Using Machine Learning To Identify Neural Mechanisms Underlying the Development of Cognition in Children and Adolescents With ADHD

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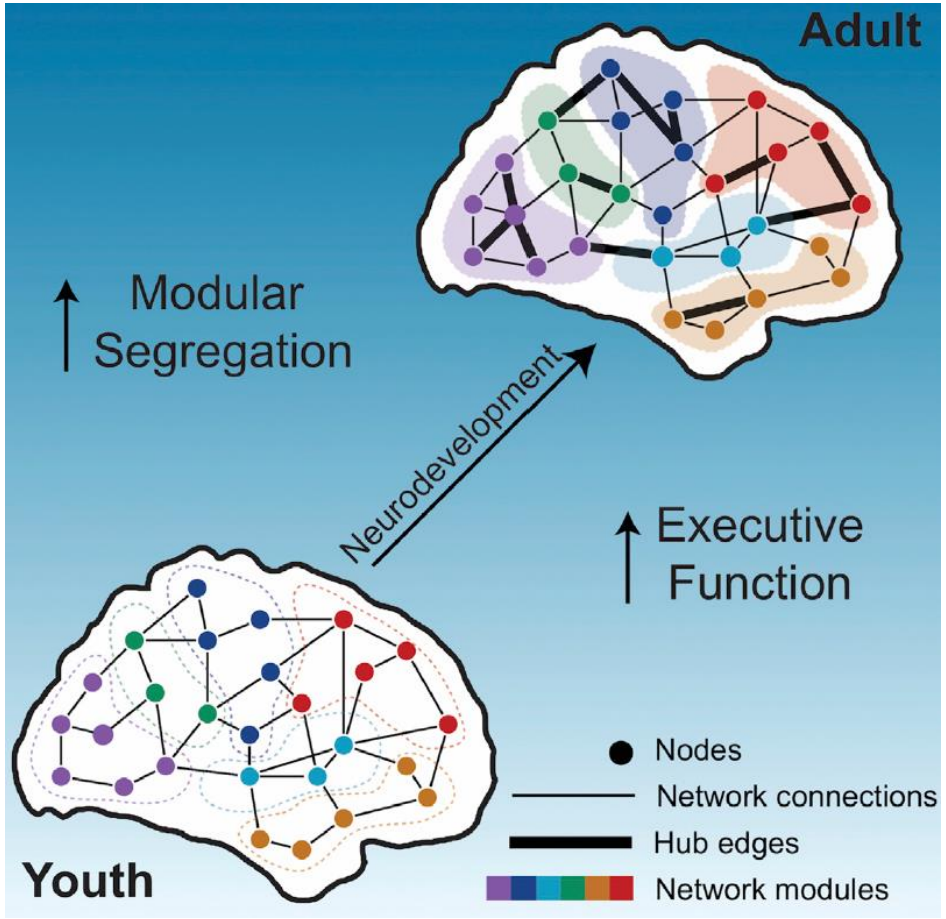
Introduction: Cognitive Development

- Childhood and adolescence are periods marked by improvements to cognition
  - E.g. Executive function, working memory
- Atypical cognitive development is associated with neurodevelopmental disorders
  - E.g. Attention Deficit Hyperactivity Disorder (ADHD)



Baum et al. (2017)

Cognition and ADHD

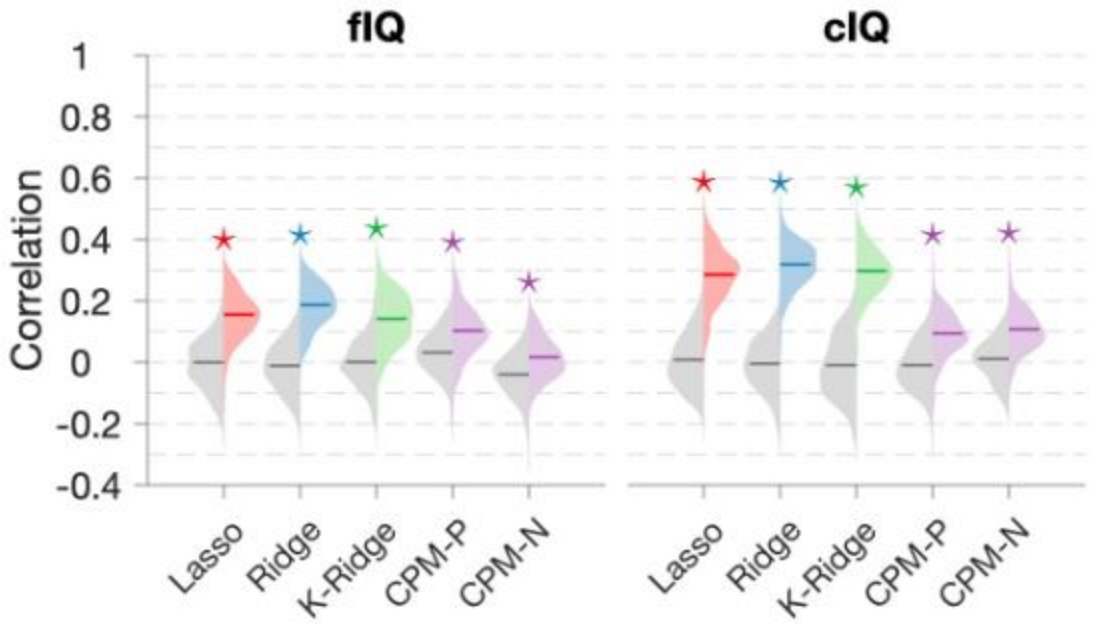
- Symptoms of ADHD
  - Inattention
  - Impulsivity
  - Hyperactivity

- ADHD is associated with deficits in cognition
  - E.g. Inhibitory control, cognitive flexibility, and working memory
  - E.g. Processing speed

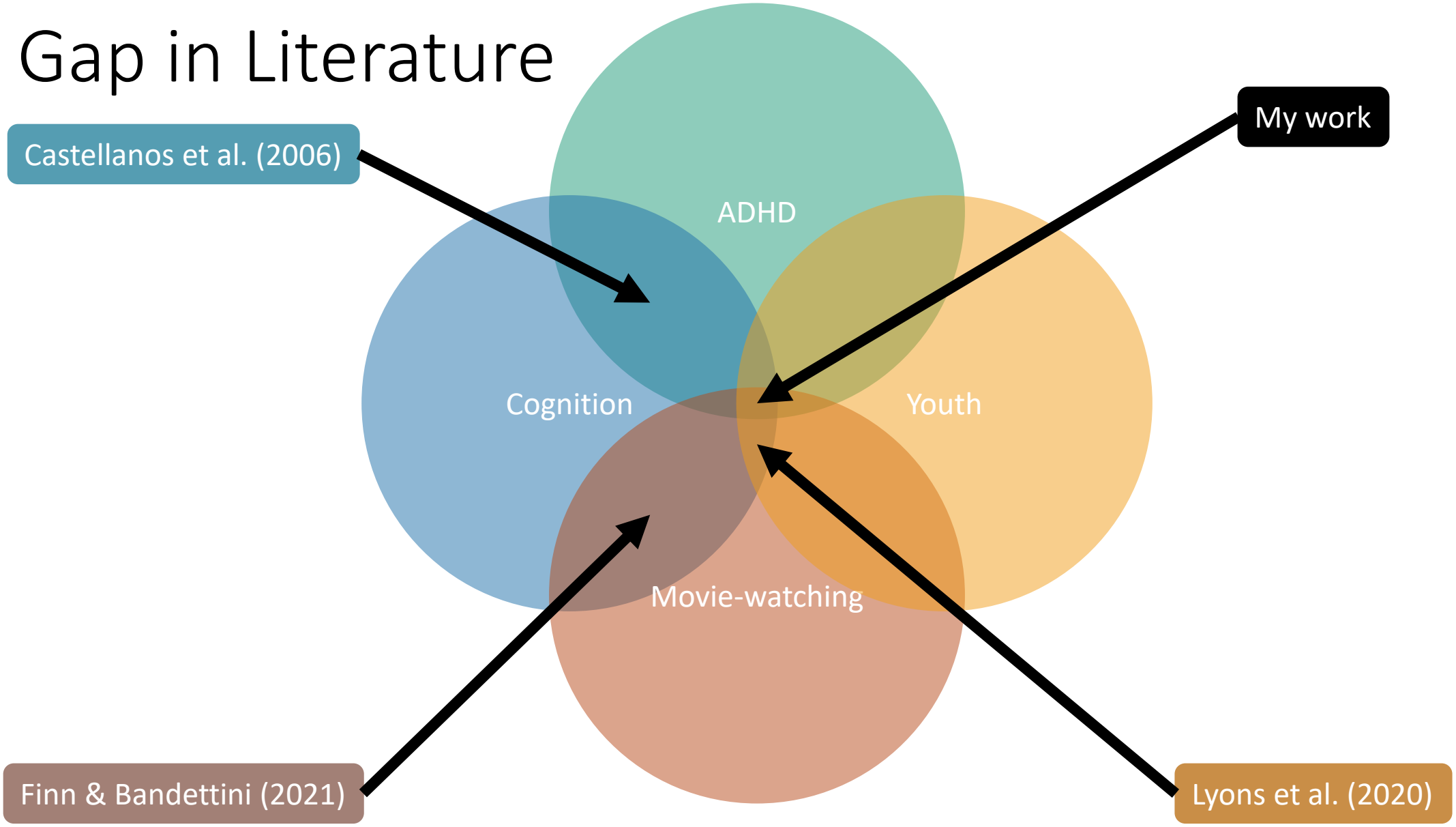
Modeling and Predicting Cognition

- Computational models can capture the relationship between brain activity and cognitive ability
  - E.g. Ridge regression

- Literature
  - Resting-state + Adults (Tian & Zalesky, 2021)
  - Resting-state + Youth (Sripada et al., 2019)
  - Movie-watching + Adults (Finn & Bandettini, 2021)



Gap in Literature



Objectives

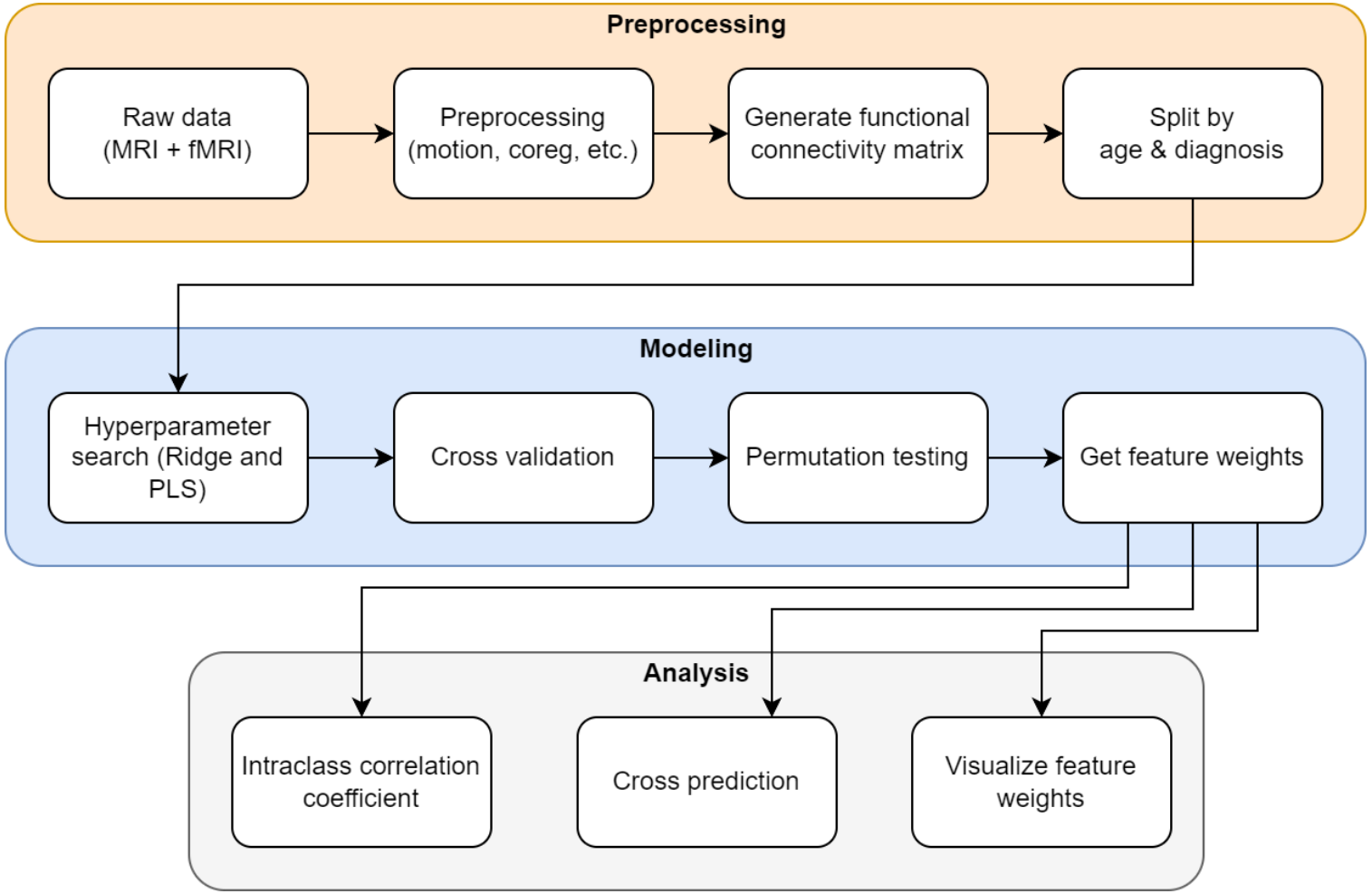
1. Can cognition be predicted in a large group of children and adolescents diagnosed with ADHD using functional neural activity during movie watching?
2. Does prediction accuracy remain constant across development?
3. If not, what are the neural mechanisms associated with developmental differences in predicting cognition?

