Brain Connectivity Patterns in Children Linked to Neurocognitive Abilities

Chandra Sripada MD, PhD^{1}, Mike Angstadt MS¹, Saige Rutherford BS¹, Aman Taxali MS¹, D. Angus Clark PhD¹, Tristan Greathouse BS¹, Alex Weigard PhD¹, Luke Hyde PhD², Mary Heitzeg PhD¹*

¹Department of Psychiatry, University of Michigan, Ann Arbor, ²Department of Psychology, University of Michigan, Ann Arbor, MI

**Correspondence:*

*Chandra Sripada
Department of Psychiatry
University of Michigan
4250 Plymouth Road
Ann Arbor MI 48109
sripada@umich.edu*

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ABSTRACT

The development of objective brain-based measures of individual differences in psychological traits is a longstanding goal of clinical neuroscience. Here we show that reliable objective markers of children's neurocognitive abilities can be built from measures of brain connectivity. The sample consists of 5,937 9- and 10-year-olds in the Adolescent Brain Cognitive Development multi-site study with high-quality functional connectomes that capture brain-wide connectivity. Using multivariate methods, we built predictive neuromarkers for a general factor of neurocognitive ability as well as for a number of specific cognitive abilities (e.g., spatial reasoning, working memory). Neuromarkers for the general neurocognitive factor successfully predicted scores for held-out participants at 19 out of 19 held-out sites, explaining over 14% of the variance in their scores. Neuromarkers for specific neurocognitive abilities also exhibited statistically reliable generalization to new participants. This study provides the strongest evidence to date that objective quantification of psychological traits is possible with functional neuroimaging.

INTRODUCTION

Psychological traits and abilities arise from complex patterns in the structure and function of the human brain. A central goal for clinical neuroscience is to objectively measure these brain patterns in order to assess and predict individual differences in traits and abilities. Recent studies provide hints that objective quantification of psychological traits is possible with non-invasive functional neuroimaging¹⁻⁵ (see ⁶ for a review), but modest sample sizes and inconsistent results have prevented any strong conclusions.

In the present work, we take a significant step forward. We establish the strongest evidence to date for the effectiveness and generalizability of brain-based objective markers ("neuromarkers") for neurocognitive abilities, a set of inter-related abilities for reasoning, problem solving, manipulating representations, and learning and recall of information⁷⁻⁹. Individual differences in these abilities are important because they are associated with diverse life outcomes. Better neurocognitive abilities are associated with health, well-being, and occupational success^{10,11}, while deficits in neurocognition, and closely related constructs such as executive functioning^{7,9}, are associated with a broad range of psychopathologies¹²⁻¹⁶.

Traditionally, neurocognitive abilities were studied in functional imaging with task-based studies and locationist methodology¹⁷⁻²⁰—participants are given tasks that engage neurocognitive processing with the aim of localizing task-associated processing to specific brain regions. Our work here differs in three respects. First, we take a network neuroscience approach^{21,22}, examining interconnections among distributed large-scale networks measured when participants are at rest²³. Second, we apply recently developed multivariate predictive modeling methods that aggregate (typically small) units of information across the entire brain,

creating an overall best prediction of scores on individual difference variables.²⁴ Such methods provide a substantial improvement in effect size compared to traditional mass univariate approaches (which conduct separate statistical tests at each brain feature), potentially allowing clinically meaningful predictions of individual differences at the level of the single subject. Third, we do not study how brain features are associated with a single neurocognitive task. Rather, we examine how brain connectivity is linked to an overarching general factor of neurocognitive ability^{25–28} that contributes to performance across diverse neurocognitive tasks, as well as several specific factors of neurocognitive ability^{29,30}.

