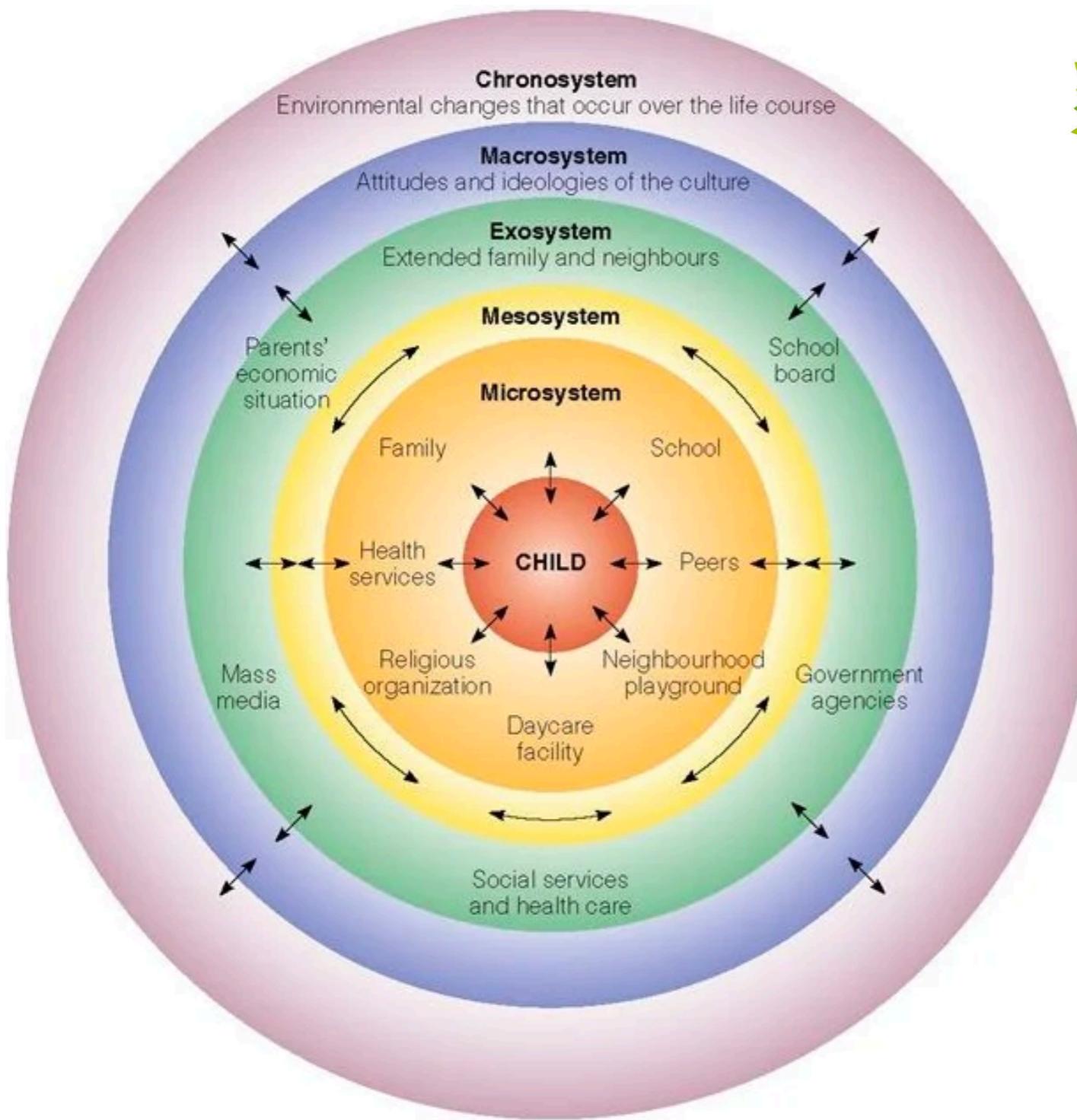


# A general exposome factor explains individual differences in functional brain network topography and cognition in youth

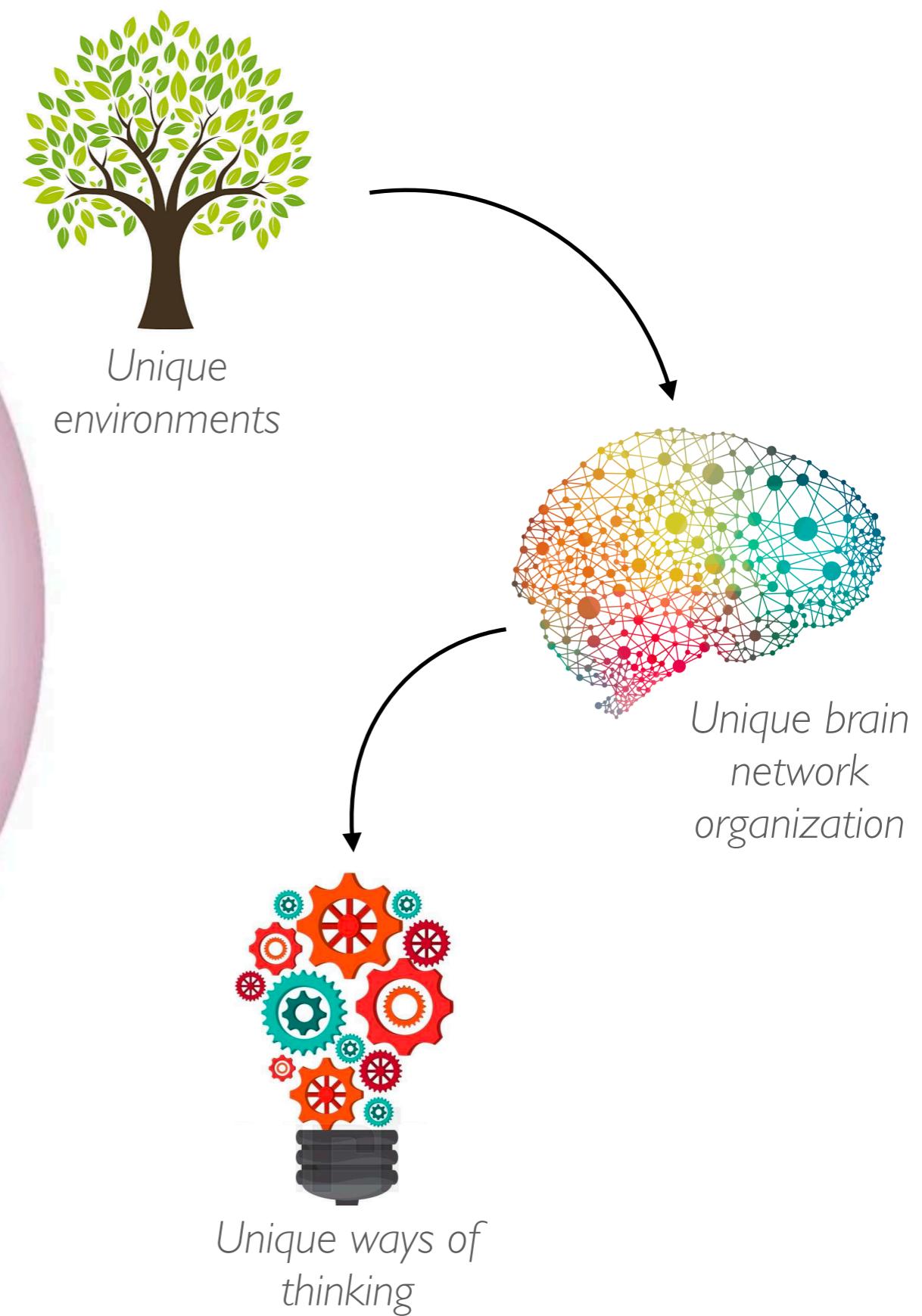
Arielle S. Keller  
07.18.23



# Our brains develop in unique, complex environments



Bonfenbrenner's Ecological Systems Theory



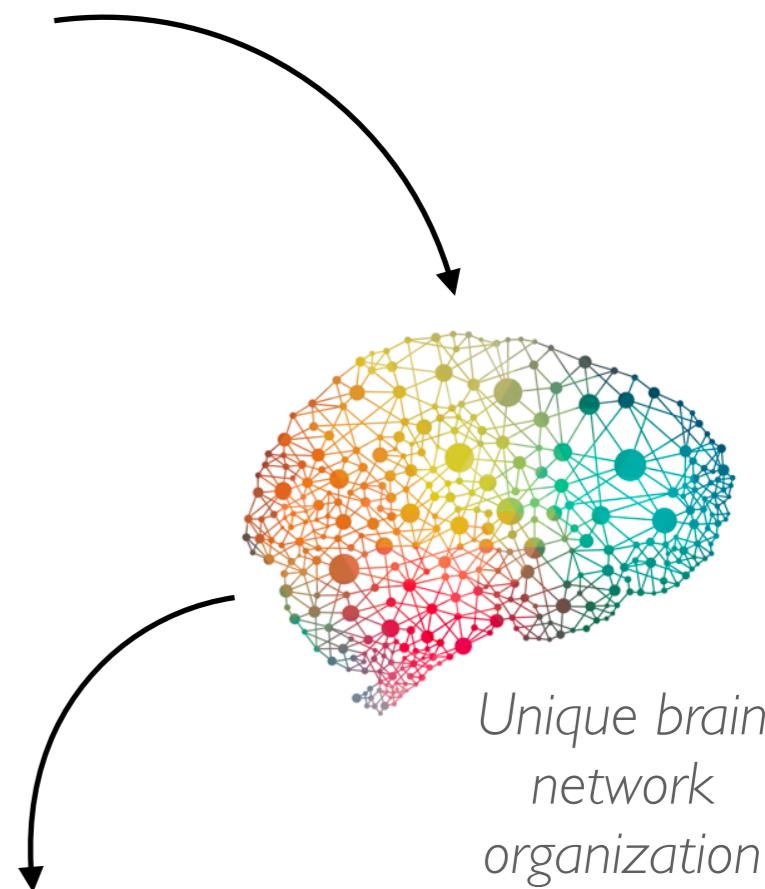
# Our brains develop in unique, complex environments

