



OHBM 2024
JUNE 23~27, SEOUL, KOREA

OHBM 2024
EDUCATIONAL COURSES

Charting life-course functional connectome using normative modeling

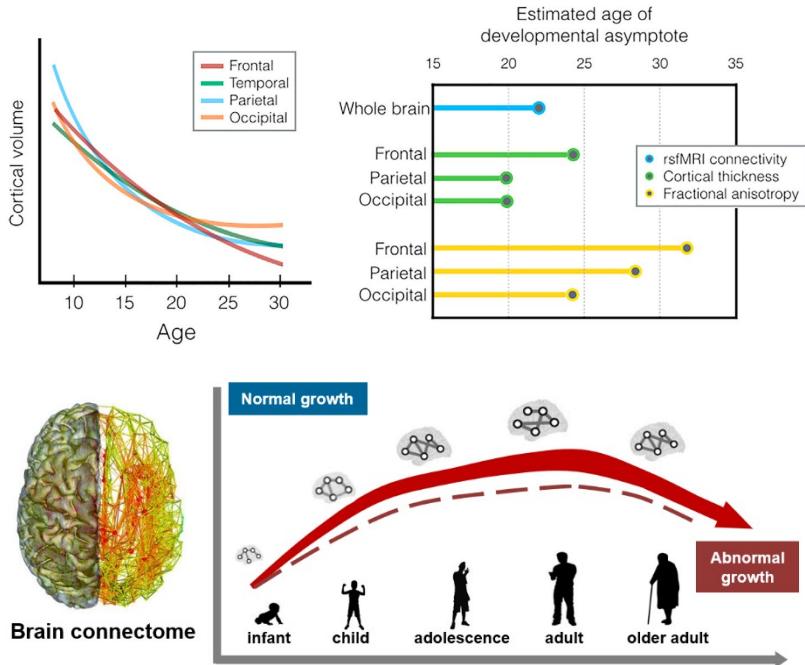


Lianglong Sun

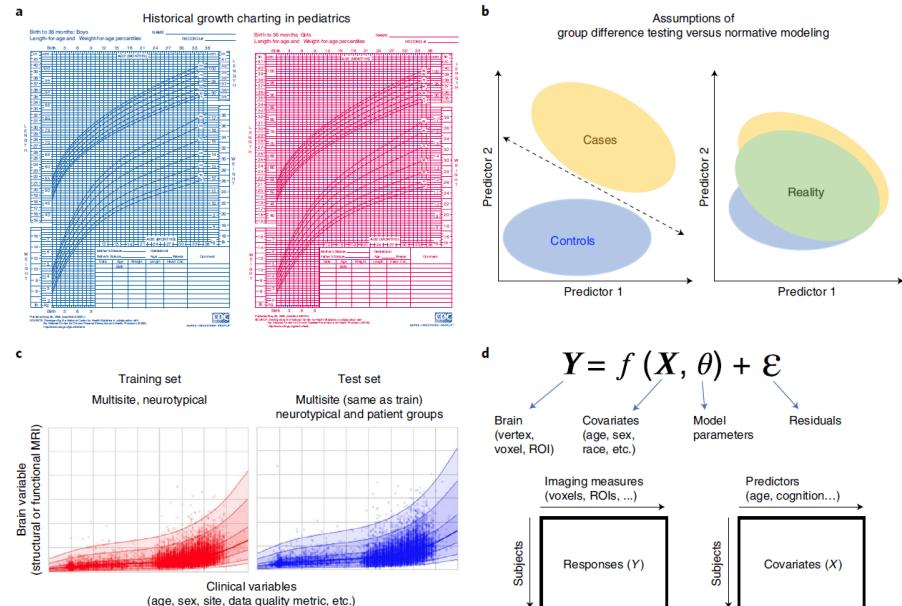
State Key Laboratory of Cognitive
Neuroscience and Learning,
Beijing Normal University

Background

The emergence, development, and aging of the intrinsic connectome architecture throughout the lifespan



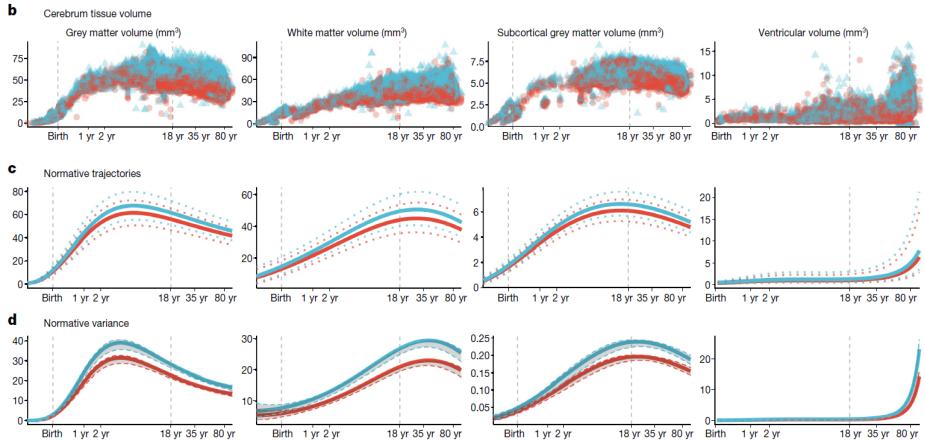
The growth chart framework provides an invaluable tool for charting normative reference curves in the human brain



Somerville *et al* (2016) *Neuron*; Zuo *et al* (2017) *Trends Cogn Sci*; Cao *et al* (2017) *Trends Neurosci*; Vogel *et al* (2023) *Nat Rev Neurosci*

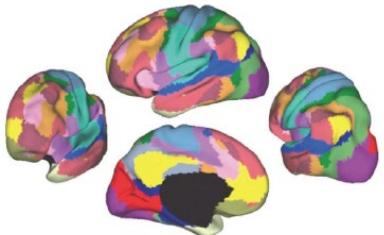
Marquand *et al* (2016) *Biol Psychiatry*; Rutherford *et al* (2022) *Nat Protoc*

Background

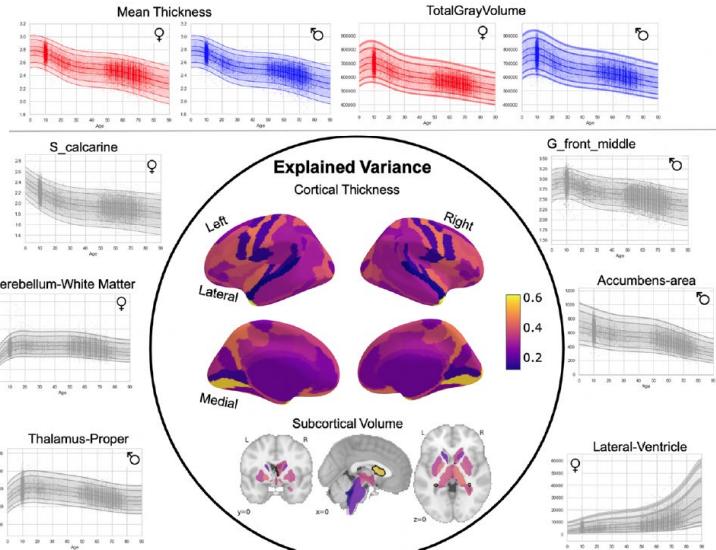


Bethlehem, Seidlitz, White et al (2022) *Nature*

Yeo-17 network parcellation



Rutherford et al (2023) *eLife*



Rutherford et al (2022) *eLife*

The normative growth pattern of the functional brain connectome across the human lifespan

