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EDUCATIONAL COURSES

Charting life-course functional connectome using normative modeling

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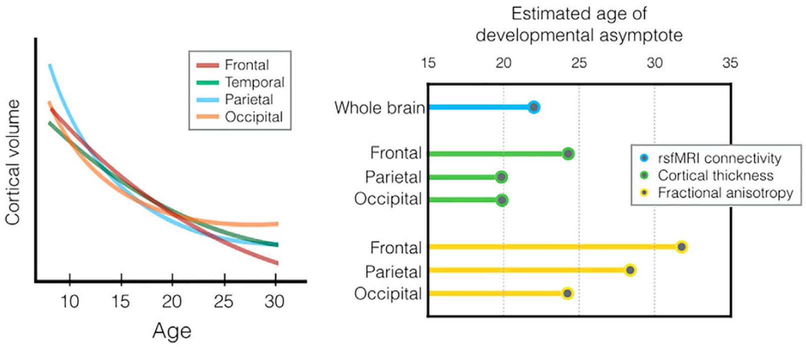
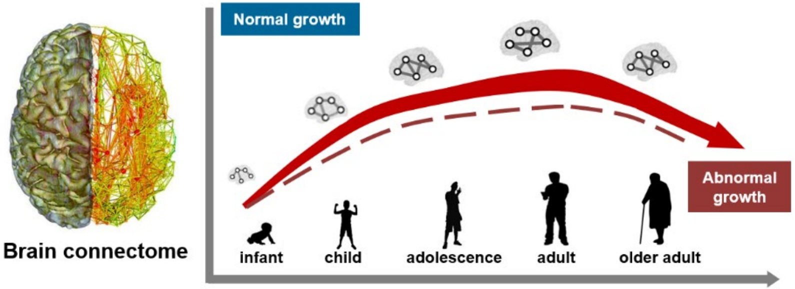
Content

- Background
- Lifespan normative growth of the global functional connectome
- The fine-grained, lifespan-wide suite of system-level atlases
- Lifespan growth of system-specific functional segregation
- Lifespan growth of regional level functional connectivity
- Identifying clinical relevance in brain disorders using connectome-based normative models

Background

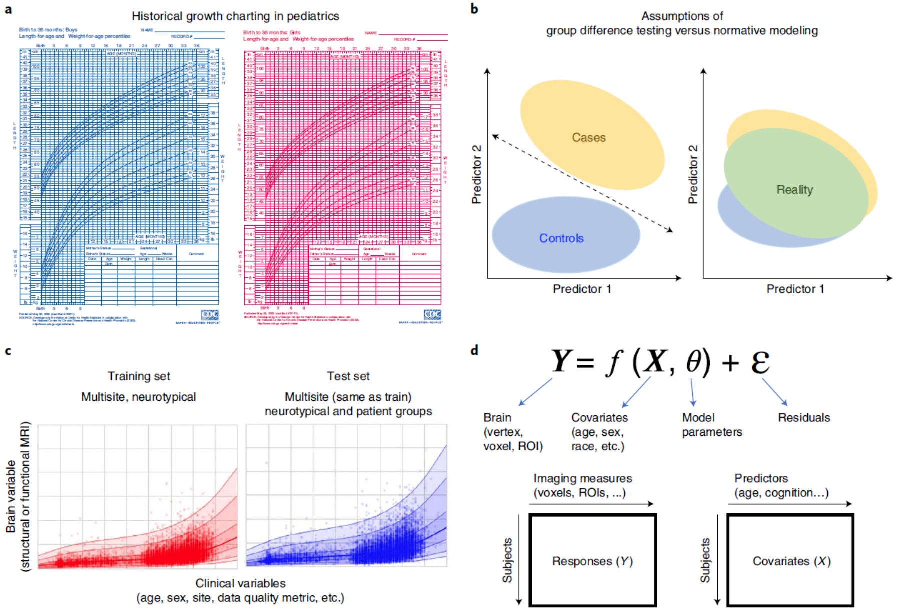
The emergence, development, and aging of the intrinsic connectome architecture throughout the lifespan