## Why this matters:

- Poorer youth cognition is associated with
  - poorer adult cognition (Agha et al., 2019)
  - diverse psychopathology (Shanmugan et al., 2016)
  - increased risk-taking (Shamosh et al., 2008)
  - cardiovascular disease (Hart et al., 2004)
  - all-cause mortality (Batty et al., 2007)
  - health, wealth, and public safety (Moffitt et al., 2011)
- Adverse childhood experiences (e.g., abuse/neglect) and environmental disparities (e.g., SES) can impact both cognition (Pechtel et al., 2011) and functional brain networks (Murtha et al., 2022)



Unique environments



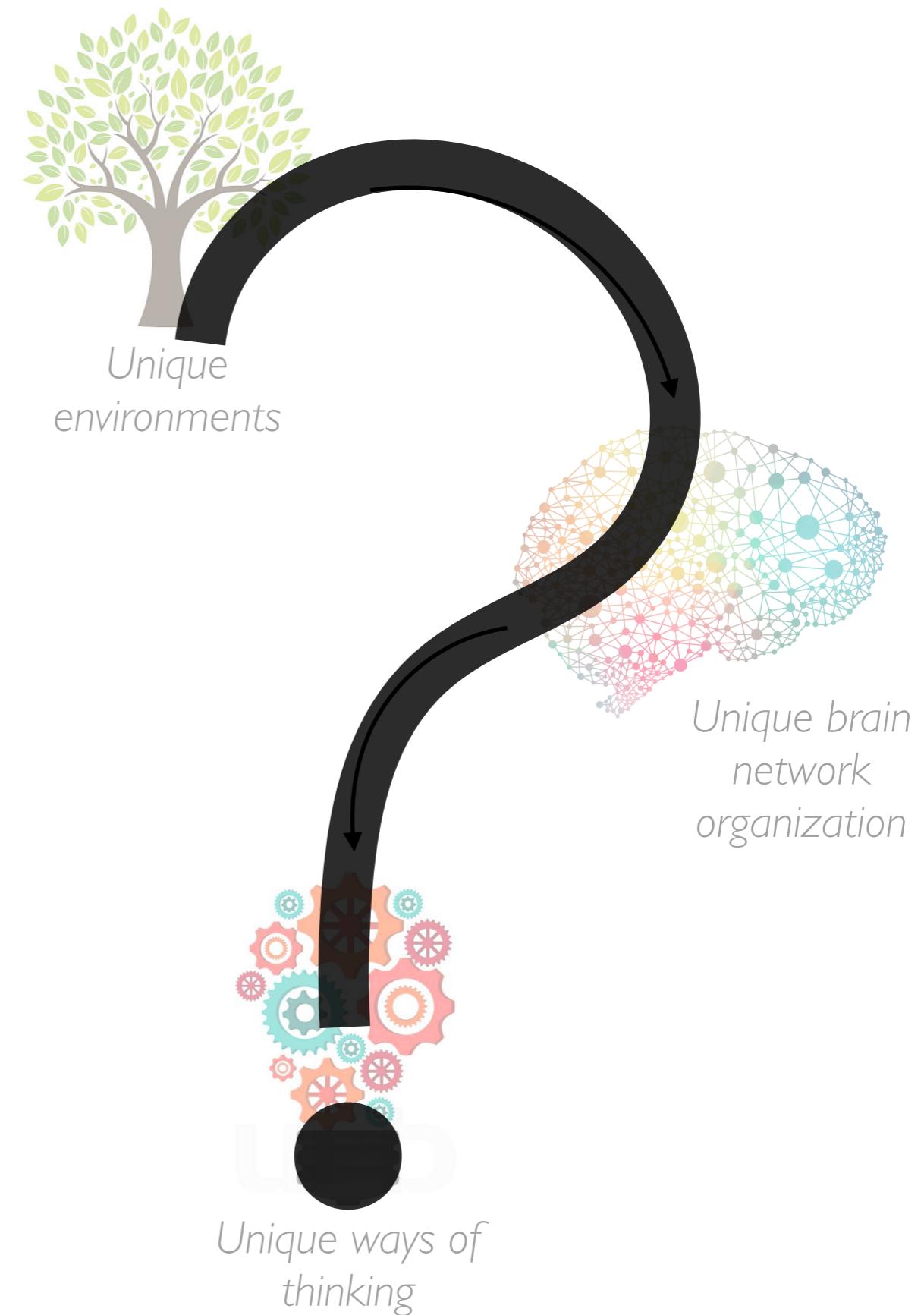
Unique brain network organization



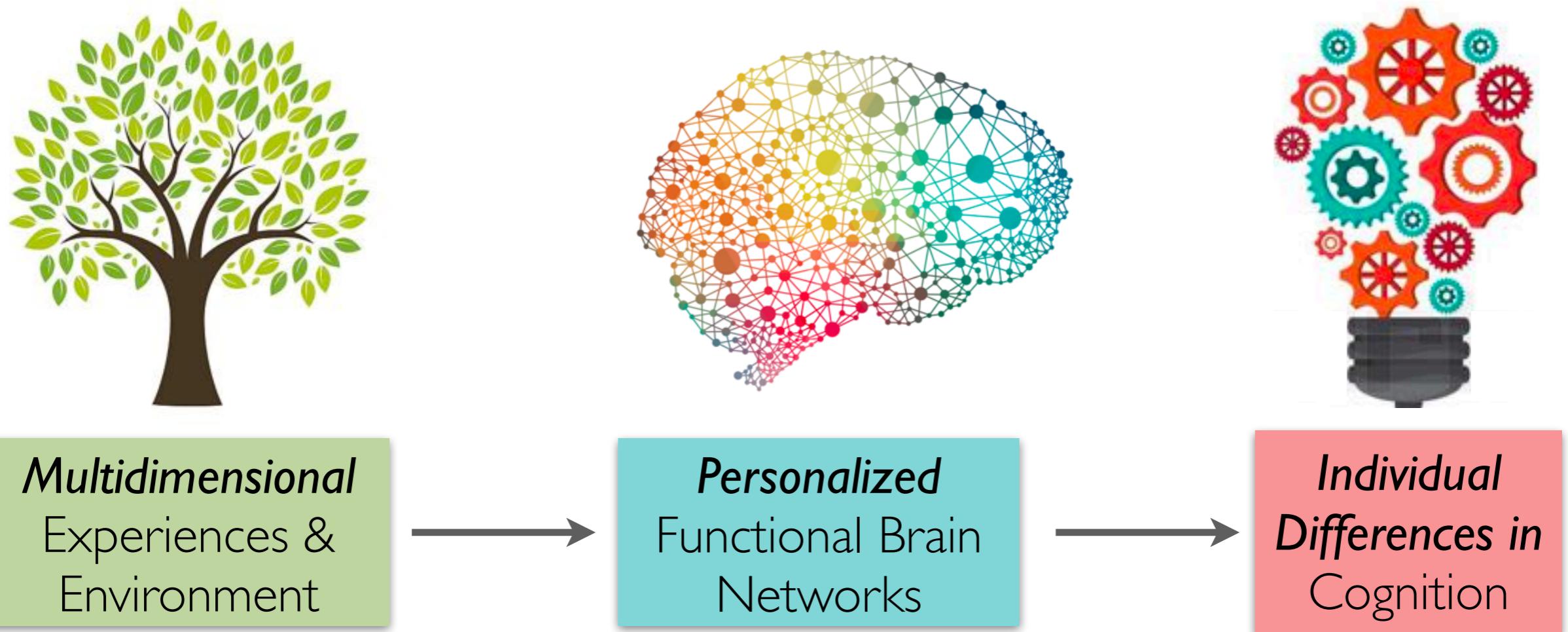
Unique ways of thinking

# The big, broad, burning question

*How do the unique,  
complex environments  
we grow up in shape  
our developing brains  
and minds?*



# Motivation



- **Reproducibility/Generalizability:** access to large cross-sectional and longitudinal datasets
- **Specificity:** granular measures of early experiences/environment and subtypes of cognition
- **Personalized Neuroscience:** charting of individuals' functional brain development

# My journey to this point



Cognition (Attention)



Functional Brain Networks



Experiences & Environment

- Individual differences in cognition in adults are associated with:
  - depression
  - anxiety
  - specific EEG markers
  - functional connectivity patterns
- Individual differences in the cortical layout of functional brain networks are associated with cognition in kids
- Hierarchical functional brain network development may support cognitive development
- Certain aspects of early life experiences (e.g., specific caregiving styles) are associated with cognition in kids
- Cognitive impairments in adults are associated with self-reports of stressful early life experiences

# Motivation



***Multidimensional***  
Experiences &  
Environment



***Personalized***  
Functional Brain  
Networks



***Individual***  
***Differences in***  
Cognition

*How do the unique, complex environments we grow up in shape our developing brains and minds?*