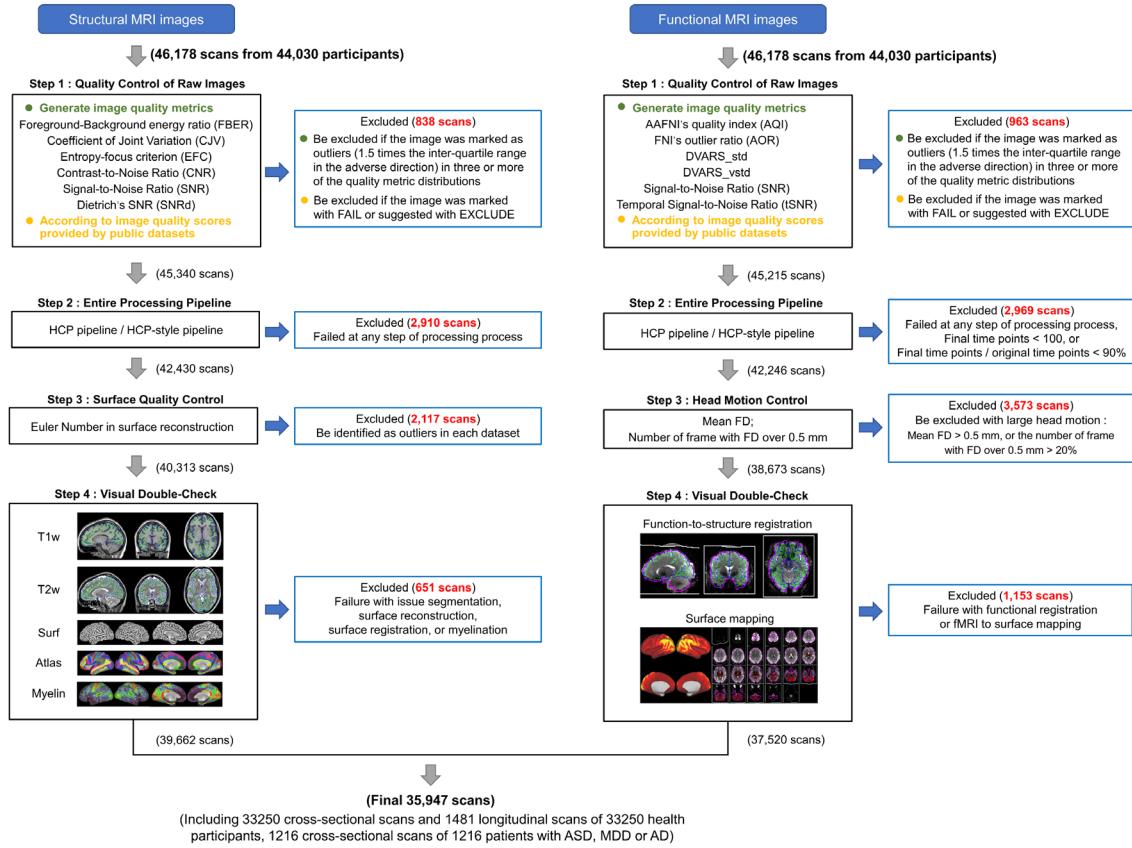
Datasets and imaging quality control

We aggregated 3T multi-modal imaging data from 44,030 individuals.

Imaging quality control framework

- Combining automated assessment and expert manual review

- The final sample included **33,250 healthy individuals**, ranging in age from 32 postmenstrual weeks to 80 years, from 132 sites.
- 414 ASD patients (aged 5-59 y)
- 622 MDD patients (aged 11-77 y)
- 180 AD patients (aged 51-80 y)



Datasets and imaging quality control

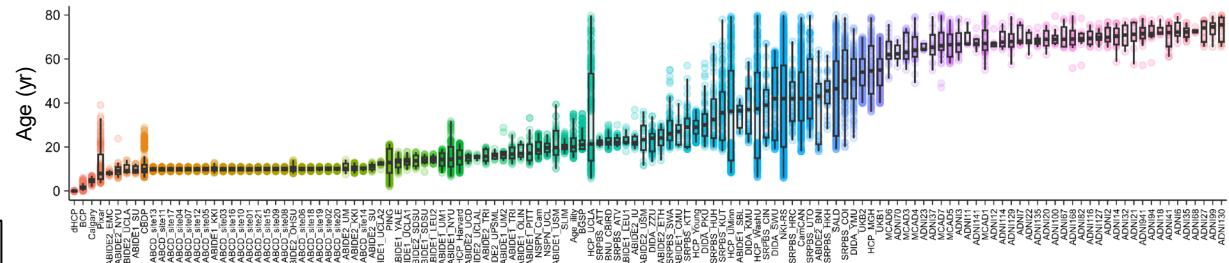
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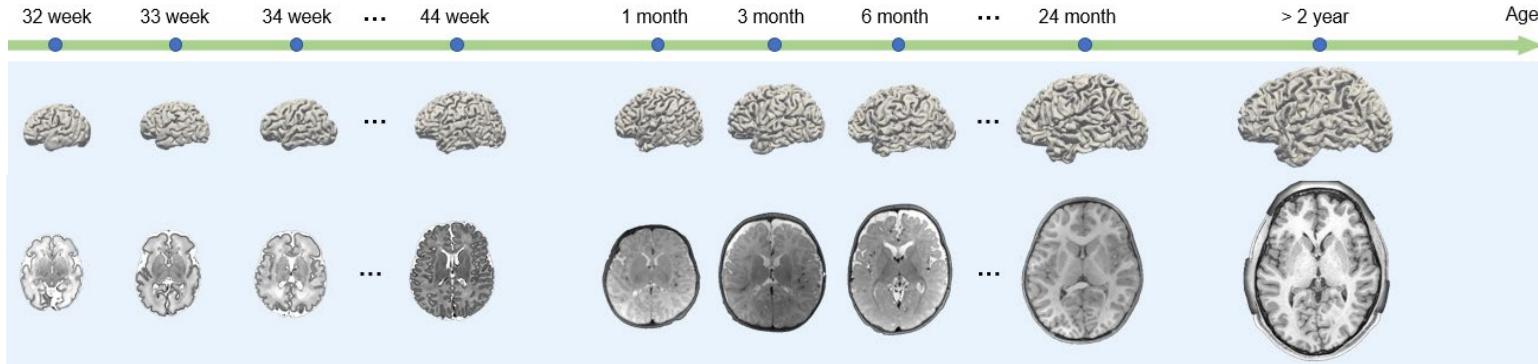
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Aggregated data across 132 sites (after quality control)



Data processing



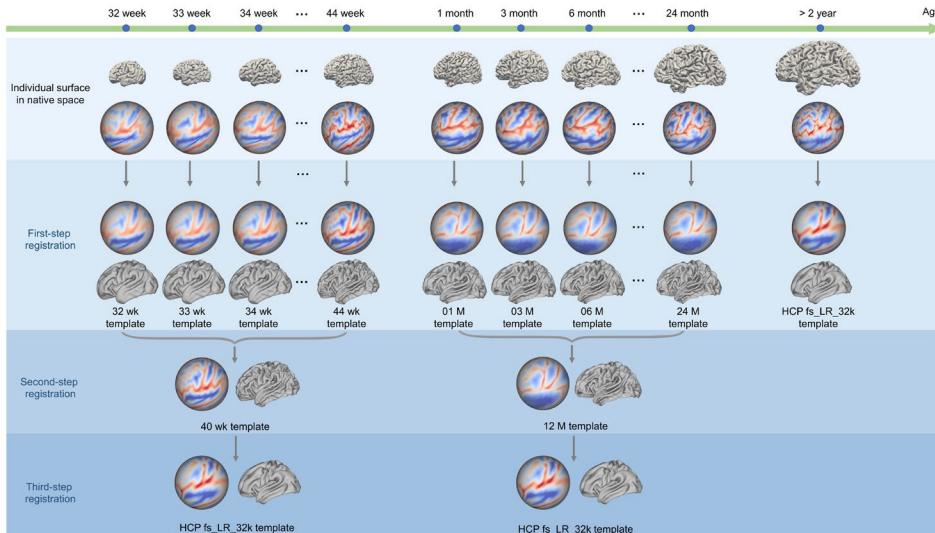
Considerable changes of the human brain in early development

Challenges:

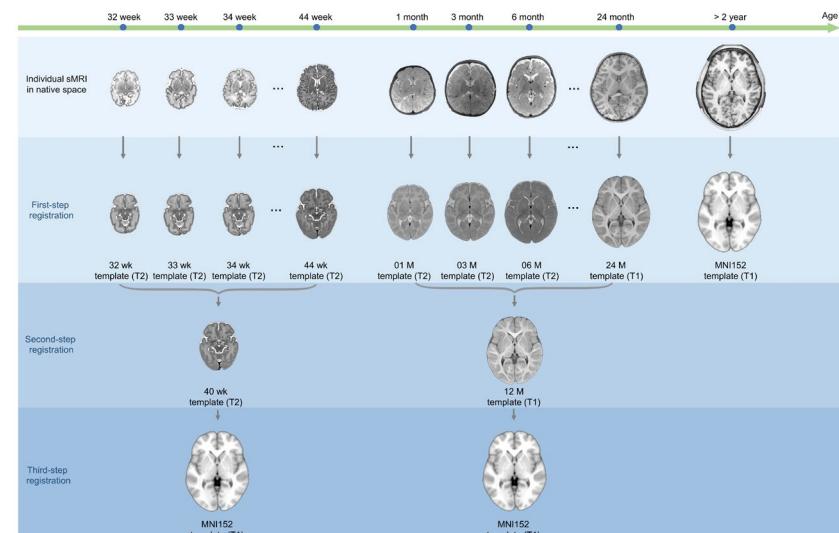
- Lack of a lifespan-appropriate preprocessing pipeline
- Lack of a set of standard templates for registration across lifespan
- Lack of a set of functional atlases across lifespan

Data processing

Participants aged 32 to 44 postmenstrual weeks



Participants aged 1 to 24 months

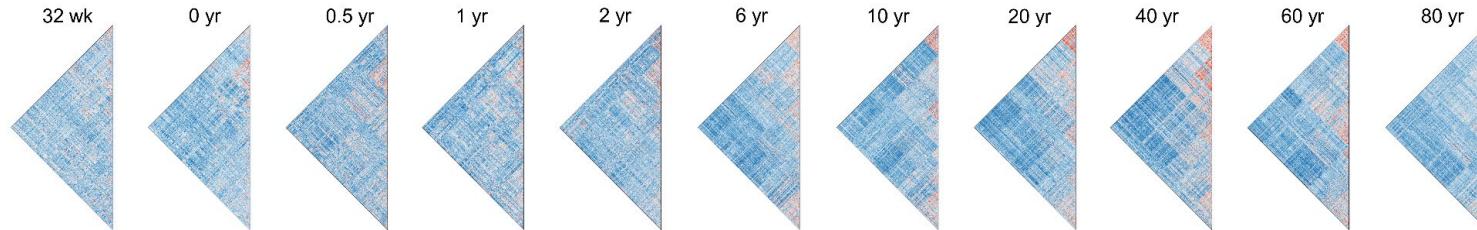


Individual cortical surface registration framework

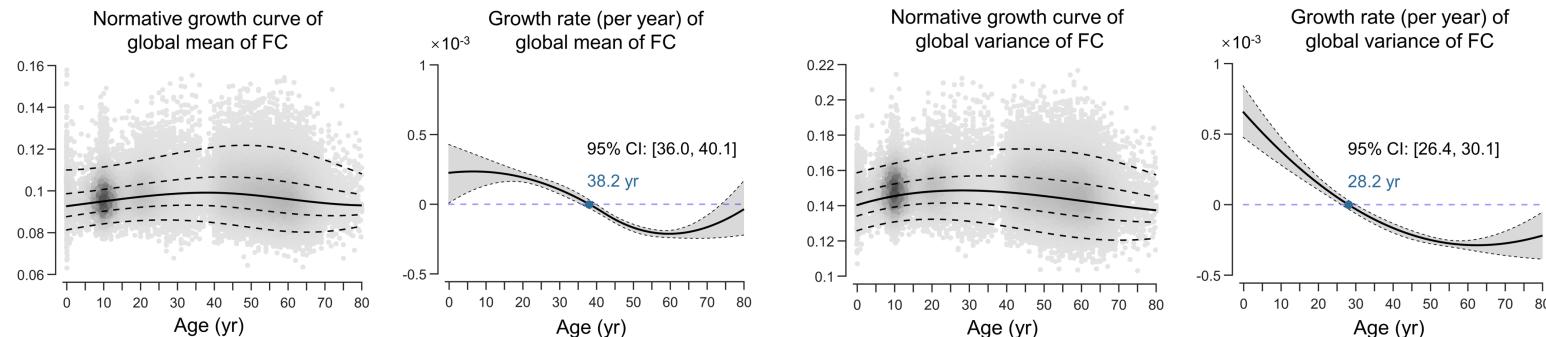
Individual volume registration framework

Lifespan normative growth of the global functional connectome

Functional connectome matrices at different growth ages



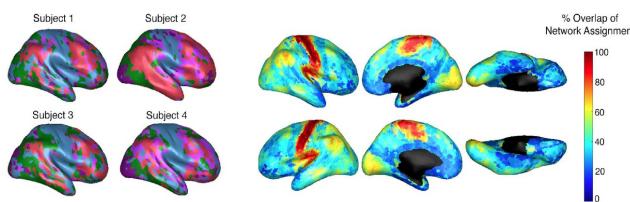
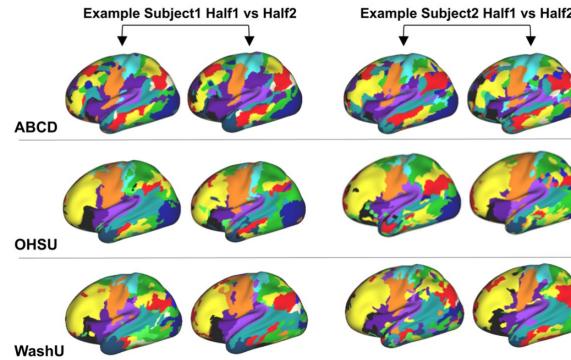
Normative models of global functional connectome ($N = 33,250$)



- The lifespan curve of the global mean of functional connectome exhibited a nonlinear increase from 32 postmenstrual weeks onward, **peaking in the late fourth decade of life** (38.2 years, 95% bootstrap CI 36.0-40.1), followed by a nonlinear decline.
- The global variance of functional connectome also exhibited a nonlinear growth pattern, **reaching its peak in the late third decade of life** (28.2 years, 95% bootstrap CI 26.4-30.1).

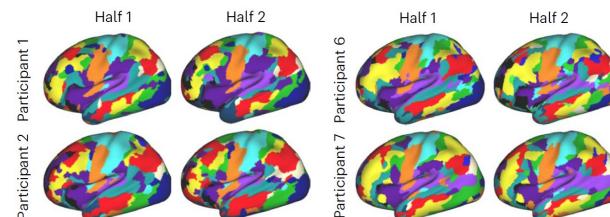
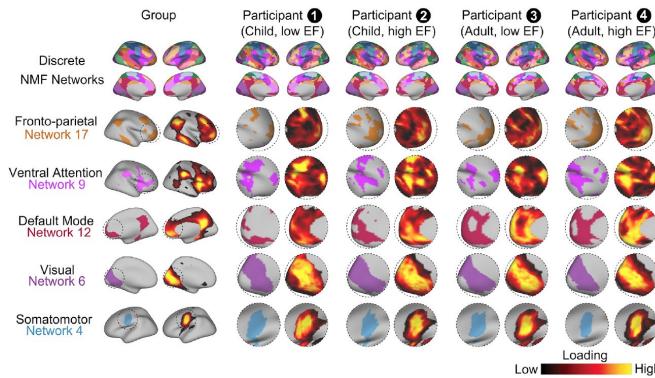
Personalized functional mapping is critical for the entire lifespan

Mutual information calculated between within-subject network maps:



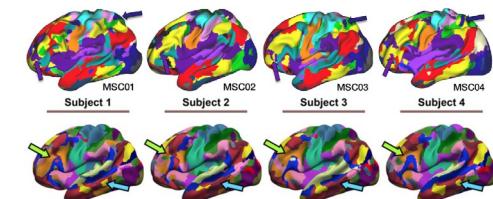
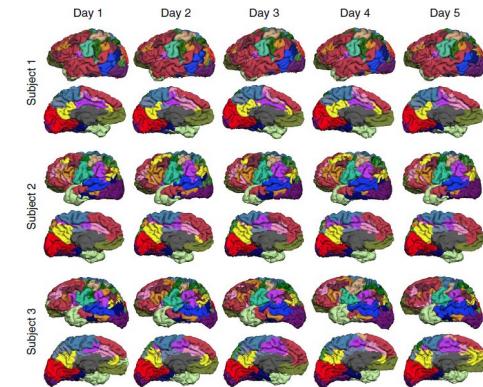
Neonates