Methods: Healthy Brain Network Biobank Data

- Participants ages 6 to 16 years old
- fMRI captured while participants watched a 10-minute movie clip from “Despicable Me”
- Collected variables: age, sex, IQ, Visual Spatial (VSI), Verbal Comprehension (VCI), Fluid Reasoning (FRI), Working Memory (WMI), Processing Speed (PSI)
- Groups: ADHD (n=373) and TD (n=106)

CHILD MIND® INSTITUTE
healthy brain network

Data Pipeline



Result 1: Predicting Age and Sex

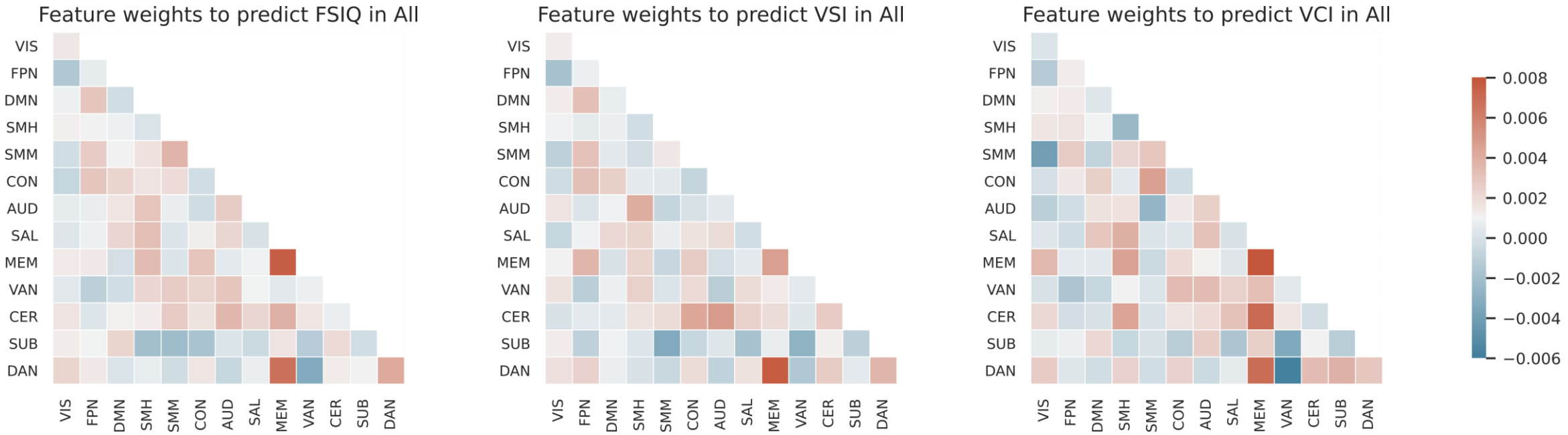
- ADHD (n=373)
  - Age: r^2=0.45
  - Sex: 74% accuracy
- TD (n=106)
  - Age: r^2=0.13
  - Sex: 60% accuracy
- Lower explained variance for age and lower accuracy for sex in TD
- Suggests the TD group is more heterogeneous

Result 2: Predicting Cognition

WISC	ADHD (n=373)	TD (n=106)
Intelligence Quotient (FSIQ)	0.38*	0.04
Visual Spatial (VSI)	0.31*	0.16
Verbal Comprehension (VCI)	0.39*	0.20
Fluid Reasoning (FRI)	0.30*	-0.07
Working Memory (WMI)	0.21*	0.12
Processing Speed (PSI)	0.05	-0.06

Values are Pearson correlation (r)
Starred (*) values indicate statistically significant at $p<.05$ max-statistic corrected

Result 2: Predicting Cognition in ADHD



Values are the weight assigned to each feature (network connection)

Network Legend

- VIS = Visual
- FPN = Frontoparietal
- DMN = Default mode
- SMH = Sensorisomatomotor (hand)
- SMM = Sensorisomatomotor (mouth)
- CON = Cingulo-opercular
- AUD = Auditory
- SAL = Salience
- MEM = Memory retrieval
- VAN = Ventral attention
- CER = Cerebellum
- SUB = Subcortical
- DAN = Dorsal attention

WISC Legend

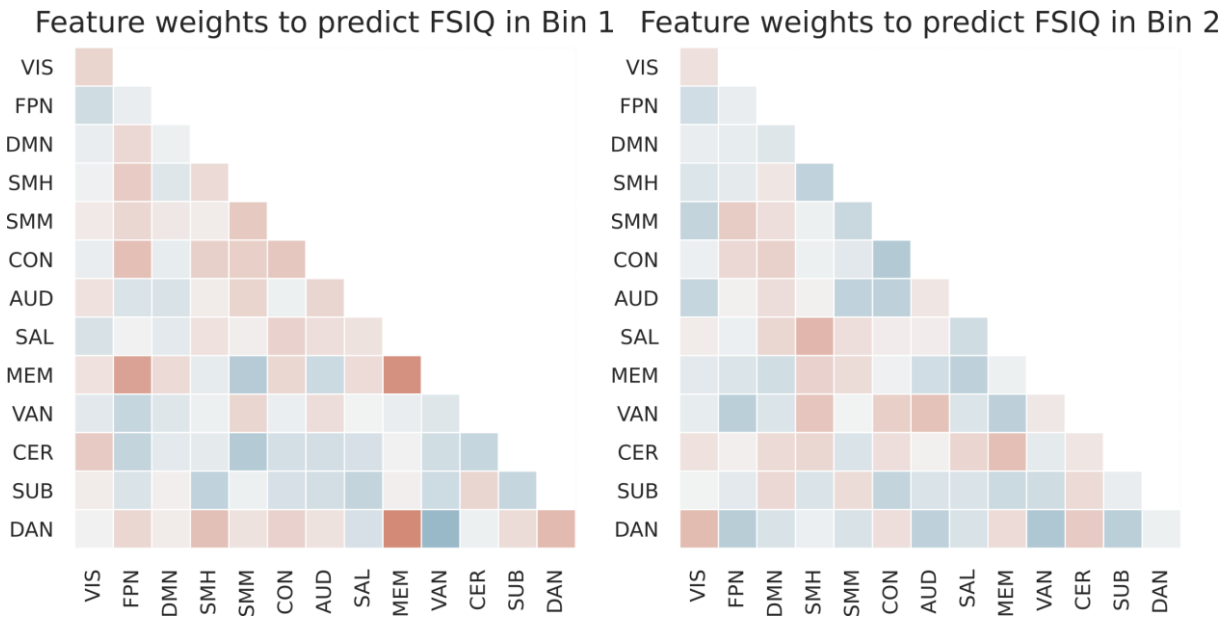
- FSIQ = Intelligence quotient
- VSI = Visual spatial
- VCI = Verbal comprehension

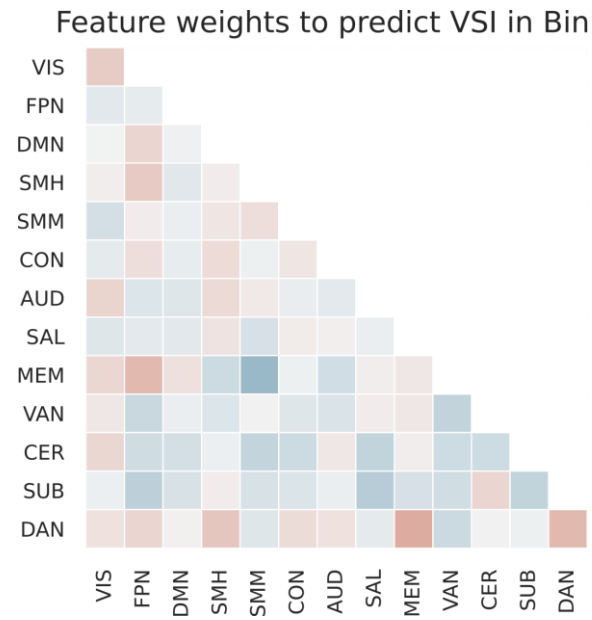
Result 3: Development of Cognition in ADHD

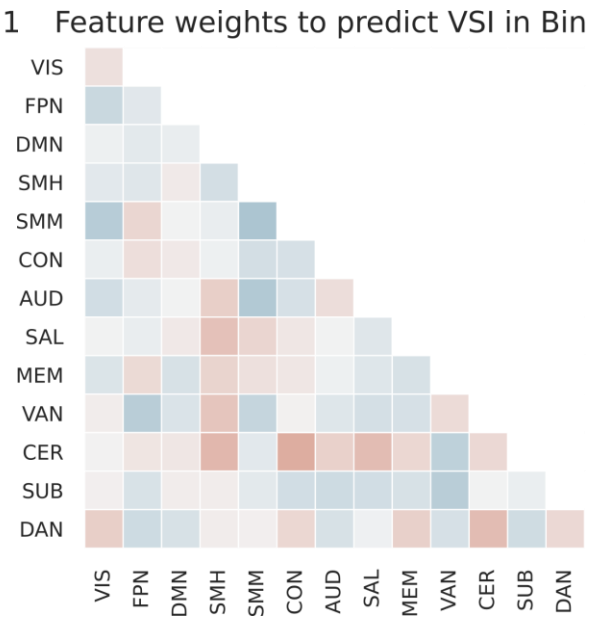
WISC	Bin 1 (n=114)	Bin 2 (n=147)	Bin 3 (n=112)
Intelligence Quotient (FSIQ)	0.27*	0.35*	0.11
Visual Spatial (VSI)	0.24*	0.21*	0.09
Verbal Comprehension (VCI)	0.22*	0.35*	0.04
Fluid Reasoning (FRI)	0.05	0.31*	-0.01
Working Memory (WMI)	0.05	0.29*	0.10
Processing Speed (PSI)	-0.09	0.06	0.09

Values are Pearson correlation (r)
Starred (*) values indicate statistically significant at $p<.05$ max-statistic corrected

Development of Cognition in ADHD (Bin 1 & 2)