Our study leverages imaging and behavioral data from 11,875 9 and 10-year olds in the Adolescent Brain and Cognitive Development (ABCD) national consortium study, Release 2.1^{31,32}. We applied bifactor modeling to the comprehensive ABCD 11-task neurocognitive battery³³ to quantify individual differences in a dominant general factor of neurocognitive ability, which captured 75% of the variation in task scores (coefficient ω hierarchical³⁴), as well as three domain-specific factors that together accounted for 13% of the variation in task scores (Figure 1). We also produced resting state connectomes for 5,937 youth who met stringent neuroimaging quality control standards; these connectomes capture tens of thousands of functional connections between hundreds of brain regions. We next applied a multivariate approach predictive modeling approach, brain basis set (BBS)^{35,5,36}, to build neuromarkers for neurocognitive abilities from whole-brain functional connectivity patterns. To guard against identifying spurious relationships and to provide evidence of generalizability, we coupled BBS with leave-one-site-out cross-validation, in which we construct neuromarkers in all sites except one, test the marker at the held-out site, and repeat until each site is held out.

RESULTS

Figure 1: Factor Model of the ABCD Neurocognitive Battery. The comprehensive 11-task ABCD neurocognitive battery was factor analyzed yielding a general factor of neurocognitive ability and three specific factors.

Figure 2: Correlations Between Predicted and Actual General Factor Scores in Leave-One-Site-Out Cross-Validation Analysis. Neuromarkers for the general factor of neurocognitive ability were constructed based on whole brain connectivity patterns. (Left Panel) These neuromarkers generalized to 19 out of 19 held out sites. The overall mean correlation between predicted and observed general factor scores for 5,937 held out subjects was 0.36, $p_{\text{PERM}} < 0.0001$ (observed correlation was higher than 10,000 correlations in the permutation distribution). (Right Panel) Scatter plots for the four largest held-out sites show highly consistent performance.

Connectivity-based neuromarkers for the general factor of neurocognitive ability are highly effective in predicting scores in held-out subjects

In leave-one-site-out cross-validation, the correlation between actual versus predicted general factor scores, averaging across folds of the cross-validation, was 0.36 (Figure 1, left panel). That is, brain connectivity patterns accounted for 14.2% of the variance in general factor scores in held-out samples of youth (variance explained was calculated with the r-squared cross-validated metric³⁷). Cross-site generalizability was remarkably consistent (Figure 1, right panel). Correlations between predicted and actual scores were statistically significant in 19 out of 19 held-out sites (all 19 site-specific p values < 0.0001 ; observed correlations were higher than all 10,000 correlations in the permutation distribution).

Predictive performance of neuromarkers for the general factor of neurocognition remained highly statistically significant across multiple robustness checks

Analysis	General Factor of Neurocognitive Ability	Number of Participants (N)
1. Main Analysis	$r=0.36$; $p<0.0001^*$	5,937
2. Additional Demographic Controls	$r=0.30$; $p<0.0001^*$	5,468
3. White/European-American (non-Hispanic) Subsample	$r=0.27$; $p<0.0001^*$	3,480
4. Leave-One-Site Out General Factor	$r=0.36$; $p<0.0001^*$	5,937
5. Ultra-Low Motion Subsample	$r=0.32$; $p<0.0001^*$	2,847

Table 1: Summary of Additional Analyses to Assess Robustness. The sensitivity of our main analyses (top row) to modeling choices was assessed with a number of robustness checks (rows 2-5). Correlations between actual and predicted neurocognitive scores remained statistically significant and similar in size across all these analyses. * = observed correlation was higher than all 10,000 correlations in the permutation distribution.

We next assessed the robustness of our leave-one-site-out cross-validation analysis via sensitivity checks that modified key elements of the analysis stream. We tested alternative analyses that utilized: 1) Additional ABCD demographic covariates (household income, highest parental education, household marital status), and 2) A subsample restricted to participants who reported their race as White/European-American (non-Hispanic), to confirm that findings were not driven by potentially confounding demographic factors; 3) Bifactor models of neurocognition learned in the training sample and applied to the held-out sample (to create total separation between training and test samples); and 4) An ultra-low head motion sample (mean framewise displacement < 0.2; to confirm motion was not responsible for any associations). As shown in Table 1, all results remained highly statistically significant across these changes, confirming the robustness of our analysis stream.