Molloy & Saygin (2022) *Neuroimage*;
Moore et al (2024) *Imaging Neurosci*



Children and adolescents

Cui et al (2020) *Neuron*;
Hermosillo et al (2024) *Nat Neurosci*



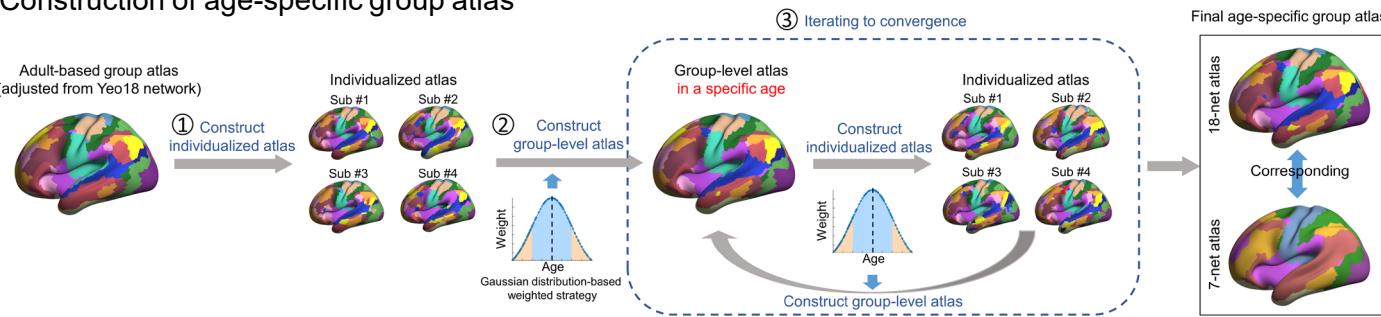
Adults

Wang et al (2015) *Nat Neurosci*;
Gordon et al (2017) *Neuron*;
Kong et al (2019) *Cereb Cortex*

Constructing population-based and individual-based functional atlas

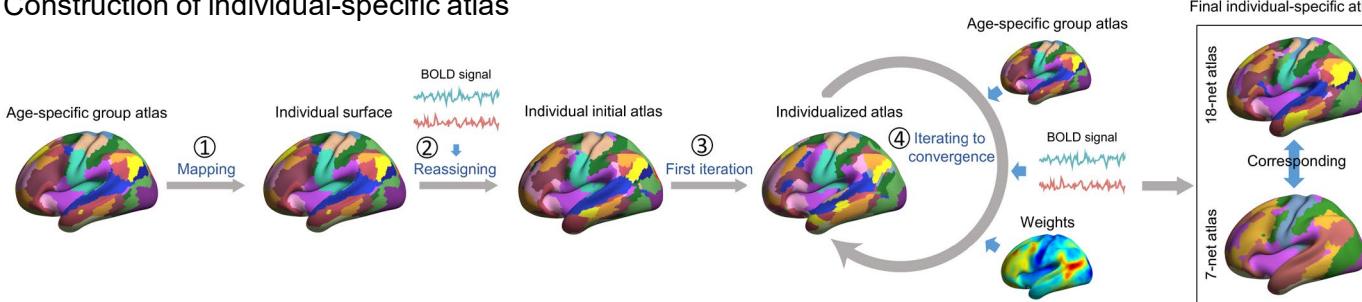
- For **age-specific group atlas**, we developed a Gaussian-weighted iterative age-specific group atlas (GIAGA) generation approach
- For **individual-specific atlas**, we used the individualized atlas approach proposing by Wang *et al* (2015) *Nat Neurosci*
- Functional homogeneity:** individual-specific atlas > age-specific group atlas > adult-based group atlas (all $p < 10^{-8}$)

Construction of age-specific group atlas



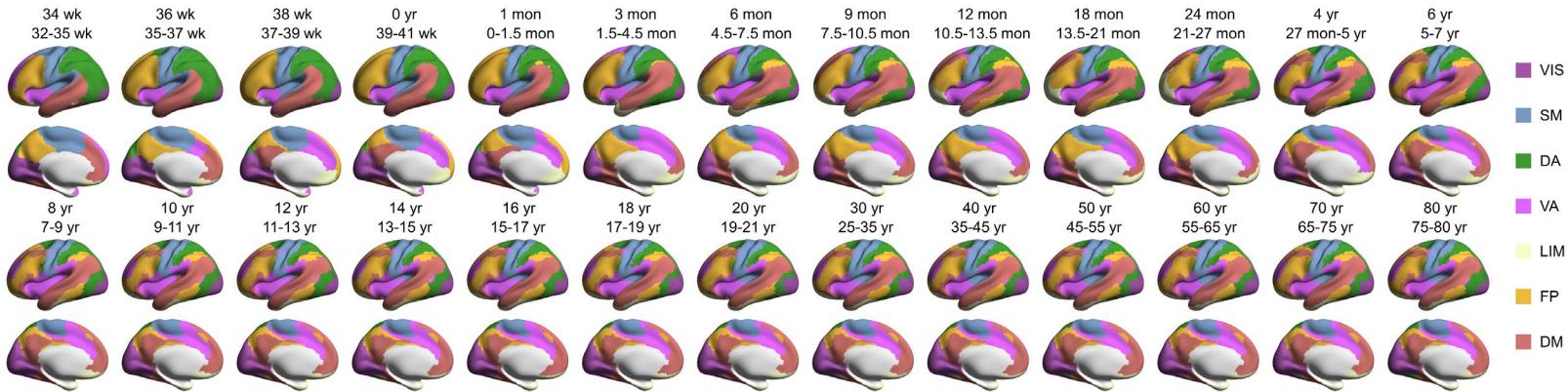
18-net	7-net
VIS_Cent	VIS
VIS_Per	SM
SM_A	DA
SM_B	VA
SM_C	LIM
DA_A	FP
DA_B	DM
VA_A	LIM_A
VA_B	LIM_B
LIM_A	FP_A
LIM_B	FP_B
FP_A	FP_C
FP_B	DM_A
FP_C	DM_B
DM_A	DM_C
DM_B	DM_D