# Outline

I. How do we measure environment, brain, and behavior?

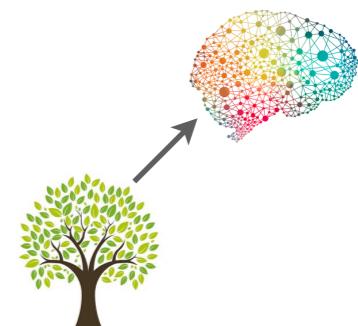


2. How does the environment shape cognition?

and I will sneak in some pics of my puppy

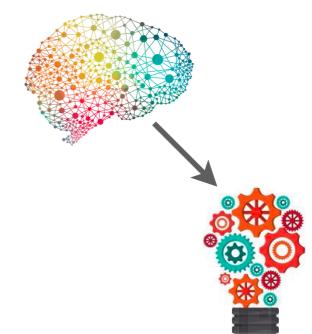


3. How does the environment shape brain organization?

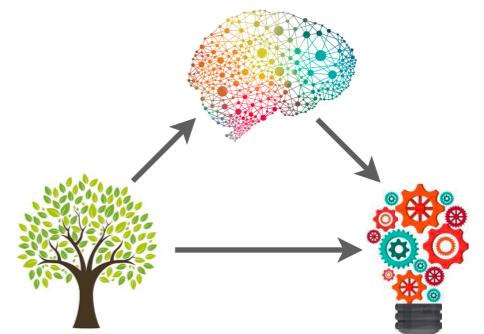


4. How does brain organization relate to cognitive abilities?

and I will sneak in pics of someone else's pet

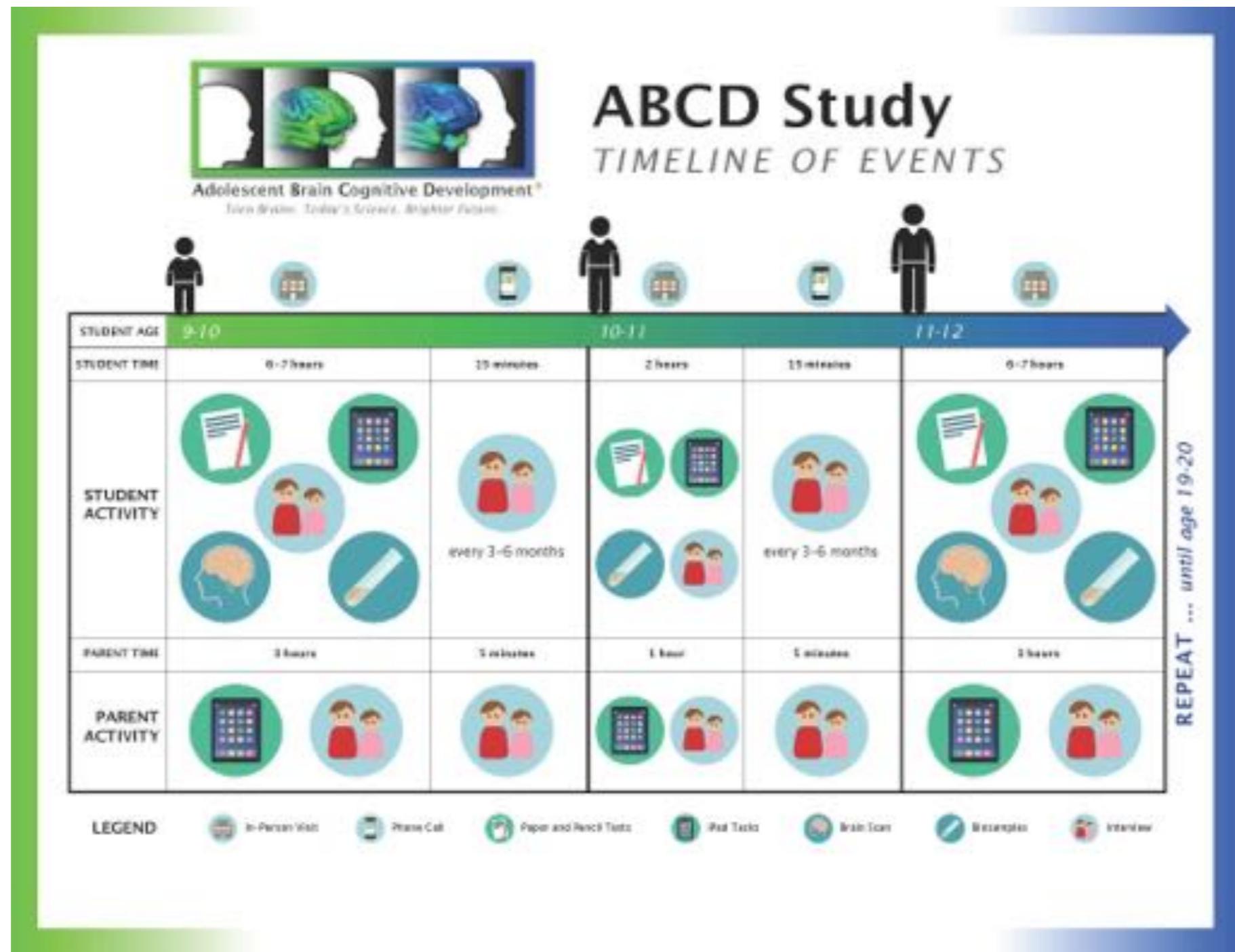


5. Putting it all together!



# Large Cross-Sectional and Longitudinal Data

$n = 11,878$



All analyses conducted in matched Discovery and  
Replication samples (Feczko et al., 2021)

# Dimensionality Reduction

## ENVIRONMENT

each child's unique multi-dimensional environment



longitudinal bifactor analysis

general exposome  
Exp-Factor

exposome sub-factors

- School
- Family Values
- Family Turmoil
- Dense Urban Poverty
- Extracurriculars
- Screen Time

## COGNITION

cognitive tasks

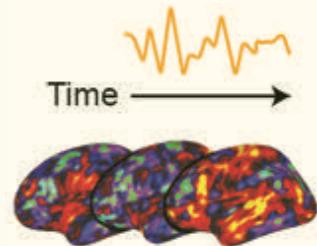
- Picture Vocabulary
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- Picture Sequence
- Pattern Comparison
- Reading Recognition
- Card Sorting
- List Learning
- Little Man Task
- RAVLT

Bayesian PCA  
(Thompson et al., 2019)