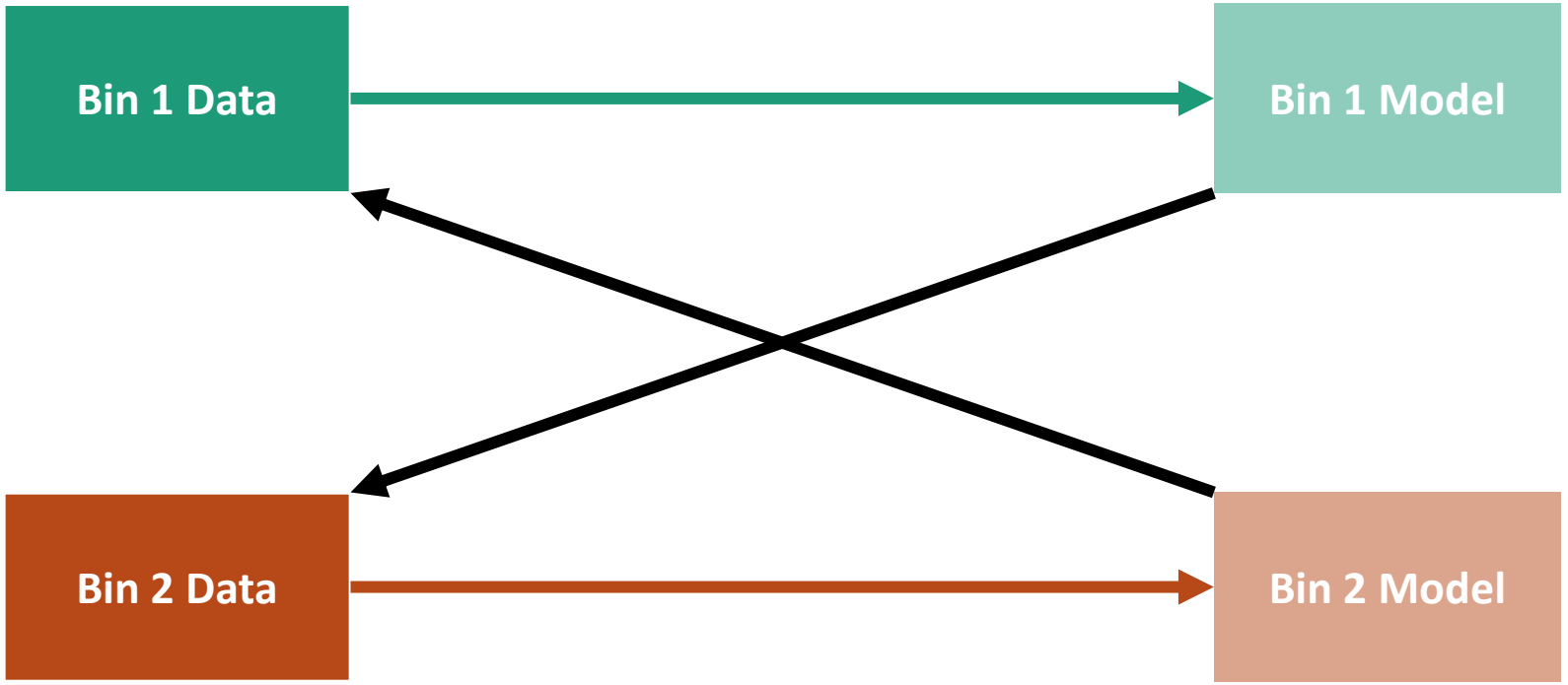




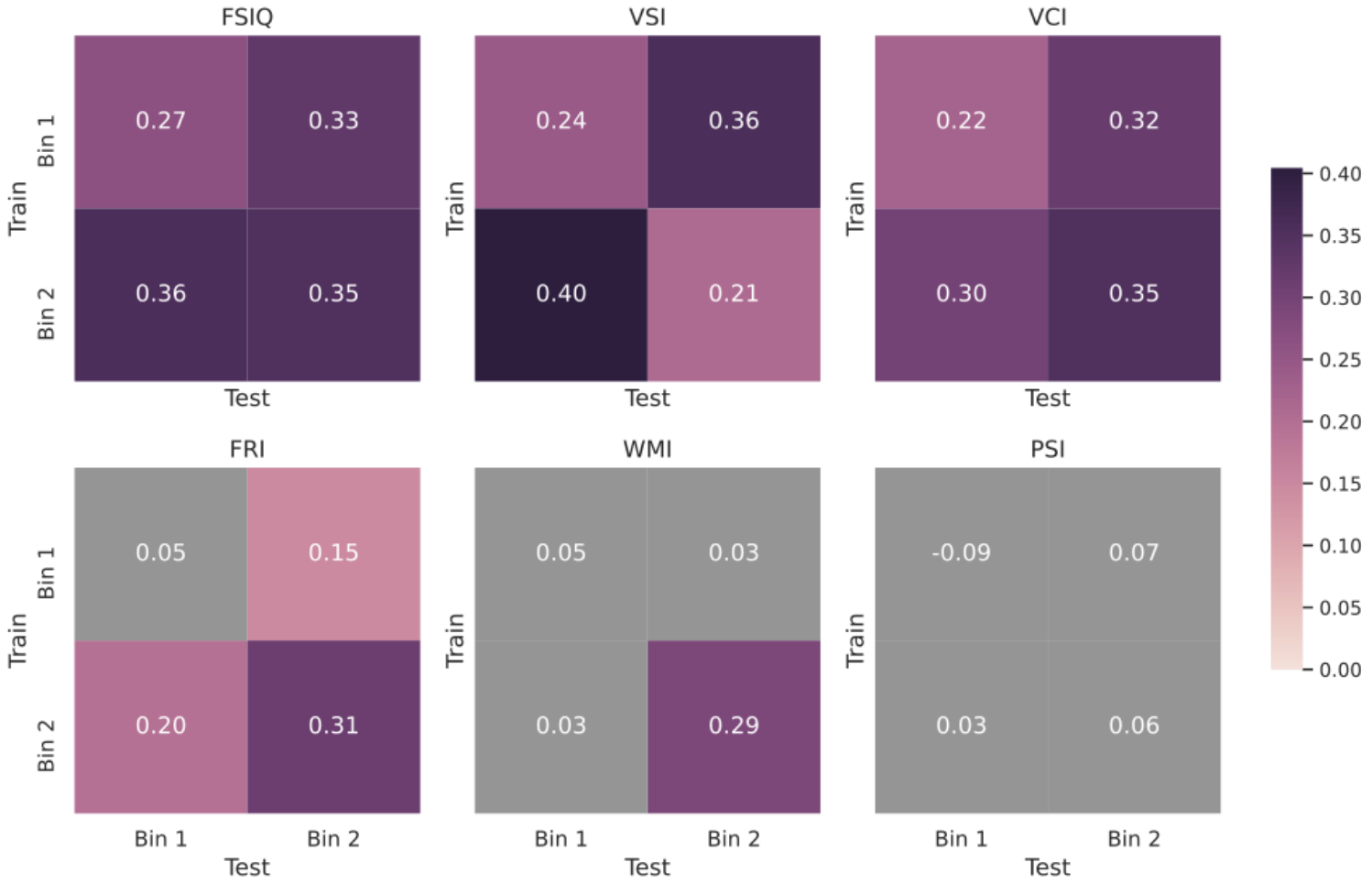


Values are the weight assigned to each feature (network connection)

Cross Prediction

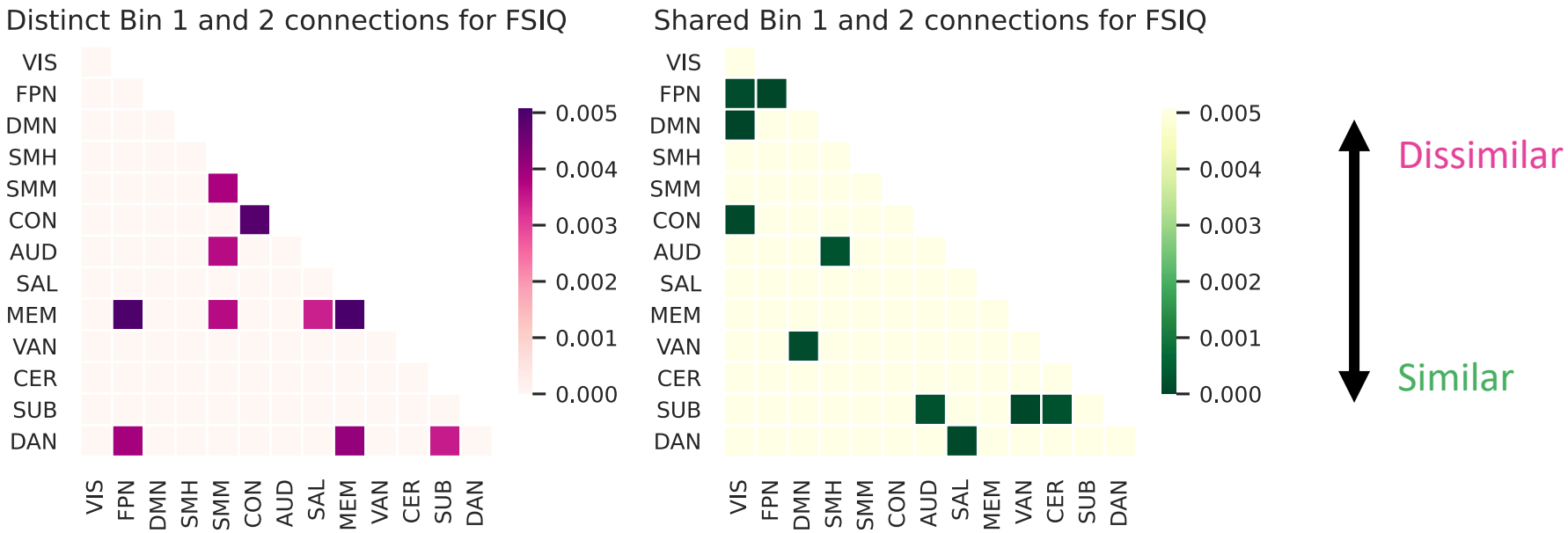


Result 4: Cross Prediction



Values are Pearson correlation (r)
Purple values indicate statistically significant at p<.05 max-statistic corrected

Feature Weight Differences & Similarities (FSIQ)



Values are the difference between two sets of feature weights

Network Legend

- VIS = Visual
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- SMM = Sensorisomatomotor (mouth)
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Conclusion

1. Can cognition be predicted in a large group of children and adolescents diagnosed with ADHD using functional neural activity during movie watching?
   - **Yes**
2. Does prediction accuracy remain constant across development?
   - **No**
3. If not, what are the neural mechanisms associated with developmental differences in predicting cognition?
   - **Shared: frontoparietal, default mode, subcortical, dorsal attention**
   - **Distinct: sensory/somatomotor, cingulo-opercular, memory retrieval**

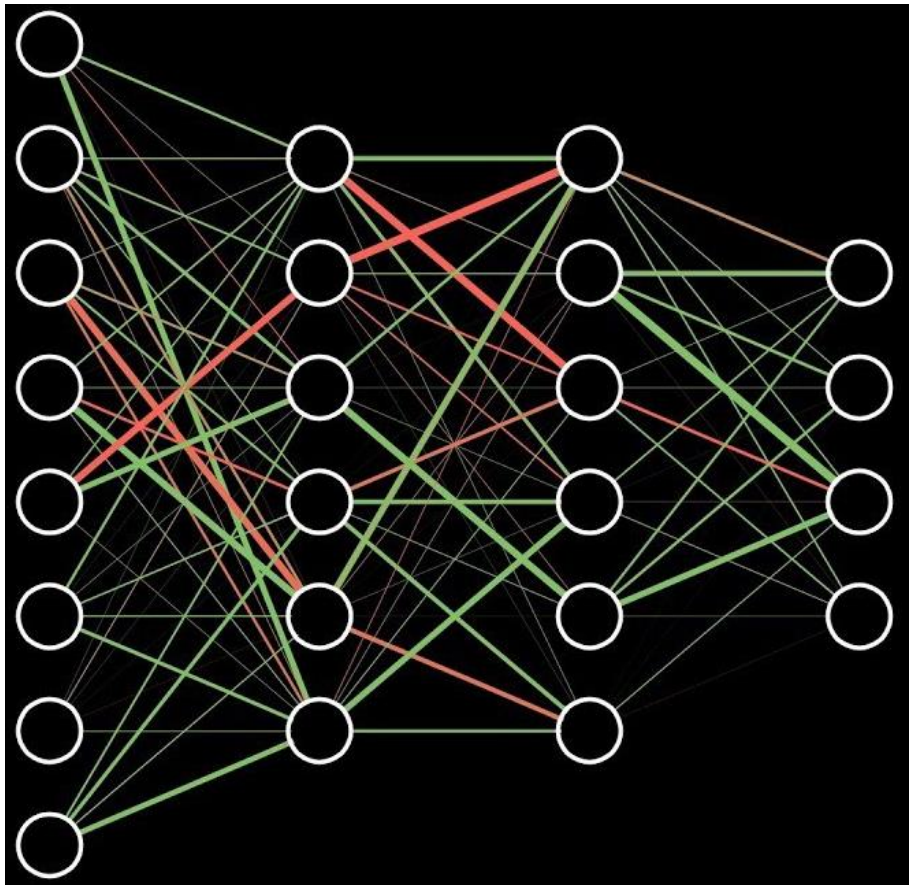
Significance

- We can model and predict various cognitive abilities in a large group of children and adolescents diagnosed with ADHD using functional neural activity during movie watching.
- Different sets of neural mechanisms are associated with different developmental periods.
- A better understanding of how cognition, development, and ADHD are related.