Construction of individual-specific atlas

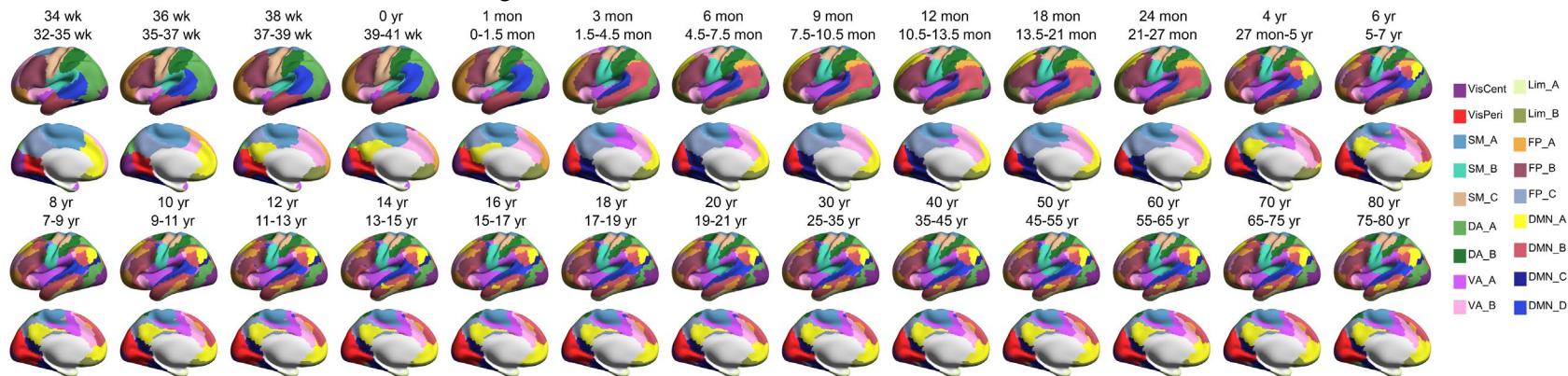


The fine-grained, lifespan-wide suite of system-level atlases

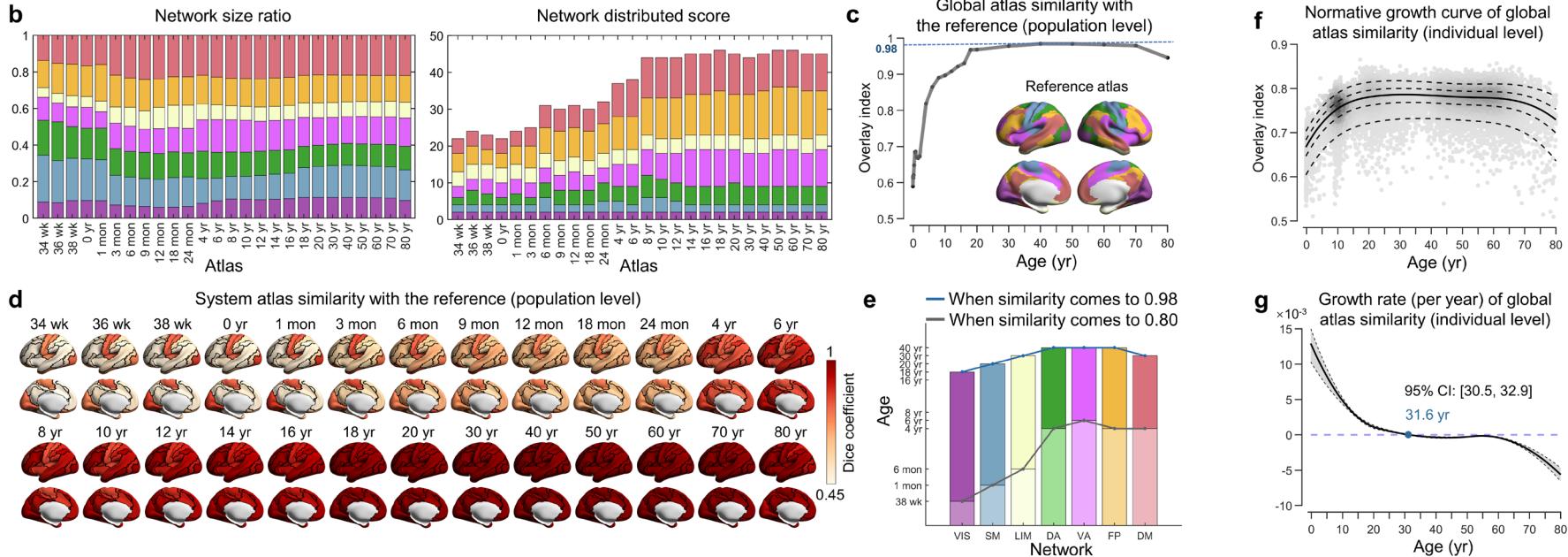
Seven-network functional atlases



Eighteen-network functional atlases



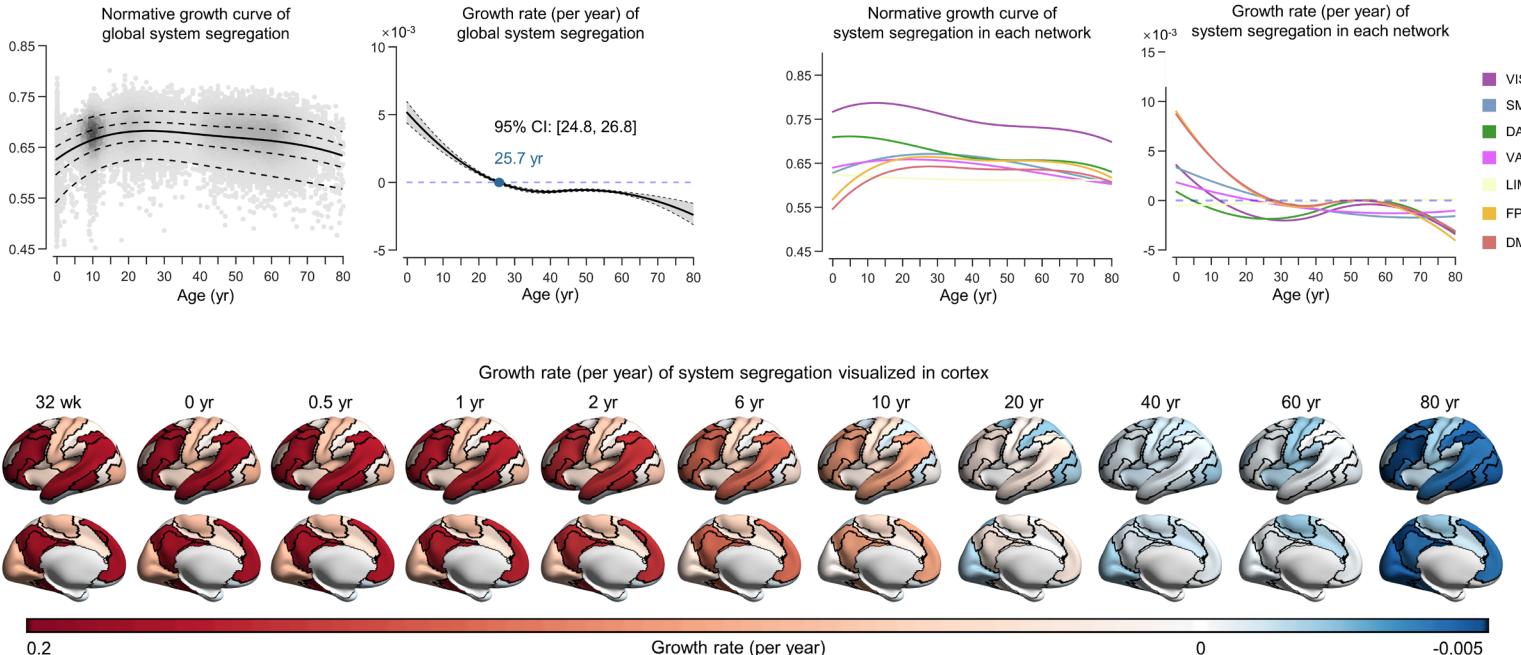
The fine-grained, lifespan-wide suite of system-level atlases



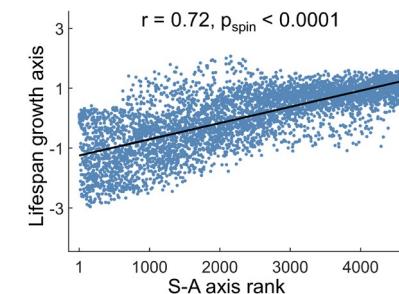
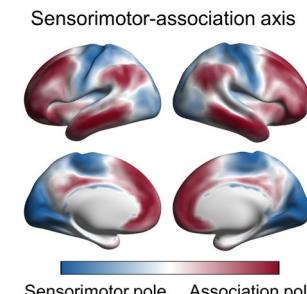
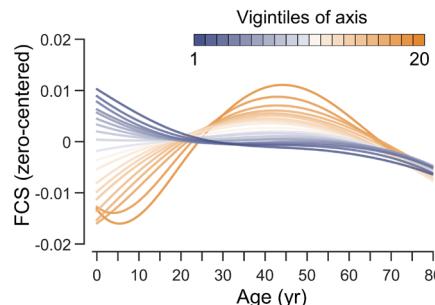
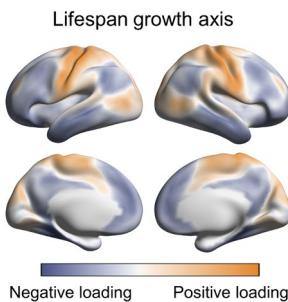
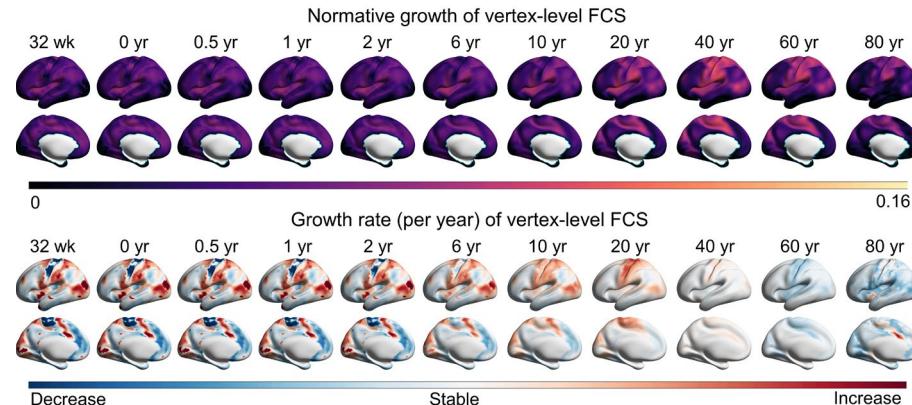
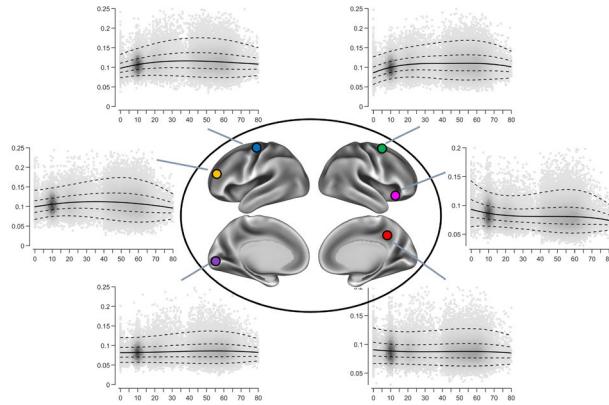
- (Population level) The overall similarity of the whole-cortical atlas exhibited a rapid increase during the first two decades of life, followed by a plateau, and a subsequent slight decrease with age.
- (Individual level) The global similarity of the individualized atlas to the reference increased from 32 postmenstrual weeks and reached a peak in adulthood (31.6 years, 95% bootstrap CI 30.5-32.9).

