

Connectome-Based Predictive Modeling and Aggressive in Adolescence Brain

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Using connectome-based predictive modeling to predict individual behavior from brain connectivity



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Using connectome-based predictive modeling to predict individual behavior from brain connectivity

[Xilin Shen](#), [Emily S Finn](#), [Dustin Scheinost](#), [Monica D Rosenberg](#), [Marvin M Chun](#), [Xenophon Papademetris](#) & [R Todd Constable](#) 

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Todd Constable is a Professor of Radiology and Biomedical Imaging and of Neurosurgery; Director of MRI Research that focused on technical advances in imaging, such as fast imaging sequences and methodology development applied to the body or the brain. One lab is a neuroscience lab focused on mapping the functional organization of the brain through functional MRI measurements and understanding the relationship between this functional organization and behavior. Other lab is focused on the development of novel MRI devices with projects around low field MRI's that can be placed in doctor's offices, with the potential to make MRI much more accessible than it is in its current form.

Large-scale functional brain networks of maladaptive childhood aggression identified by connectome-based predictive modeling



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Large-scale functional brain networks of maladaptive childhood aggression identified by connectome-based predictive modeling

[Karim Ibrahim](#) ✉, [Stephanie Noble](#), [George He](#), [Cheryl Lacadie](#), [Michael J. Crowley](#), [Gregory McCarthy](#), [Dustin Scheinost](#) & [Denis G. Sukhodolsky](#) ✉

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Denis Sukhodolsky is an Associate Professor in the Yale Child Study Center. His research concerns the efficacy and biomarkers of behavioral interventions for children with autism spectrum disorder, irritability, and related neurodevelopmental disorders.

Functional connectivity during frustration: a preliminary study of predictive modeling of irritability in youth



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Functional connectivity during frustration: a preliminary study of predictive modeling of irritability in youth

[Dustin Scheinost](#), [Javid Dadashkarimi](#), [Emily S. Finn](#), [Caroline G. Wambach](#), [Caroline MacGillivray](#), [Alexandra L. Roule](#), [Tara A. Niendam](#), [Daniel S. Pine](#), [Melissa A. Brotman](#), [Ellen Leibenluft](#) & [Wan-Ling Tseng](#) ✉

[Neuropsychopharmacology](#) **46**, 1300–1306 (2021) | [Cite this article](#)

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Wan-Ling Tseng is an Assistant Professor at the Yale Child Study Center. Her research focuses on understanding the brain mechanisms mediating abnormal psychological processes associated with irritability and aggression in children and adolescents and how these behaviors and symptoms change over time.

Connectome-based Predictive Modeling (CPM)

Connectome-based Predictive Modeling (CPM) is a data-driven protocol for developing predictive models of brain-behavior relationships from connectivity data using cross-validation.

The protocol includes the following steps:

- (1) feature selection,
- (2) feature summarization,
- (3) model building,
- (4) assessment of prediction significance.

CPM and Multimodal Data

Resting-state fMRI

Task fMRI

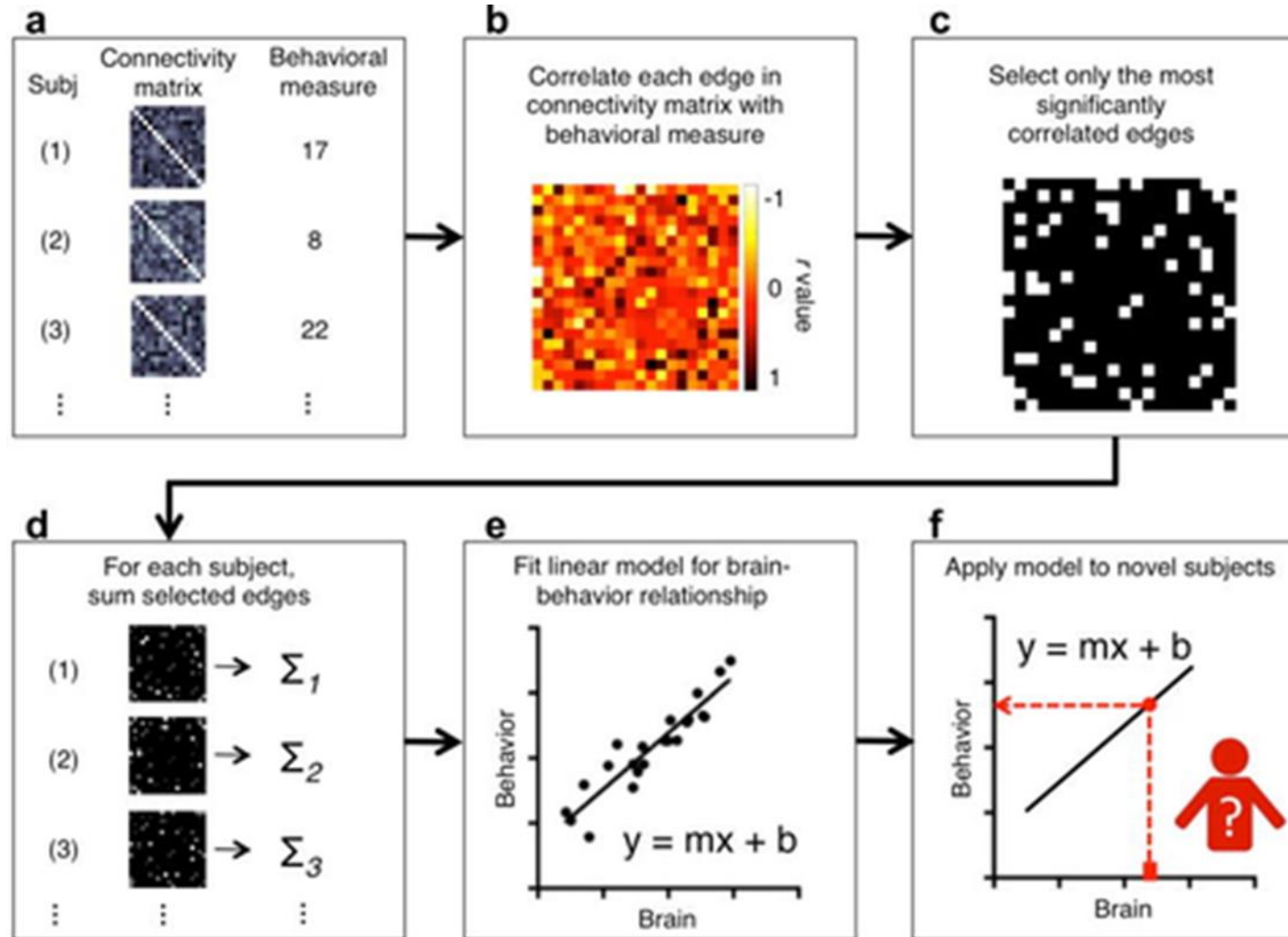
DTI (Diffusion Tensor Imaging)

EEG (ElectroEncephaloGram)

MEG (MagnetoEncephaloGraphy)

fNIRS (functional Near-Infrared Spectroscopy)

Schematic of CPM



Scripts and Tools

BioImage Suite is a web-based medical image analysis software package with image processing , image registration and visualization capabilities.

NITRC: <https://www.nitrc.org/projects/bioimagesuite/>

GitHub: <https://github.com/YaleMRRC/CPM>

Web: <https://bioimagesuiteweb.github.io/webapp/>

Manual: <https://bioimagesuiteweb.github.io/bisweb-manual/>



[\[BioImage Suite Web Manual Table Of Contents \]](#)

Why to Predictive Power of Brain-Behavior Correlations

Standpoint of Scientific Rigor

Cross-validation is a more conservative way to infer the presence of a brain–behavior relationship than is correlation.

Cross-validation is designed to protect against overfitting by testing the strength of the relationship in a novel sample, increasing the likelihood of replication in future studies.

A Practical Standpoint

Establishing predictive power is necessary to translate neuroimaging findings into tools with practical utility.

In part, fMRI has struggled as a diagnostic tool because of low generalizability of results to novel subjects.

Comparison with other Methods

Multivariate-Prediction and Univariate-Regression Method

Support Vector Regression (SVR)

The strengths of CPM include its use of linear operations and its purely data-driven approach.

First, from a practical standpoint, CPM is simpler to implement and requires less expertise in machine learning.

The second major advantage of the CPM approach, as compared with multivariate methods, is that the predictive networks obtained by CPM can be clearly interpreted.

Limitations

1. The predictive models may not be optimal for capturing complex, nonlinear relationships between connectivity and behavior.
2. The predictive models tend to produce predicted values with a range that is smaller than the range of true values.
3. Multivariate approaches may outperform CPM in terms of prediction accuracy for certain data sets. In deciding whether CPM is suitable for their purposes.

Recent literature on machine learning has suggested that combined results from different prediction models (classification models) usually outperform results obtained from a single 'best' approach.

Experimental design

Sample size

These methods have the most utility in studies with moderate to large sample sizes ($N > 100$).

The time of scanning and of behavioral testing

In most cases, the neuroimaging data and behavioral measures should be collected in a short temporal window in order to minimize differences in 'state' behaviors between the time of scanning and of behavioral testing.

CPM may also be applied when 'trait' behavioral measures are collected a considerable time after scanning, such as using connectivity data to predict long-term symptom changes after an intervention.

Discovery cohort and test cohort

A particularly powerful experimental design is to use two (or more) data sets, with one data set serving as the discovery cohort on which the model is built, and the second serving as the test cohort.

Evaluating the predictive power of CPM

The correlation between predicted values and true values is calculated as a test statistic.

A permutation test should be used to generate an empirical null distribution to assess the significance.

Head movement and other potential variables

Researchers need to ensure that motion is not correlated with the behavioral data and that connectome-based models cannot predict motion.

If there is an association between motion and the behavioral or connectivity data, additional controls for motion, such as removing high-motion subjects from analysis, need to be performed.

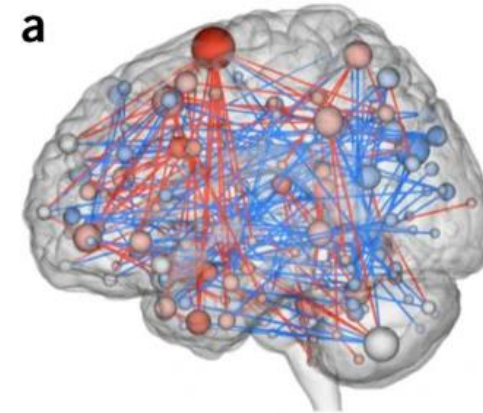
Other potential variables that could be correlated with the behavior of interest include age, gender, and IQ. The effects of these confounding factors could be removed using partial correlation.