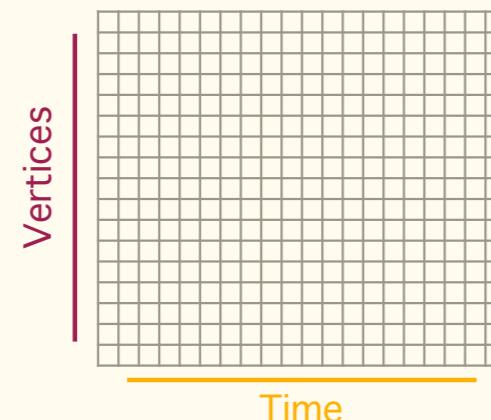
cognitive domains

- General Cognition
- Executive Function
- Learning and Memory

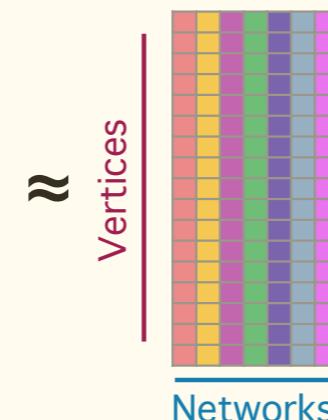
functional neuroimaging



BOLD timeseries at each vertex



network topography



Vertices

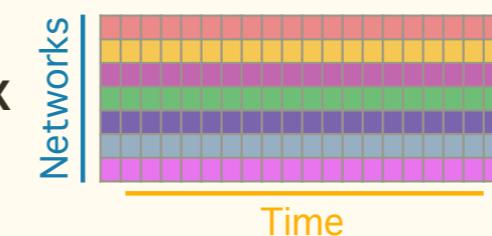
Networks

X

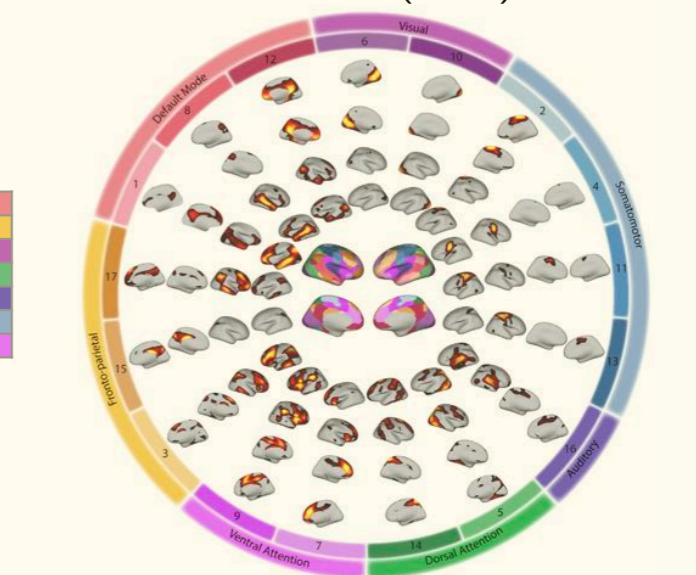
Time

## BRAIN NETWORKS

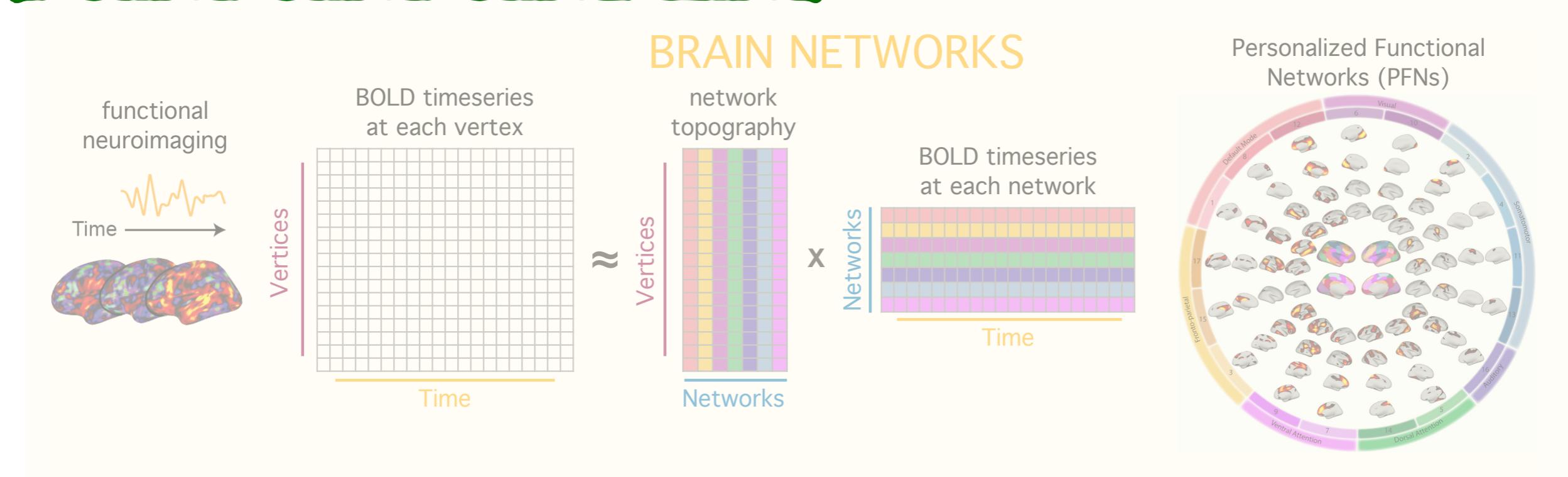
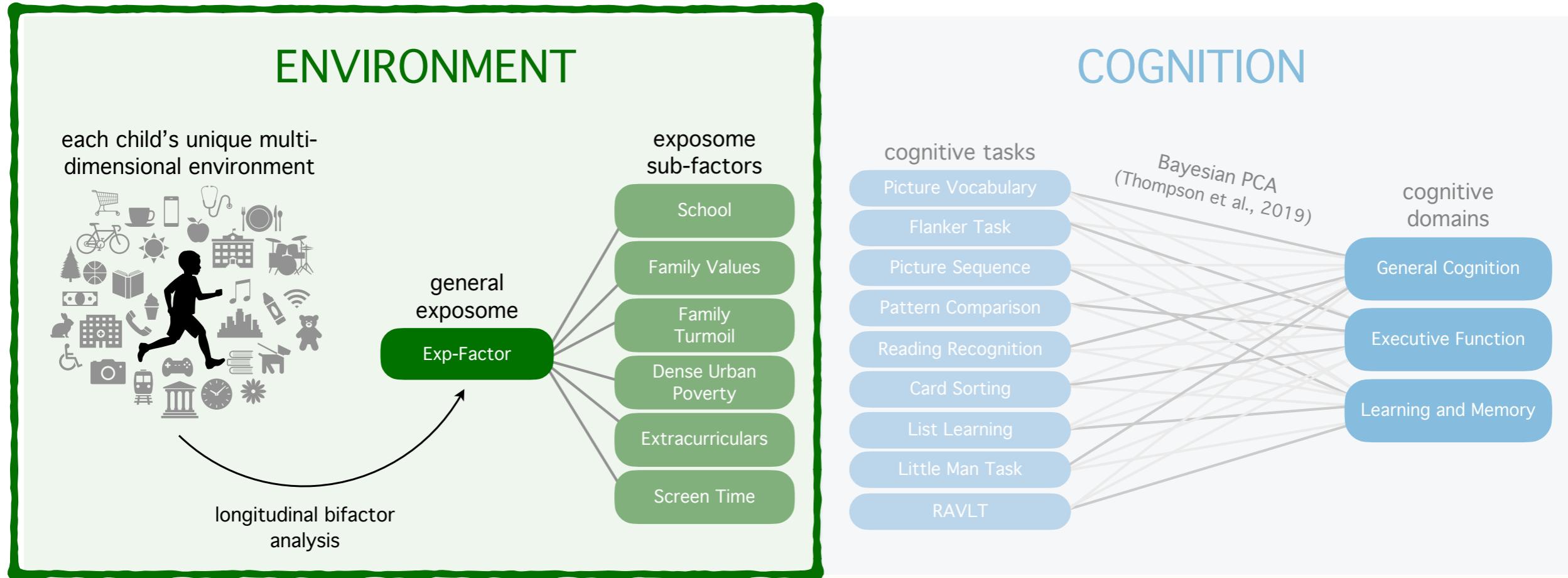
BOLD timeseries at each network



Personalized Functional Networks (PFNs)



# Dimensionality Reduction



# Measuring the “Exposome”

*How do we characterize a child's unique, complex, multi-dimensional environment?*



**Multidimensional**  
Experiences &  
Environment

# Measuring the “Exposome”

## Ecosystems

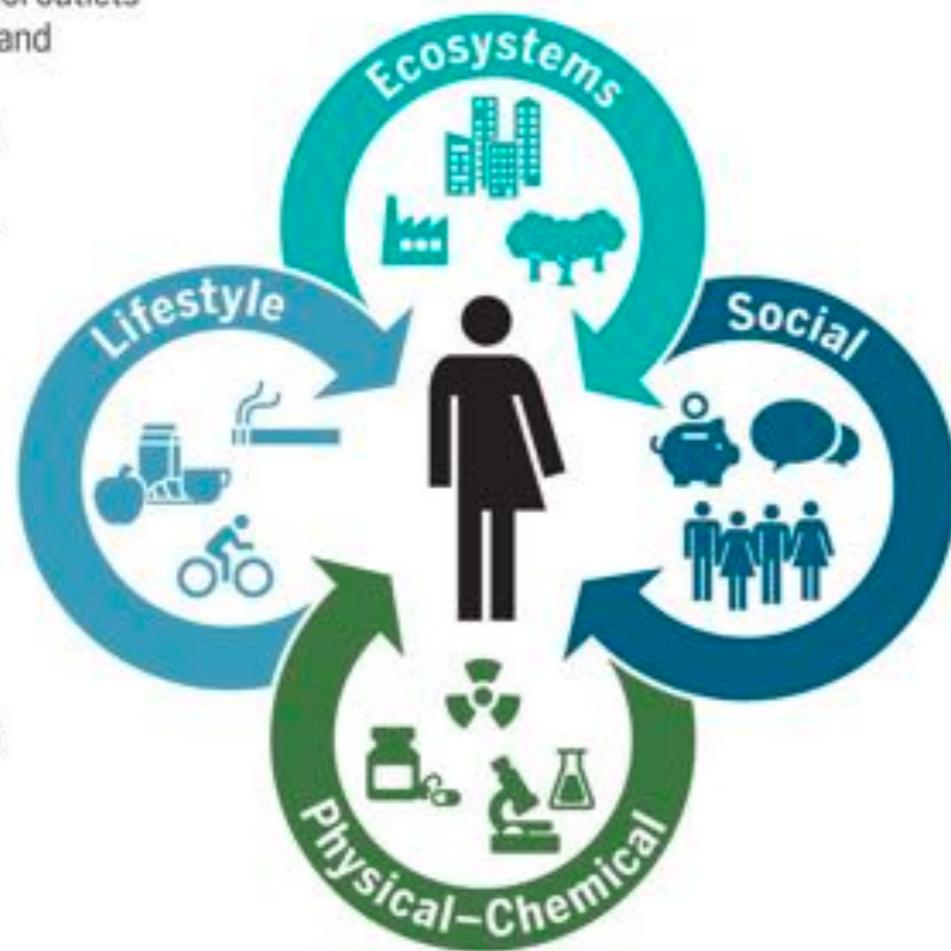
Food outlets, alcohol outlets  
Built environment and urban land uses  
Population density  
Walkability  
Green/blue space

## Lifestyle

Physical activity  
Sleep behavior  
Diet  
Drug use  
Smoking  
Alcohol use

## Social

Household income  
Inequality  
Social capital  
Social networks  
Cultural norms  
Cultural capital  
Psychological and mental stress



## Physical-Chemical

Temperature/humidity  
Electromagnetic fields  
Ambient light  
Odor and noise  
Point, line sources, e.g., factories, ports  
Outdoor and indoor air pollution  
Agricultural activities, livestock  
Pollen/mold/fungus  
Pesticides  
Fragrance products  
Flame retardants (PBDEs)  
Persistent organic pollutants  
Plastic and plasticizers  
Food contaminants  
Soil contaminants  
Drinking water contamination  
Groundwater contamination  
Surface water contamination  
Occupational exposures

### Initial work focused on:

- physical/chemical exposures
- physical health outcomes (e.g., cancer)
- studies in adults

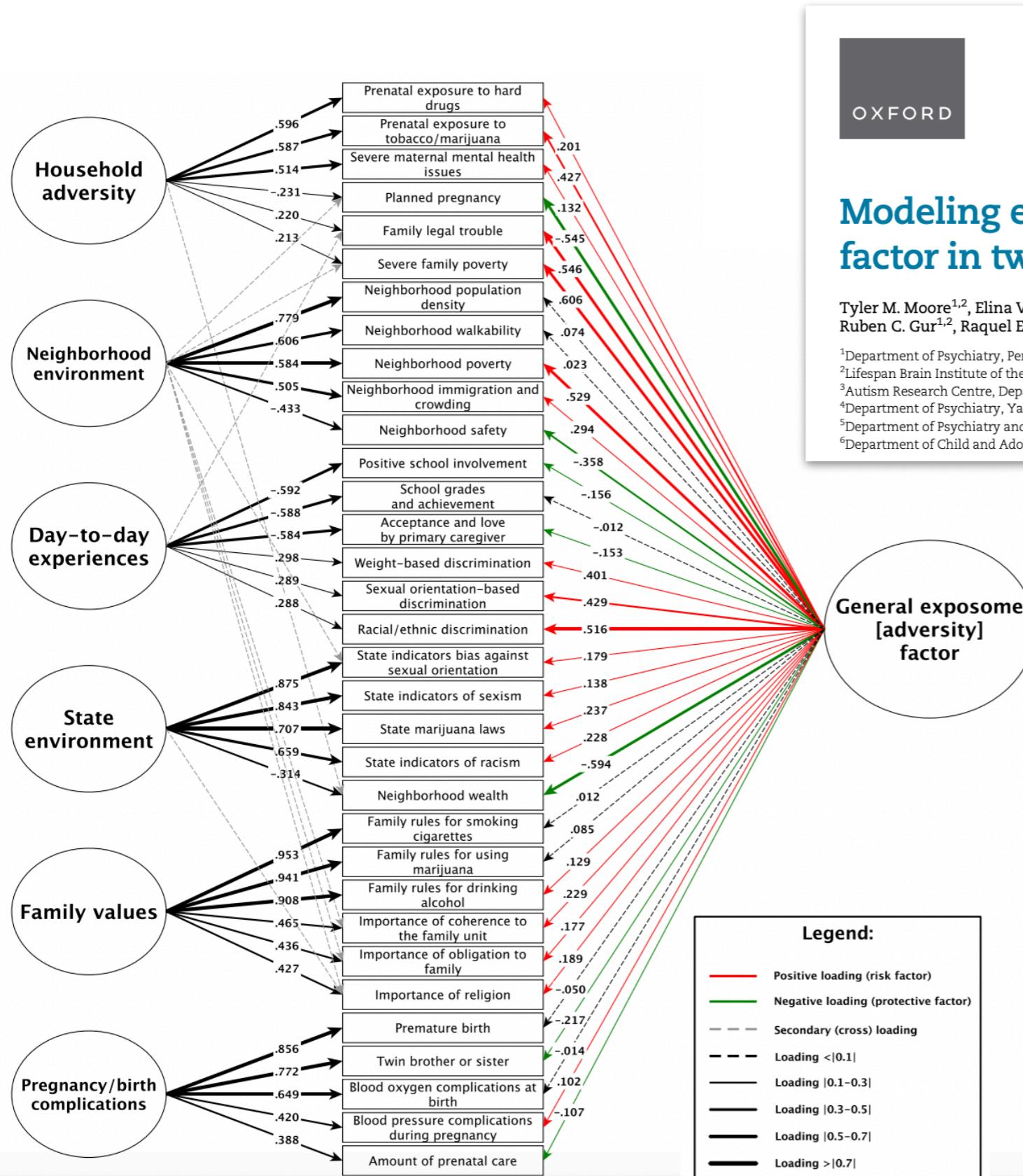
### Recent work has taken this to:

- psychosocial exposures
- mental health outcomes (e.g., psychosis)
- studies in children

"The exposome is an integrated function of exposures on our body, including what we eat and do, our experiences, and where we live and work."