Lifespan growth of system-specific functional segregation

$$\text{System segregation} = \frac{FC_W - FC_B}{FC_W}$$

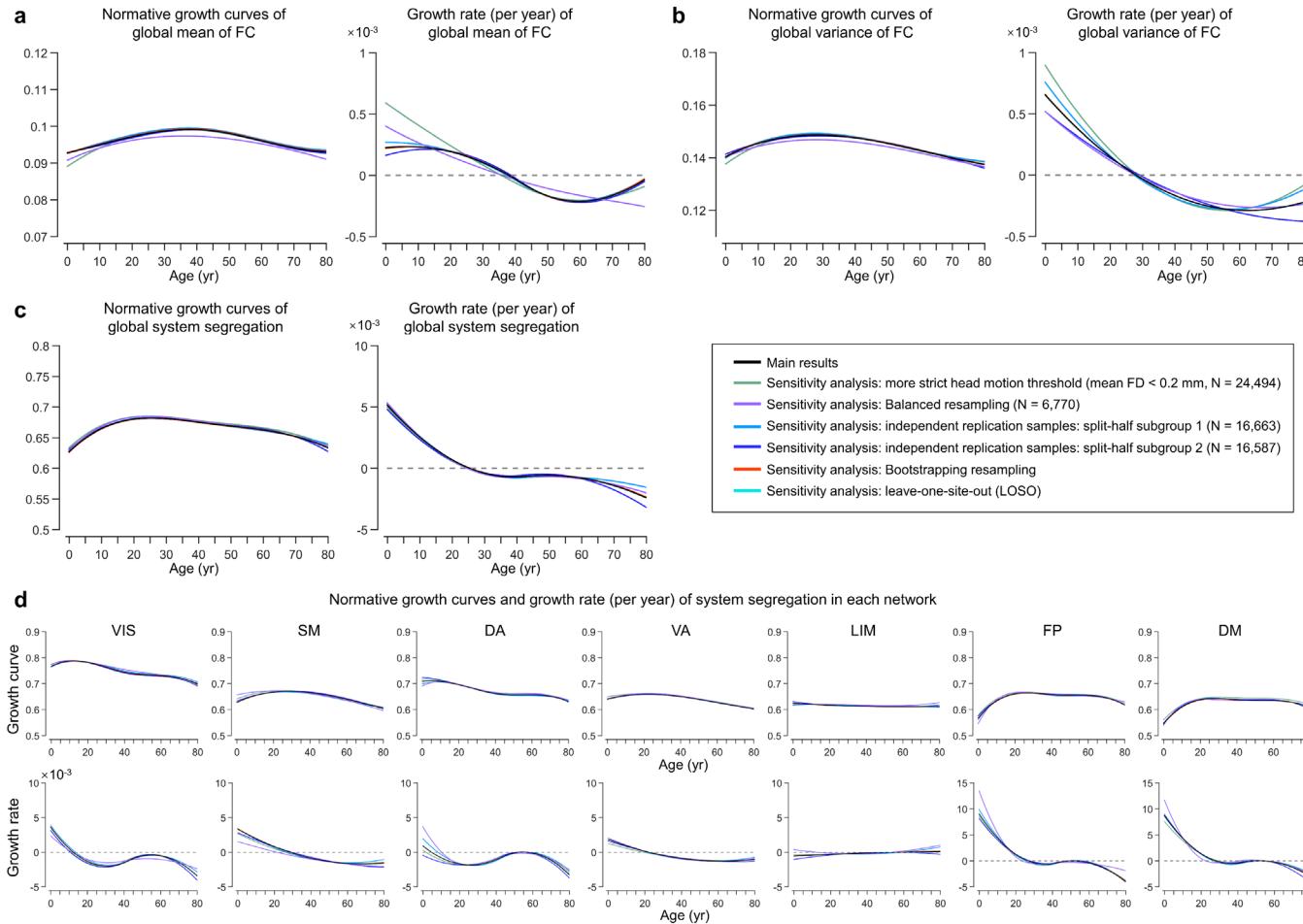


Lifespan growth of regional level functional connectivity



- Lifespan growth of functional connectivity at the regional level reveals a spatial gradient pattern that from primary to association cortex

Sensitivity analyses for the lifespan normative growth patterns



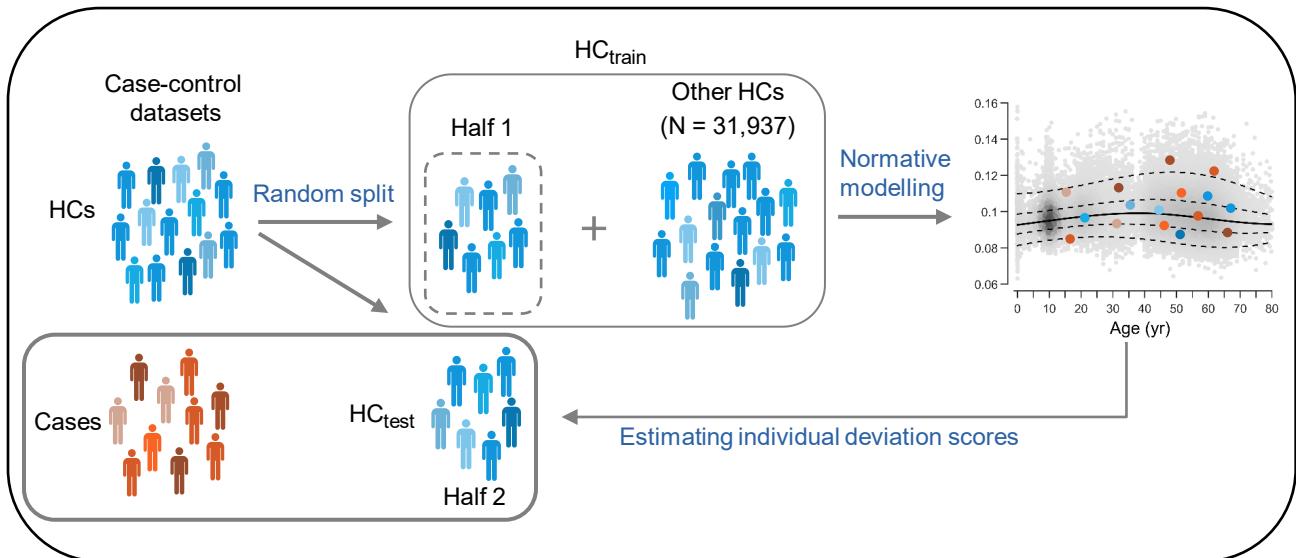
Identifying individual heterogeneity in brain disorders

Case-control datasets:

with ASD ($N_{ASD} = 414$; $N_{HC} = 591$)

with MDD ($N_{MDD} = 622$; $N_{HC} = 535$)

with AD ($N_{AD} = 180$; $N_{HC} = 187$)



This process was repeated 100 times, generating 100 models and 100 sets of deviation scores.