Visualizing selected connectivity features

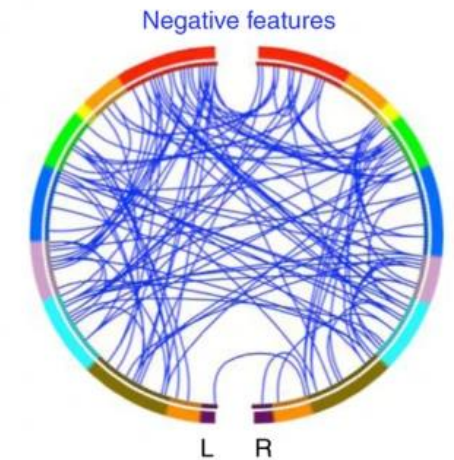
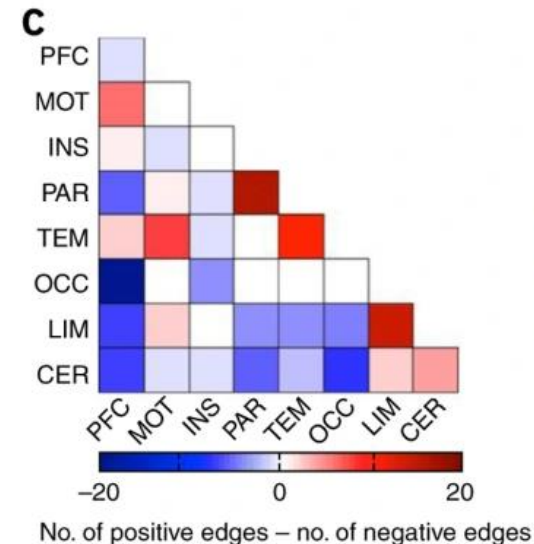
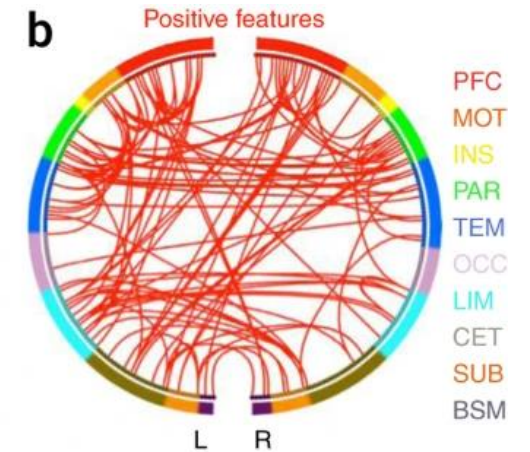
The most conservative approach is to visualize only edges that were selected in all iterations of the analysis (i.e., the overlap of all the models).

A looser threshold may be set such that edges are included if they appear in at least 90% of the iterations.

glass brain plots



circle plots



matrix plots

Materials

Individual connectivity matrices

Behavioral measures

Head-motion estimates

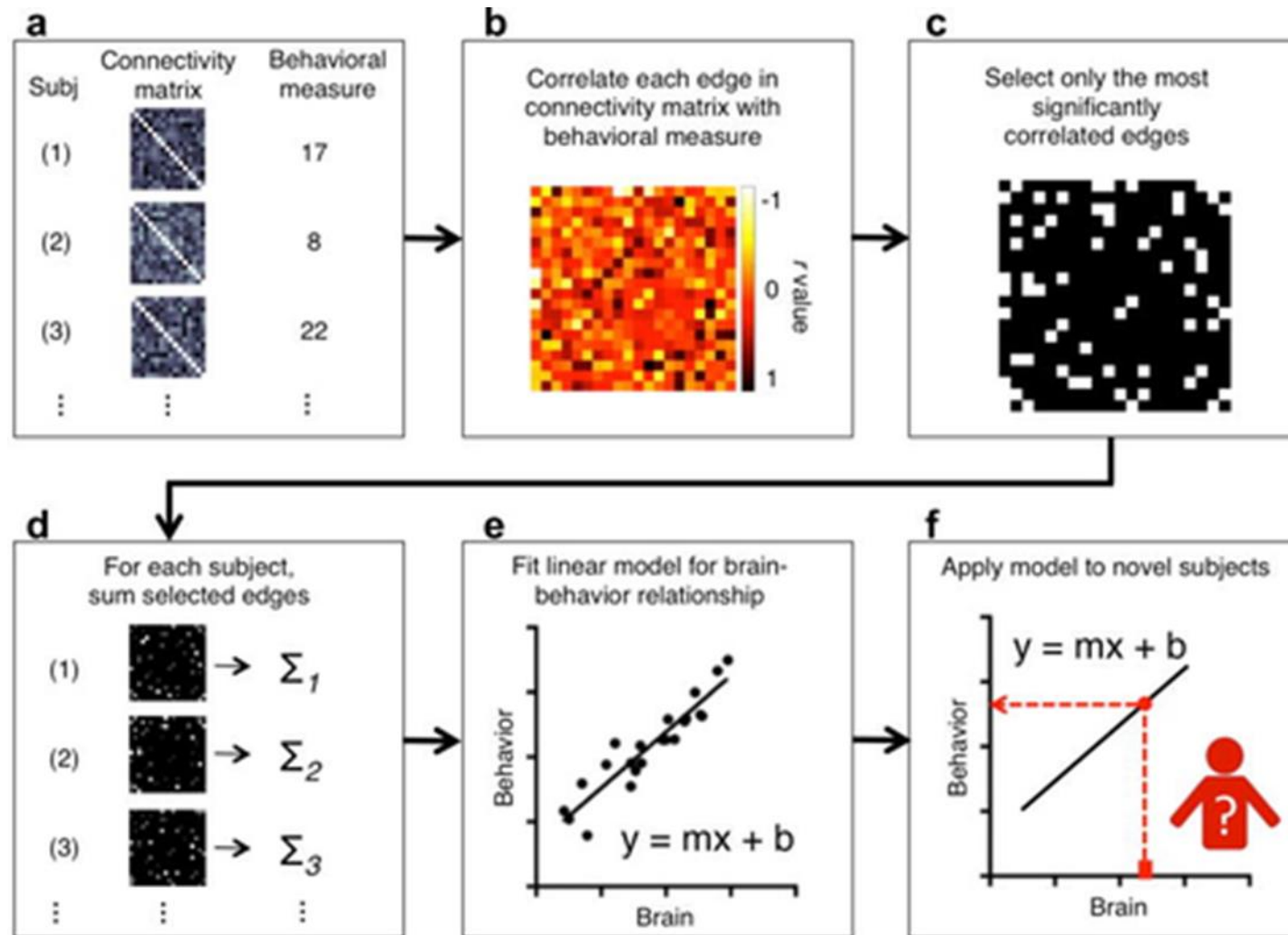
Anatomical labels

Network labels

Build the predictive model with cross-validation using CPM

Permutation testing

Online visualization tool

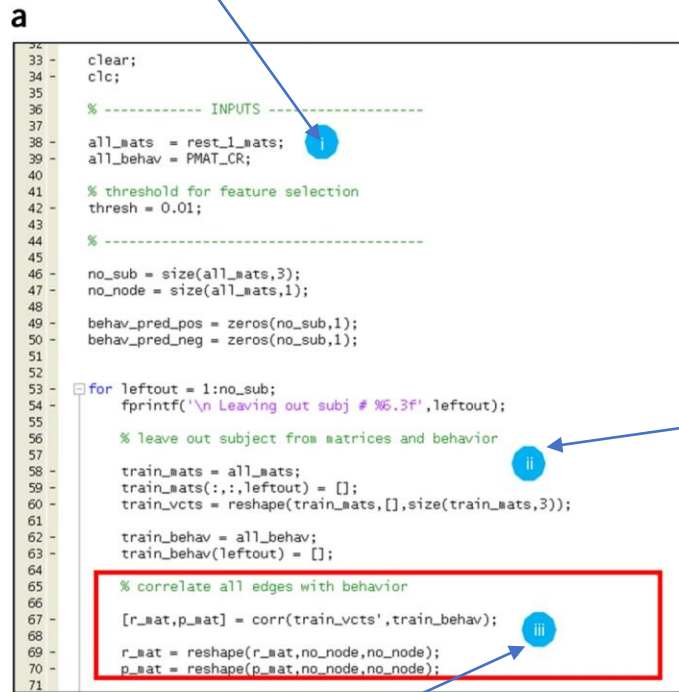


Overview of the Procedure

Load connectivity matrices and behavioral data into memory

a

```
33 - clear;
34 - clc;
35
36 % ----- INPUTS -----
37
38 all_mats = rest1_mats;
39 all_behav = PMAT_CR;
40
41 % threshold for feature selection
42 thresh = 0.01;
43
44 % -----
45
46 no_sub = size(all_mats,3);
47 no_node = size(all_mats,1);
48
49 behav_pred_pos = zeros(no_sub,1);
50 behav_pred_neg = zeros(no_sub,1);
51
52
53 for leftout = 1:no_sub;
54     fprintf('\n Leaving out subj # %5.3f',leftout);
55
56     % leave out subject from matrices and behavior
57
58     train_mats = all_mats;
59     train_mats(:, :, leftout) = [];
60     train_vcts = reshape(train_mats, [], size(train_mats,3));
61
62     train_behav = all_behav;
63     train_behav(leftout) = [];
64
65     % correlate all edges with behavior
66
67     [r_mat, p_mat] = corr(train_vcts', train_behav);
68
69     r_mat = reshape(r_mat, no_node, no_node);
70     p_mat = reshape(p_mat, no_node, no_node);
71
```



b

Alternative 1

```
65 % correlate all edges with behavior using rank correlation
66
67 [r_mat, p_mat] = corr(train_vcts', train_behav, 'type', 'Spearman');
68
69 r_mat = reshape(r_mat, no_node, no_node);
70 p_mat = reshape(p_mat, no_node, no_node);
71
```

c

Alternative 2

```
65 % correlate all edges with behavior using partial correlation
66
67 train_age = all_age;
68 train_age(leftout) = [];
69
70 [r_mat, p_mat] = partialcorr(train_vcts', train_behav, train_age);
71
72 r_mat = reshape(r_mat, no_node, no_node);
73 p_mat = reshape(p_mat, no_node, no_node);
74
```

d

Alternative 3

```
65 % correlate all edges with behavior using robust regression
66
67 edge_no = size(train_vcts,1);
68 r_mat = zeros(1, edge_no);
69 p_mat = zeros(1, edge_no);
70
71 for edge_i = 1: edge_no;
72     [~, stats] = robustfit(train_vcts(edge_i,:), train_behav);
73     cur_t = stats.t(2);
74     r_mat(edge_i) = sign(cur_t)*sqrt(cur_t^2/(no_sub-1-2+cur_t^2));
75     p_mat(edge_i) = 2*tcdf(cur_t, no_sub-1-2); %two tailed
76 end
77
78 r_mat = reshape(r_mat, no_node, no_node);
79 p_mat = reshape(p_mat, no_node, no_node);
80
```

Divide data into training and testing sets for cross-validation. In this example, leave-one-out cross-validation is used