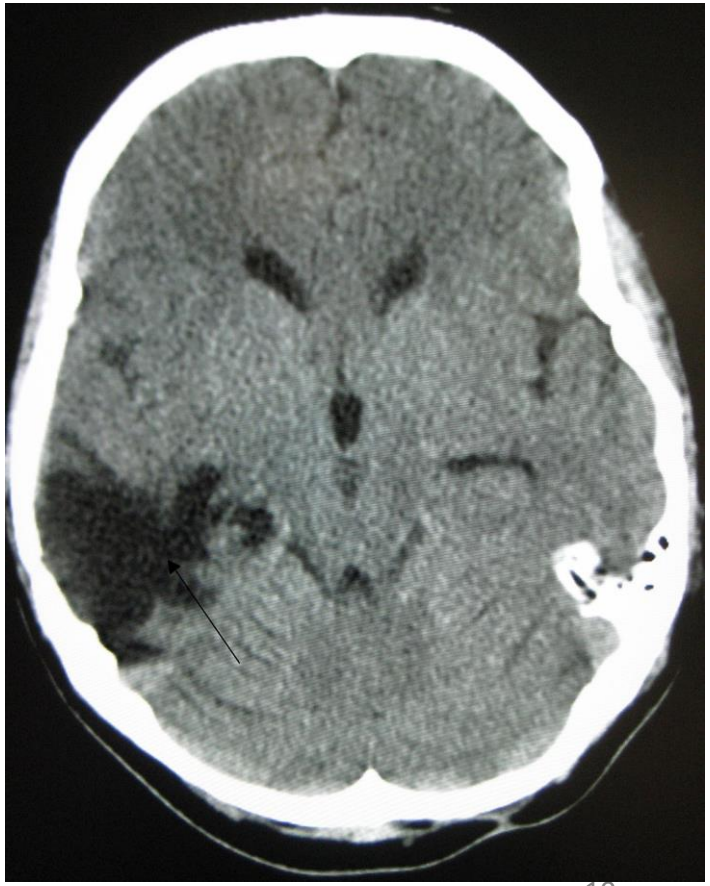
Future Directions

Other disorders

Other models



Causal approach



Acknowledgements

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  - Dr. Bobby Stojanoski
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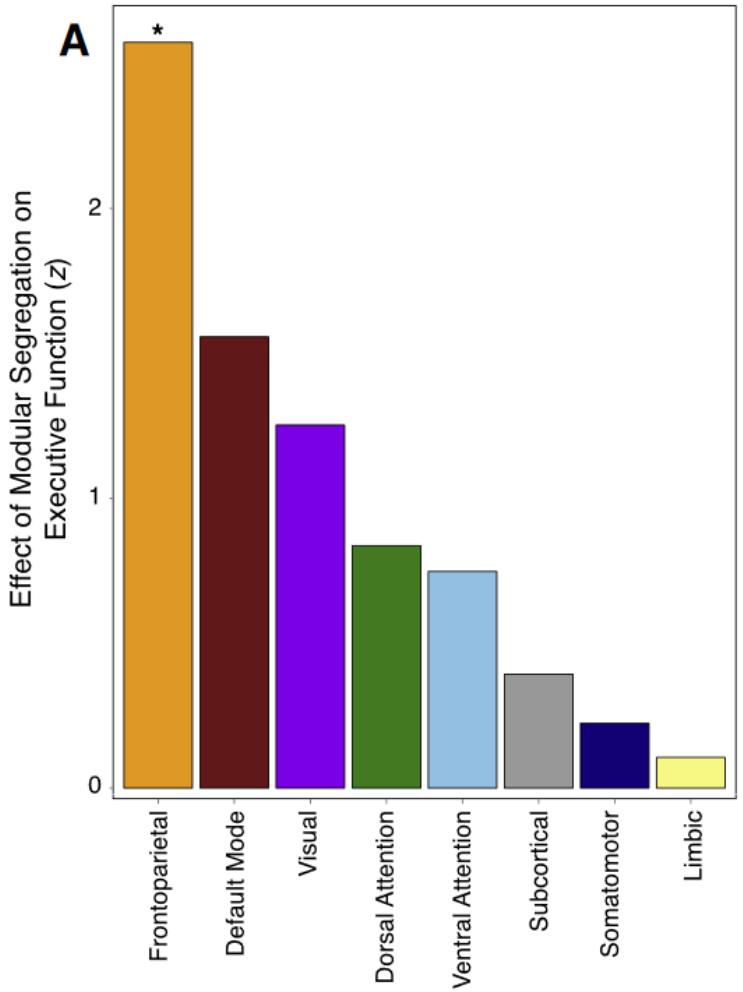
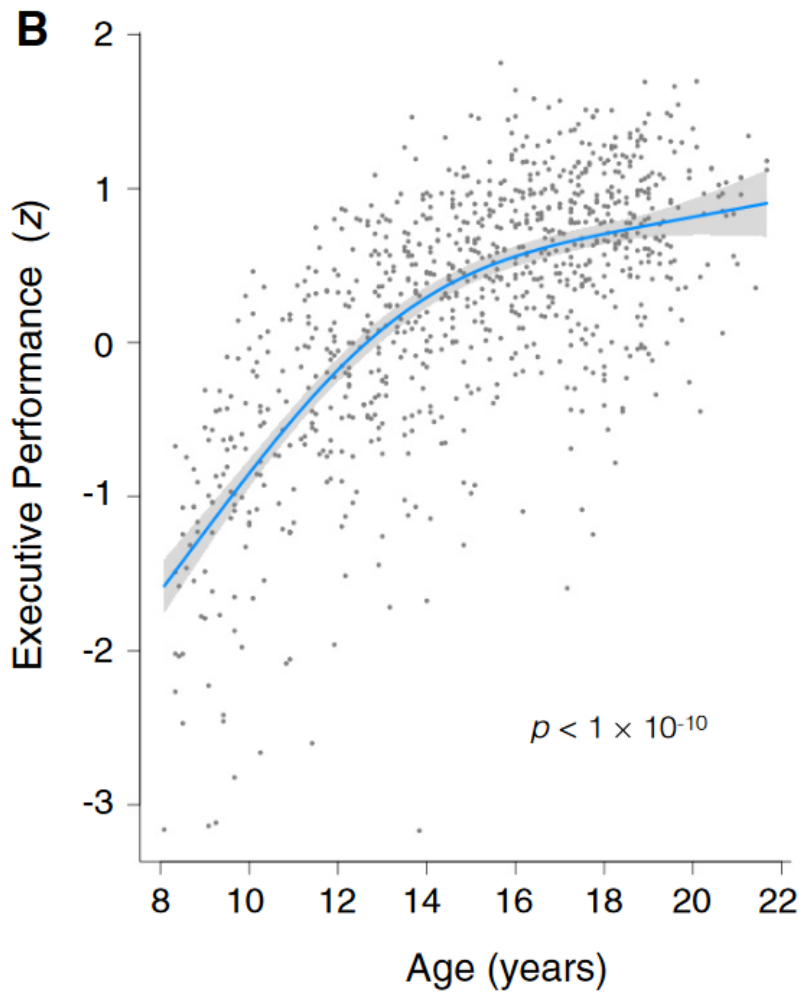
- Advisory Committee
  - Dr. Ryan Stevenson
  - Dr. Jorn Diedrichsen
  - Dr. Ali Khan
- The Child and Mind Institute for creating the Healthy Brain Biobank.

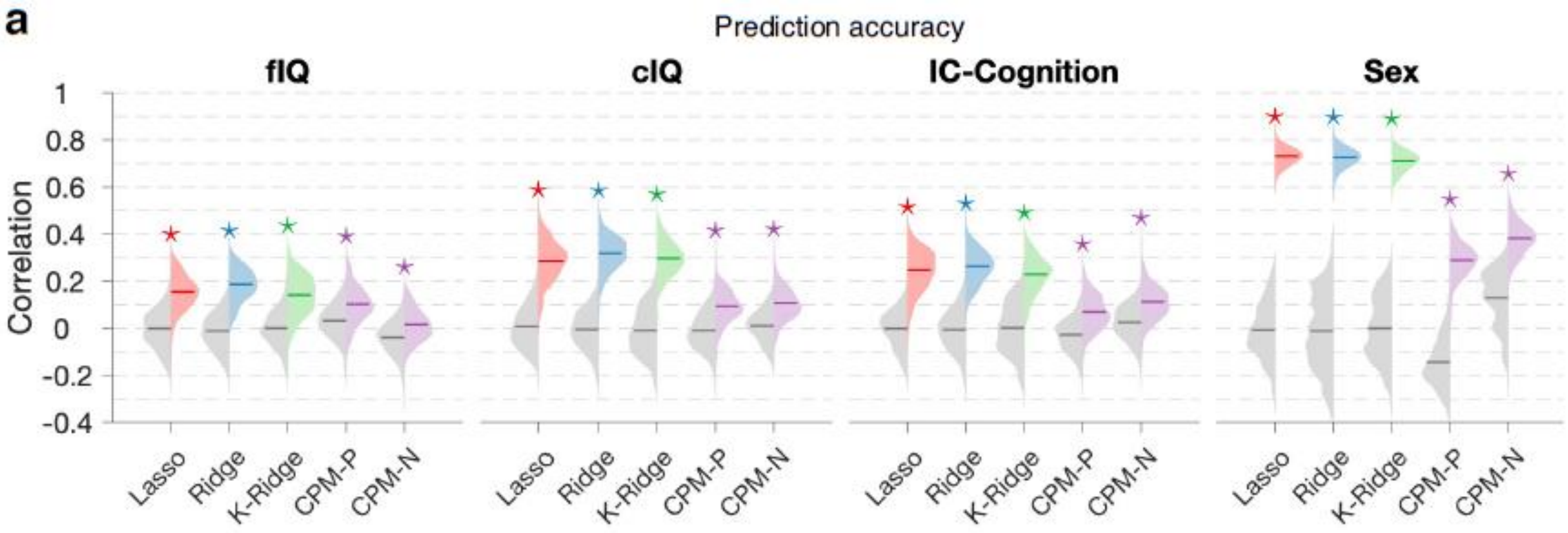
Executive Function Development





Baum et al. (2017)

Machine learning prediction of cognition from functional connectivity: Are feature weights reliable?



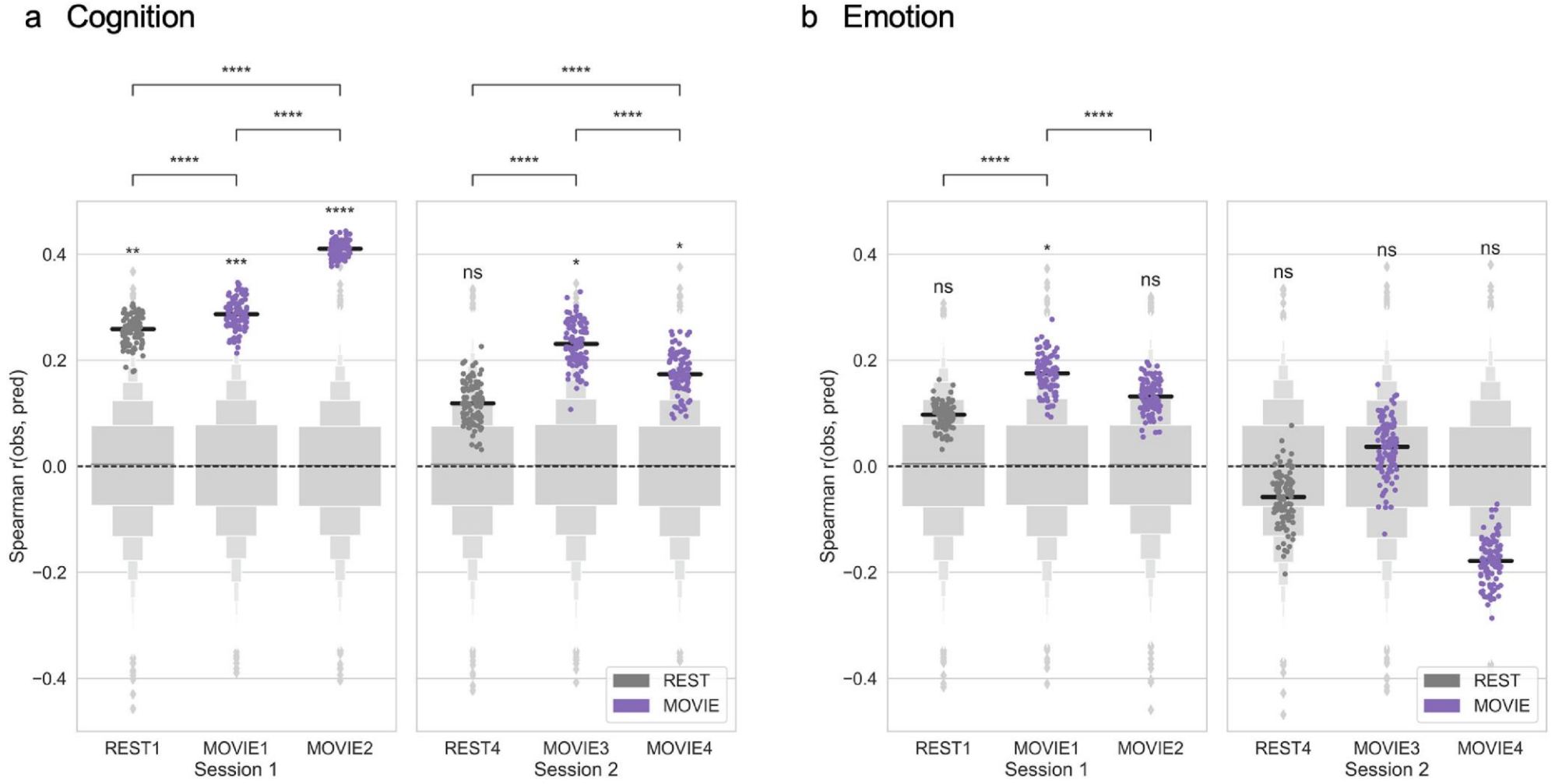
Tian & Zalesky (2021)

Prediction of neurocognition in youth from resting state fMRI

Analysis	General Ability	Speed/flexibility	Learning/memory
1. Main (leave-one-site-out)	$\boldsymbol{r = 0.31;\ p < 0.0001}$*	$\boldsymbol{r = 0.06;\ p = 0.02}$	$\boldsymbol{r = 0.15;\ p < 0.0001}$*
2. Demographic controls	$\boldsymbol{r = 0.29;\ p < 0.0001}$*	$r = 0.05;\ p = 0.11$	$\boldsymbol{r = 0.10;\ p = 0.01}$
3. Split-half - train 1, test 2	$\boldsymbol{r = 0.30;\ p < 1 \times 10^{-6}}$	$r = 0.05;\ p = 0.10$	$\boldsymbol{r = 0.12;\ p < 0.0001}$*
4. Split-half - train 2, test 1	$\boldsymbol{r = 0.33;\ p < 1 \times 10^{-6}}$	$\boldsymbol{r = 0.09;\ p = 0.005}$	$\boldsymbol{r = 0.15;\ p < 1 \times 10^{-6}}$
5. Low motion, 75 subj. min	$\boldsymbol{r = 0.30;\ p < 0.0001}$*	$r = 0.04;\ p = 0.27$	$r = 0.01;\ p = 0.58$
6. Low motion, 50 subj. min	$\boldsymbol{r = 0.30;\ p < 0.0001}$*	$r = 0.02;\ p = 0.64$	$r = 0.04;\ p = 0.22$