Neuromarkers for specific cognitive abilities also exhibited statistically reliable generalization to unseen subjects, with neuromarkers for verbal abilities performing the best

Figure 3: Correlations Between Predicted and Actual Scores for 14 Specific Neurocognitive Abilities in Leave-One-Site-Out Cross-Validation Analysis. Neuromarkers for 14 specific ability variables were constructed based on whole brain connectivity patterns. All 14 neuromarkers exhibited statistically reliable generalization to unseen subjects.

We next assessed the predictivity of neuromarkers for specific neurocognitive abilities, in particular the three specific factors as well as the 11 individual neurocognitive tasks (Figure 1). Neuromarkers were constructed in 14 separate BBS models, each tested with leave-one-site-out cross-validation. We found that neuromarkers for all 14 specific ability variables exhibited

statistically reliable generalization to unseen subjects (Figure 3). Neuromarkers for verbal abilities (vocabulary and reading) performed the best, each accounting for more than 9% of the variance in scores in held out participants. To address the fact that the general factor is correlated (to varying degrees) with some of the 14 specific ability variables, we constructed additional neuromarkers for all 14 specific ability variables, this time performing leave-one-site-out cross-validation controlling for the effect of the general factor of neurocognitive ability. We found 13 of the 14 neuromarkers continued to exhibit statistically reliable generalization to unseen subjects (the 14th neuromarker, working memory, was trend significant at $p_{\text{PERM}}=0.10$, Figure S3). This result demonstrates that resting state connectivity patterns contain unique information about multiple specific domains of neurocognitive abilities over and above information about the general factor.

Functional connections involving control networks and processing networks were prominent in the general factor neuromarker. Additionally, these connections varied the most across the fifteen neuromarkers for different neurocognitive abilities.

Figure 4: Connections Between Brain Networks in the Neuromarker for the General Factor of Neurocognition. (Left Panel) Supra-threshold connections linking large-scale networks are shown as red and blue dots. The map shows a distributed set of brain-wide connections is related to the general factor for neurocognitive ability. Connections involving control networks (fronto-parietal, ventral attention, dorsal attention, and cingulo-opercular) and processing networks (visual, default) are especially prominent. (Right Panel) Network map highlighting connections involving control networks and processing networks. Width of chords represents number of suprathreshold connections linking the indicated pair of networks. Red shades = connections at which higher connectivity predicts higher neurocognitive scores; Blue shades = connections at which lower connectivity predicts higher neurocognitive scores.

We next examined consensus connectomes, importance-weighted composite maps associated each neuromarker (see Methods, §9). For the general factor neuromarker, its consensus connectome (Figure 4) showed prominent representation of connections involving control

networks (fronto-parietal, cingulo-opercular, ventral attention, and dorsal attention) and processing networks (visual, default). Connections involving these networks were 56.4% of the suprathreshold connections in the general factor neuromarker, even though make up only 22.6% of the connections in the connectome.

Figure 5: Connections Involving Control Networks and Processing Networks Differentiate Neuromarkers for Different Neurocognitive Abilities. We identified pairs of networks (listed in rows) in which inter-network connections varied the most across the fifteen neuromarkers for neurocognitive abilities (listed in columns). The size of the gray circles indicates the number of suprathreshold connections linking the pair of networks for each neuromarker. Red network labels indicate positive connections and blue indicate negative connections. The figure shows that connections involving control networks (Fronto-parietal, Cingulo-opercular, Dorsal Attention, Ventral Attention) and processing networks (Default, Visual, Somatomotor-Hand) play a major role in differentiating neuromarkers for distinct neurocognitive abilities.

