SUPPLEMENTARY INFORMATION

Brain-based Predictions of Psychiatric Illness-Linked Behaviors Across the Sexes

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Supplemental Methods

Sample Construction

The ABCD dataset is a large community-based sample of children and adolescents who were assessed on a comprehensive set of neuroimaging, behavioral, developmental, and psychiatric batteries. This study used minimally preprocessed data from the Adolescent Brain Cognitive Development (ABCD). Specifically, data were obtained from the NIMH Data Archive for ABCD Release 2.0.1. The ABCD 2.0.1 Data Release included a total of 11,875 participants. MR images were acquired across 21 sites in the United States using harmonized protocols for GE and Siemens scanners. In line with our prior work(1, 2), exclusion criteria were used to ensure quality control. As recommended by the ABCD consortium, we excluded individuals who were scanned using Philips scanners due to incorrect preprocessing [\(https://github.com/ABCD-](https://github.com/ABCD-STUDY/fMRI-cleanup)[STUDY/fMRI-cleanup\)](https://github.com/ABCD-STUDY/fMRI-cleanup). For the T1 data, individuals who did not pass recon-all quality control(3) were removed. For the functional connectivity data, functional runs with boundary-based registration (BBR) costs greater than 0.6 were excluded. Further, volumes with framewise displacement (FD) > 0.3 mm or voxel-wise differentiated signal variance (DVARS) > 50, along with one volume before and two volumes after, were marked as outliers and subsequently censored. Uncensored segments of data containing fewer than five contiguous volumes were also censored(4, 5). Functional runs with over half of their volumes censored and/or max FD > 5mm were removed. Individuals who did not have at least 4 minutes of data were also excluded from further analysis. Individuals who did not have all behavioral measures were also excluded. Finally, we excluded siblings to prevent unintended biases due to inherent heritability in neurobiological and/or behavioral measures. Our final sample included comprised 5260 children (2689 males, 2571 females; 9-10 years old).

Behavioral Data

The Child Behavior Checklist is a widely used clinical scale for identifying problematic behaviors in children and adolescents(6), and includes eight empirically-based syndrome scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems Rule-Breaking Behavior, and Aggressive Behavior. These scores are further summarized into Internalizing, Externalizing, and Total Problems. The Internalizing domain summarizes Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints. The Externalizing domains summarizes Rule-Breaking and Aggressive Behaviors. Finally, the Total Problems score is based on responses to all of the eight syndrome scales. The CBCL also includes six Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented scales consistent with DSM-5 categories: Affective (Depressive), Anxiety, Somatic, Oppositional Defiant, Conduct, and Attention Deficit/Hyperactivity (ADHD) Disorders.

Preprocessing

Minimally preprocessed T1 data were further processed using FreeSurfer 5.3.0(7-10) to generate cortical surface meshes for each individual, which were then registered to a common spherical coordinate system(9, 10). Minimally preprocessed fMRI data were further processed with the following steps: (1) removal of initial frames, with the number of frames removed depending on the type of scanner(3) and (2) alignment with the T1 images using boundarybased registration(11) with FsFast. Framewise displacement (FD)(12) and voxel-wise differentiated signal variance (DVARS)(13) were computed using fsl_motion_outliers. Respiratory pseudomotion was filtered out using a bandstop filter (0.31-0.43 Hz) before computing FD(14-16). A total of 18 nuisance covariates were also regressed out of the fMRI time series: global signal, six motion correction parameters, averaged ventricular signal, averaged white matter signal, and their temporal derivatives. Regression coefficients were estimated from the non-censored volumes. Global signal regression was performance as we are interested in behavioral prediction, and global signal regression has been shown to improve behavioral prediction performance(17, 18). Finally, the brain scans were interpolated across censored frames using least squares spectral estimation(19), band-pass filtered (0.009 Hz ≤ f ≤ 0.08 Hz), projected onto FreeSurfer fsaverage6 surface space, and smoothed using a 6 mm fullwidth half maximum kernel. All processing as described was completed on a local server.

Predictive Modeling

For each sex, we split the data into 100 distinct train and test sets (at approximately a 2:1 ratio) without replacement. Imaging site was considered when splitting the data such that we placed all participants from a given site either in the train or test set but not split across the two. Within each train set, we optimized the regularization parameter using three-fold cross-validation while similarly accounting for imaging site as in the initial train-test split. Once optimized, we evaluated models on the corresponding test set. We repeated this process for each of 100 distinct train-test splits to obtain a distribution of prediction accuracy. To evaluate model significance, for each set of predictive models, a corresponding set of null models was generated as follows: the behavioral score was randomly permuted 1000 times, and each permutation was used to train and test a null model using a randomly selected regularization parameter from the set of selected parameters from the original model. Prediction accuracy from each of the null models was then compared to the average accuracy from the corresponding distribution of model accuracies and model generalizabilities from the original (true) models. The p-value for each model's significance is defined as the proportion of null models with prediction accuracies greater than or equal to corresponding average accuracy from the original (true) distribution. All p-values were corrected for multiple comparisons across all measures of model accuracy and generalizability (i.e., 17 train behaviors x 2 train sexes x 17 test behaviors x 2 test sexes = 1156 comparisons) using the Benjamini-Hochberg False Discovery Rate (q=0.05) procedure(20).