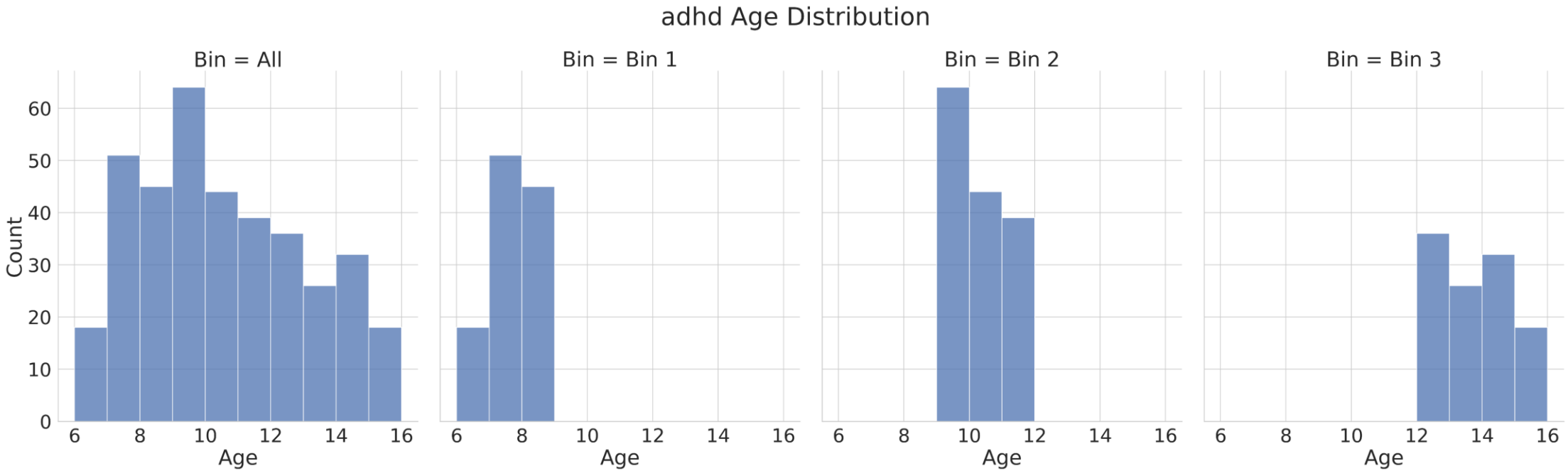
Sripada et al. (2020)

Movie-watching outperforms rest for functional connectivity-based prediction of behavior

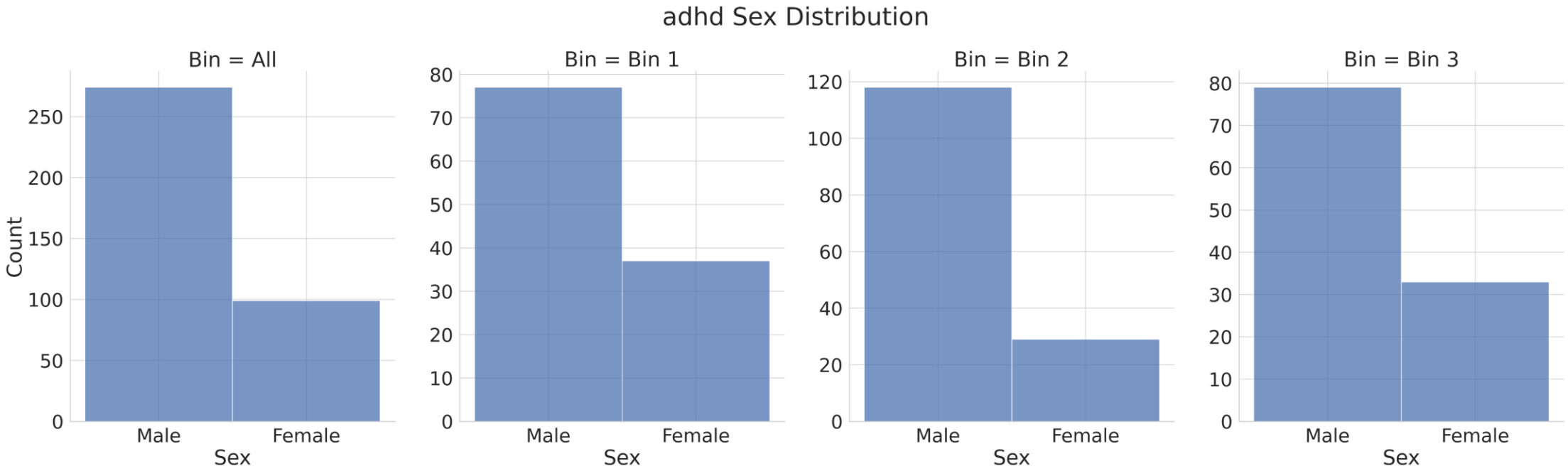


Finn & Bandettini (2021)