Relate connectivity to behavior

Edge selection

Forming single-subject
summary values

Model fitting

Prediction in novel subjects

a

```
68 - r_mat = reshape(r_mat,no_node,no_node);
69 - p_mat = reshape(p_mat,no_node,no_node);
70 -
71 -
72 - % set threshold and define masks
73 -
74 - pos_mask = zeros(no_node,no_node);
75 - neg_mask = zeros(no_node,no_node);
76 -
77 - pos_edges = find(r_mat > 0 & p_mat < thresh);
78 - neg_edges = find(r_mat < 0 & p_mat < thresh);
79 -
80 - pos_mask(pos_edges) = 1;
81 - neg_mask(neg_edges) = 1;
82 -
83 - % get sum of all edges in TRAIN subs (divide by 2 to control for the
84 - % fact that matrices are symmetric)
85 -
86 - train_sumpos = zeros(no_sub-1,1);
87 - train_sumneg = zeros(no_sub-1,1);
88 -
89 - for ss = 1:size(train_sumpos);
90 -     train_sumpos(ss) = sum(sum(train_mats(:,:,ss).*pos_mask))/2;
91 -     train_sumneg(ss) = sum(sum(train_mats(:,:,ss).*neg_mask))/2;
92 - end
93 -
94 - % build model on TRAIN subs
95 -
96 - fit_pos = polyfit(train_sumpos, train_behav,1);
97 - fit_neg = polyfit(train_sumneg, train_behav,1);
98 -
99 - % run model on TEST sub
100 -
101 - test_mat = all_mats(:,:,leftout);
102 - test_sumpos = sum(sum(test_mat.*pos_mask))/2;
103 - test_sumneg = sum(sum(test_mat.*neg_mask))/2;
104 -
105 - behav_pred_pos(leftout) = fit_pos(1)*test_sumpos + fit_pos(2);
106 - behav_pred_neg(leftout) = fit_neg(1)*test_sumneg + fit_neg(2);
107 -
108 - end
109 -
110 - % compare predicted and observed scores
111 -
112 - [R_pos, P_pos] = corr(behav_pred_pos,all_behav);
113 - [R_neg, P_neg] = corr(behav_pred_neg,all_behav);
114 -
115 - figure(1); plot(behav_pred_pos,all_behav,'r. '); %line
116 - figure(2); plot(behav_pred_neg,all_behav,'b. '); %line
117 -
118 -
119 -
120 -
121 -
```

b

Alternative

```
80 - %-----sigmoidal weighting-----
81 - pos_edges = find(r_mat > 0 );
82 - neg_edges = find(r_mat < 0 );
83 -
84 - % covert p threshold to r threshold
85 - T = tinv(thresh/2, no_sub-1-2);
86 - R = sqrt(T^2/(no_sub-1-2+T^2));
87 -
88 - % create a weighted mask using sigmoidal
89 - % weight = 0.5, when correlation = R/3;
90 - % weight = 0.88, when correlation = R;
91 - pos_mask(pos_edges) = sigmf( r_mat(pos_e
92 - neg_mask(neg_edges) = sigmf( r_mat(neg_e
93 - %-----sigmoidal weighting-----
```

c

Alternative

```
92 - % build model on TRAIN subs
93 - % combining both positive and negative features
94 - b = regress(train_behav, [train_sumpos, train_sumneg]);
95 -
96 - % run model on TEST sub
97 -
98 -
99 - test_mat = all_mats(:,:,leftout);
100 - test_sumpos = sum(sum(test_mat.*pos_mask))/2;
101 - test_sumneg = sum(sum(test_mat.*neg_mask))/2;
102 -
103 - behav_pred(leftout) = b(1)*test_sumpos + b(2)*test_sumneg;
104 -
105 -
106 - end
107 -
```

d

Alternative

```
133 - % compare predicted and observed scores
134 -
```

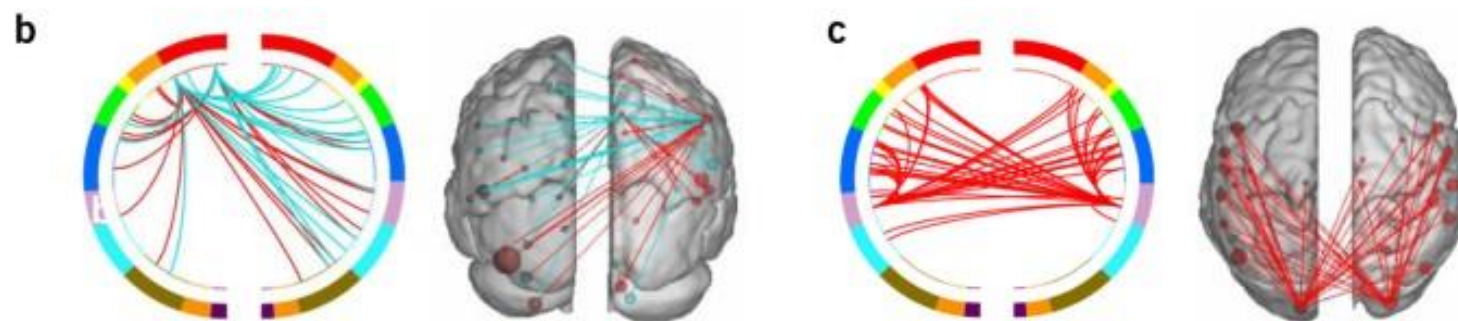
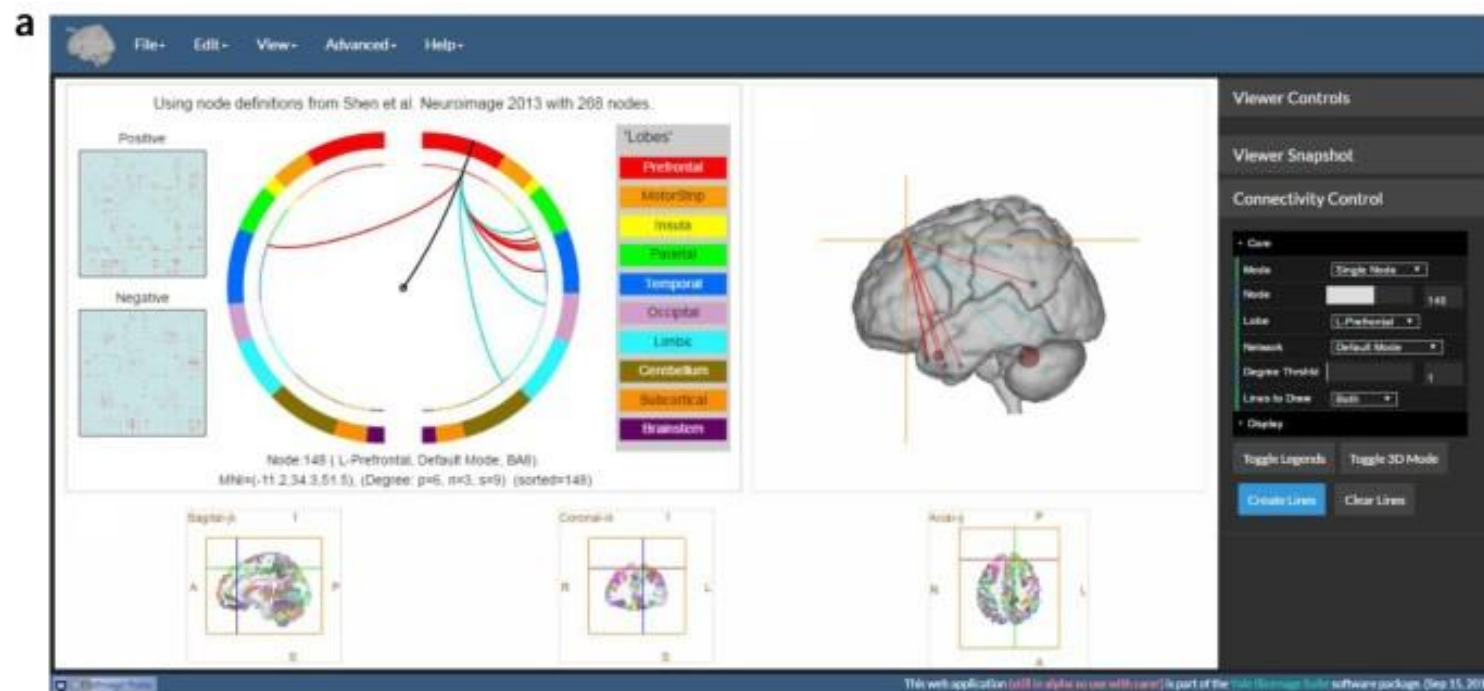
Calculate the true prediction correlation

Shuffle data labels, calculate correlation coefficient, and repeat for 100–10,000 iterations

Calculate P values

```
37
38 - all_mats = rest_1_mats;
39 - all_behav = PMAT_CR;
40
41 - no_sub = size(all_mats,3);
42
43 - % calculate the true prediction correlation
44 - [true_prediction_r_pos, true_prediction_r_neg] = predict_behavior(all_mats, all_behav);
45
46 - % number of iterations for permutation testing
47 - no_iterations = 1000;
48 - prediction_r = zeros(no_iterations,2);
49 - prediction_r(1,1) = true_prediction_r_pos;
50 - prediction_r(1,2) = true_prediction_r_neg;
51
52 - % create estimate distribution of the test statistic
53 - % via random shuffles of data labels
54 - for it=2:no_iterations
55 -     fprintf('\n Performing iteration %d out of %d', it, no_iterations);
56 -     new_behav = all_behav(randperm(no_sub));
57 -     [prediction_r(it,1), prediction_r(it,2)] = predict_behavior(all_mats, new_behav);
58 - end
59
60 - sorted_prediction_r_pos = sort(prediction_r(:,1),'descend');
61 - position_pos = find(sorted_prediction_r_pos==true_prediction_r_pos);
62 - pval_pos = position_pos(1)/no_iterations;
63
64 - sorted_prediction_r_neg = sort(prediction_r(:,2),'descend');
65 - position_neg = find(sorted_prediction_r_neg==true_prediction_r_neg);
66 - pval_neg = position_neg(1)/no_iterations;
67
```

Visualizing selected connectivity features



Paper List

Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity

A neuromarker of sustained attention from whole-brain functional connectivity

Functional connectivity during frustration: a preliminary study of predictive modeling of irritability in youth

Large-scale functional brain networks of maladaptive childhood aggression identified by connectome-based predictive modeling

Connectome-based individualized prediction of temperament trait scores

Robust prediction of individual creative ability from brain functional connectivity

Brain connectivity fingerprinting and behavioural prediction rest on distinct functional systems of the human connectome

Large-scale functional brain networks of maladaptive childhood aggression identified by connectome-based predictive modeling

The term “aggression” refers to a broad category of behaviors that can result in harm to self or others. **Maladaptive aggression** can also be viewed as the behavioral component of anger outbursts, which includes developmentally and socially inappropriate verbal behaviors, such as yelling and verbal threats, and physical behaviors, such as pushing, hitting, or kicking.



Maladaptive aggression

Introduction

Maladaptive aggression is among the most common reasons for referral to mental health services and spans across childhood psychiatric disorders, most notably disruptive behavior disorders, mood disorders, and autism spectrum disorder.

Neuroimaging studies have identified neural dysfunction in ventral and lateral prefrontal regulatory regions in children with aggressive behavior. the search for brain-based predictors has not yielded reliable neural biomarkers of childhood aggression that could inform treatment.

While previous research has focused on specific brain regions, the new study identifies patterns of neural connections across the entire brain that are linked to aggressive behavior in children.