# Measuring the “Exposome”



Exposome, 2022, 2(1), osac010

<https://doi.org/10.1093/exposome/osac010>

Advance Access Publication Date: 14 December 2022

Research Article

## Modeling environment through a general exposome factor in two independent adolescent cohorts

Tyler M. Moore<sup>1,2</sup>, Elina Visoki<sup>2</sup>, Stirling T. Argabright<sup>2</sup>, Grace E. Didomenico<sup>2</sup>, Ingrid Sotelo<sup>2</sup>, Jeremy D. Wortzel<sup>2</sup>, Areebah Naeem<sup>2</sup>, Ruben C. Gur<sup>1,2</sup>, Raquel E. Gur<sup>1,2</sup>, Varun Warrier<sup>3</sup>, Sinan Guloksuz<sup>4,5</sup>, Ran Barzilay <sup>1,2,6\*</sup>

<sup>1</sup>Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

<sup>2</sup>Lifespan Brain Institute of the Children's Hospital of Philadelphia (CHOP) and Penn Medicine, Philadelphia, PA, USA

<sup>3</sup>Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, UK

<sup>4</sup>Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

<sup>5</sup>Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands

<sup>6</sup>Department of Child and Adolescent Psychiatry and Behavioral Science, Children's Hospital of Philadelphia (CHOP), Philadelphia, PA, USA

Inclusion of exposome factors greatly increased variance explained in overall psychopathology compared with models relying solely on demographics and parental education (from <4% to >38% in ABCD)

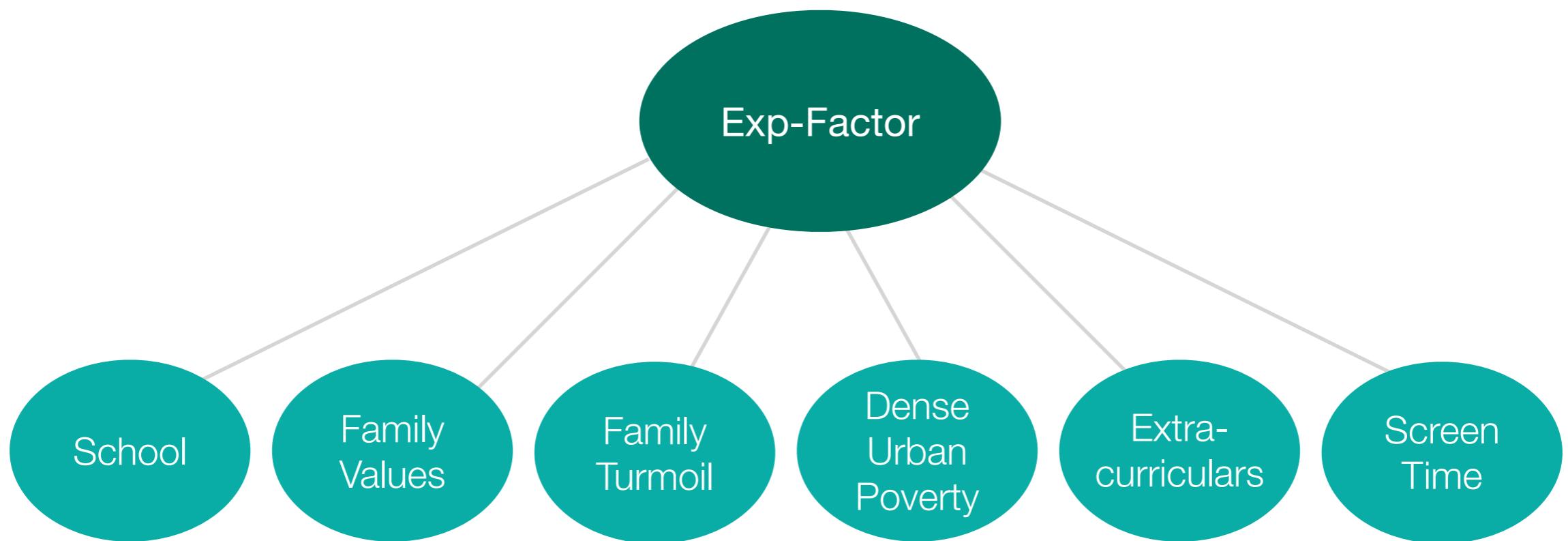


Multidimensional Experiences & Environment

# Measuring the “Exosome”

## Longitudinal Bifactor Analysis

354 variables → 32 subscores/variables



**Multidimensional**  
Experiences &  
Environment

# Measuring the “Exosome”

Variable	Exp-Factor	School	Family Values	Family Turmoil	Dense Urban Poverty	Extracurriculars	Screen Time
SRPF: Feel Involved in School	0.075	0.641	0.012	0.023	0.003	-0.043	0.065
SRPF: Good Grades	-0.063	0.628	0.037	-0.010	-0.009	-0.019	-0.042
SRPF: Enjoy School	0.090	0.625	0.010	-0.034	0.016	0.050	-0.060
SRPF: Positive Feedback in School	-0.104	0.581	0.019	-0.002	-0.010	0.072	0.018
Parental Monitoring	0.208	0.435	0.039	-0.069	0.037	-0.068	0.014
FES: Family Non-Conflict - Youth Repor	-0.182	-0.278	-0.034	0.259	-0.068	0.035	0.033
MACV: Family Image	<b>-0.437</b>	0.032	0.739	0.001	0.040	-0.010	0.018
MACV: Caring/Security	-0.147	0.017	0.737	-0.029	-0.027	0.024	-0.015
MACV: Religiosity	<b>-0.465</b>	0.046	0.397	-0.011	-0.141	-0.014	-0.047
MACV: Independence	-0.247	0.000	0.385	0.030	0.111	-0.007	0.020
Parental Rules on Substance Use	0.201	-0.021	-0.129	0.024	0.109	0.022	0.017
FES: Family Conflict - Parent Report	-0.180	-0.019	-0.008	0.551	0.013	0.019	-0.008
FES: Family Non-Conflict - Parent Repor	0.012	-0.030	-0.071	0.474	0.025	0.023	0.012
FES: Family Conflict - Youth Report	-0.271	-0.257	-0.014	0.347	-0.150	0.086	0.011
Substance Use Attitudes	0.225	-0.036	-0.101	0.154	0.080	-0.083	0.025
ABGD: Dense/Suburban	-0.121	0.036	0.029	0.051	0.553	0.006	-0.008
ABGD: Crowding and Crime	<b>-0.311</b>	0.016	0.100	-0.085	0.499	-0.047	-0.050
ABGD: Retirement and Group Living	-0.009	-0.021	-0.042	-0.023	0.486	0.018	0.016
ABGD: Poverty	<b>-0.695</b>	0.012	-0.026	-0.022	0.393	0.007	0.010
Neighborhood Safety	<b>0.398</b>	-0.016	0.122	-0.085	-0.352	0.025	0.022
ABGD: Air Polution	-0.043	0.019	-0.023	0.071	0.352	-0.003	0.057
ABGD: Traditional South and Midwest	<b>-0.415</b>	0.040	0.035	0.018	-0.293	-0.079	-0.020
Parents Married	<b>0.572</b>	-0.002	0.059	-0.013	-0.264	-0.064	-0.130
ABGD: Ozone	0.122	-0.049	0.011	-0.066	0.253	0.024	0.037
Household Income	<b>0.780</b>	-0.022	0.008	0.034	-0.240	0.001	-0.017
Parental Education	<b>0.680</b>	-0.028	-0.044	0.060	-0.214	0.096	-0.016
SAIQ: Miscellaneous Sports/Activities	<b>0.507</b>	0.004	0.032	0.065	-0.004	0.433	0.018
SAIQ: Arts and Individual Sports/Activiti	<b>0.475</b>	0.052	0.003	0.016	0.043	0.379	-0.003
SAIQ: Competitive/High-Impact Athleti	0.223	-0.008	0.047	0.084	-0.085	0.337	0.021
TBIs	0.085	-0.034	-0.007	0.053	-0.013	0.178	-0.003
Screen Time	-0.235	-0.063	-0.006	0.018	-0.004	0.032	0.393
Peer Deviance	-0.086	-0.086	-0.016	0.046	-0.006	0.017	0.099

Youth Report  
Parent Report  
Geocoded Data



Tyler Moore

*Exp-Factor*



Multidimensional  
Experiences &  
Environment

# A useful feature of this approach



All the general and specific factors are orthogonal!



