dynamics can accurately separate symptom fingerprints, subgraphs 2 through 5 (paneled rows). (**A**) Classification accuracies closely match main text **Fig. 4**, where dots represent *n*=43 held-out test-set participants. Effect sizes (ESM) of each model (*D*) are listed on the top, along with theoretical chance and empirical chance near dashed grey lines. Average model accuracy across 1000 permutations is listed on the bottom of each plot. All models were significant and thus $p<0.001$; Cohen's *D* ESMs are listed on top of each model to provide a scale-free index to compare model accuracies. (**B**) Following main text **Fig. 5**, case-control classification accuracy varies with amount of connectivity data inputted to NMF; primary diagnoses are classified with varying patterns across models; and fingerprints are best separated by brain network dynamics across states involving shifts from resting-state to Stroop inhibitory cognitive control task.

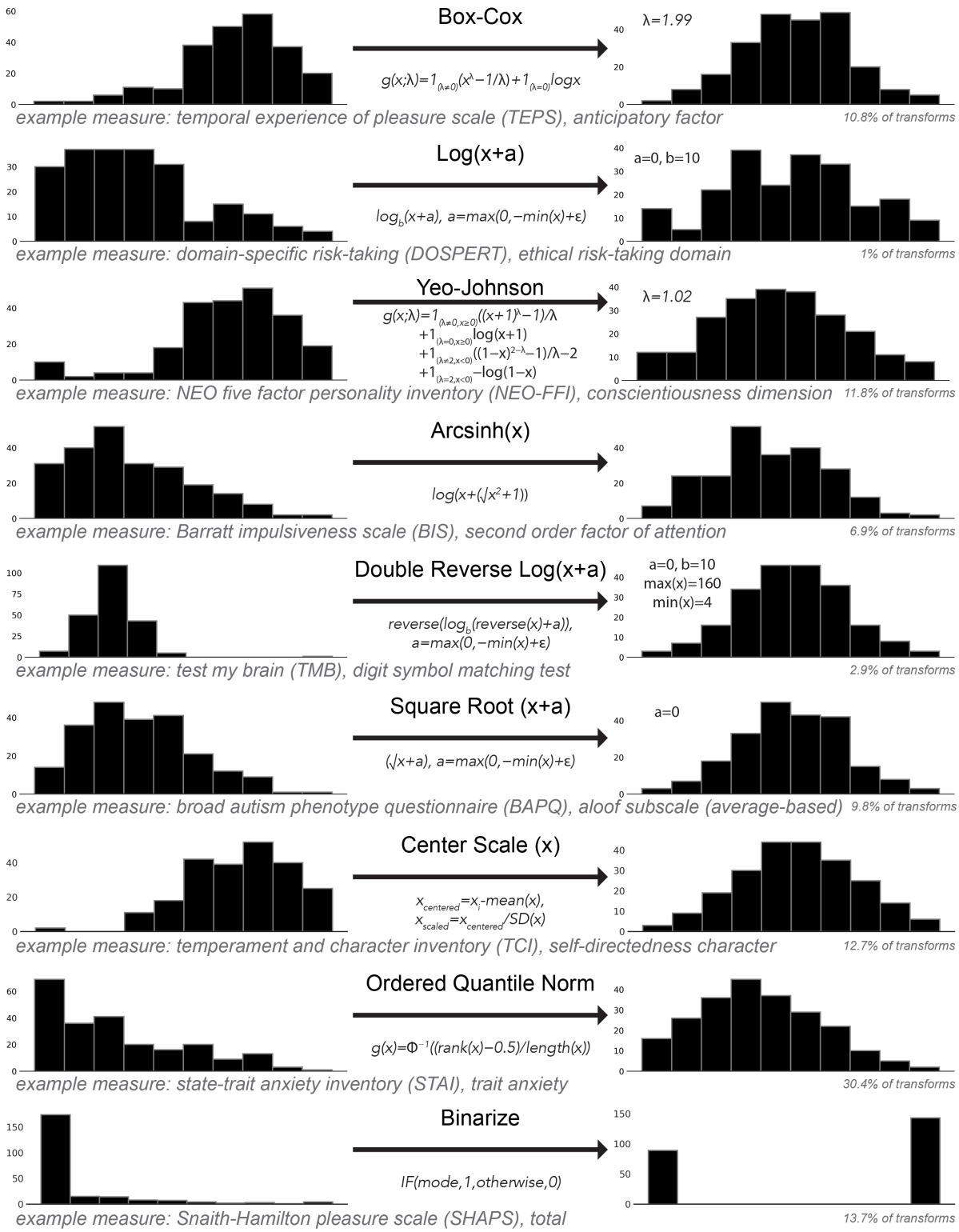

Figure S3. Normalizing transformations applied to behavioral, cognitive, and clinically-relevant measures for the symptom fingerprinting pipeline. Using the R package bestNormalize[6], the shown transformation-estimating functions were used on select behavioral measures. In each case, an example implementation is shown along with mathematical formula to demonstrate the transformation process.