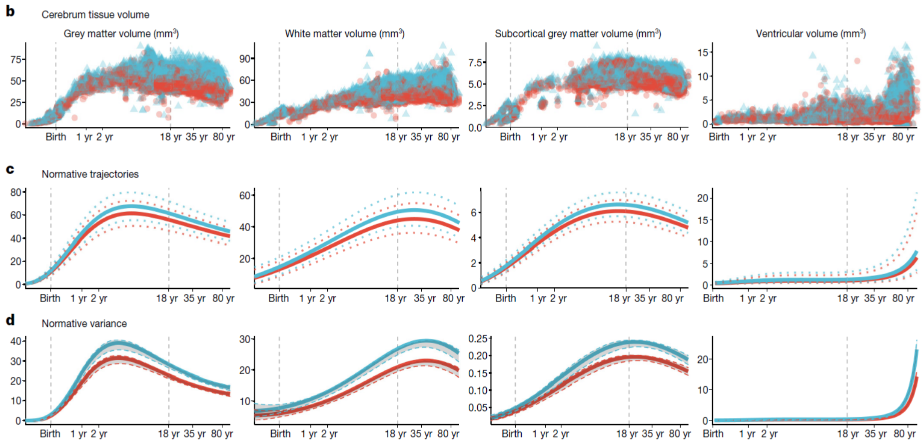
Somerville *et al* (2016) *Neuron*; Zuo *et al* (2017) *Trends Cogn Sci*;
Cao *et al* (2017) *Trends Neurosci*; Vogel *et al* (2023) *Nat Rev Neurosci*

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

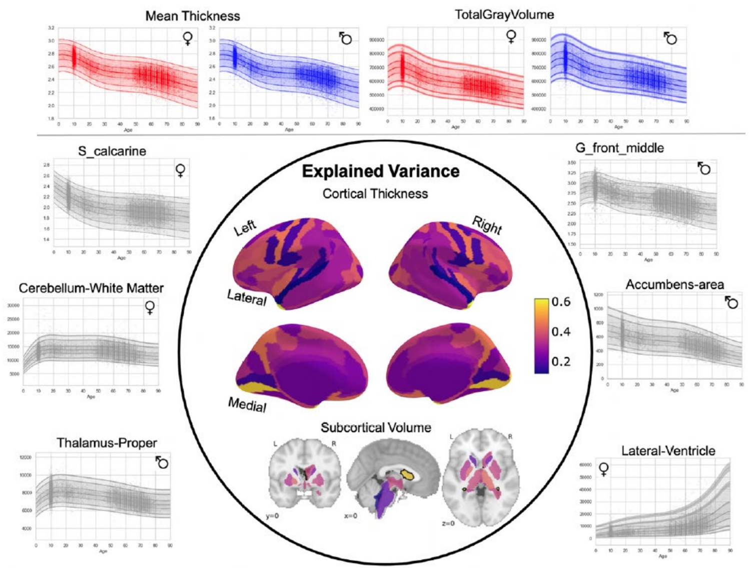


Marquand *et al* (2016) *Biol Psychiatry*
Rutherford *et al* (2022) *Nat Protoc*

Background

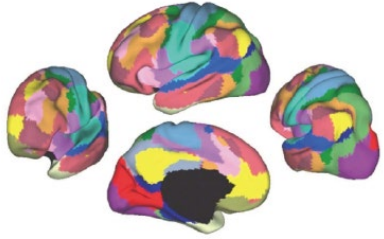


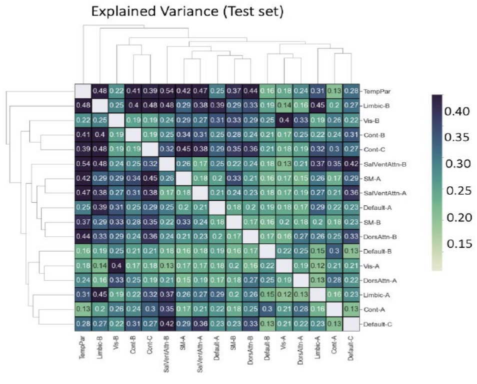
Bethlehem, Seidlitz, White *et al* (2022) *Nature*