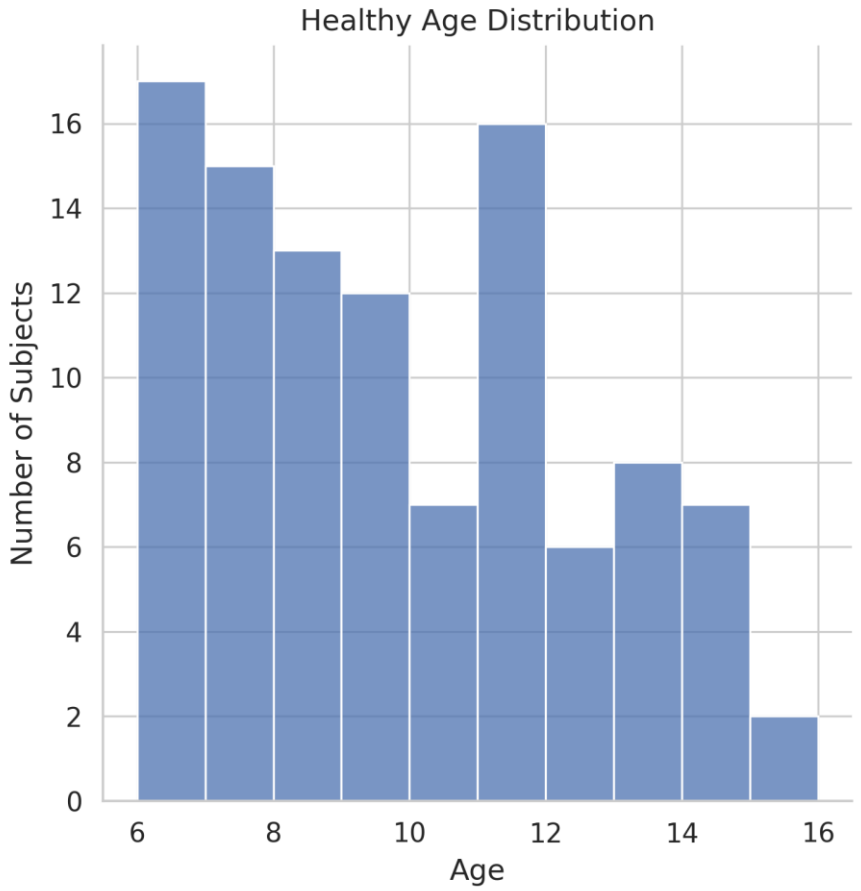
ADHD Age Distribution



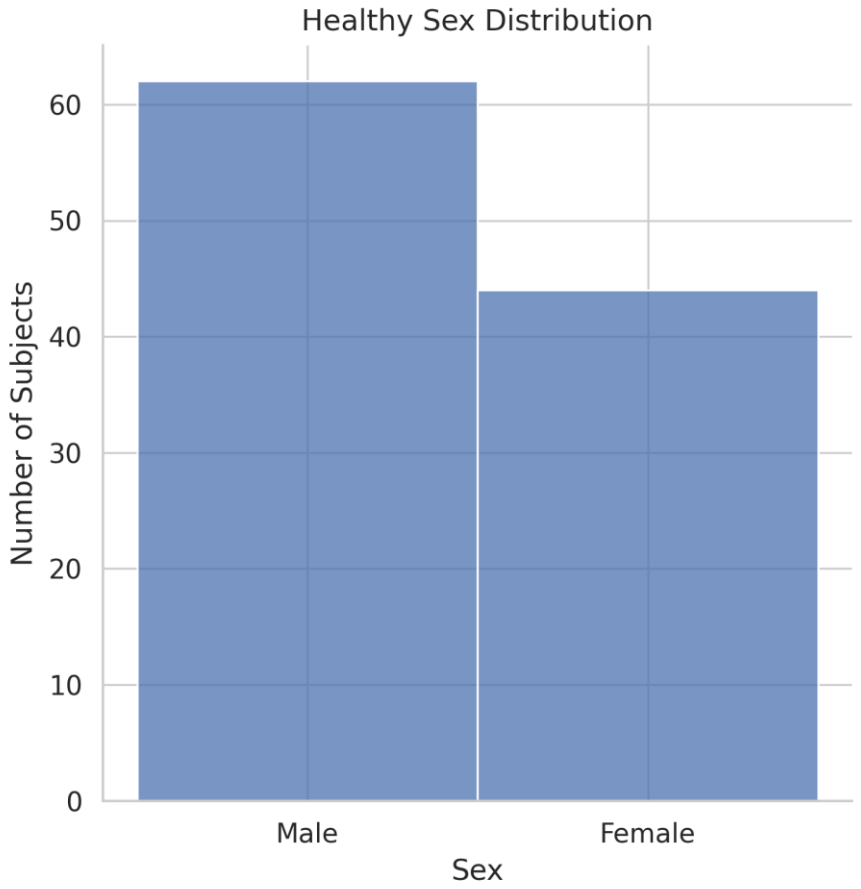
ADHD Sex Distribution



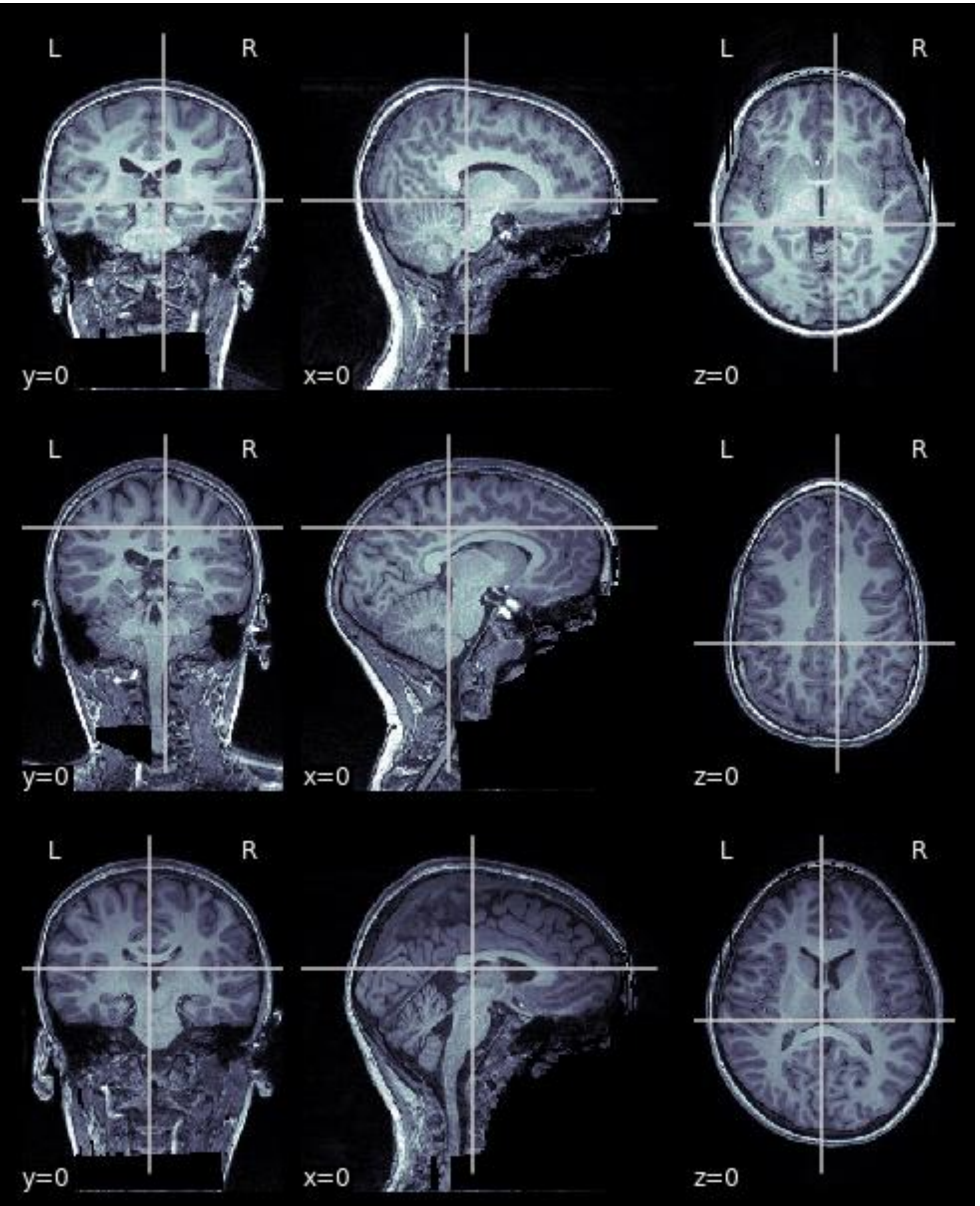
TD Age Distribution

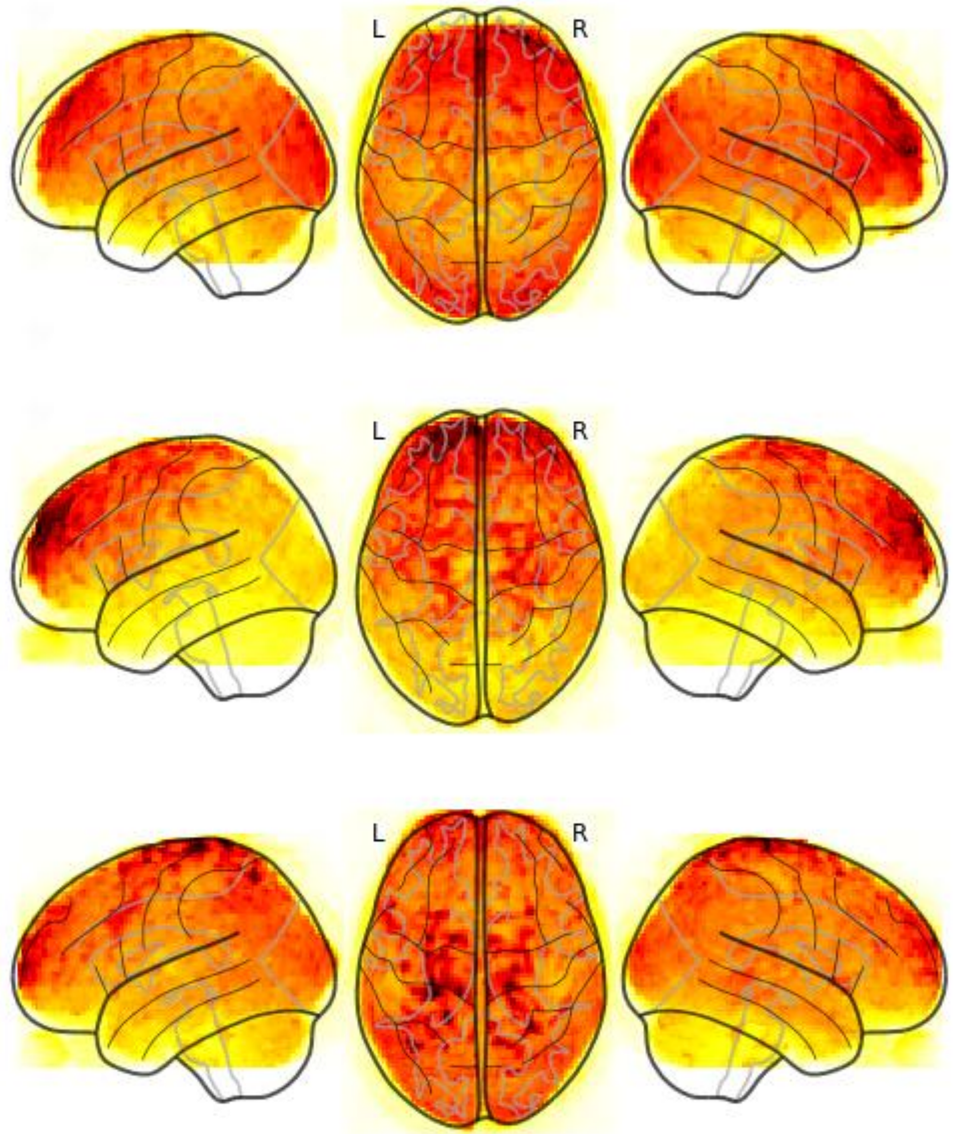


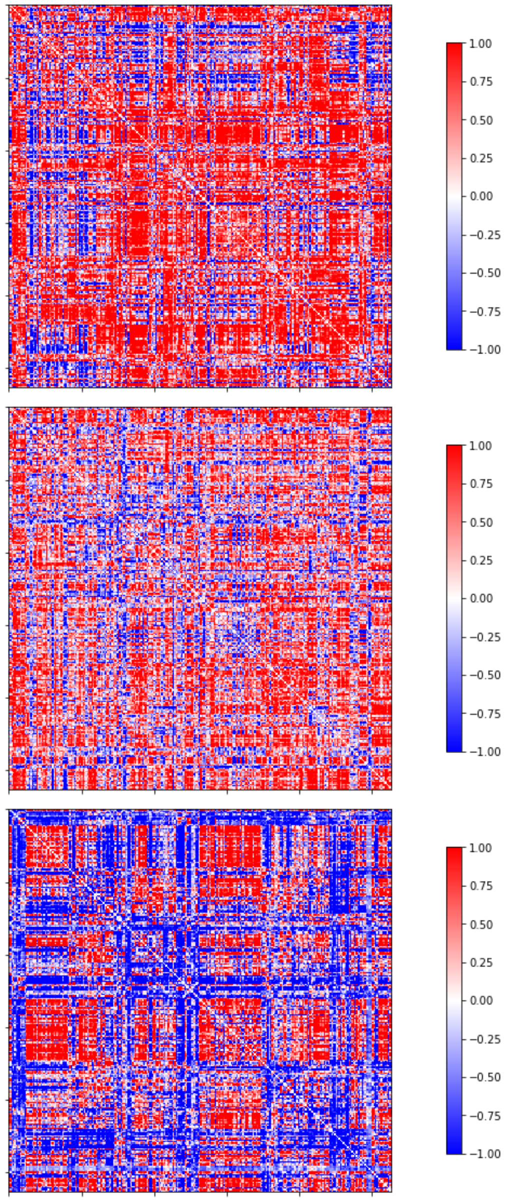
TD Sex Distribution



Brain Data







WISC-V

Full Scale

Verbal Comprehension	Visual Spatial	Fluid Reasoning	Working Memory	Processing Speed
Similarities	Block Design	Matrix Reasoning	Digit Span	Coding
Vocabulary	*Visual Puzzles*	Figure Weights	*Picture Span*	*Symbol Search*
Information		*Picture Concepts*	*Letter–Number Sequencing*	*Cancellation*
Comprehension		*Arithmetic*		

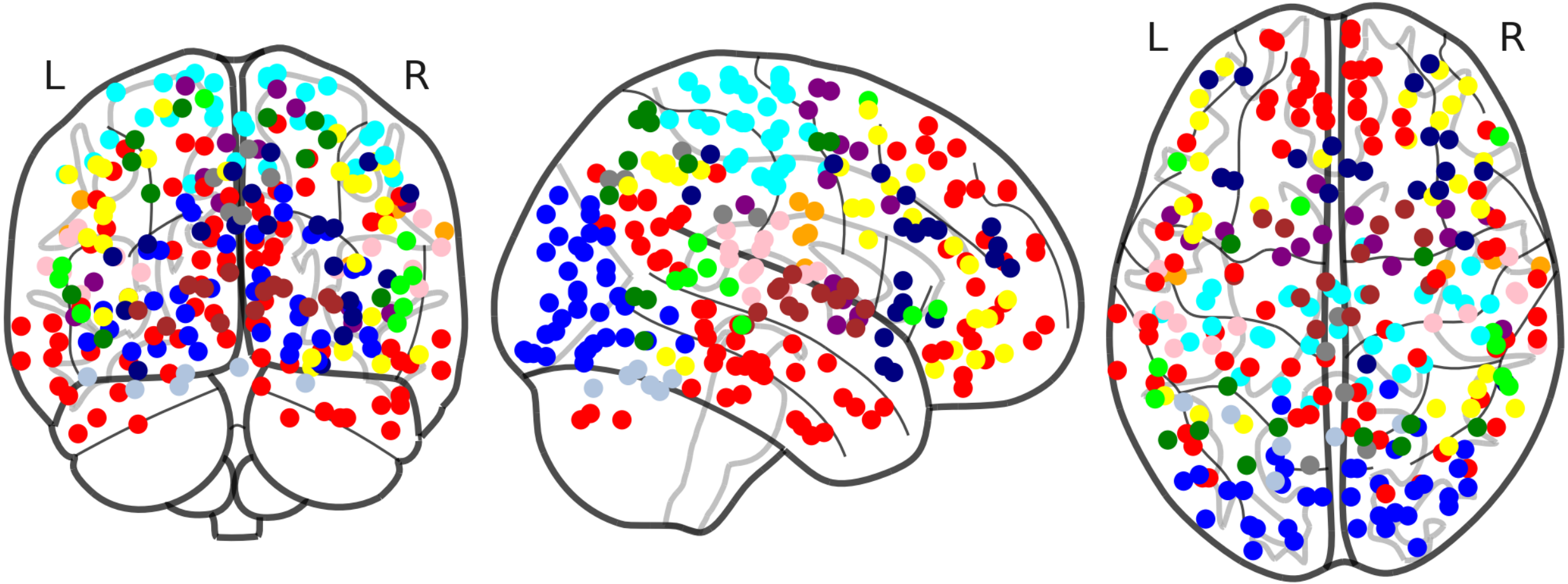
Primary Index Scales

Verbal Comprehension	Visual Spatial	Fluid Reasoning	Working Memory	Processing Speed
Similarities	Block Design	Matrix Reasoning	Digit Span	Coding
Vocabulary	Visual Puzzles	Figure Weights	Picture Span	Symbol Search

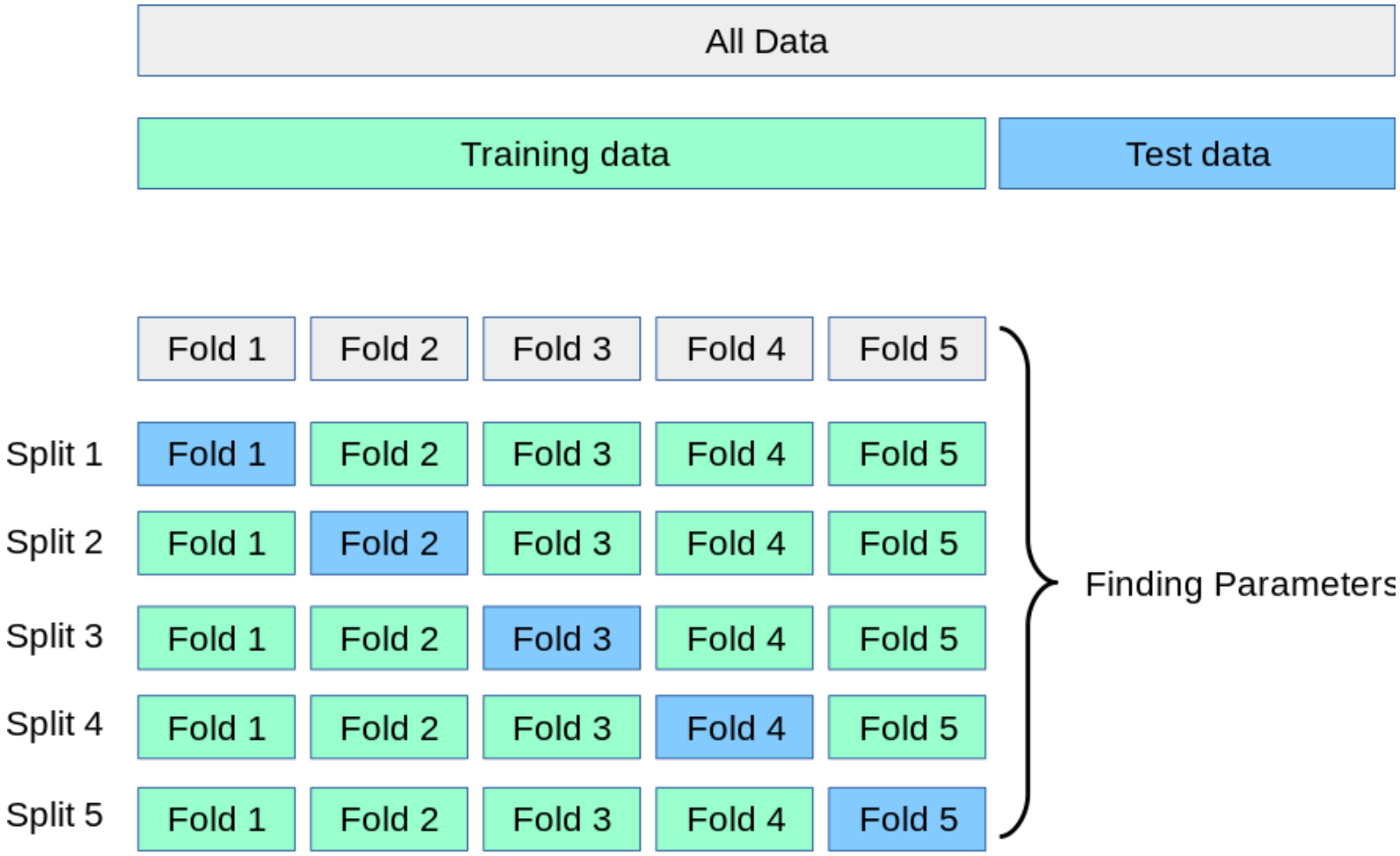
AA Preprocessing Modules

- Data
  - aamod_structuralfromnifti: find structural input files from nifti.
  - aamod_epifromnifti: find EPI input files from nifti.
  - aamod_tsdiffana: calculate measurements of noise in time series.
  - aamod_realign: uses SPM realignment to perform motion correction on fMRI data, realigning each image to the first one.
- Structural
  - aamod_coreg_noss: spatially align (coregister) the mean fMRI volume with the structural.
  - aamod_norm_noss: normalization. Scale and warp the structural image so that each brain region matches the corresponding one in the MNI standard template (average brain).
- Functional
  - aamod_bet: use the FSL brain extraction tool (BET).
  - aamod_bet_epi_reslicing: skull stripping with BET.
  - aamod_mask_fromstruct: create different threshold masks from the segmentation.
  - aamod_compSignal: get the signal from the CSF, WM, GM, and OOB.
  - aamod_norm_write: apply the scaling and warping derived by norm_noss to the fMRI images.
  - aamod_smooth: spatially smooths the fMRI data.
- Modelling
  - aamod_listspikes: lists spikes (big changes from one image to the next) in the MRI data.
  - aamod_firstlevel_scrubbingmodel_BS: cleans and filters time series.
  - aamod_firstlevel_modelestimate_saveresids: estimate a specified model and save the residuals.