Participants

Variable	Total sample (N = 129)	Aggressive behavior (n = 100)	Healthy controls (n = 29)	p value ^b
Age, years (SD)	11.9 (2.2)	11.7 (2.3)	12.8 (1.8)	0.02 ^c
Male, %	69	73	55.2	0.07
Mean IQ ^a (SD)	107.8 (13.8)	106.4 (14.1)	112.5 (12.3)	0.04 ^c
Race, %				0.45
White	76	78	69	
Black	13.2	12	17.2	
American Indian/Alaska native	1.6	2	0	
Asian/Pacific Islander	1.6	2	0	
Other/more than one race	7.8	6	13.8	
Ethnicity				1
Hispanic	15.5	16	13.8	
Non-Hispanic	84.5	84	86.2	
Mean CBCL aggressive behavior T score (SD)	69.8 (12.2)	75.3 (7.6)	51 (2.7)	<0.001 ^d
Mean CBCL internalizing behavior T score (SD)	58.6 (13.1)	63.3 (10.3)	42.4 (7.3)	<0.001 ^d
Mean SRS-2 SCI total T score (SD)	60.7 (13.8)	65.5 (11.3)	44.1 (7.8)	<0.001 ^d
RPQ aggression total (SD)	15.7 (9.3)	19.4 (6.9)	2.8 (3.1)	

Variable	Total sample (N = 129)	Aggressive behavior (n = 100)
DSM-5 diagnoses ^e , %		
Oppositional defiant disorder		76
Conduct disorder		4
DBD-NOS		3
DMDD		18
ASD		18
ADHD		78
Anxiety disorder		26
Depression disorder		4
Type of medication, %		
Stimulants		31
Antidepressant		13
Neuroleptics		13
Non-stimulants		20
Mood stabilizers		4
Benzodiazepines		2

Measures

The [Reactive-Proactive Aggression Questionnaire \(RPQ\)](#) total score was used as the primary continuous measure of severity of aggressive behavior in CPM analyses.

The RPQ is a 23-item parent-report scale that measures proactive and reactive aggression on a 3-point Likert scale.

Task

Emotionally expressive faces from the NimStim Face Stimulus Set

The task uses a pseudorandomized block design with 12 blocks that each contains two randomly selected faces exhibiting the same expression: 6 calm emotion and 6 fearful emotion blocks. The face-expression pair images are randomly selected throughout the blocks and no individual face-expression image is displayed more than once throughout the paradigm



Data acquisition and preprocessing

Siemens MAGNETOM Tim Trio 3 Tesla scanner

1. The first four volumes of each functional run were discarded to allow for the magnetization to reach a steady state.
2. Functional data were temporally realigned to correct for interleaved slice acquisition.
3. Motion was corrected using FSL MCFLIRT linear realignment tool.
4. Data were spatially smoothed with a 5-mm full width at half maximum isotropic Gaussian kernel with a non-linear high-pass filter (60 s cut-off).
5. Functional images were registered to co-planar images, which were then registered to the high-resolution T1-weighted images and normalized to the Montreal Neurological Institute 152 template.
6. Several covariates of no interest were regressed out from the data including the 12 motion parameters, mean white matter signal, mean cerebrospinal fluid signal, mean global signal, and the linear, quadratic, and cubic drifts.

Global signal regression was performed as it strengthens the association between functional connectivity and behavior, leading to better performing and generalizing predictive models.

There were also no significant correlations between **RPQ aggression severity and motion** ($r = 0.07$, $p = 0.45$) or CBCL aggression severity and motion ($r = 0.02$, $p = 0.81$).

Connectivity matrices and Connectome-based predictive modeling (CPM)

1. Network nodes were defined using the Shen 268-node brain atlas
2. The atlas was warped from MNI space into single-subject space
3. Task connectivity was calculated on the basis of the “raw” task time courses, with no regression of task-evoked activity, which emphasizes individual differences in connectivity
4. This involved computation of the mean time courses for each of the 268 nodes (i.e., averaging the time courses of all constituent voxels)
5. Node-by-node pairwise correlations were computed, and Pearson correlation coefficients were Fisher z-transformed to yield symmetric 268×268 connectivity matrices.

Significance of CPM performance

Model performance was assessed using Pearson's correlation (r) and root mean square error

Permutation testing was performed. To generate null distributions for significance testing, we randomly shuffled the correspondence between behavioral variables and connectivity matrices by permuting subject assignments for behavioral variables 1000 times and re-ran the CPM analysis with the shuffled data. Based on these null distributions, the p values for predictions were calculated

External replication and validation

They applied the CPM aggression network models to a sample from the ABCD study of task-based fMRI from 1701 children (920 females) using the SST and from 1791 children (958 females) using the emotional n-back task (EN-back) (age range 9–10 years).

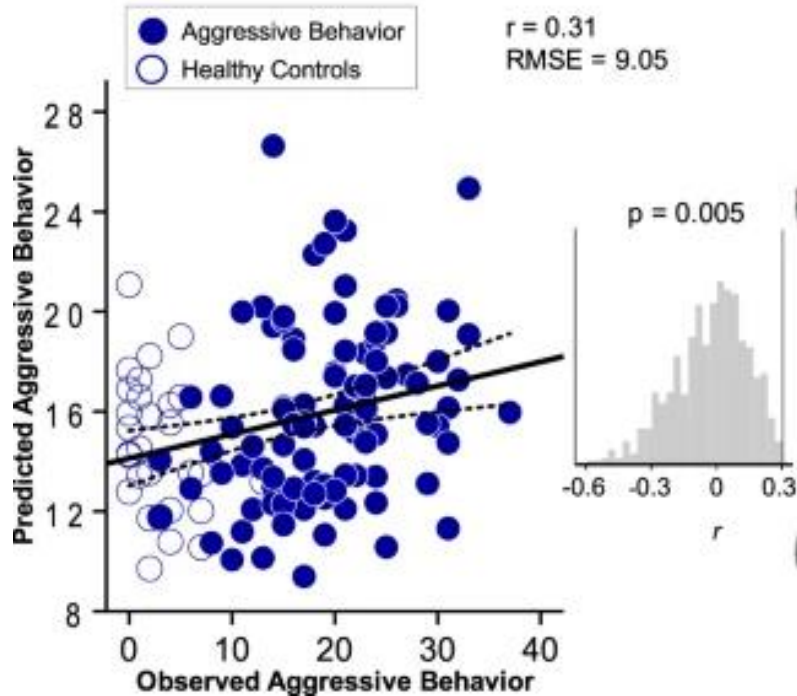
They selected these tasks for replication and validation purposes for the following reasons.

1. The SST and EN-back tasks tap frontoparietal and fronto-amygdala circuitry that are relevant to aggressive behavior
2. The EN-back task stimuli included a set of happy, fearful, and neutral expressions drawn in part from the NimStim Stimulus Set.
3. In addition, the SST taps the construct of response inhibition that is also implicated in childhood aggressive behavior