Multidimensional  
Experiences &  
Environment

# Dimensionality Reduction

## ENVIRONMENT

each child's unique multi-dimensional environment



longitudinal bifactor analysis

general exposome  
Exp-Factor

exposome sub-factors

- School
- Family Values
- Family Turmoil
- Dense Urban Poverty
- Extracurriculars
- Screen Time

## COGNITION

cognitive tasks

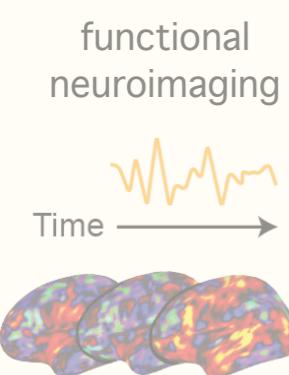
- Picture Vocabulary
- Flanker Task
- Picture Sequence
- Pattern Comparison
- Reading Recognition
- Card Sorting
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- Little Man Task
- RAVLT

*Bayesian PCA  
(Thompson et al., 2019)*

cognitive domains

- General Cognition
- Executive Function
- Learning and Memory

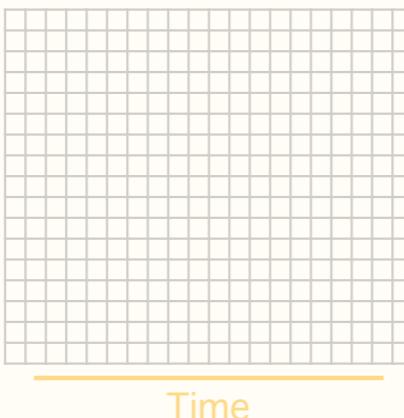
## BRAIN NETWORKS



functional neuroimaging

BOLD timeseries  
at each vertex

Vertices



network topography

Vertices

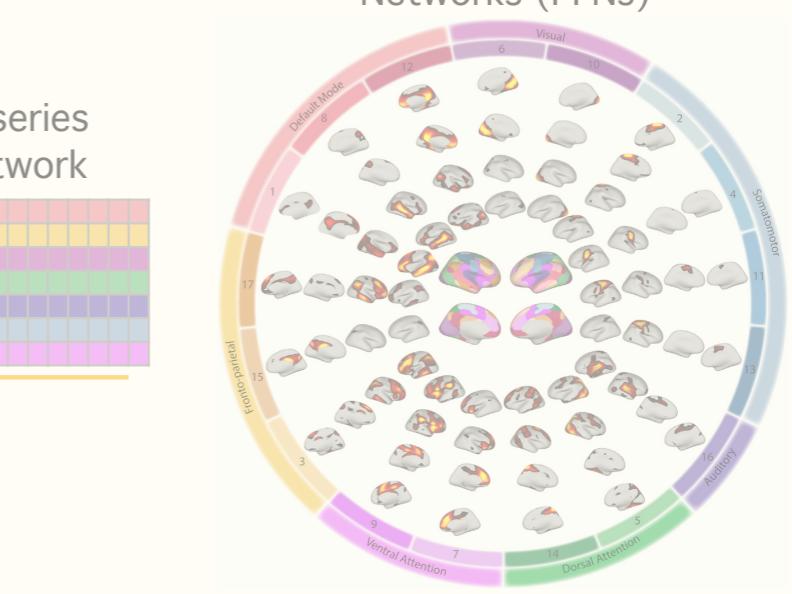
Networks

BOLD timeseries  
at each network

Networks

Time

Personalized Functional Networks (PFNs)



# Measuring Cognition

**Top three dimensions of variability in cognition across 9 tasks**

## General Cognition

- 1. Reading
- 2. Picture Vocabulary
- 3. Little Man Task

## Executive Function

- 1. Pattern Comparison
- 2. Flanker
- 3. Card Sorting

## Learning/Memory

- 1. Picture Memory
- 2. Rey Aud./Verbal Learning
- 3. List Learning



*Individual  
Differences in  
Cognition*

# Measuring Cognition

Year 2

## Neurocognition

### NIH Toolbox Tasks:

- Picture Vocabulary
- Flanker Inhibitory Control & Attention
- Pattern Comparison Processing Speed
- Picture Sequence Memory Form B
- Oral Reading Recognition

Rey Auditory Verbal Learning Test

Little Man Task

RAVLT Delayed Recall

Game of Dice Task

Social Influence Task

**PicVocab:** Language, Verbal Intellect

**Flanker:** Cognitive Control/Attention

**Pattern:** Processing Speed; Information Processing

**Picture:** Visuospatial Sequencing/Memory

**Reading:** Reading Ability/Language



*Individual  
Differences in  
Cognition*

# Dimensionality Reduction

## ENVIRONMENT

each child's unique multi-dimensional environment



longitudinal bifactor analysis

general exposome  
Exp-Factor

exposome sub-factors

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## COGNITION

cognitive tasks

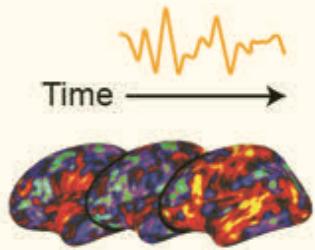
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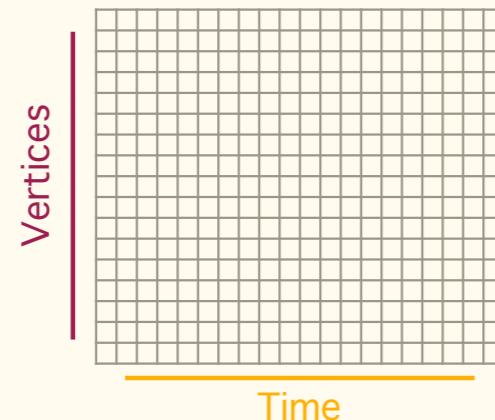
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- Learning and Memory

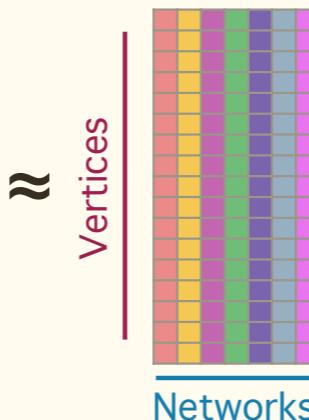
functional neuroimaging



BOLD timeseries at each vertex



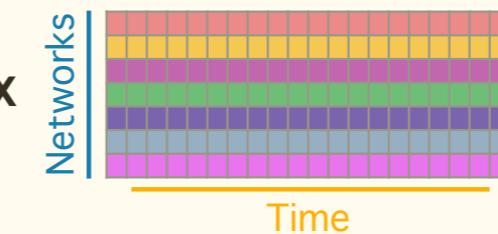
network topography



Vertices

Networks

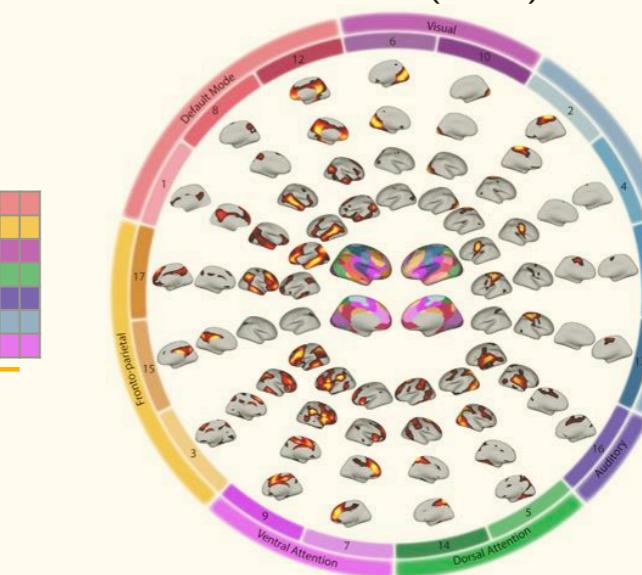
BOLD timeseries at each network



Networks

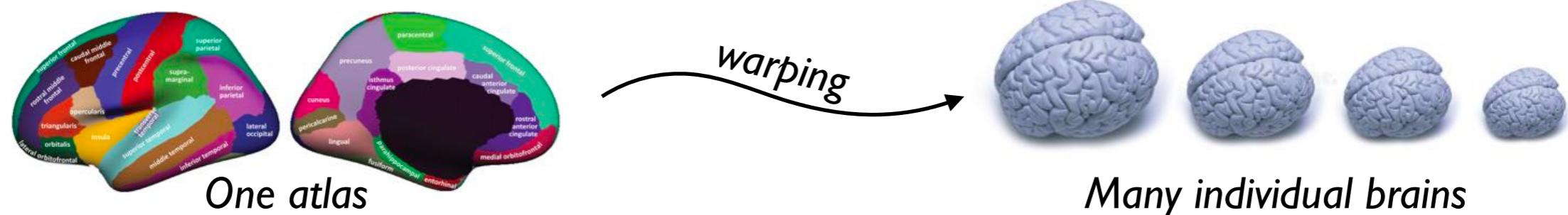
Time

Personalized Functional Networks (PFNs)