We next calculated a variability index (Methods, §10) that identifies pairs of networks whose connections varied the most across the 15 neuromarkers for neurocognitive abilities (the index separates positive and negative inter-network connections, and is thus calculated over 240 inter-network values). This index illuminates the main network connectivity patterns that best

differentiate the neuromarkers. We found the top 21 inter-network relationships (out of 240 total) accounted for over 50% of the variance in inter-network connectivity across the 15 neuromarkers. These 21 highly varying inter-network relationships are shown in Figure 5, which in addition highlights interesting patterns of specificity for different domains of neurocognition. For example, the Speed/Flexibility factor is heavily represented in negative connections involving fronto-parietal and cingulo-opercular connections with default network. The Learning/Memory factor, in contrast, is most represented in negative connections within default network and positive connections linking default network with fronto-parietal network. Similar patterns of specificity are found for other specific neurocognitive abilities. Additionally, we found connections linking control networks and processing networks (see Figure 5 caption), which were heavily represented in the general factor neurosignature (see Figure 4), were also the most variable across neuromarkers.

DISCUSSION

This study examined behavioral and resting state imaging data for 5,937 9- and 10-year-old participants across 19 sites in the ABCD Consortium study^{33,38}. Using a multivariate predictive modeling approach, we aimed to build neuromarkers for neurocognitive abilities from resting state connectivity patterns and validate their performance with leave-one-site cross-validation. Our main findings are that multivariate neuromarkers of neurocognitive abilities are effective at predicting multiple domains of neurocognition and reliably generalize to held out subjects. In addition, neuromarkers for the general factor of neurocognition were particularly effective, explaining over 14% of variance in scores in held out subjects, a clinically meaningful level of predictivity, and remained highly predictive after a number of robustness checks. Our results provide the strongest evidence yet that neuroimaging can be used to build reliable and generalizable brain-based markers for psychological traits and abilities. Moreover, these findings set the stage for additional investigation in the longitudinal ABCD dataset to better understand how the connectivity patterns here linked to neurocognitive abilities change and mature over the course of adolescence.

Previous studies also identified links between brain imaging features, including resting state functional connectivity, and neurocognitive phenotypes¹⁻⁶. The present study adds to the literature in three key ways. First, this is the largest study ever examining links between brain connectivity and cognitive abilities in youth. Larger samples enable estimation of effects with less variability³⁹, yielding especially reproducible insights into brain-behavior relationships. Second, this study provides unique evidence about generalizability, showing that neuromarkers trained in one set of subjects effectively and consistently generalize to new subjects (with successful generalization in 19 out of 19 held out ABCD sites). The utility of imaging-based markers for psychological traits and abilities depends heavily on their applicability to new datasets collected at heterogeneous sites with different subject characteristics and scanners, and this study confirms that strong generalizability is possible. Third, most previous neuroimaging studies exclusively examined a single aspect of cognition, such as a single neurocognitive ability^{1,4,40}, or a general factor of cognitive ability^{3,36,41}. This study is among the first to shed

light on how brain connectivity contributes to the general factor of neurocognition, several specific factors, as well as a number of individual neurocognitive abilities.

To this point, we found that neuromarkers across different domains of neurocognition exhibited varying levels of performance. Predictivity was highest for the general factor of neurocognitive ability, explaining over 14% of the variance in scores in out of sample subjects. Strong predictivity was also observed for a verbal/spatial specific factor as well as for several individual tasks, especially for the crystallized abilities of reading and vocabulary. Relatively poorer performance, on the other hand, was observed for two other neurocognitive domains, the Speed/Flexibility domain and the Learning/Memory domain, as well as the individual task associated with these domains (Figure 3).