Rutherford *et al* (2022) *eLife*

Yeo-17 network parcellation





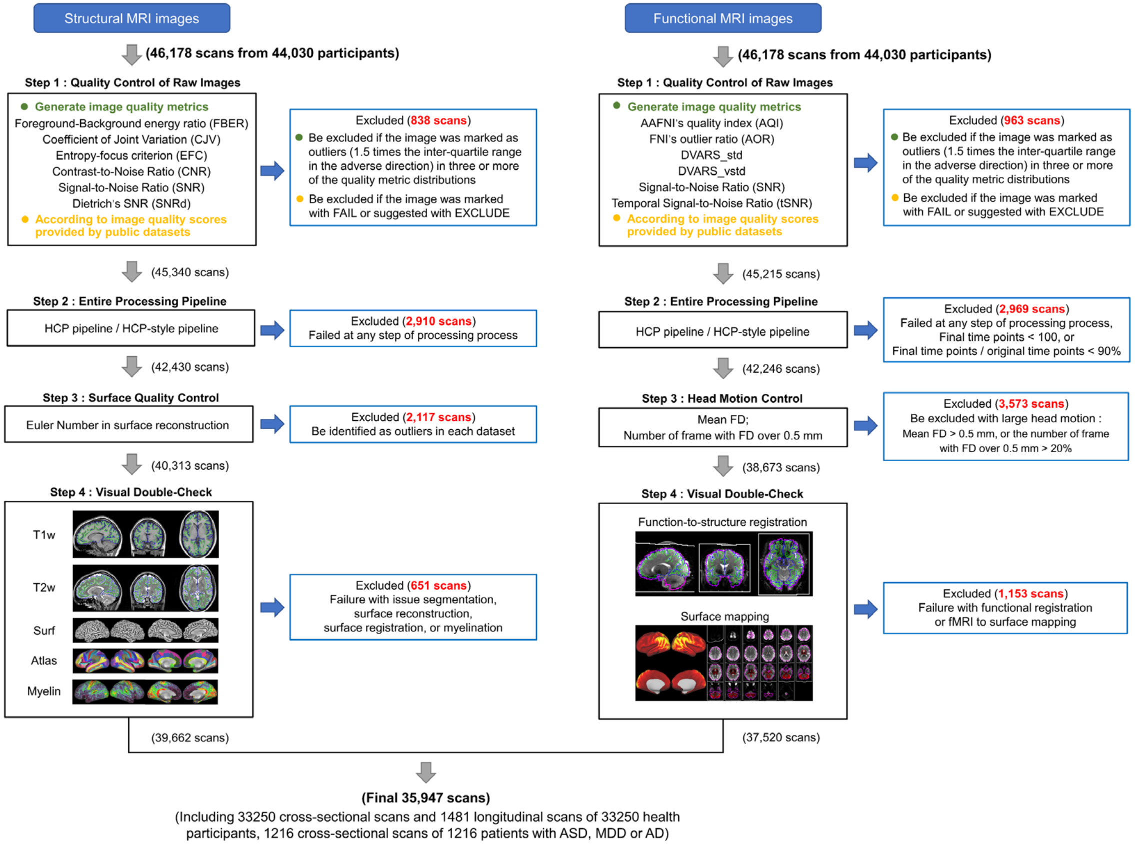
Rutherford *et al* (2023) *eLife*

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



https://github.com/sunlianglong/BrainChart-FC-Lifespan/blob/main/QC/README.md

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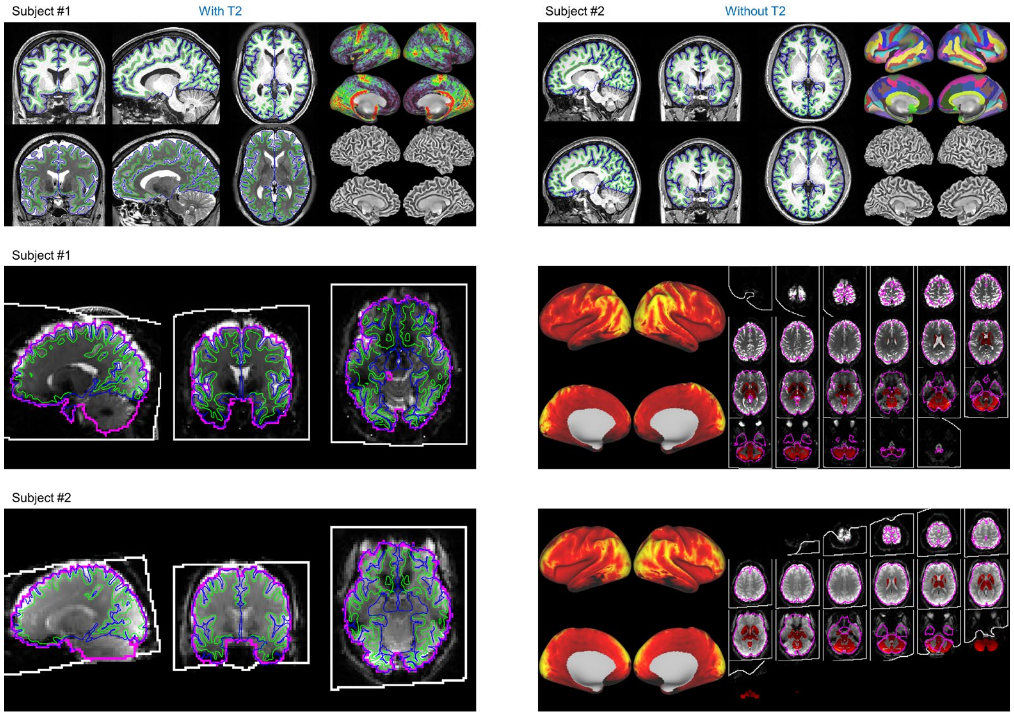

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Glasser *et al* (2013) *NeuroImage*

Datasets and imaging quality control

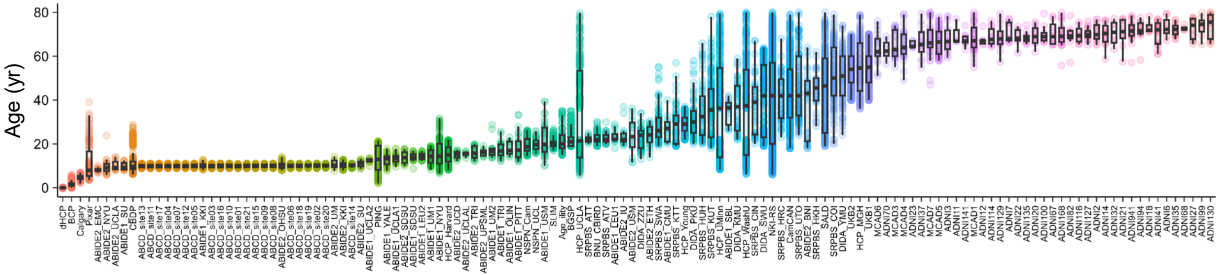
We aggregated 3T multi-modal imaging data from 44,030 individuals.

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.