High reproducibility was observed among the 100 repetitions (mean $R > 0.95$, mean MSE < 0.1 of the growth curves) and the 100 sets of deviation scores (mean $R > 0.97$, mean MSE < 0.2).

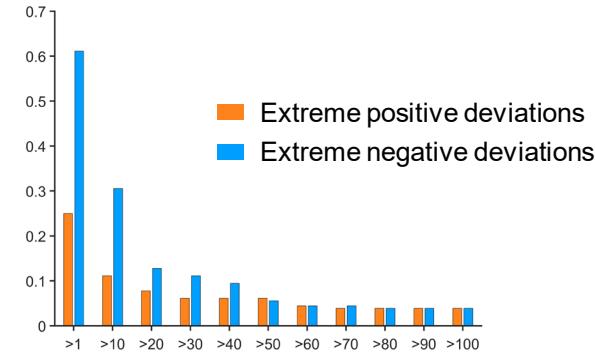
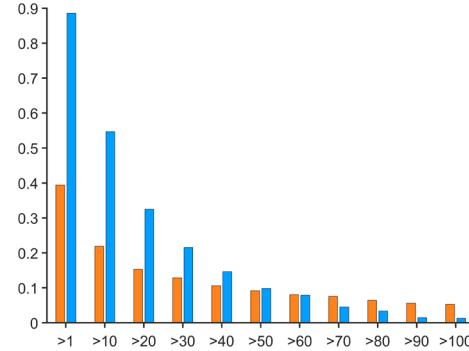
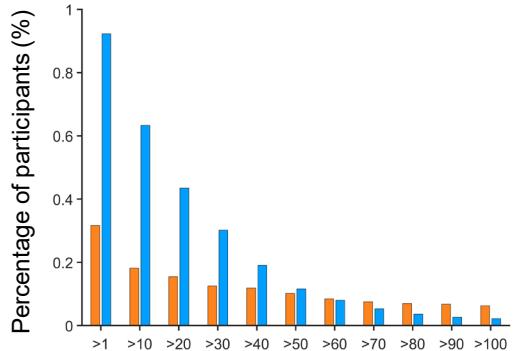
Identifying individual heterogeneity in brain disorders

ASD

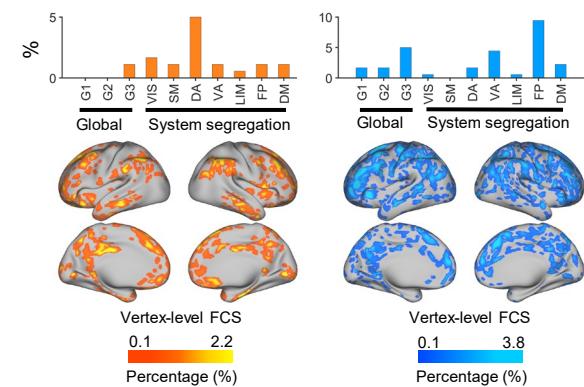
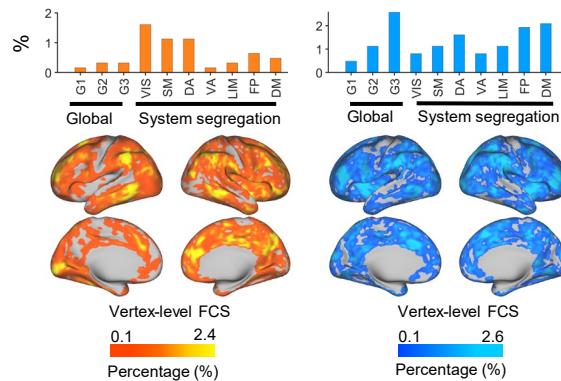
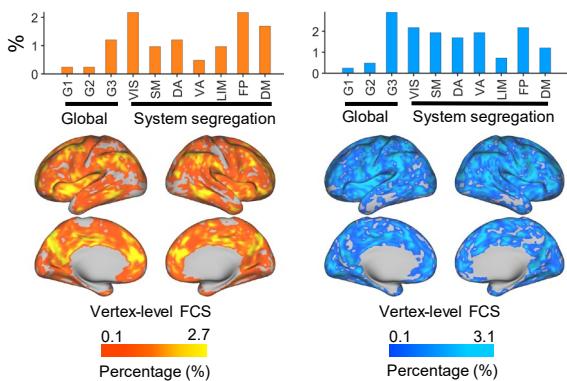
MDD

AD

The percentage of participants with extremely deviations under different number of functional metrics



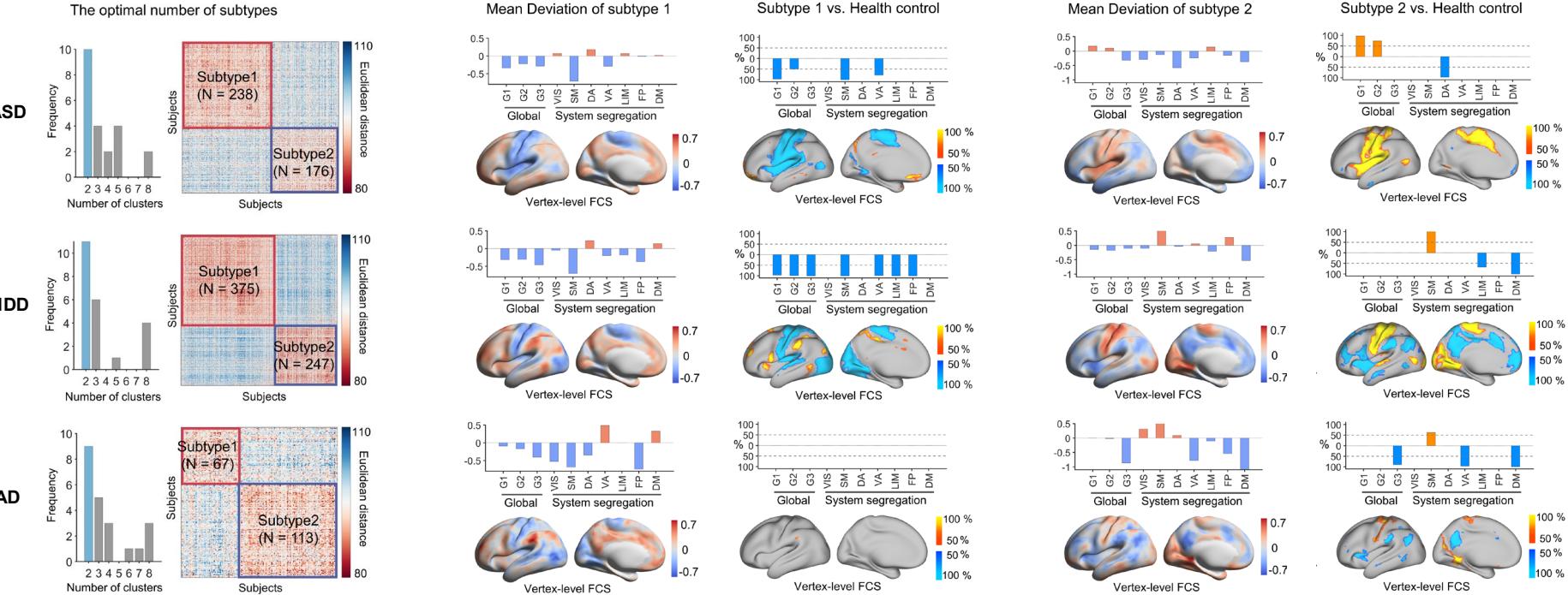
The percentage of extreme FC deviations of global, system, and vertex levels