In explaining these differences, it is possible that these neurocognitive variables that were less well predicted simply do not have sizable signatures in resting state connectomes in 9- and 10-year old youth. There is some evidence that neurocognitive abilities remain fairly undifferentiated²⁷, unspecialized⁴², or underdeveloped^{43,44} in late childhood/early adolescence. Thus, it is possible that performance for a number of specific factors and individual tasks will improve as the architecture of neurocognition becomes more refined over the course of adolescence and the specific abilities reflected in these factors/tasks separate out from the general factor. An alternative explanation is that the multivariate classifiers used for the present analysis are not sensitive to signatures for certain specific factors and individual tasks. For example, if resting state signatures of certain neurocognitive abilities are mainly localized in small, spatially discrete structures (e.g., striatum or hippocampus), classifiers that rely on distributed whole-connectome information, including the BBS method used in the present report, will be unlikely to recover them. In future studies, alternative classifiers (e.g., supervised methods), modalities (e.g., task-based methods), or search strategies (e.g., regions of interest approaches) could be utilized.

The connectivity neurosignatures for the general factor of neurocognition and other neurocognitive variables were highly distributed across the connectome, but there was nonetheless a concentration of connections involving control networks (such as fronto-parietal network and cingulo-opercular network) and processing networks (such as default network and visual network). Additionally, we found control network/processing network connections were the most variable across the set of neurosignatures for different neurocognitive domains. Control networks^{45,46} are proposed to be the source of cognitive control signals that modulate responses in other networks based on contextual demands—a function that is consistent with the observation that these networks are implicated in higher-order cognitive abilities. Additionally, connections involving control networks and default network are found to be among the most variable across individuals.⁴⁷ These connections also exhibit substantial maturation across childhood and adolescence^{48,49}, and their maturational trajectories exhibit significant inter-individual differences^{4,50,51}. Taken together, these observations align well with our finding that connections involving control networks and processing networks are a primary locus of individual differences in neurocognitive abilities.

One important potential application for neuromarkers of neurocognition is in elucidating psychological, neural, and developmental mechanisms of cognitive abilities^{43,52}. Neuromarkers summarize complex distributed whole-brain connectivity patterns with a small number of quantitative metrics²⁴, opening the door to sophisticated statistical modeling methods that assess genetic and environmental (e.g., poverty, family environment) contributions to neuromarker expression and, in turn, the contributions of neuromarker expression to subsequent outcomes. Critically, a major strength of the 10-year longitudinal ABCD study³¹ is that it allows researchers to track the maturational patterns across adolescence of the connections implicated in our neurocognitive markers. This will facilitate future work that delineates in detail the role of neuromarker expression in mediating the relationship between genetic and environmental risk factors (e.g., poverty, family environment) and the subsequent emergence of behavioral (e.g., substance initiation) or psychopathological (e.g., psychosis) endpoints.

Additionally, neuromarkers of the type demonstrated here could one day find more direct clinical application. There is growing evidence that impaired neurocognitive abilities are associated with diverse forms of psychopathology^{12–16}, including schizophrenia^{53–55}, externalizing disorders such as ADHD^{56,57} and substance use disorders^{58,59}, and internalizing disorders such as depression^{60,61}. Notably, in this same ABCD baseline sample, we recently showed⁶² that reduced scores on the general factor of neurocognition were associated with elevation in the general factor of psychopathology^{63–65} (widely termed the “P factor”), which confers vulnerability to nearly all prevalent psychiatric symptoms. The possibility thus exists that neuromarkers for neurocognitive abilities could find clinical use in identifying individuals at risk for negative psychiatric outcomes, potentially at an early age well before overt signs and symptoms have emerged.

In sum, in a large rigorously characterized sample of youth, we established that neuromarkers of neurocognitive abilities built from distributed brain network connectivity patterns consistently generalize to new subjects across different data collection sites, are robust across a number of sensitivity checks, and capture clinically meaningful quantities of variation in general and specific neurocognitive abilities.

METHODS

1. Sample and Data

The ABCD study is a multisite longitudinal study with 11,875 children between 9–10 years of age from 21 sites across the United States. The study conforms to the rules and procedures of each site’s Institutional Review Board, and all participants provide informed consent (parents) or assent (children). Detailed description of recruitment procedures⁶⁶, assessments⁶⁷, and imaging protocols³⁸ are available elsewhere.