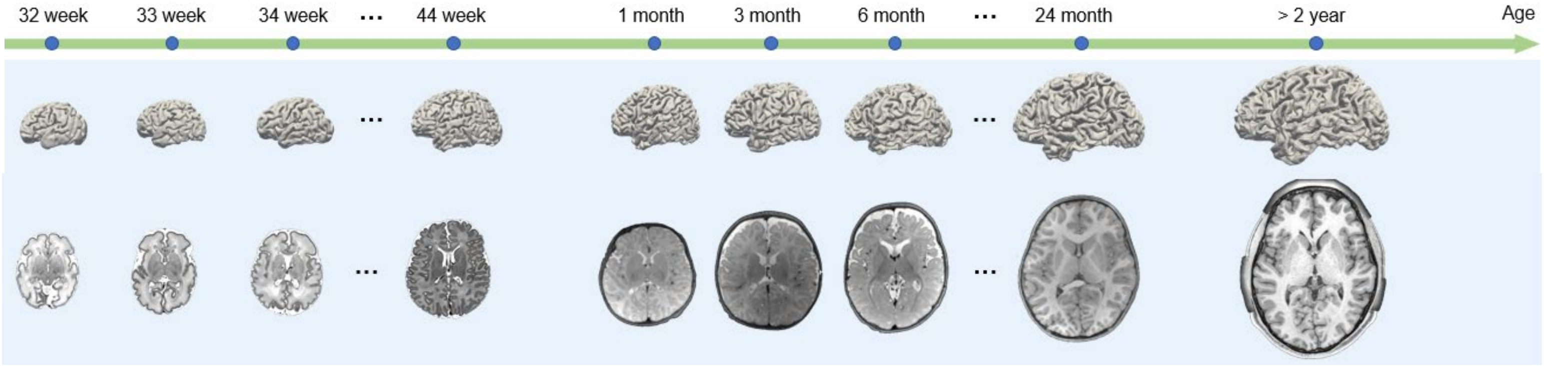
- 414 ASD patients (aged 5-59 y)
- 622 MDD patients (aged 11-77 y)
- 180 AD patients (aged 51-80 y)

Aggregated data across 132 sites (after quality control)



https://github.com/sunlianglong/BrainChart-FC-Lifespan/blob/main/QC/README.md

Data processing



Considerable changes of the human brain in early development

Challenges:

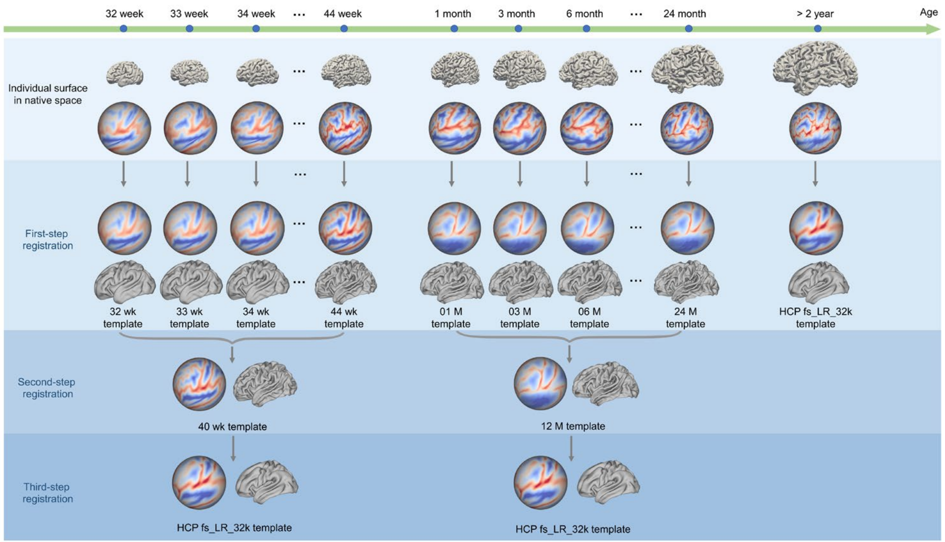
- Lack of a lifespan-appropriate preprocessing structural pipeline
- Lack of a set of standard templates for registration across lifespan
- Lack of a set of functional atlases across lifespan