Identifying individual heterogeneity in brain disorders

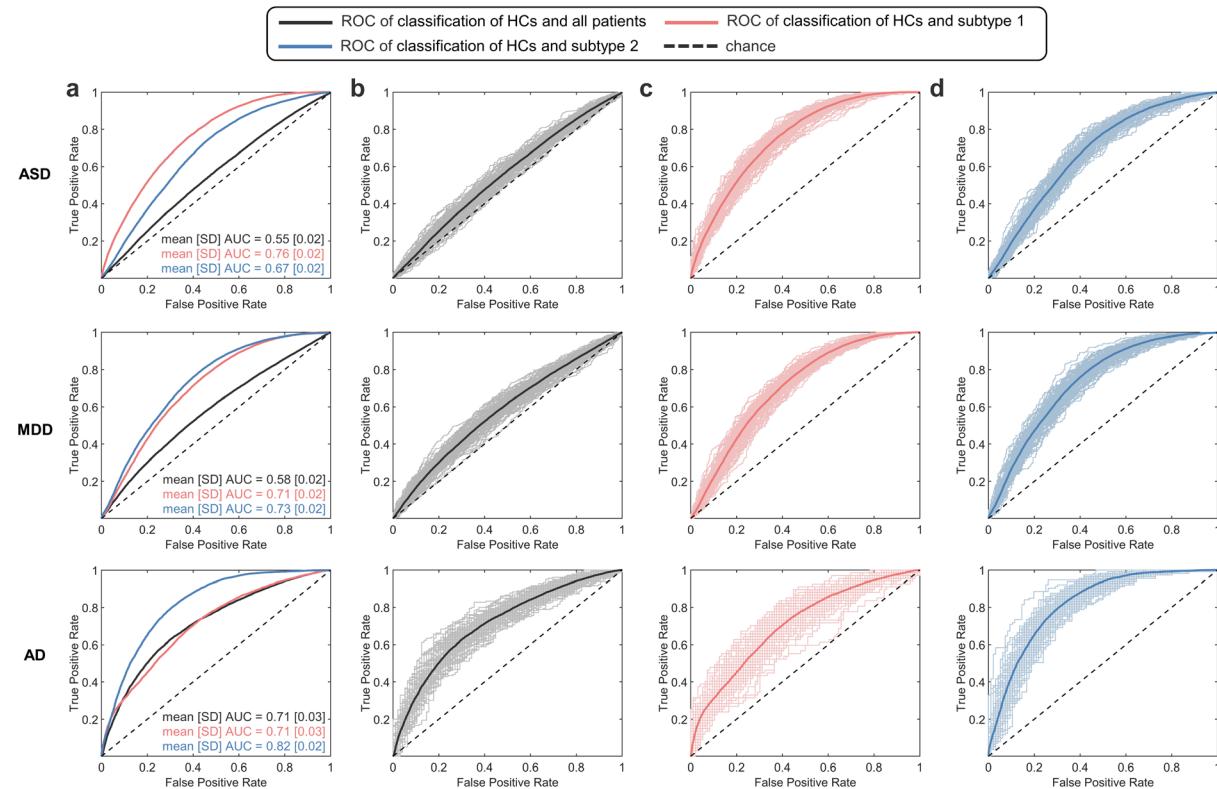
Subtyping analysis

- For each disorder, different subtypes showed distinct patterns of deviation and case-control differences in the functional connectome



Identifying clinical relevance in brain disorders

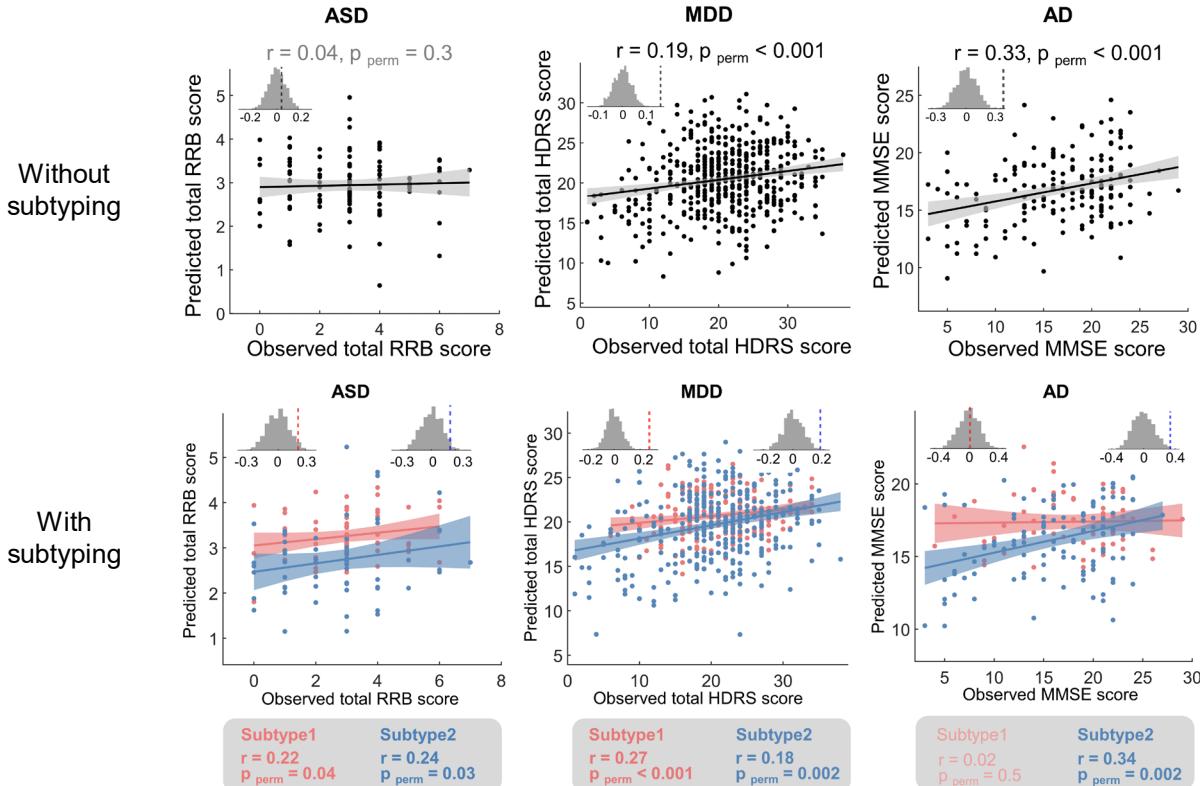
Classification analysis



- The mean AUCs for ASD subtypes 1 and 2 were 0.76 and 0.67, respectively, but 0.55 without subtyping.
- The mean AUCs for MDD subtypes 1 and 2 were 0.71 and 0.73, respectively, but 0.58 without subtyping.
- The mean AUCs for AD subtypes 1 and 2 were 0.71 and 0.82, respectively, but 0.71 without subtyping.

Identifying clinical relevance in brain disorders

Prediction analysis



Summary

- The global mean and variance of functional connectivity show continuous nonlinear changes across the lifespan, peaking in the late of fourth decade and the late of third decade, respectively.
- The default mode and frontoparietal networks undergo more rapid development of system segregation during infancy, childhood, and adolescence, peak later, and decline precipitously during aging.
- The lifespan growth pattern of regional FCS is constrained by its position along the S-A axis, highlighting the role of the S-A axis as a key organizational principle that influences cortical development and aging.
- The connectome-based normative model is useful in capturing individual heterogeneity within the clinical populations, underscoring its potential to advance our understanding of neuropsychiatric disorders.

For more details on this study, please refer to the preprint available at:
<https://www.biorxiv.org/content/10.1101/2023.09.12.557193v2>

Abstract: Functional connectome through the human life span

Poster number: **1269** [Monday, June 24 | 12:15 -14:15 & Tuesday, June 25 | 13:00 -15:00]

Acknowledgments



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- Xuhong Liao (Beijing Normal University)
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The Alzheimer's Disease Neuroimaging Initiative,
The Age_ility Project,
The Baby Connectome Project,
The Brain Genomics Superstruct Project,
The Calgary Preschool MRI Dataset,
The Cambridge Centre for Ageing and Neuroscience Dataset,
The Connectivity-based Brain Imaging Research Database,
The Children Brain Development Project,
The Developing Human Connectome Project,
The Disease Imaging Data Archiving: major depressive disorder Working Group
The Human Connectome Project,
The Lifespan Human Connectome Project,
The Multi-center Alzheimer Disease Imaging (MCADI) Consortium,
The Nathan Kline Institute-Rockland Sample Dataset,
The Neuroscience in Psychiatry Network Dataset,
The Pediatric Imaging, Neurocognition, and Genetics Data Repository,
The Pixar Dataset,
The Strategic Research Program for Brain Sciences Dataset,
The Southwest University Adult Lifespan Dataset,
The Southwest University Longitudinal Imaging Multimodal Brain Data Repository,
The UK Biobank Brain Imaging Dataset,

Thanks!