Feature Weights

We used the Haufe transformation(21) to transform feature weights obtained from the linear ridge regression models to increase their interpretability and reliability(2, 22, 23). For each train split, we used feature weights obtained from the model, W , the covariance of the input data (functional connectivity), Σ_{x} , and the covariance of the output data (behavioral score), Σ_{y} , to compute the Haufe-transformed feature weights, A, as follows:

$A = \Sigma_x W \Sigma_y^{-1}$

We then averaged these Haufe-transformed feature weights across the 100 splits to obtain a mean feature importance value. We computed full correlations between mean feature importance obtained from the different models to evaluate whether they relied on shared or unique features to predict the behavioral scores. For all models, we also summarized pairwise regional feature importance at a network-level to support interpretability as previously described(24). Briefly, cortical parcels were assigned to one of 17 networks from the Yeo 17 network parcellation(25), and subcortical, brainstem, and cerebellar parcels were assigned to a single subcortical network for convenience. Regional pairwise positive and negative feature weights were separately averaged to yield network-level estimates of positive and negative associations between functional connectivity and behavioral scores.

Supplementary Table 1: Demographic information.

Demographic information (age, race/ethnicity, and socioeconomic status/income) for all subjects from the ABCD 2.0.1 Data Release. Demographic information are reported separately for subjects who are included (n=5260) and excluded (n=6615) from these analyses based on the criteria described in the Supplemental Methods. Data are further reported separately for males and females in both the included and excluded criteria. Reported proportions (%) may not sum to exactly 100% due to rounding.

Supplementary Table 2: Males and females exhibit largely overlapping behavioral scores. Mean, median, standard deviation (SD), interquartile range (IQR), and corrected p values (*p*) corresponding to significant sex differences in behavioral scores. Sex differences with corrected p values < 0.01 were considered statistically significant. Behaviors with significant sex differences are bolded.

Supplementary Table 3: Motion is not related to psychopathological behavior.

Correlation coefficient between mean framewise displacement (FD) and behavioral scores for males and females.

Supplementary Table 4: Shared network-level features underlie psychiatric illness-linked behaviors across the sexes.

Correlation coefficient between network-level feature weights from models trained on males and females. Correlations were computed separately for positive associations and negative associations. Corresponding network-level positive and negative associations for all behaviors for males and females are shown in Figures 5-7 and Supplementary Figures 1-14.

A. Distribution of Behavioral Scores

Supplementary Figure 1: Males and females exhibit similar behavioral trends.

(A) Violin plots display the distribution of all behavioral scores for males (left) and females (right). The shape of the violin plots indicates the entire distribution of values, dashed lines indicate the median, and dotted lines indicate the interquartile range. (B) The 2D grids display the correlation coefficient for each pair of behavioral scores for males (left) and females (right). ADHD – Attention deficit/hyperactivity disorder.

Supplementary Figure 2: Shared network-level functional connections underlying internalizing behaviors in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and internalizing behaviors in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive}=0.66. Correlations between negative associations across sexes, r_{negative}=0.72.

Supplementary Figure 3: Shared network-level functional connections underlying anxious/depressed behaviors in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and anxious/depressed behaviors in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, $r_{positive} = 0.55$. Correlations between negative associations across sexes, r_{negative}=0.73.

Supplementary Figure 4: Shared network-level functional connections underlying somatic complaints in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and somatic complaints in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.78. Correlations between negative associations across sexes, r_{negative} =0.54.

Supplementary Figure 5: Shared network-level functional connections underlying externalizing behaviors in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and externalizing behaviors in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.87. Correlations between negative associations across sexes, r_{negative} =0.89.

Supplementary Figure 6: Shared network-level functional connections underlying aggressive behaviors in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and aggressive behaviors in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.80. Correlations between negative associations across sexes, r_{negative} =0.75.

Supplementary Figure 7: Shared network-level functional connections underlying thought problems in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and thought problems in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.91. Correlations between negative associations across sexes, r_{negative} =0.86.

Supplementary Figure 8: Shared network-level functional connections underlie attention problems in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and attention problems in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.95. Correlations between negative associations across sexes, r_{negative} =0.94.

Supplementary Figure 9: Shared network-level functional connections underlying social problems in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and social problems in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.82. Correlations between negative associations across sexes, r_{negative} =0.90.

Supplementary Figure 10: Shared network-level functional connections underlying total problems in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and total problems in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.95. Correlations between negative associations across sexes, r_{negative} =0.88.

Supplementary Figure 11: Shared network-level functional connections underlying affective scores in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and affective scores in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.81. Correlations between negative associations across sexes, r_{negative} =0.75.

Supplementary Figure 12: Shared network-level functional connections underlying anxiety scores in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and anxiety scores in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.38. Correlations between negative associations across sexes, r_{negative} =0.53.

Supplementary Figure 13: Shared network-level functional connections underlying somatic scores in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and somatic scores in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.76. Correlations between negative associations across sexes, r_{negative} =0.56.

Supplementary Figure 14: Shared network-level functional connections underlying oppositional defiant scores in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and oppositional defiant scores in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.50. Correlations between negative associations across sexes, r_{negative}=0.27.

Supplementary Figure 15: Shared network-level functional connections underlying conduct scores in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and conduct scores in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.89. Correlations between negative associations across sexes, r_{negative} =0.93.

Supplementary Figure 16: Shared network-level functional connections underlying ADHD scores in males and females.

Positive (top) and negative (bottom) associations between network-level functional connectivity and ADHD scores in males (left) and females (right). Regional feature weights were summarized to a network-level by assigning cortical regions to one of 17 Yeo networks, and subcortical regions to a subcortical network. Colors next to the network labels along the vertical and horizontal axes correspond to the network colors from Figure 1C. Warmer colors within the heatmap indicate a positive association and cooler colors indicate a negative association. For visualization, values within each matrix were divided by the absolute maximum value across the positive and negative matrices for each sex. Correlations between positive associations across sexes, r_{positive} =0.91. Correlations between negative associations across sexes, r_{negative} =0.94.

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