2. Data Acquisition, fMRI Preprocessing, and Connectome Generation

Imaging protocols were harmonized across sites and scanners. High spatial (2.4 mm isotropic) and temporal resolution (TR=800 ms) resting state fMRI was acquired in four separate runs (5min per run, 20 minutes total, full details are described in ⁶⁸). The entire data pipeline described below was run through automated scripts on the University of Michigan's high-performance cluster, and is described below, with additional detailed methods automatically generated by fMRIPrep software provided in the Supplement. Code for running the analyses can be found at Code for running the analyses can be found at https://github.com/SripadaLab/ABCD_Resting_Neurocognition.

Preprocessing was performed using fMRIPrep version 1.5.0⁶⁹, a Nipype⁷⁰ based tool. Full details of the fMRIPrep analysis can be found in supplemental materials. Briefly, T1-weighted (T1w) and T2-weighted images were run through recon-all using FreeSurfer v6.0.1. T1w images were also spatially normalized nonlinearly to MNI152NLin6Asym space using ANTs 2.2.0. Each functional run was corrected for fieldmap distortions, rigidly coregistered to the T1, motion corrected, and normalized to standard space. ICA-AROMA was run to generate aggressive noise regressors. Anatomical CompCor was run and the top 5 principal components of both CSF and white matter were retained. Functional data were transformed to CIFTI space using HCP's Connectome Workbench. All preprocessed data were visually inspected at two separate stages to ensure only high-quality data was included: After co-registration of the functional data to the structural data and after registration of the functional data to MNI template space.

Connectomes were generated for each functional run using the Gordon 333 parcel atlas⁷¹, augmented with parcels from high-resolution subcortical⁷² and cerebellar⁷³ atlases. Volumes exceeding a framewise displacement threshold of 0.5mm were marked to be censored. Covariates were regressed out of the time series in a single step⁷⁴, including: linear trend, 24 motion parameters (original translations/rotations + derivatives + quadratics), aCompCorr 5 CSF and 5 WM components and ICA-AROMA aggressive components, high pass filtering at 0.008Hz, and censored volumes. Next, correlation matrices were calculated for each run. Each matrix was then Fisher r-to-z transformed, and then averaged across runs for each subject yielding their final connectome.

3. Bifactor Modeling of the ABCD Neurocognition Task Battery

Preliminary exploratory factor analyses (EFA) were first conducted (maximum likelihood estimation with oblique geomin rotation) to explore the latent structure of the 11 ABCD neurocognitive tasks. In addition, a parallel analysis with 1,000 random draws was also run that suggested the presence of three factors. The optimal factor structure was determined by considering the scree plot, parallel analysis, model fit, and the interpretability of different factor solutions (including consistency with past research). Overall, three broad factors best characterize these tasks, corresponding to spatial/verbal, speed/flexibility, and learning/memory; in the bifactor models these three factors served as the specific factors. Follow-up confirmatory factor analysis showed very good fit by conventional standards (χ^2 (34)=443.16, $p<0.001$, RMSEA=0.03, CFI=0.99, TLI=0.98, SRMR=0.02), with the general factor capturing 75% of the variation in task scores (coefficient ω hierarchical³⁴), and the three

domain-specific factors together accounting for 13% of the variation in task scores (see Figure S3).

4. Inclusion/Exclusion

There are 11,875 subjects in the ABCD Release 2.0.1 dataset. Screening was initially done using ABCD raw QC to limit to subjects with 2 or more good runs of resting data as well as a good T1 and T2 image (QC score, protocol compliance score, and complete all =1). This resulted in 9598 subjects with 2 or more runs that entered preprocessing. Each run was subsequently visually inspected for registration as well as for warping quality, and only those subjects who still had 2 or more good runs were retained (N=8858). After connectome generation, runs were excluded if they had less than 4 minutes of uncensored data, and next subjects were retained only if they had 2 or more good runs (N=6568). Next, sites with fewer than 75 subjects were dropped. This left us with N=6449 subjects across 19 sites to enter PCA. Finally, subjects with missing values for neurocognitive scores or nuisance covariates were excluded. This left 5937 subjects to enter our main BBS predictive modeling analysis. Number of subjects for alternative analysis streams conducted as part of our robustness checks are reported in Table 1.