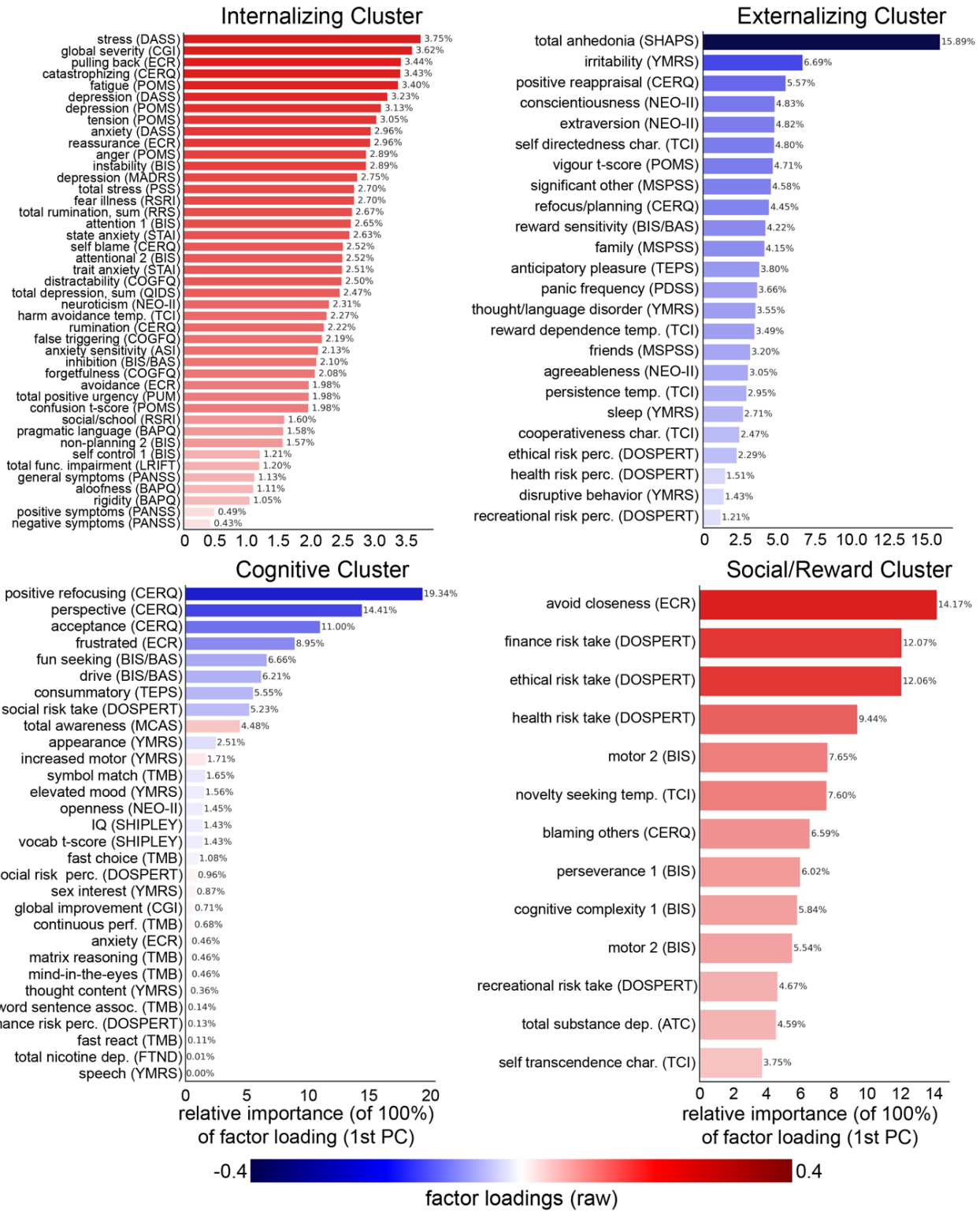

Figure S4. Uncovering dimensional symptom profiles: expanded PCA loadings. Corresponding to Results **Fig. 3**, all of the measures in each cluster are shown as well as the relative importance of their factor loadings in the first PC of each cluster. Scale and subscale names (y-axes) are expanded in **Supplemental Table S1,** along with *a priori* domain mapping technique.