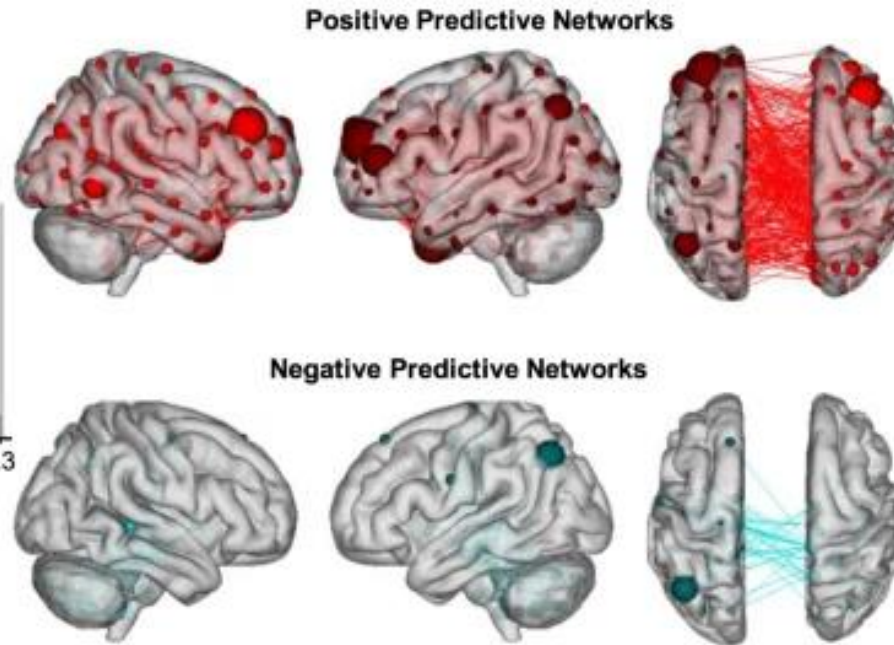
Results

Brain-wide functional connectivity predicts severity of aggressive behavior

A) Model Fit: Predicted vs. Observed



B) Positive and Negative Networks Predicting Aggression



Age

Sex

Motion

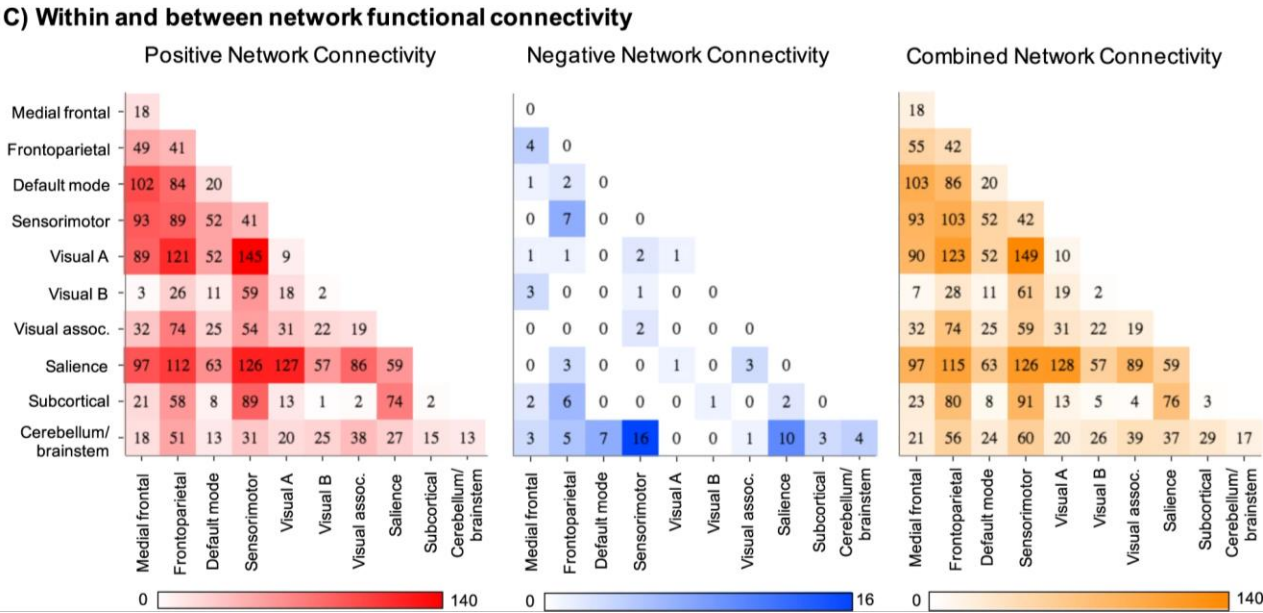
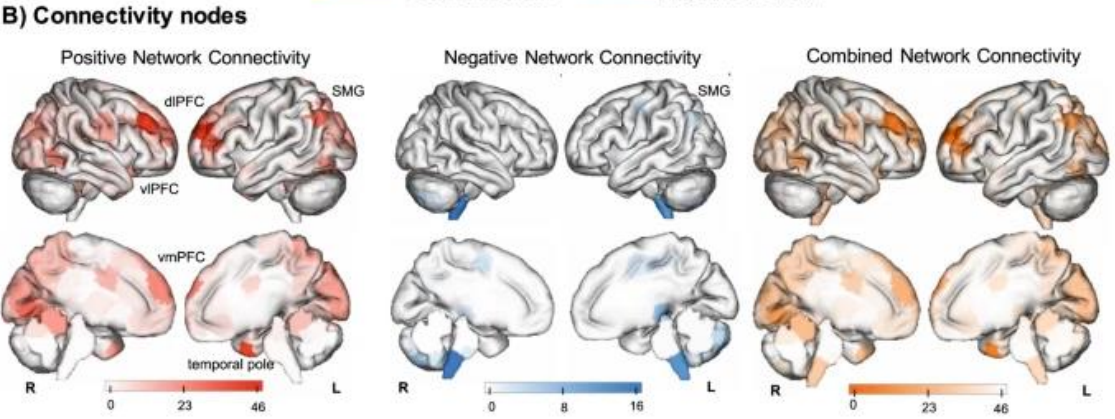
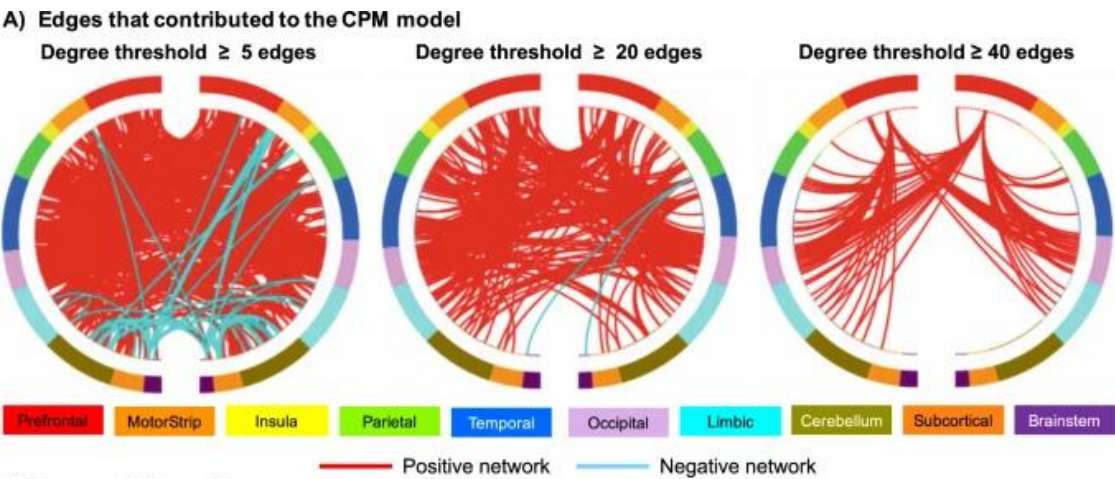
Psychiatric medication

ASD vs. non-ASD

ASD social behavior impairments

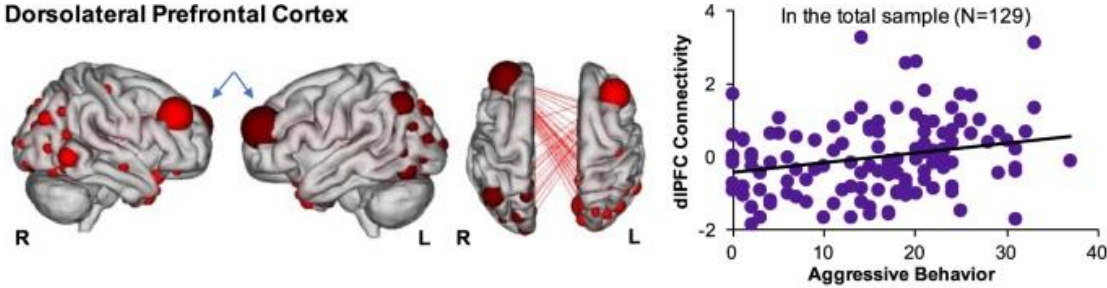
Ten-fold cross-validation

Networks predicting aggression summarized by connectivity between macroscale brain regions and networks

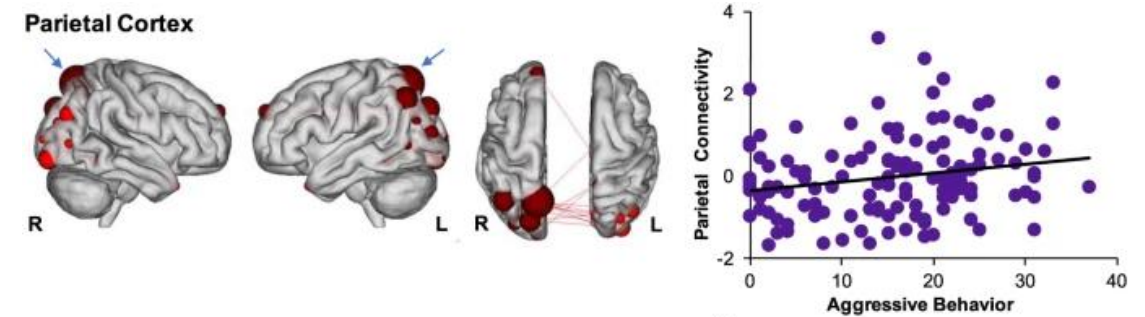


Follow-up analyses for high-degree nodes contributing to the connectome model in the discovery sample of 129 children