5. Constructing a Brain Basis Set (BBS)

BBS is a validated multivariate method that uses principal components dimensionality reduction to produce a basis set of components that are then associated with phenotypes^{4,35}. We select the top 250 components for our basis set based on previous work showing that 50-100 components per 1000 subjects captures most meaningful variance without overfitting^{35,36}.

6. Leave-One-Site-Out Cross Validation

To assess generalizability of BBS-based regression models, we used leave-one-site-out cross-validation. In each fold of the cross-validation, data from one of the 19 sites served as the held-out test dataset and data from the other 18 sites served as the training dataset. Additionally, to ensure separation of train and test datasets, at each fold of the cross-validation, a new PCA was performed on the training dataset yielding a 250-component basis set. We assessed the performance of BBS models with Pearson's correlation, cross-validated r-squared (see Supplement), and mean squared error.

7. Accounting for Covariates in Cross-Validation Framework

In each fold of cross-validation, BBS models were trained in the train partition with the following covariates: gender, race, age, age squared, mean FD and mean FD squared. To maintain strict separation between training and test datasets, regression coefficients for the covariates learned from the training sample are applied to the test sample, and the variance they explain is subtracted away. This procedure, described in detail in our previous publication³⁶, yields an estimate of the contribution of brain components alone in predicting test subject P factor scores, excluding the contribution of the nuisance covariates. Note that by employing leave-one-site-out, members of twinships and sibships are never present in both training and test samples.

8. Permutation Testing

We assessed the significance of all cross-validation-based correlations with non-parametric permutation tests in which we randomly permuted the 5,880 subjects' P factor scores 10,000 times, as described in detail in the Supplement.

9. Consensus Connectome Maps

To help convey overall patterns across entire BBS multiple regression models with 250 components, we constructed “consensus” component maps. We used multi-level multiple regression modeling, with the neurocognitive scores as outcome variables and expression scores for the 250 components as predictors. Gender, race, age, mean FD, and mean FD squared were entered as fixed effect covariates, with family id and ABCD site entered as random effects (family nested within site). We next multiplied each connectomic component with its associated regression coefficient. We then summed across all 250 components yielding a single map, and thresholded the entries at $z=2$. We in addition created circular visualizations of consensus connectomes (see Figure 4, right panel) using the *circlize* software library in R, restricting the visualization to a subset of networks of interest.

10. Identifying Highly Varying Network Pairs

We quantified variation of pairs of networks across 15 connectomic neuromarkers (4 for the factor model and 11 for individual tasks). For each neuromarker, we summed suprathreshold connections for each pair of networks separately for positive and negative connections, yielding 240 values per neuromarker. We next calculated the variance of these values across the 15 neuromarkers. We selected the 21 most varying network pairs (which together accounted for over 50% of the variance across the 15 neuromarkers) and displayed the number of suprathreshold connections for each network pair for each neuromarker with a bubble heat map.

11. Data Availability

The ABCD data used in this report came from NDA Study 721, 10.15154/1504041, which can be found at <https://nda.nih.gov/study.html?id=721>.

COMPETING INTERESTS

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: CS, MA, AT, SR, MH; Methodology: CS, DC, MA, AT, SR; Formal Analysis: CS, DC, MA, AT, SR; Data Curation: MA, SR, TG; Writing – Original Draft: CS; Writing – Reviewing and Editing: AW, CS, LH, MA, MH, SR, TG; Visualization: MA, AT, SR; Supervision: CS, MH; Funding Acquisition: CS, MH.

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