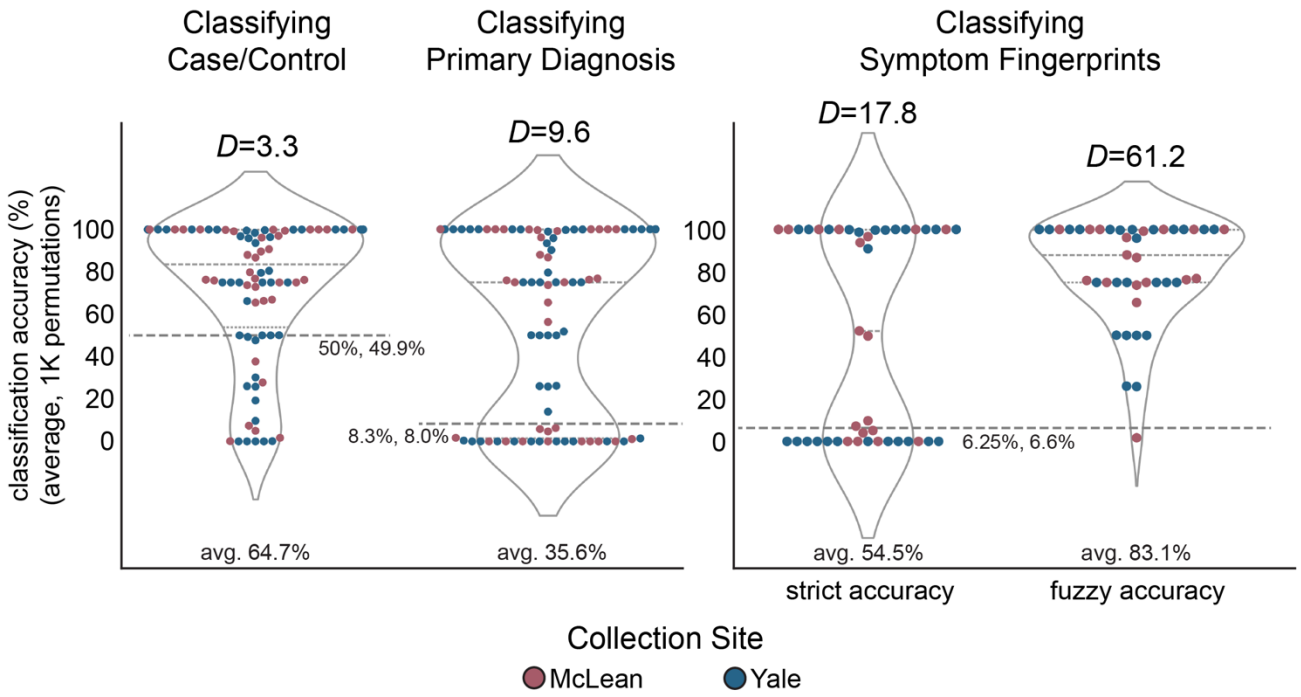

Figure S5. Model fit was proportional across data collection sites. Quality control analyses demonstrating that collection site did not influence the brain-behavior relationship between brain network dynamics and psychiatric grouping. Corresponding to Results **Fig. 4**, the primary classification model results were re-colored by collection site (dots represent *n*=43 held-out, test-set participants; red: participants recruited at McLean site, blue: those recruited at the Yale site). Given no apparent pattern or clustered distribution of classification accuracy of McLean versus Yale participants, this suggests that collection site did not drive model performances (see main Results text for further details).