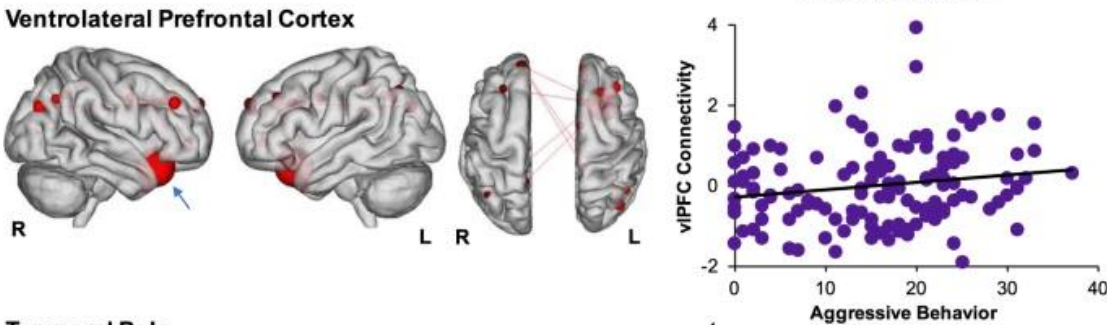
Dorsolateral Prefrontal Cortex



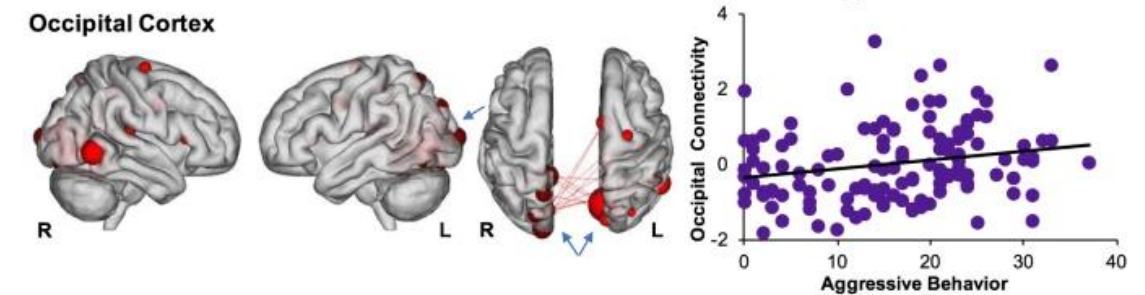
Parietal Cortex



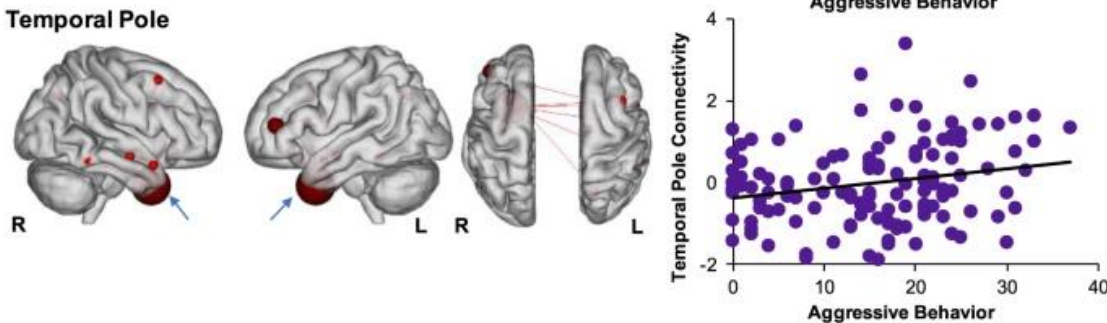
Ventrolateral Prefrontal Cortex



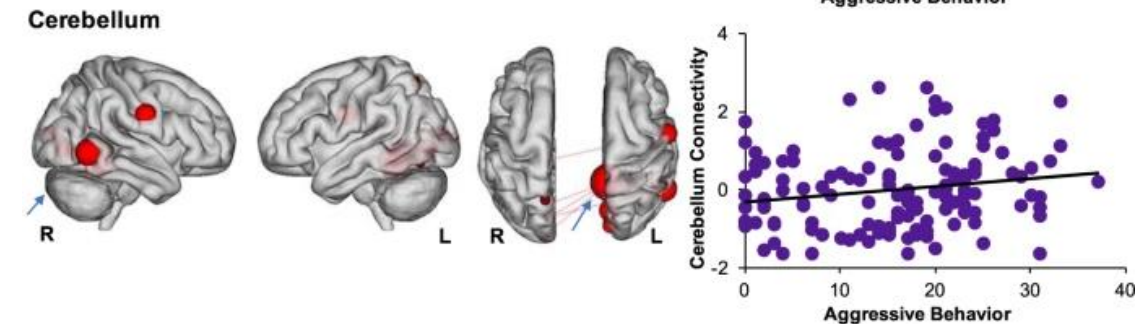
Occipital Cortex



Temporal Pole



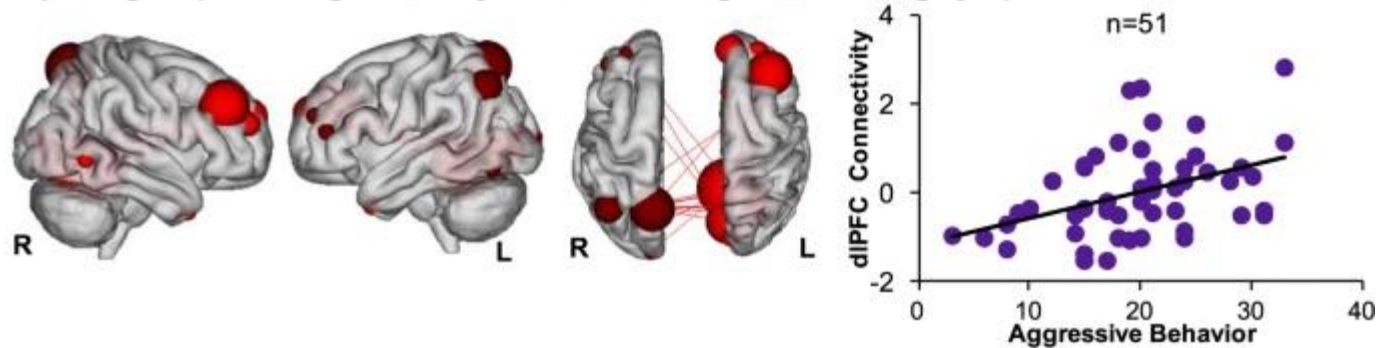
Cerebellum



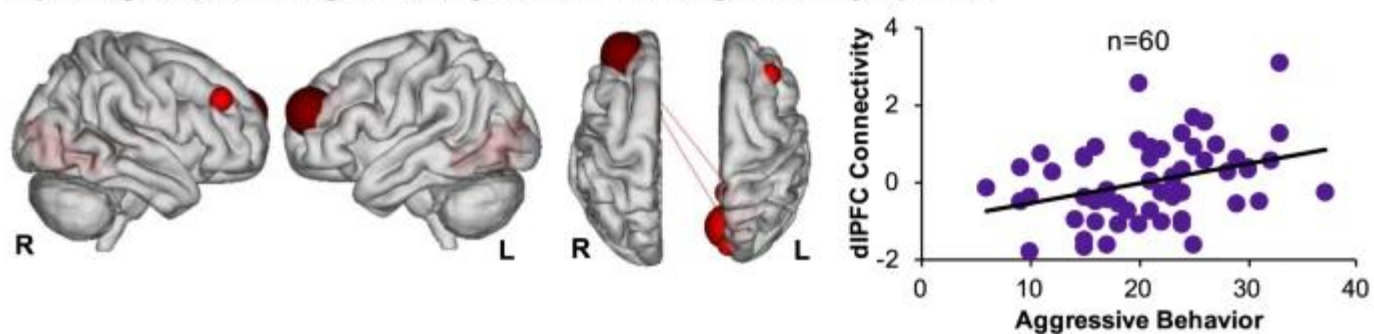
Dorsolateral prefrontal cortex connectivity predicts aggressive behavior

Dorsolateral Prefrontal Cortex Connectivity

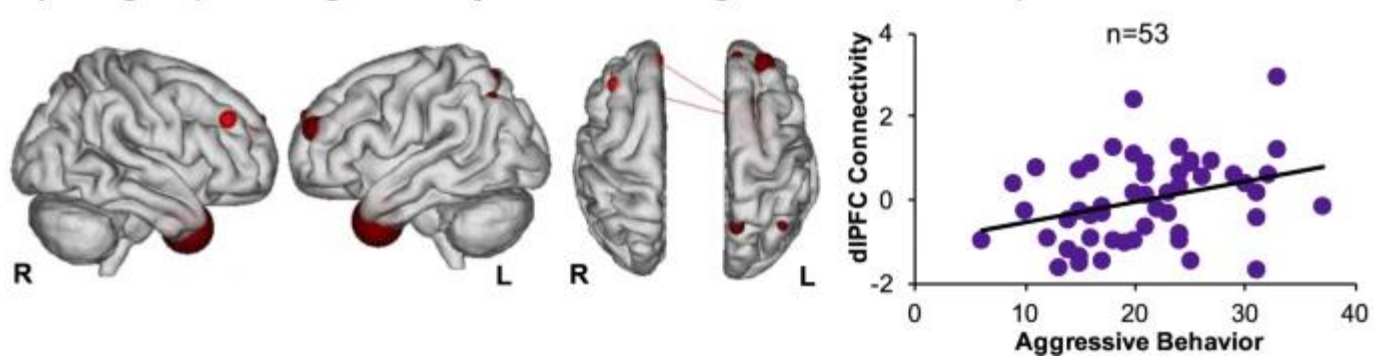
A) Subgroup with high severity of co-occurring internalizing symptoms



B) Subgroup with high severity of co-occurring ADHD symptoms

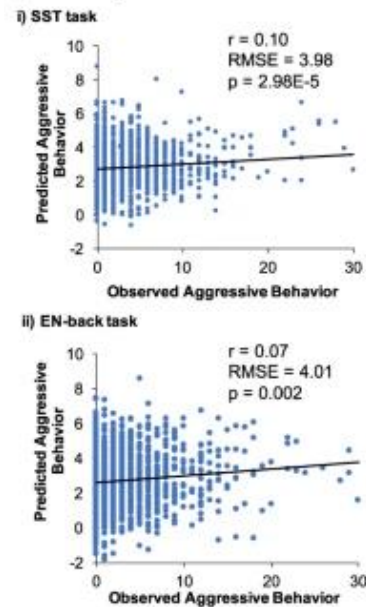


C) Subgroup with high severity of co-occurring social behavior impairments

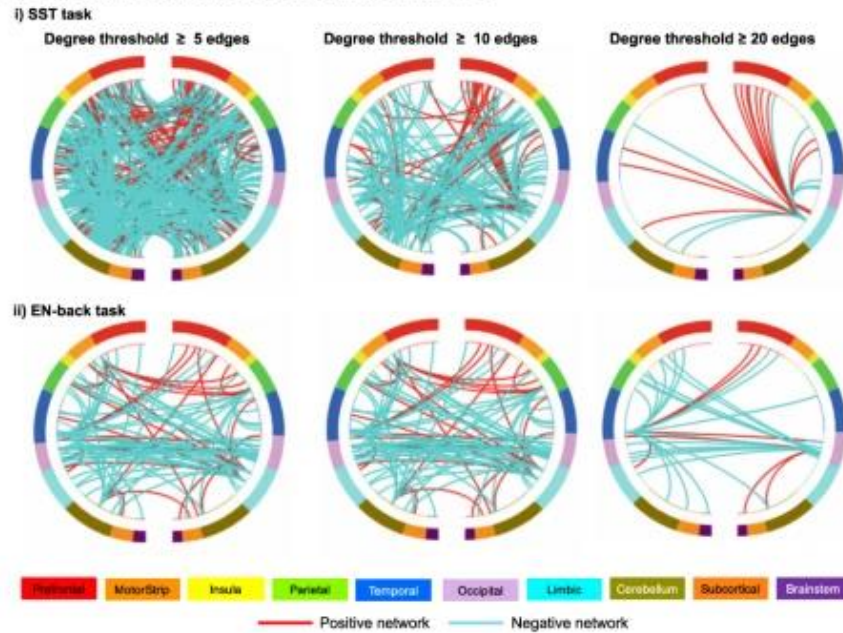


Replication of findings using CPM prediction of aggression in an out-of-sample dataset

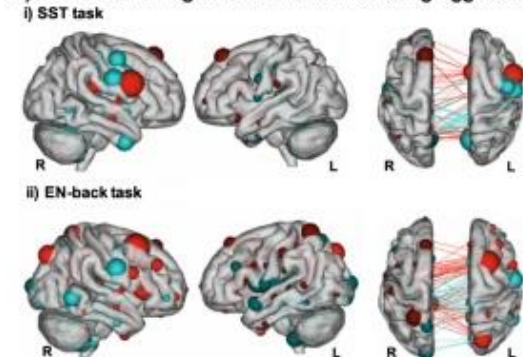
A) Model Replication: Predicted vs. Observed



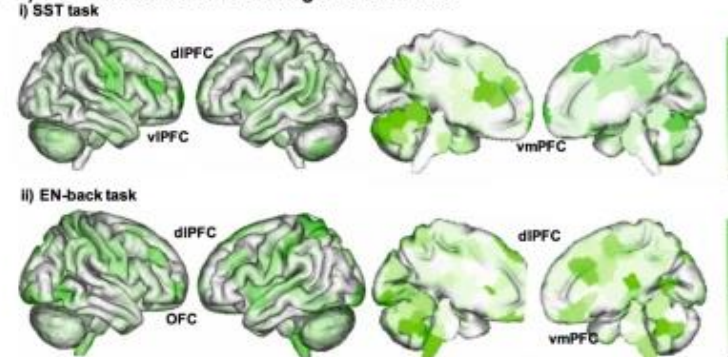
B) Edges that contributed to the CPM model in ABCD



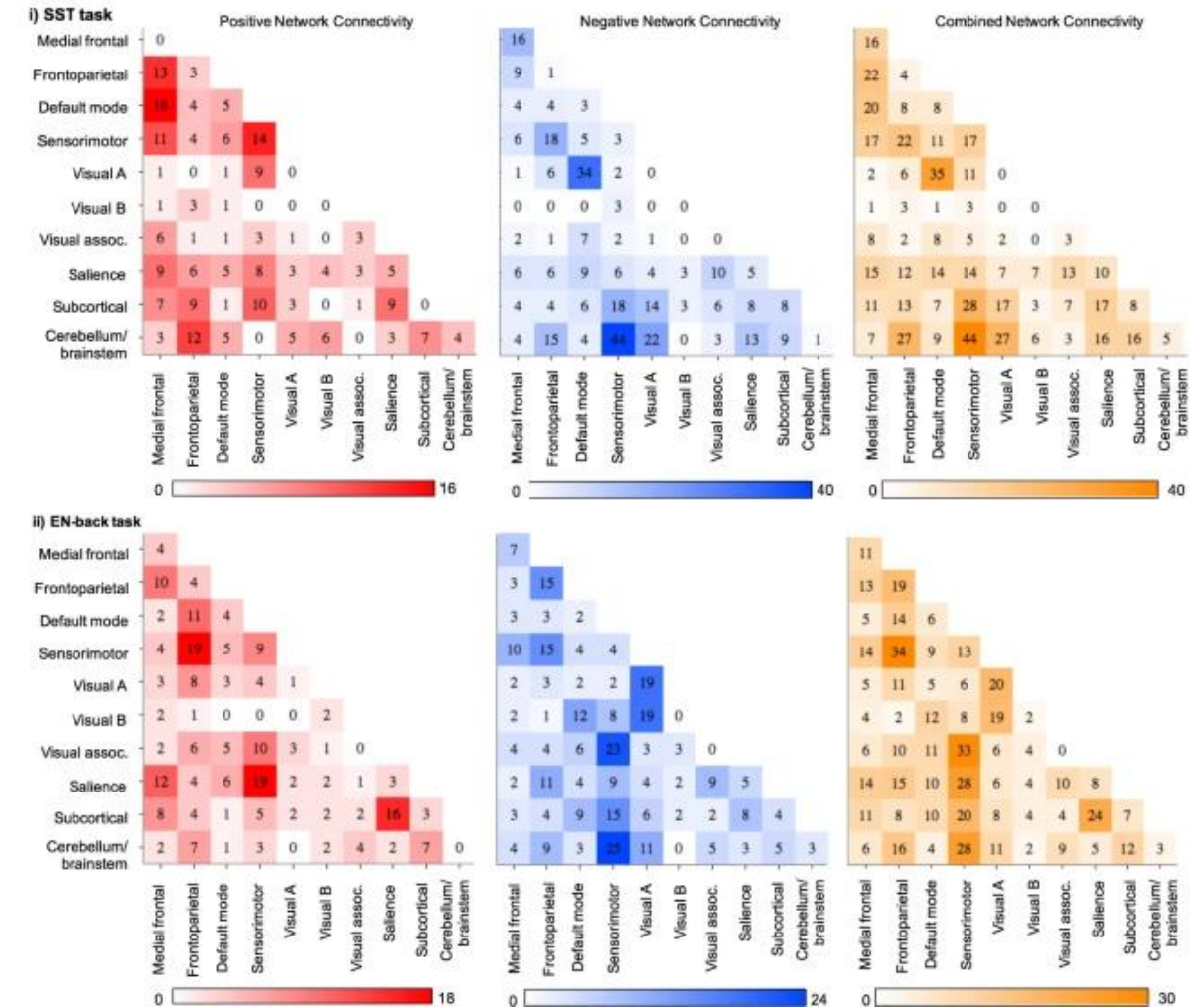
C) Positive and Negative Networks Predicting Aggression