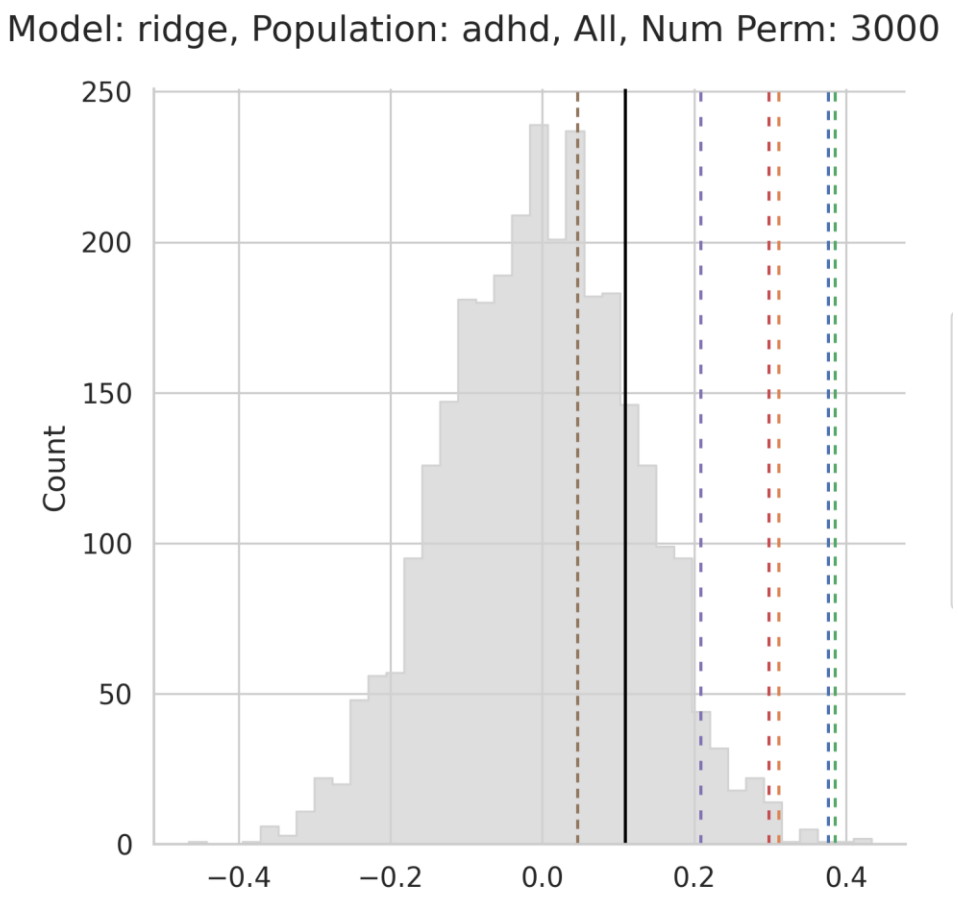
Power Atlas

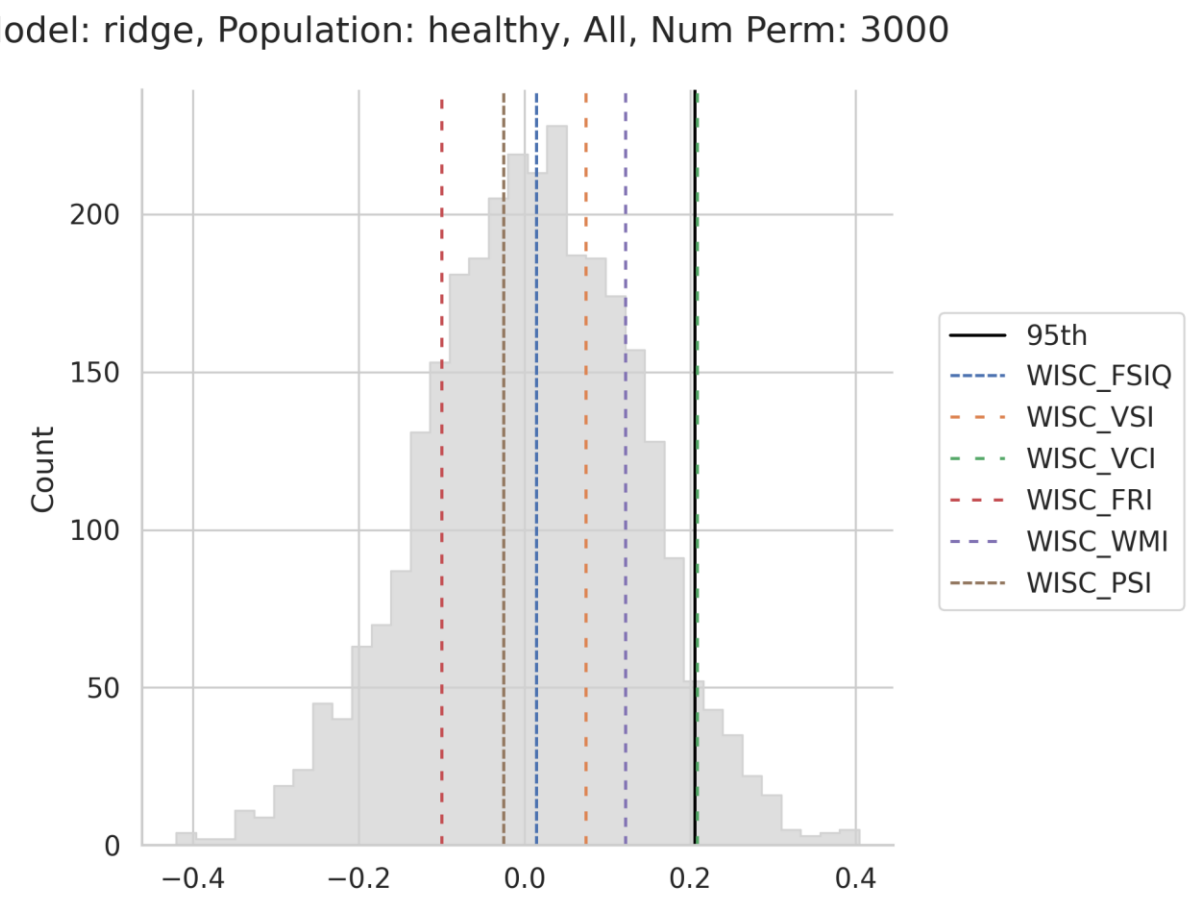


Cross Validation



Permutation Testing + Max Statistic





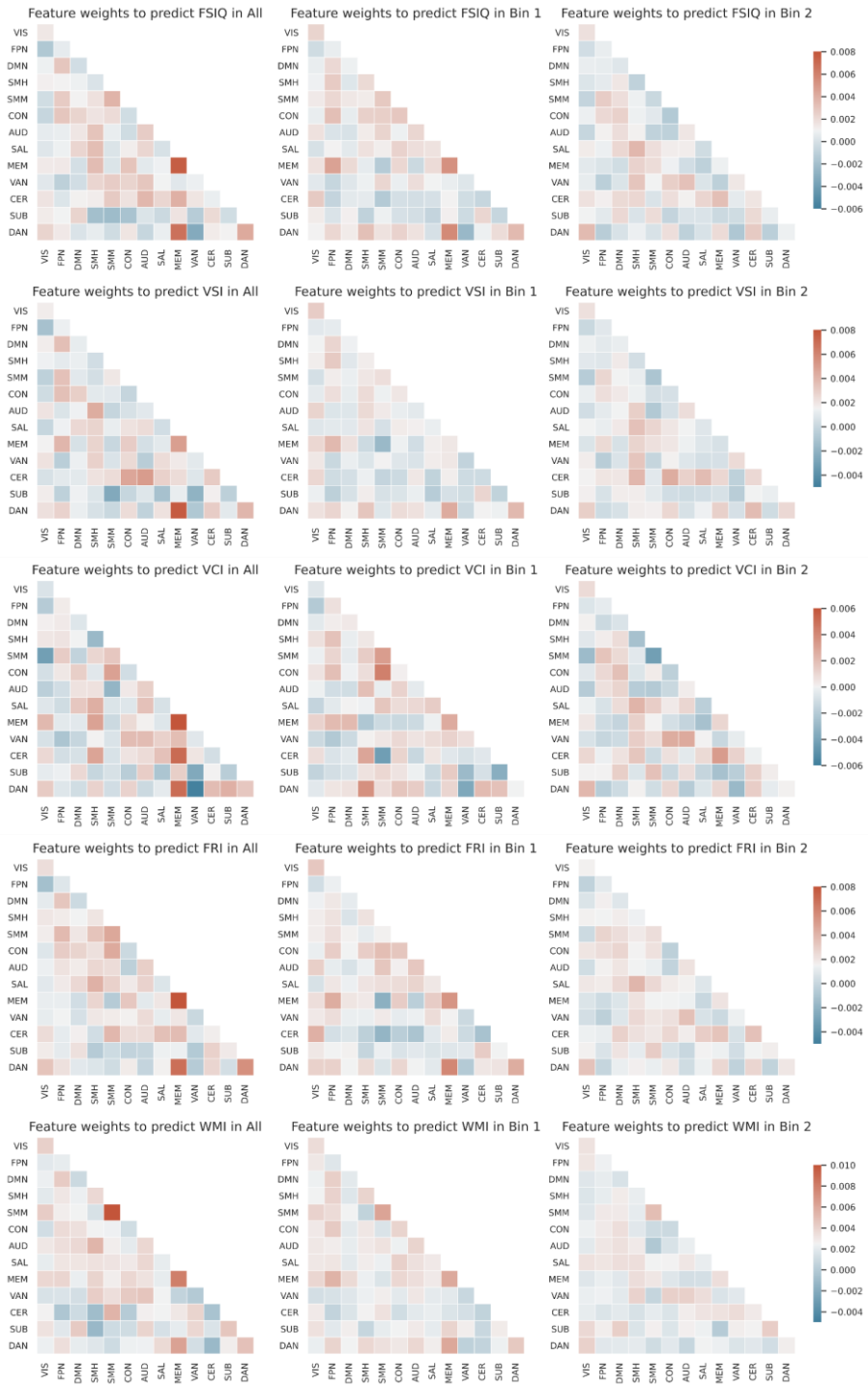
Intraclass Correlation Coefficient (ICC)

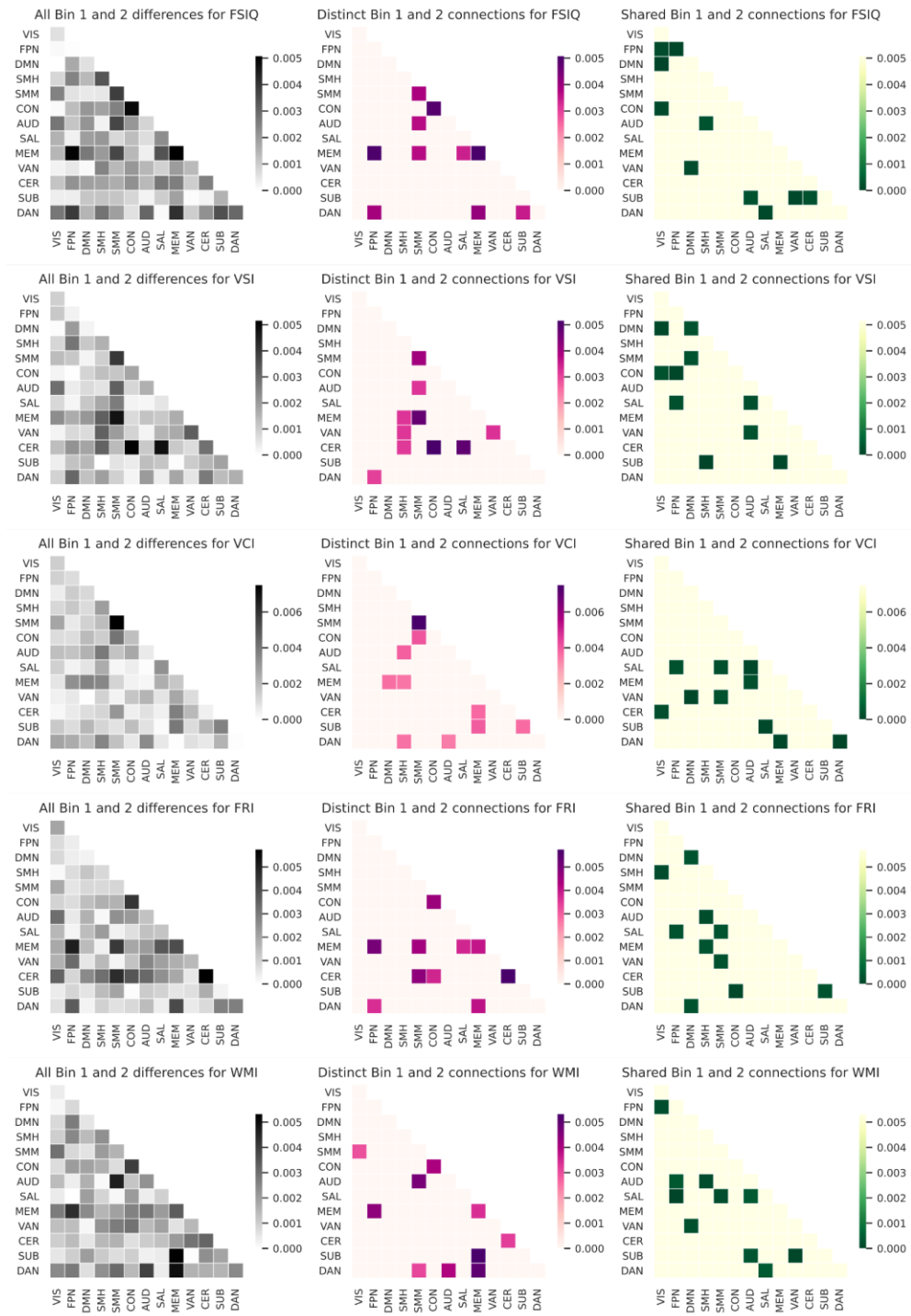
WISC	All (n=373)	Bin 1 (n=114)	Bin 2 (n=147)	Bin 3 (n=112)
Intelligence Quotient (FSIQ)	0.96	0.97	0.98	0.97
Visual Spatial (VSI)	0.96	0.95	0.94	0.93
Verbal Comprehension (VCI)	0.96	0.97	0.96	0.96
Fluid Reasoning (FRI)	0.96	0.99	0.96	0.97
Working Memory (WMI)	0.95	0.96	0.98	0.93
Processing Speed (PSI)	0.96	0.92	0.98	0.98