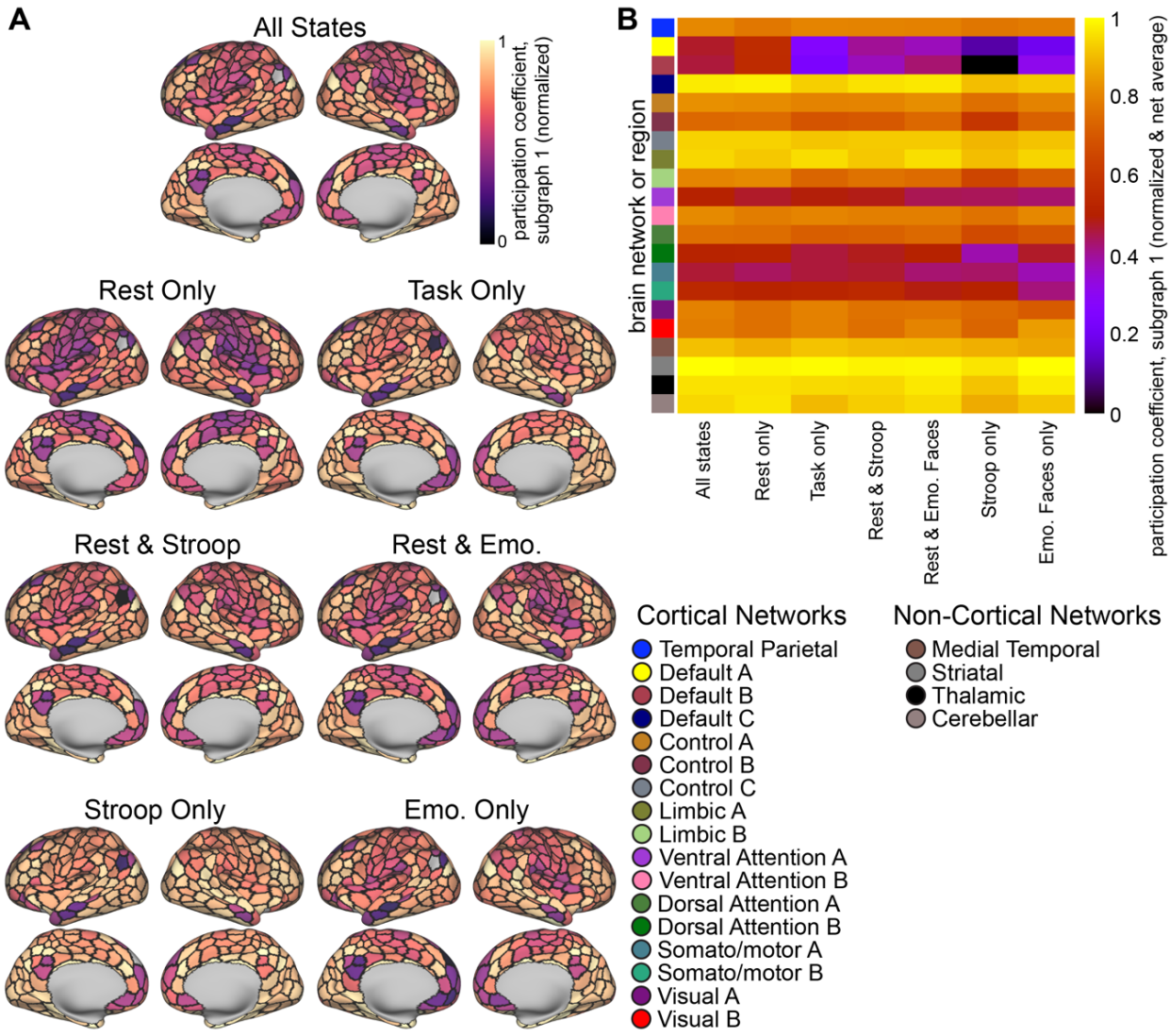

Figure S6. Hub structure underlying connectivity shifts across varied cognitive states. To explore the extent that dynamic network reconfigurations are linked with flexible processing, we applied a graph metric called participation coefficient[7], which quantifies hubs, or, how diversely connected a region is to other regions, and has been linked with integrative processes[8,9]. Applying participation coefficient to the first NMF-uncovered subgraph quantifies the extent that features underlying across-state network dynamics exhibit hub properties. (**A**) Participation coefficient (PC) of the first NMF-uncovered subgraph underlying across-state brain network dynamics, with FC estimates from different combinations of states used as inputs (i.e., the underlying network structure for the inputs in **Fig. 5** model comparisons). PC estimates were min-max normalized to a common scale of 0-1. While gross patterns were similar, regions in control network A had increased PC. (**B**) Same as panel B, but functional network averages shown. Select networks exhibited hub properties consistently across all models, such as striatal areas and control (frontoparietal) A networks, and others with more variability, such as default networks A and B. Altogether, network features constraining information processing dynamics were exhibited with different degrees of variability or stability across ranging shifts in cognitive context, depending on the functional brain system.