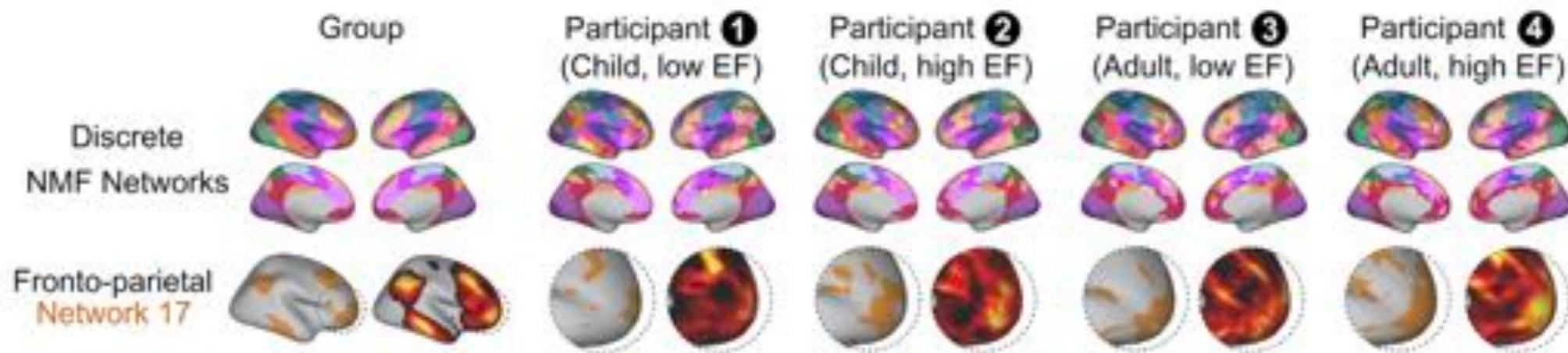


# Measuring Functional Brain Organization

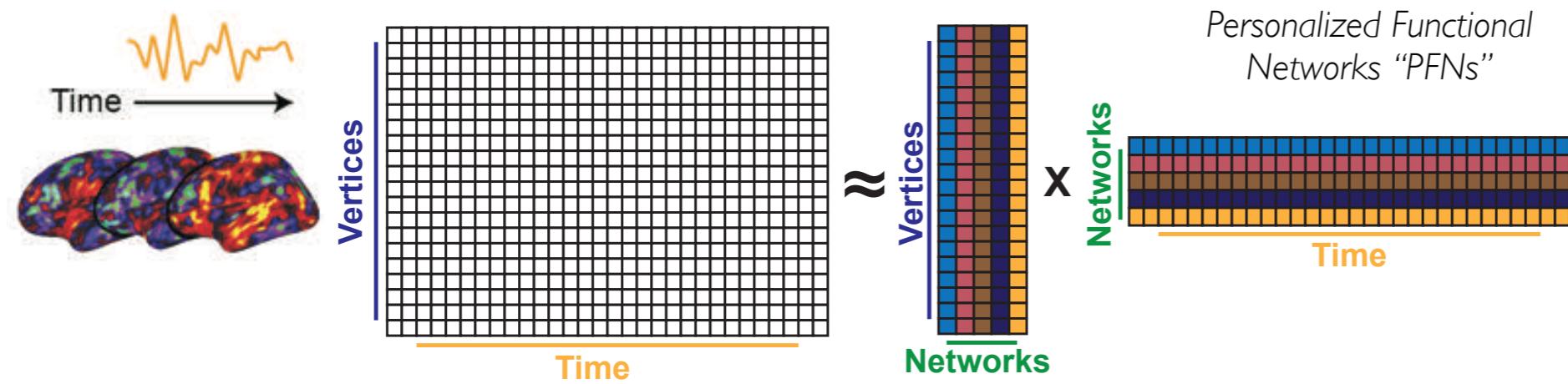
The classic approach:



Where it falls short:



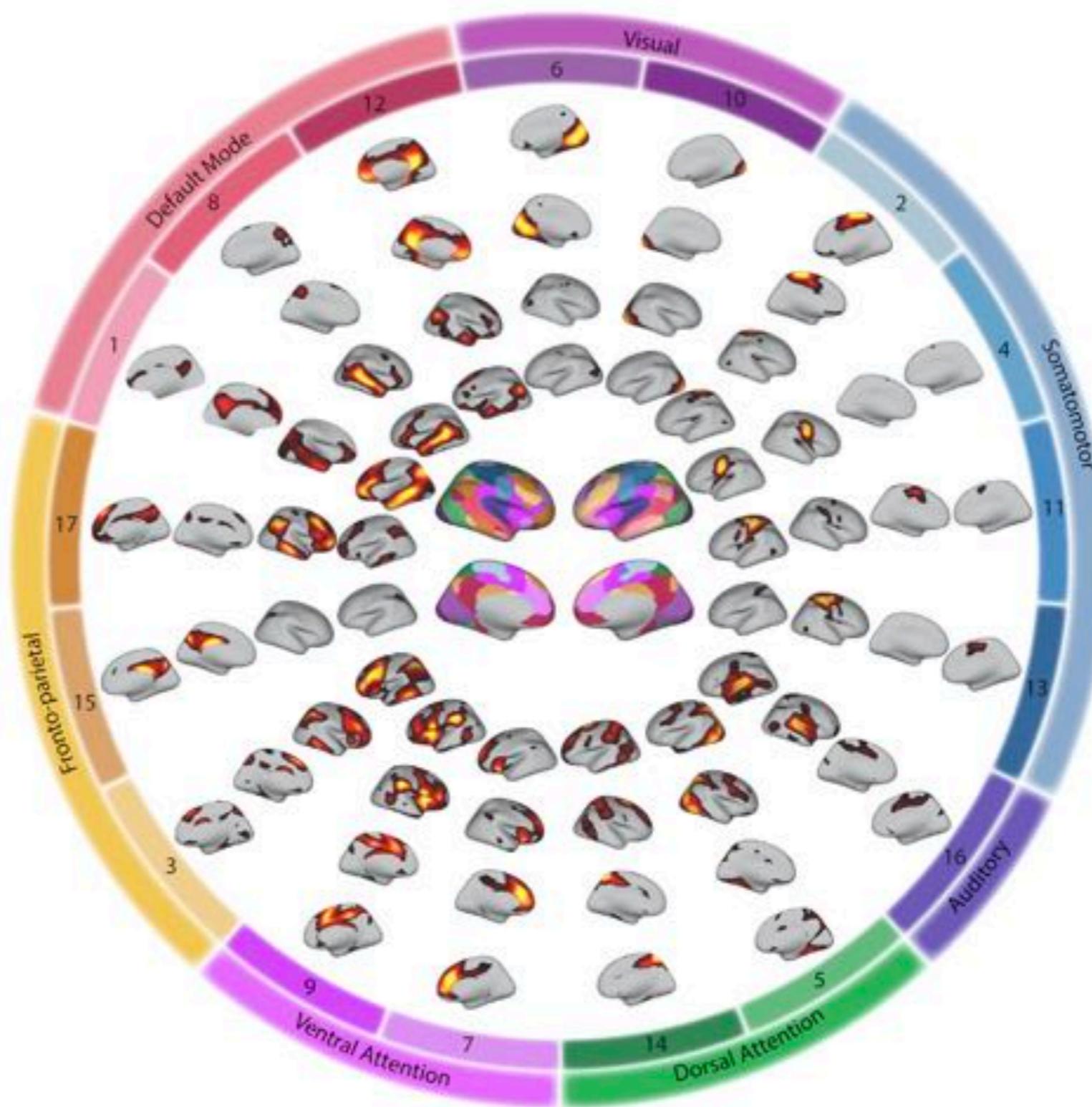
PFN approach (Non-Negative Matrix Factorization):



Cui et al., Neuron, 2020

**Personalized**  
Functional Brain  
Networks

# Personalized Functional Networks



17-Network solution named by alignment with Yeo et al., 2011 atlas

Cui et al., Neuron, 2020

# Outline

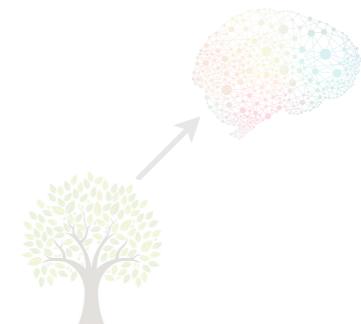
I. How do we measure environment, brain, and behavior?



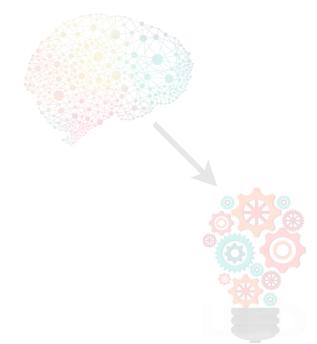
**2. How does the environment shape cognition?**



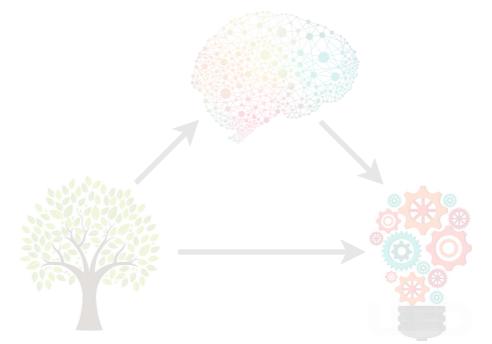
3. How does the environment shape brain organization?