Cognition in ADHD (Bin 2 Equal)

WISC	Bin 2 (n=147)	Bin 2 (n=113)
Intelligence Quotient (FSIQ)	0.35*	0.37*
Visual Spatial (VSI)	0.21*	0.24*
Verbal Comprehension (VCI)	0.35*	0.37*
Fluid Reasoning (FRI)	0.31*	0.30*
Working Memory (WMI)	0.29*	0.35*
Processing Speed (PSI)	0.06	0.04

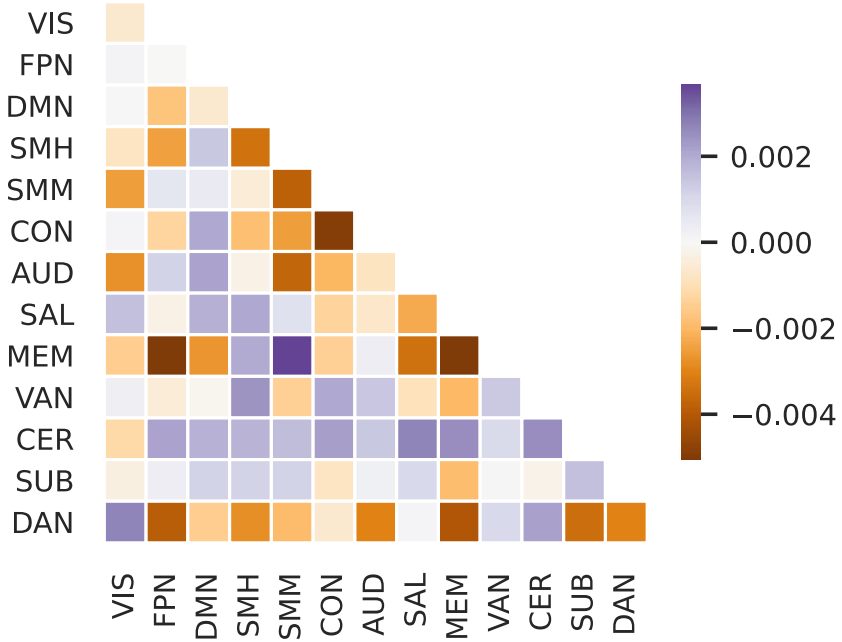
Values are Pearson correlation (r)
Starred (*) values indicate statistically significant at $p<.05$ max-statistic corrected


Feature weights to predict FSIQ in All
Feature weights to predict FSIQ in Bin 1
Feature weights to predict FSIQ in Bin 2
Feature weights to predict VSI in All
Feature weights to predict VSI in Bin 1
Feature weights to predict VSI in Bin 2
Feature weights to predict VCI in All
Feature weights to predict VCI in Bin 1
Feature weights to predict VCI in Bin 2
Feature weights to predict FRI in All
Feature weights to predict FRI in Bin 1
Feature weights to predict FRI in Bin 2
Feature weights to predict WMI in All
Feature weights to predict WMI in Bin 1
Feature weights to predict WMI in Bin 2
VIS FPN DMN SMH SMM CON AUD SAL MEM VAN CER SUB DAN

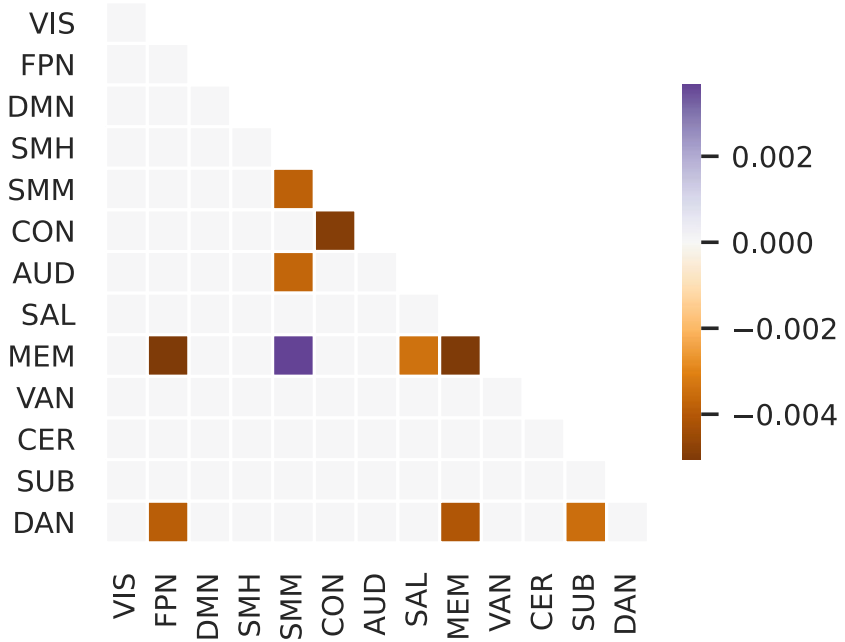

All Bin 1 and 2 differences for FSIQ
Distinct Bin 1 and 2 connections for FSIQ
Shared Bin 1 and 2 connections for FSIQ
All Bin 1 and 2 differences for VSI
Distinct Bin 1 and 2 connections for VSI
Shared Bin 1 and 2 connections for VSI
All Bin 1 and 2 differences for VCI
Distinct Bin 1 and 2 connections for VCI
Shared Bin 1 and 2 connections for VCI
All Bin 1 and 2 differences for FRI
Distinct Bin 1 and 2 connections for FRI
Shared Bin 1 and 2 connections for FRI
All Bin 1 and 2 differences for WMI
Distinct Bin 1 and 2 connections for WMI
Shared Bin 1 and 2 connections for WMI
VIS FPN DMN SMH SMM CON AUD SAL MEM VAN CER SUB DAN

Feature Weight Differences & Similarities (FSIQ)

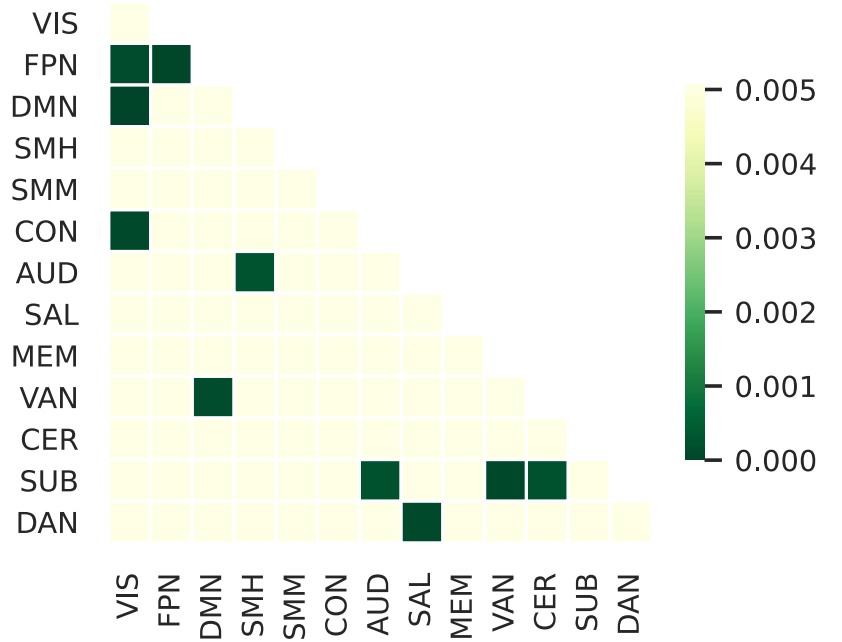
All Bin 1 and 2 differences for FSIQ

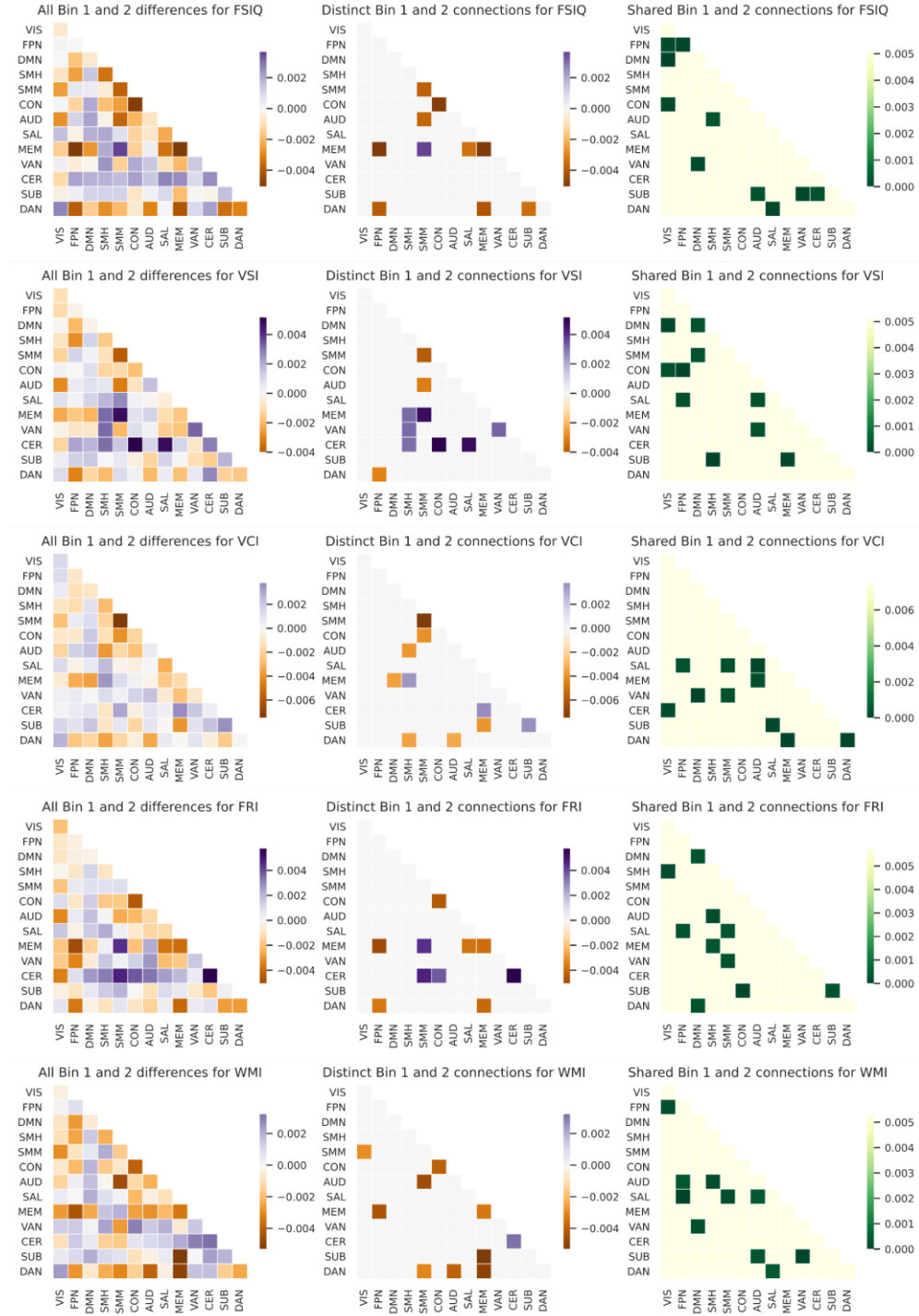


Distinct Bin 1 and 2 connections for FSIQ



Shared Bin 1 and 2 connections for FSIQ




All Bin 1 and 2 differences for FSIQ
Distinct Bin 1 and 2 connections for FSIQ
Shared Bin 1 and 2 connections for FSIQ
All Bin 1 and 2 differences for VSI
Distinct Bin 1 and 2 connections for VSI
Shared Bin 1 and 2 connections for VSI
All Bin 1 and 2 differences for VCI
Distinct Bin 1 and 2 connections for VCI
Shared Bin 1 and 2 connections for VCI
All Bin 1 and 2 differences for FRI
Distinct Bin 1 and 2 connections for FRI
Shared Bin 1 and 2 connections for FRI
All Bin 1 and 2 differences for WMI
Distinct Bin 1 and 2 connections for WMI
Shared Bin 1 and 2 connections for WMI
VIS
FPN
DMN
SMH
SMM
CON
AUD
SAL
MEM
VAN
CER
SUB
DAN