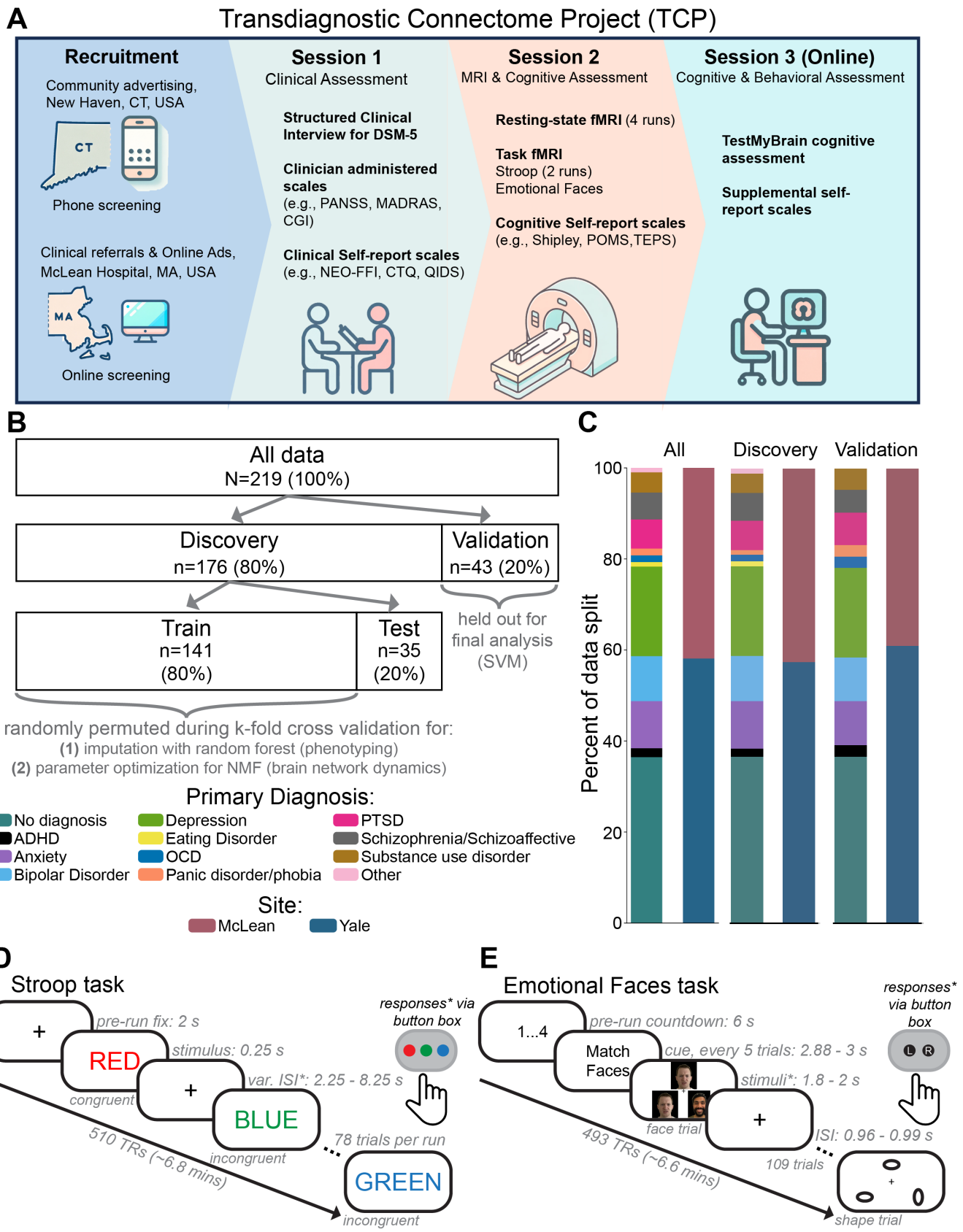

Figure S7. The Transdiagnostic Connectome Project (TCP) dataset. (**A**) Example behavioral measures, types of fMRI data, and locale information is listed for each of the three TCP sessions. (**B**)

Data were semi-randomly split (constraints to preserve proportionality of primary diagnosis and collection site) into discovery (*n*=176) and validation groups (*n*=43). Discovery data was randomly split into training and test sets for various supervised learning and/or parameter optimization steps of the pipeline, and validation data was not used until the final analyses. This ensured that the held-out testing set in classification (validation) did not "leak" information into the training set (discovery). (**C**) Percentages of participants in each primary diagnosis (as given by the SCID-V-RV) and from each collection site in the total, discovery, and validation datasets. Select primary diagnoses were collapsed based on common symptomatology, for example: substance use disorder (SUD) included cocaine use disorder and alcohol use disorder. ADHD = attention-deficit/hyperactivity disorder; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder. (**D**) The Stroop task paradigm used in task fMRI. (**E**) The Emotional Faces task paradigm used in task fMRI Var. ISI = variable interstimulus interval; TR = repetition time (1 TR = 0.8 s in TCP fMRI data). Panels A, D, and E were reproduced with permission from [1].

Supplementary References

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