D) Difference of Positive vs. Negative Networks



E) Within and between network functional connectivity

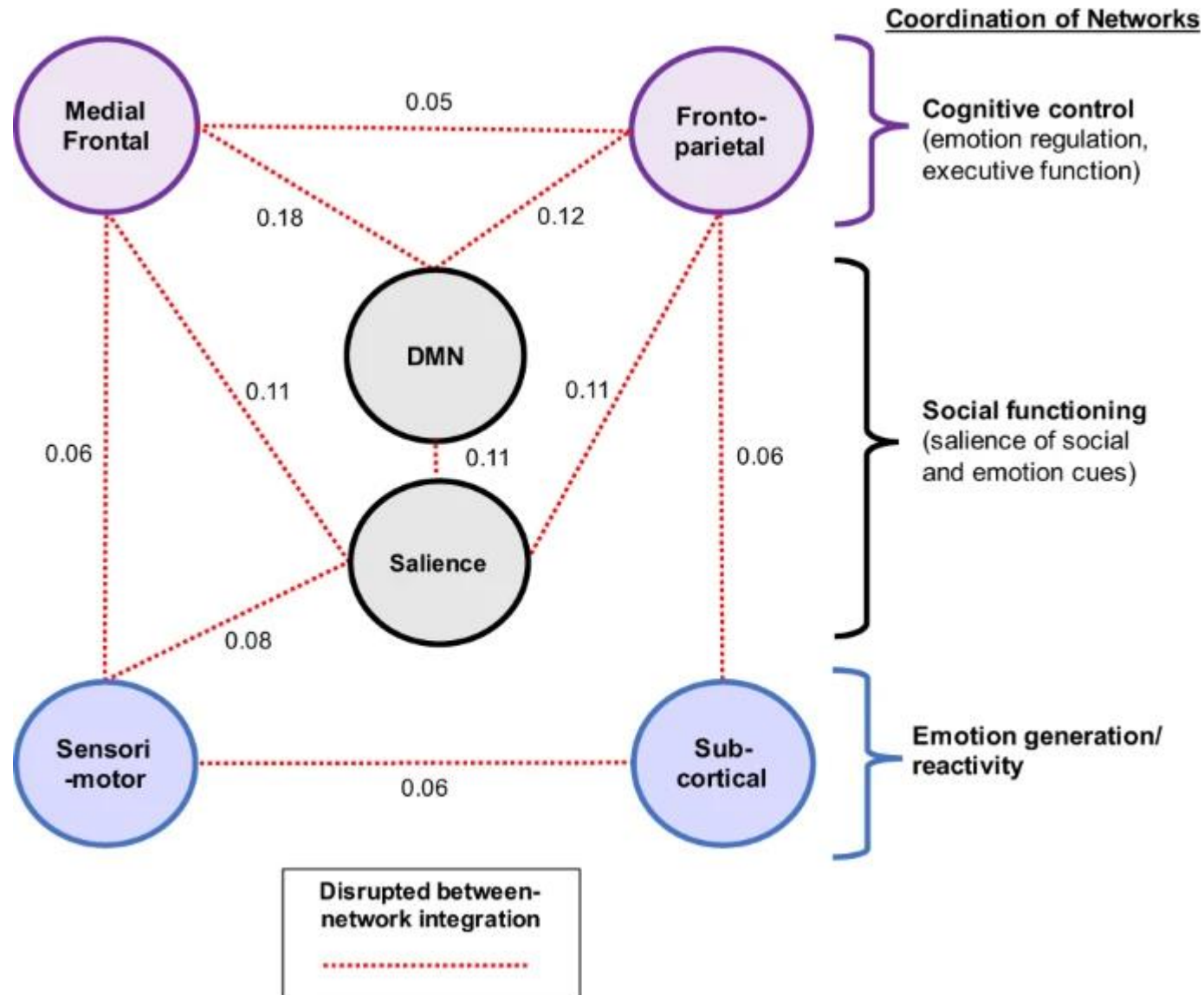


Discussion

This study is the first to apply a CPM approach to identify the functional connectomics underlying aggression in children.

1. During implicit emotion processing of faces, brain-wide connectivity predicted severity of aggressive behavior.
2. They further demonstrated that the same networks can be used to predict aggression in an independent, heterogeneous sample using similar tasks that tap into cognitive control processes of response inhibition and working memory, often impaired in children with aggressive behavior.

Network model of aggression



Study limitations

1. The present study is cross-sectional and future research is needed to understand how these findings relate to longitudinal trajectories of connectivity impairment implicated in aggression.
2. While models were robust to common co-occurring internalizing, ADHD, and ASD symptoms, the functional significance of the identified networks in relation to other forms of developmental psychopathology associated with aggression remains to be tested in larger samples.
3. These models showed modest effect sizes, capturing approximately 10% of the variance, which was reduced to 1–5% in the replication analysis.
4. The task acquisition length was relatively short.

Functional connectivity during frustration: a preliminary study of predictive modeling of irritability in youth

Irritability, defined as increased proneness to anger and frustration compared to peers, is a common presenting problem in child psychiatry.

Frustrative Nonreward, defined as the psychological state induced when an expected reward is withheld, is a construct in the negative valence systems within the research domain criteria matrix.



A recent translational model of irritability posits that a core pathophysiological deficit of irritability is aberrant responses to **frustrative nonreward** mediated by amygdala–frontostriatal dysfunction

It is important to test whether tasks involving frustrative nonreward are better suited to elicit individual differences in network abnormalities associated with irritability, compared to resting state or other tasks without a frustration component.

Modified change-signal task with rigged feedback to probe cognitive flexibility (i.e., the ability to adapt one's thinking and behavior in response to changing environmental conditions/demands) under frustrative nonreward.

- (a) it probes both motor inhibition and cognitive flexibility, two processes critical for emotion regulation
- (b) the frustration and nonfrustration blocks are interspersed randomly

Functional connectivity during a frustrating, but not nonfrustrating, state would be associated with individual differences in irritability and that networks involving the amygdala, striatum, ACC, and prefrontal cortex would be the most predictive of irritability.

Participants

	<i>n</i> (%) or mean (SD)	Range
Age, mean (SD), years	14.55 (2.85)	8–22
Gender, <i>n</i> (%) ^a	38 (55.10)	—
IQ, mean (SD) ^b	111.75 (11.45)	87–133
SES, mean (SD) ^c	38.34 (19.99)	20–114
Motion, mean (SD) ^d	0.07 (0.03)	0.02–0.16
Irritability measures, mean (SD)		
Child-reported ARI	1.79 (2.04)	0–9
Parent-reported ARI ^e	2.80 (3.35)	0–10
Primary diagnosis, <i>n</i> (%)		
DMDD	20 (28.99)	—
ADHD	14 (20.29)	—
Anxiety	12 (17.39)	—
No diagnosis	23 (33.33)	—

Measures

Irritability was measured using the parent report and child report of the [Affective Reactivity Index \(ARI\) scale](#).

Items were rated on a 0–2 scale and yielded a total score of 0–12. For >95% of the sample, these measures were collected within 1 month of scanning (>65% collected within a week of scanning).

Table 2

(A) *t*-tests for individual items in the US sample. (B) *t*-tests for individual items in the UK sample

	Mean (<i>SD</i>) parent <i>n</i> = 192	Mean (<i>SD</i>) self <i>n</i> = 192	<i>t</i> -test statistics (<i>df</i> = 191)
Easily annoyed by others	0.88 (0.83)	0.88 (0.70)	<i>t</i> = 0.00 ^{ns}
Often lose temper	0.76 (0.84)	0.61 (0.70)	<i>t</i> = 2.64 ^{**}
Stay angry for a long time	0.39 (0.59)	0.38 (0.58)	<i>t</i> = 0.31 ^{ns}
Angry most of the time	0.30 (0.60)	0.18 (0.45)	<i>t</i> = 2.50 ^{**}
Get angry frequently	0.67 (0.82)	0.48 (0.69)	<i>t</i> = 3.03 ^{**}
Lose temper easily	0.79 (0.89)	0.61 (0.79)	<i>t</i> = 3.03 ^{**}

[Stringaris, Argyris, et al. "The Affective Reactivity Index: a concise irritability scale for clinical and research settings." Journal of Child Psychology and Psychiatry 53.11 \(2012\): 1109-1117.](#)