Data processing

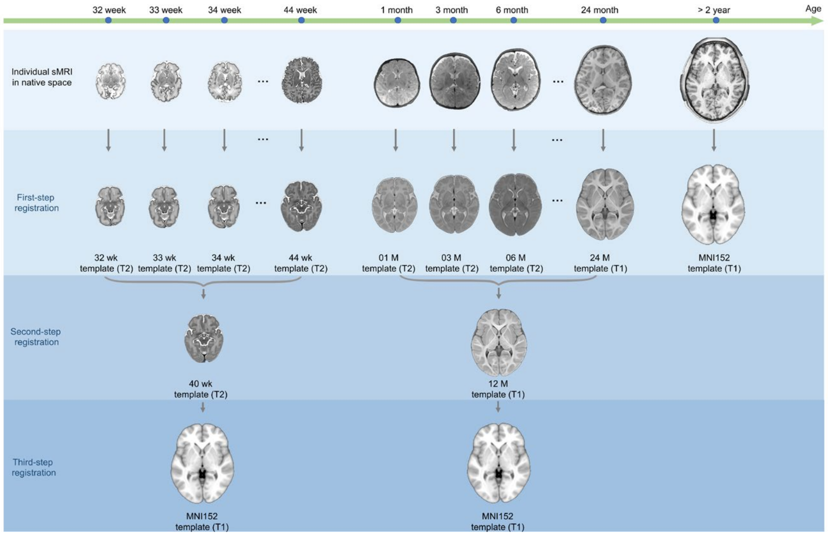
Participants aged 32 to 44 postmenstrual weeks

Participants aged 1 to 24 months

Participants aged larger than 2 years



Individual cortical surface registration framework



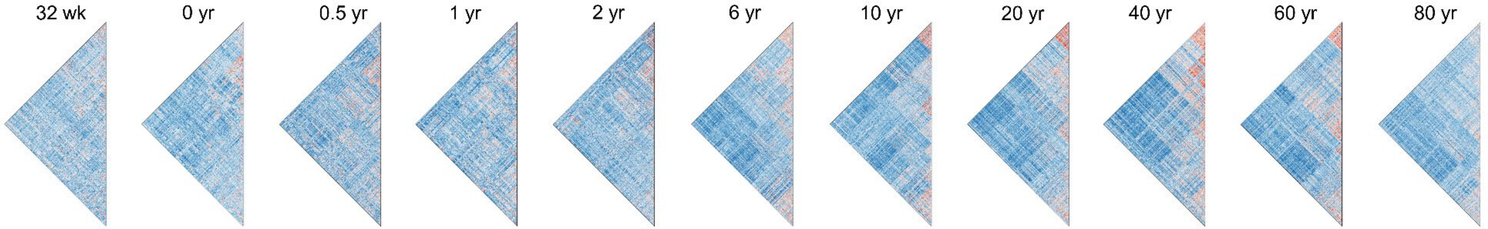
Individual volume registration framework

Templates: Williams *et al* (2023) *Nat Hum Behav;* Wu *et al* (2019) *Hum Brain Mapp*
Van Essen *et al* (2012) *Cereb Cortex;* Chen *et al* (2022) *NeuroImage*;
Schuh *et al* (2018) *BioRxiv*; Mazziotta *et al* (2001) *Philos Trans R Soc Lond B Biol Sci*

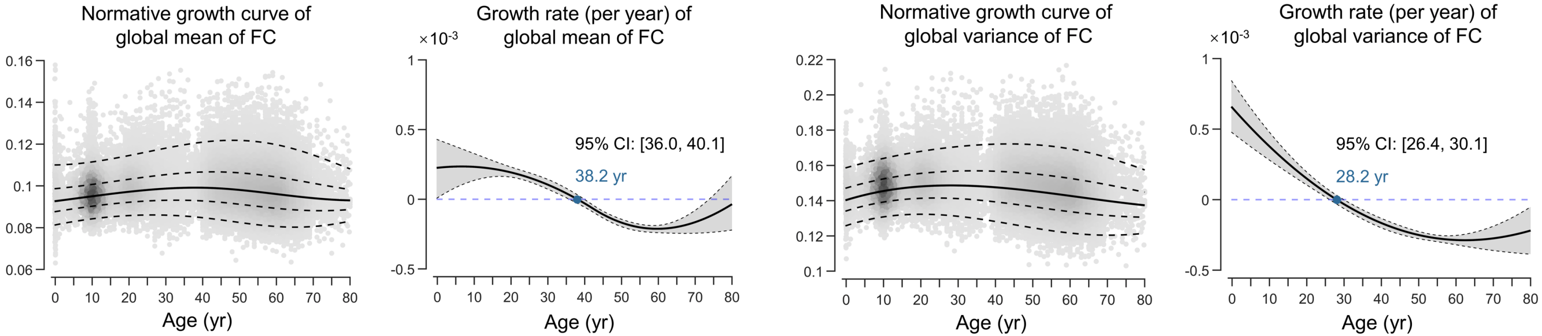
Lifespan normative growth of the global functional connectome