4. How does brain organization relate to cognitive abilities?

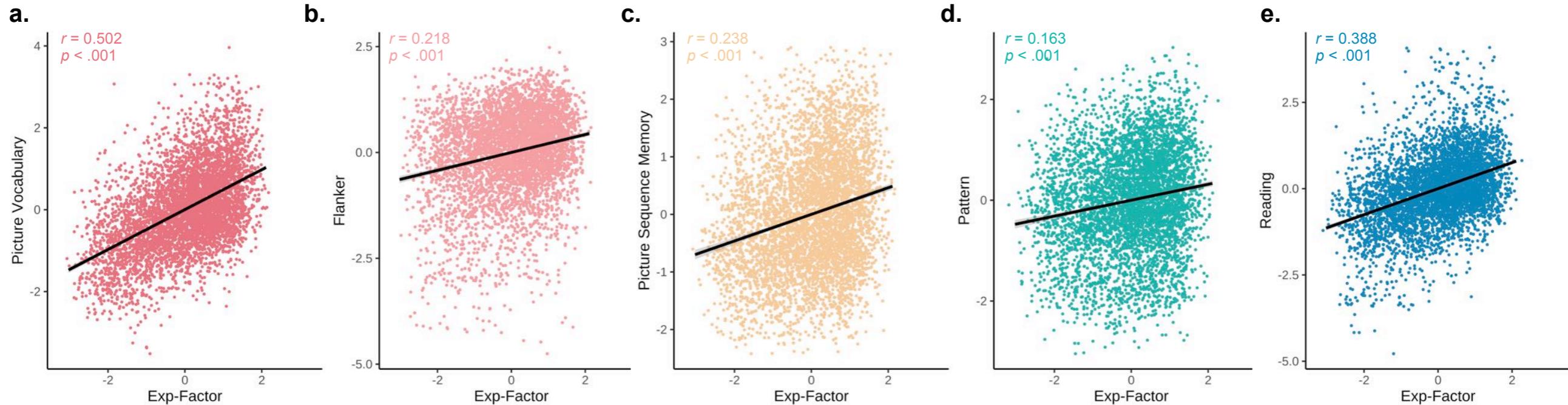


5. Putting it all together!

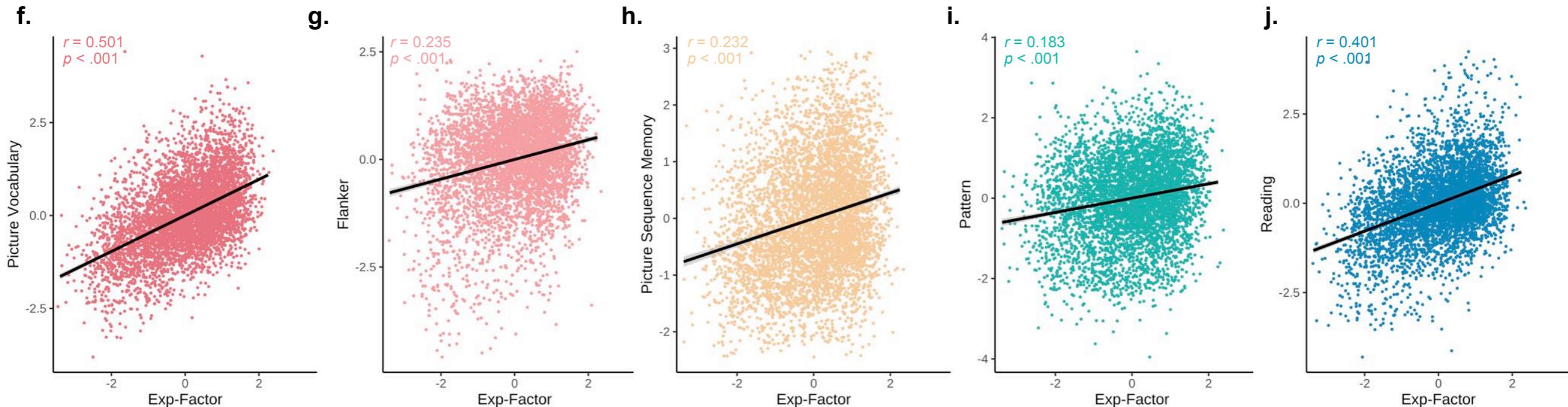


# Exp-Factor is associated with cognition

## Discovery Sample



## Replication Sample



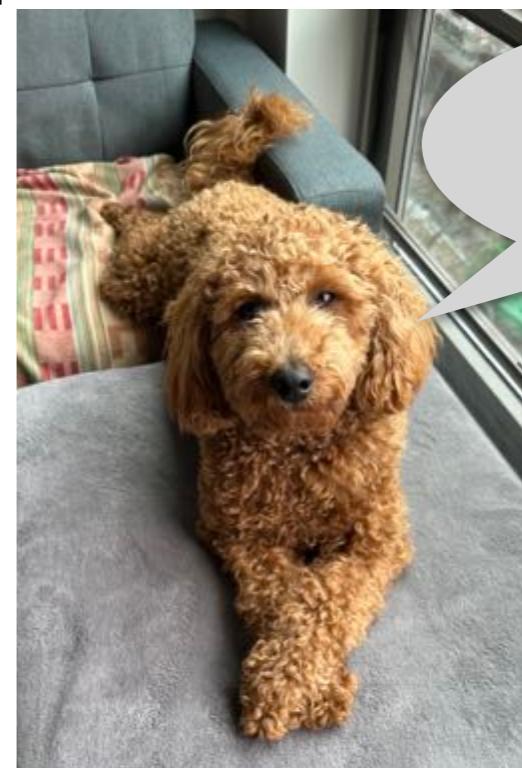
# Exp-Factor predicts cognition two years later

Predictors	Picture Vocabulary				Flanker				Picture Sequence Memory				Pattern Comparison				Reading Recognition			
	$\beta$	Std. Error	t	$p_{bonf}$	$\beta$	Std. Error	t	$p_{bonf}$	$\beta$	Std. Error	t	$p_{bonf}$	$\beta$	Std. Error	t	$p_{bonf}$	$\beta$	Std. Error	t	$p_{bonf}$
<b>Discovery Sample</b>																				
Intercept	-0.09	0.03	-2.77	0.063	-0.08	0.04	-2.08	0.418	-0.11	0.04	-2.72	0.072	0.05	0.04	1.35	1.00	-0.07	0.03	-2.00	0.501
Age	0.03	0.01	2.56	0.116	0.02	0.02	0.89	1.00	0.01	0.02	0.64	1.00	0.09	0.02	5.30	<b>1.39 x 10<sup>-6</sup></b>	0.01	0.01	0.81	1.00
Sex	0.02	0.03	0.93	1.00	0.03	0.03	0.94	1.00	-0.04	0.03	-1.28	1.00	-0.12	0.03	-3.57	<b>0.004</b>	-0.01	0.03	-0.23	1.00
Exp-Factor	0.24	0.02	14.76	<b>1.96 x 10<sup>-46</sup></b>	0.17	0.02	8.56	<b>2.07 x 10<sup>-16</sup></b>	0.20	0.02	10.25	<b>3.68 x 10<sup>-23</sup></b>	0.08	0.02	4.15	<b>3.69 x 10<sup>-4</sup></b>	0.13	0.02	8.13	<b>7.14 x 10<sup>-15</sup></b>
School	-0.03	0.01	-1.82	0.750	-0.03	0.02	-1.48	1.00	-0.01	0.02	-0.44	1.00	0.03	0.02	1.47	1.00	0.00	0.01	0.37	1.00
Family Values	-0.04	0.01	-2.91	<b>0.040</b>	-0.02	0.02	-0.88	1.00	-0.02	0.02	-0.85	1.00	-0.01	0.02	-0.47	1.00	-0.03	0.01	-2.44	0.164
Family Turmoil	-0.00	0.01	-0.06	1.00	-0.01	0.02	-0.75	1.00	-0.07	0.02	-3.76	<b>0.002</b>	0.01	0.02	0.39	1.00	-0.01	0.01	-0.65	1.00
Dense Urban Poverty	-0.00	0.01	-0.05	1.00	0.04	0.02	2.30	0.240	-0.02	0.02	-1.44	1.00	0.04	0.02	2.31	0.233	0.01	0.01	0.44	1.00
Extracurriculars	-0.01	0.02	-0.41	1.00	-0.00	0.02	-0.19	1.00	0.03	0.02	1.26	1.00	-0.02	0.02	-0.68	1.00	0.04	0.02	2.13	0.367
Screen Time	-0.03	0.02	-1.48	1.00	-0.09	0.03	-3.32	<b>0.010</b>	-0.11	0.03	-4.23	<b>2.60 x 10<sup>-4</sup></b>	-0.02	0.03	-0.62	1.00	-0.00	0.02	-0.22	1.00
T0 Picture Vocabulary	0.59	0.02	38.29	<b>1.86 x 10<sup>-256</sup></b>																
T0 Flanker					0.39	0.02	21.76	<b>5.97 x 10<sup>-96</sup></b>												
T0 Picture Sequence Memory									0.42	0.02	25.49	<b>8.84 x 10<sup>-128</sup></b>								
T0 Pattern Comparison													0.45	0.02	25.27	<b>7.72 x 10<sup>-126</sup></b>				
T0 Reading Recognition																	0.72	0.01	50.43	<b>0.00</b>

# Exp-Factor predicts cognition two years later

*Associations between exp-factor and cognition hold:*

- Cross-sectionally and longitudinally
- With Bonferroni correction for multiple comparisons
- Over and above baseline cognition
- Over and above specific exposome sub-factors
- Over and above standard covariates (age, sex, site, family)
- Over and above classic measures of SES (household income, parent education)
- Over and above psychiatric diagnoses (e.g., ADHD, anxiety) and medication use
- Across discovery and replication sub-samples
- Across groups stratified by racial identification
- Across groups stratified by biological sex
- Across all five cognitive tasks



*Seems legit*

# Outline

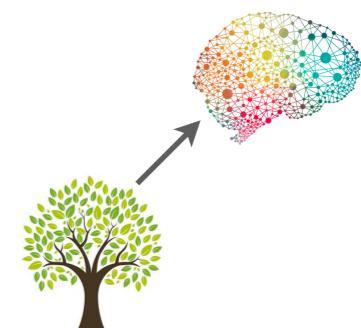
I. Dimensionality reduction of exposome, brain & behavior



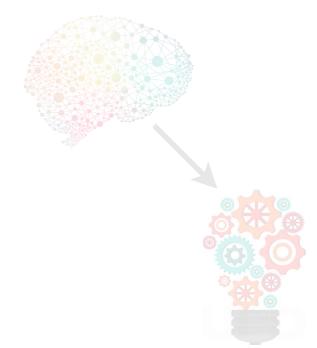
2. Exp-Factor is associated with current and future cognition



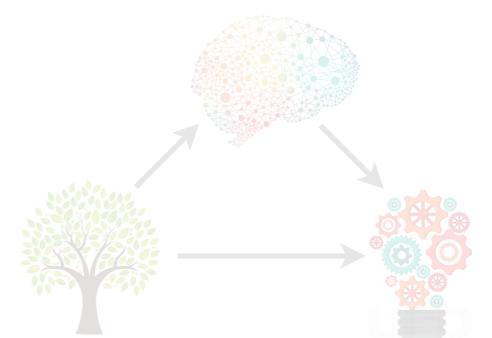
**3. How does the environment shape brain organization?**



4. How does brain organization relate to cognitive abilities?



5. Putting it all together!



# Is the exposome reflected in childrens' functional brain organization?

## *Intuition*

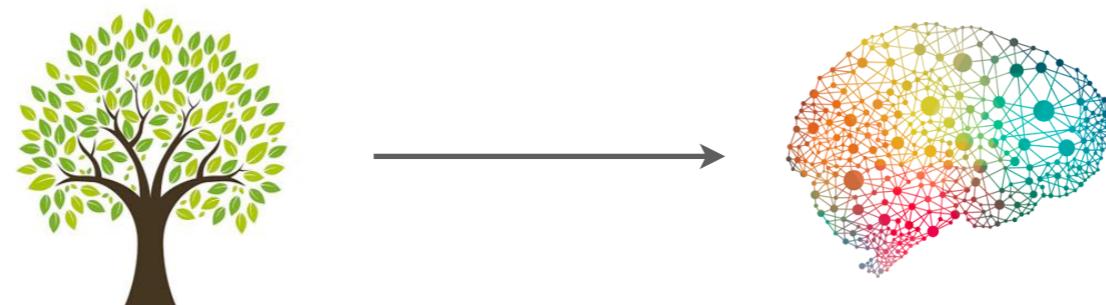
If I can accurately “guess” a child’s exp-factor score just by looking at their unique pattern of functional brain networks on the cortex, that suggests the exp-factor is reflected in functional brain organization



# Is the exposome reflected in childrens' functional brain organization?

## Back-Story

We don't yet have longitudinal brain imaging data available to see how the exposome causally relates to brain network organization, so this approach is a way of using cross-sectional data to get at the same question



# Is the exposome reflected in childrens' functional brain organization?