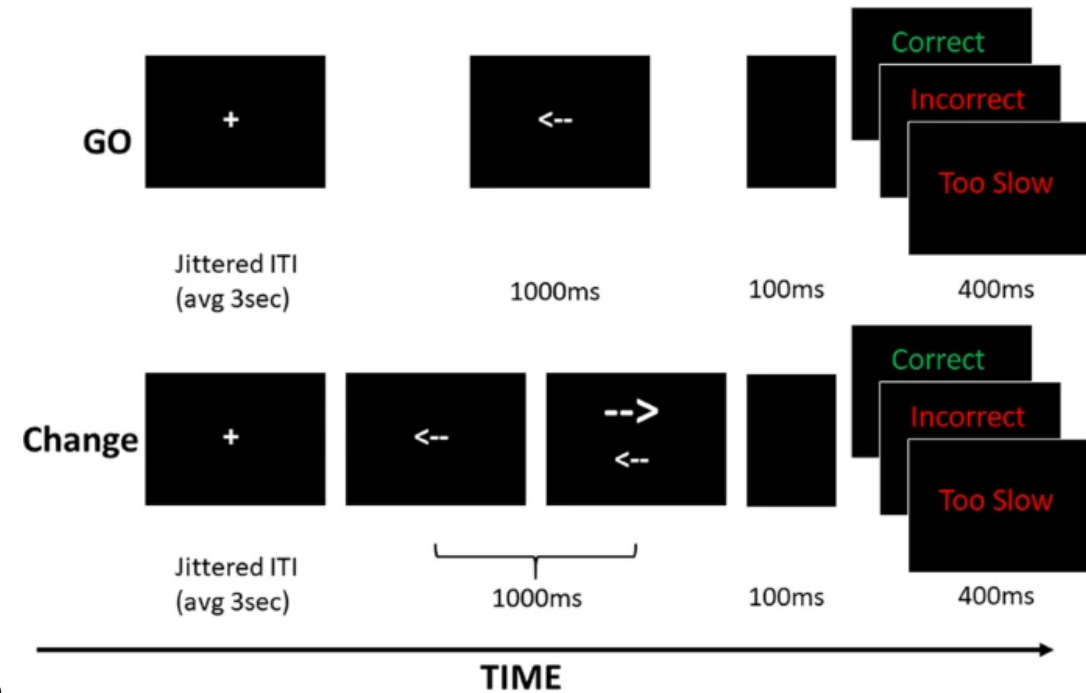
fMRI task

A modified change-signal task

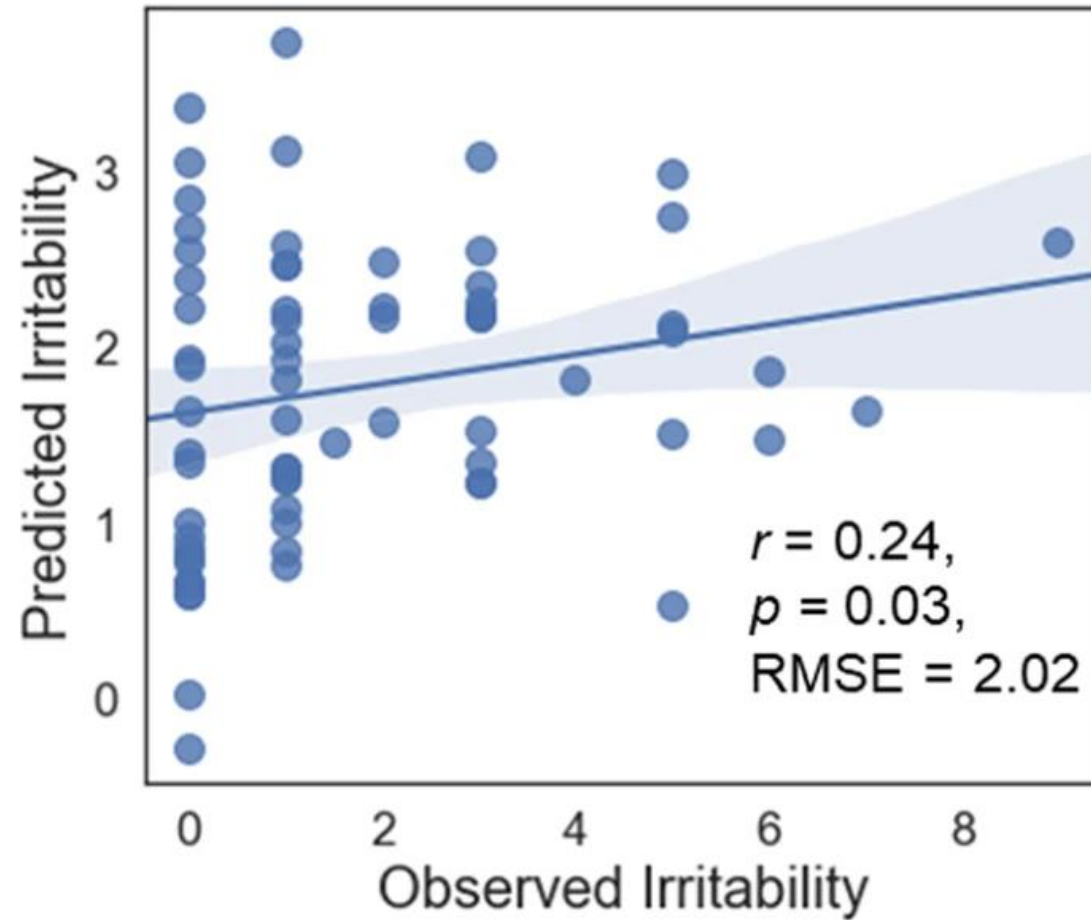
“frustration” block (50% error rate on change trials plus 20% rigged feedback on correct go trials) and a “nonfrustration” block (10% error rate on change trials), the order of which was randomized within run.

At the end of each block, participants self-reported their feelings of frustration using a nine-point Likert scale, providing a measure of state irritability.

Participants reported feeling more frustrated during frustration than nonfrustration blocks, supporting the task’s validity as a frustrative nonreward paradigm, which did not vary as a function of age



Results



Motion

Age

Sex

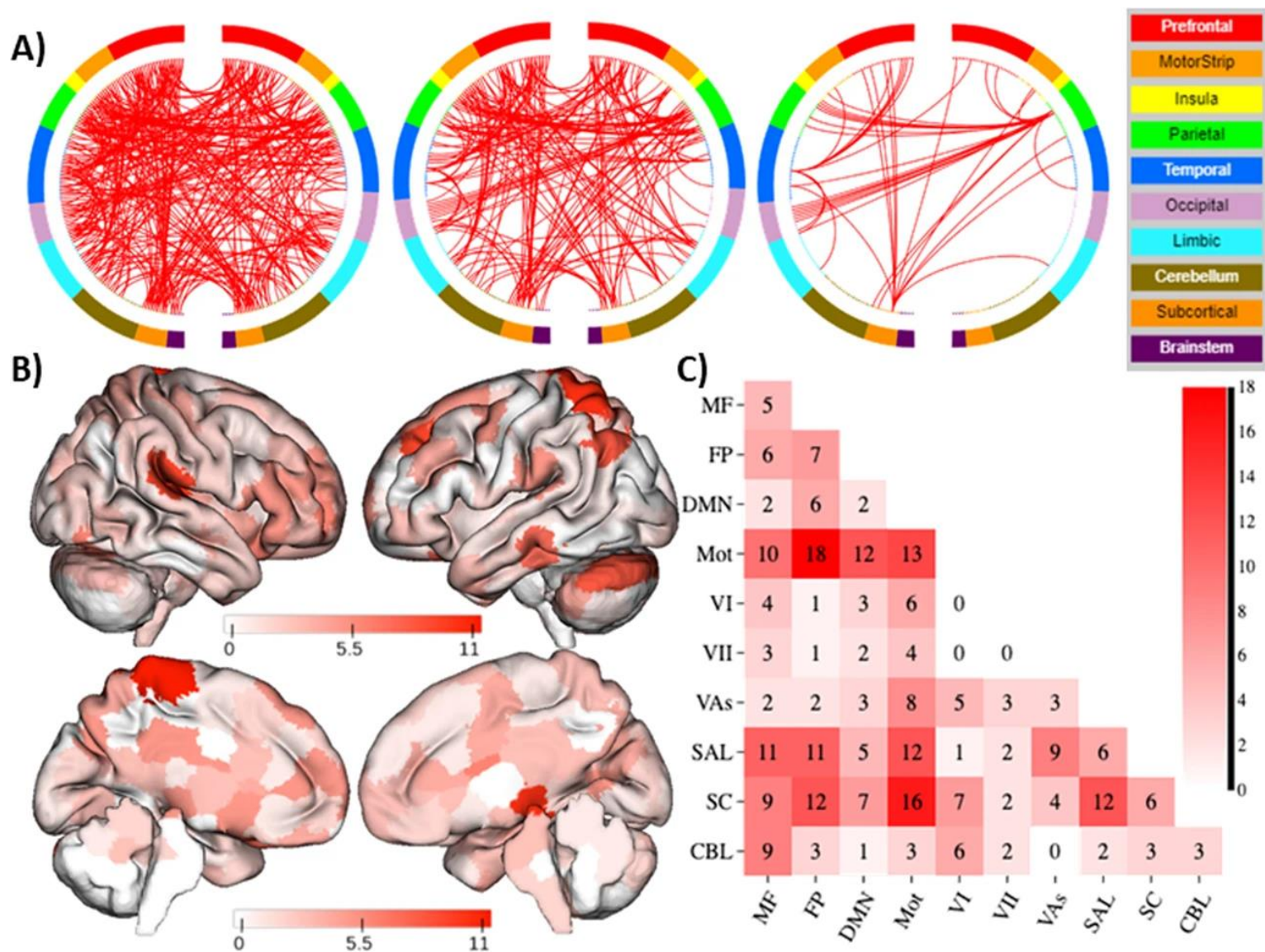
ADHD

anxiety symptoms

Medications

The overall CPM model successfully predicted child-reported ARI using functional connectivity from the frustration blocks

Anatomical and network localization of circuits predicting child-reported trait irritability



MF medial frontal,
FP frontoparietal,
DMN default mode network,
Mot motor/sensory,
VI visual A,
VII visual B,
VAs visual association,
SAL salience,
SC subcortical,
CBL cerebellum.

Discussion

The CPM approach showed that functional connectivity during frustration (but not nonfrustration) blocks was associated with child-reported irritability.

The predictive networks of child-reported irritability were primarily within the motor-sensory network; among the motor-sensory, salience, and subcortical (including amygdala, thalamus, striatum) networks; and between these networks and the frontoparietal and medial frontal networks.

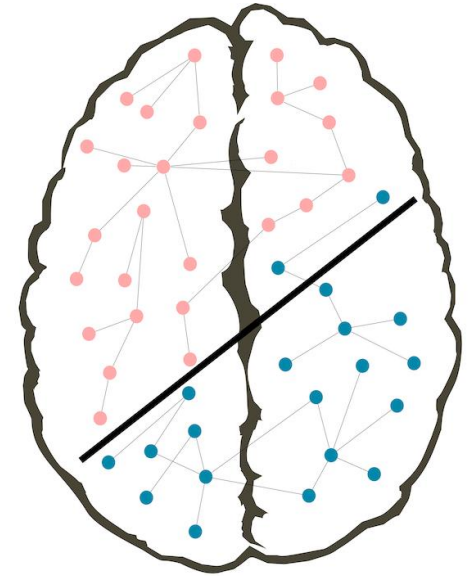
Functional connectivity during a phenotype-relevant state such as frustration to better probe individual differences in brain–behavior associations and thus facilitate biomarker discovery.

One novel finding of this study is the contribution of within motor-sensory network, and between motor-sensory and frontoparietal, subcortical, salience, and medial frontal networks to the prediction of irritability.

NBS-Predict

A prediction-based extension of the network-based statistic

Overall results showed that NBS-Predict performed comparable to or better than pre-existing feature selection algorithms (lasso, elastic net, top 5%, p-value thresholding) and **connectome-based predictive modeling (CPM)** in terms of identifying relevant features and prediction accuracy.



NBS-Predict

<https://github.com/eminSerin/NBS-Predict>

<https://www.nitrc.org/projects/nbspredict>

<https://osf.io/4ghpm>