Functional connectome matrices at different growth ages

Network size: 4609 × 4609

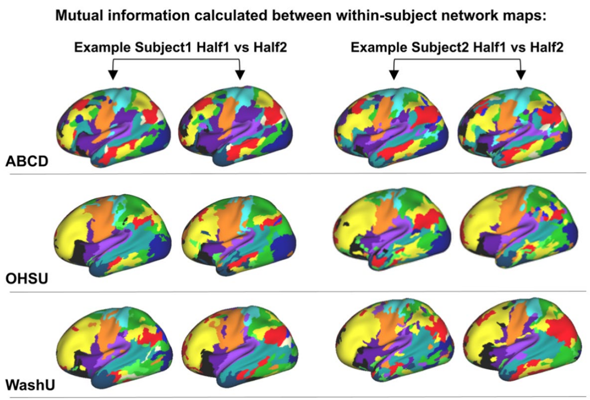


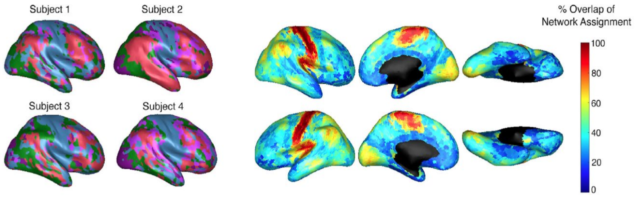
Normative models of global functional connectome (N = 33,250)



- 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 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).

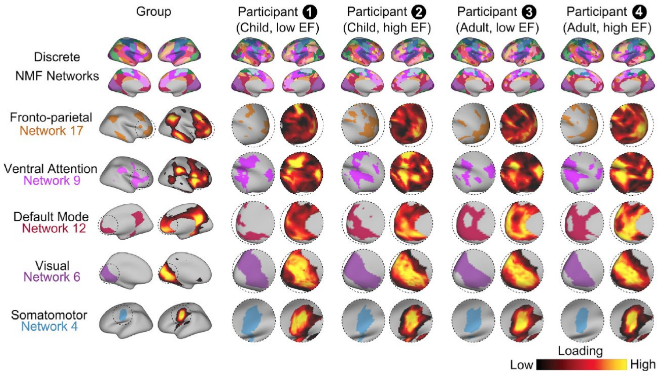
Personalized functional mapping is critical for the entire lifespan

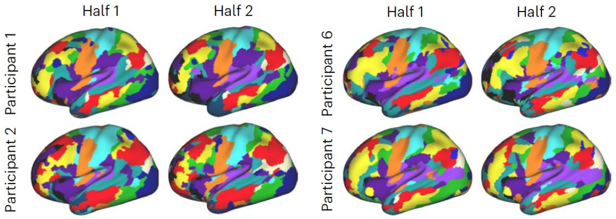




Neonates

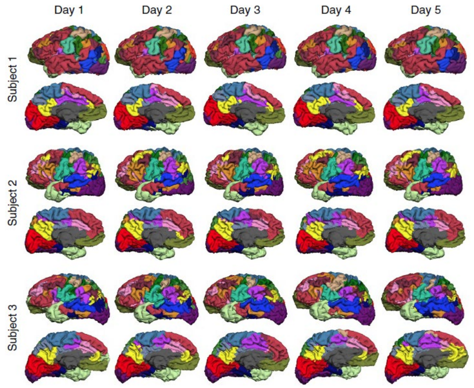
Molloy & Saygin (2022) *Neuroimage*;
Moore *et al* (2024) *Imaging Neurosci*

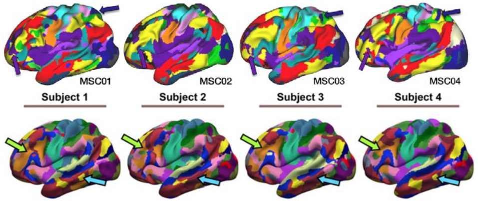




Children and adolescents

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





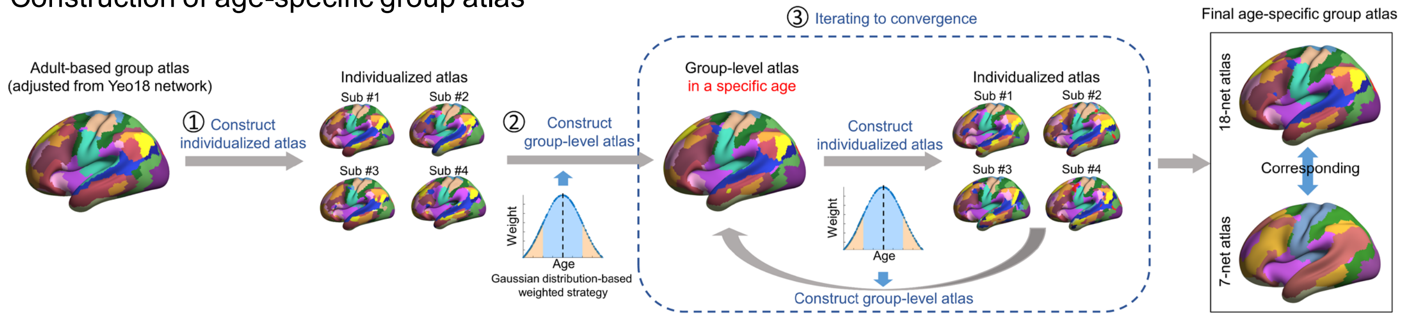
Adults

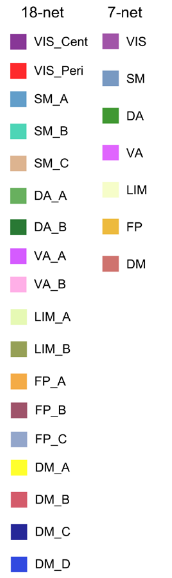
Wang *et al* (2015) *Nat Neurosci*;
Gordon *et al* (2017) *Neuron*;
Kong et al (2019) *Cereb Cortex*

Constructing population-based and individual-based functional atlas

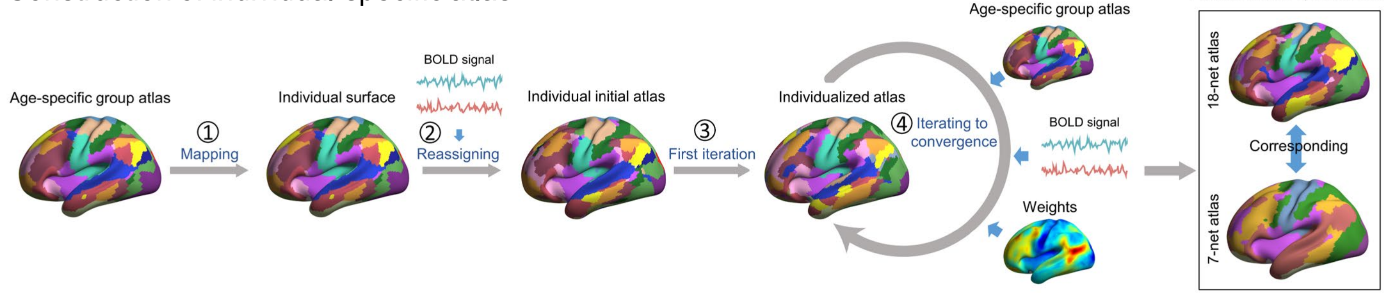
- For **age-specific group atlas**, we developed a Gaussian-weighted iterative age-specific group atlas (GIAGA) generation approach
- For **individual-specific atlas**, we used the individualized atlas approach proposing by Wang *et al* (2015) *Nat Neurosci*

Construction of age-specific group atlas





Construction of individual-specific atlas



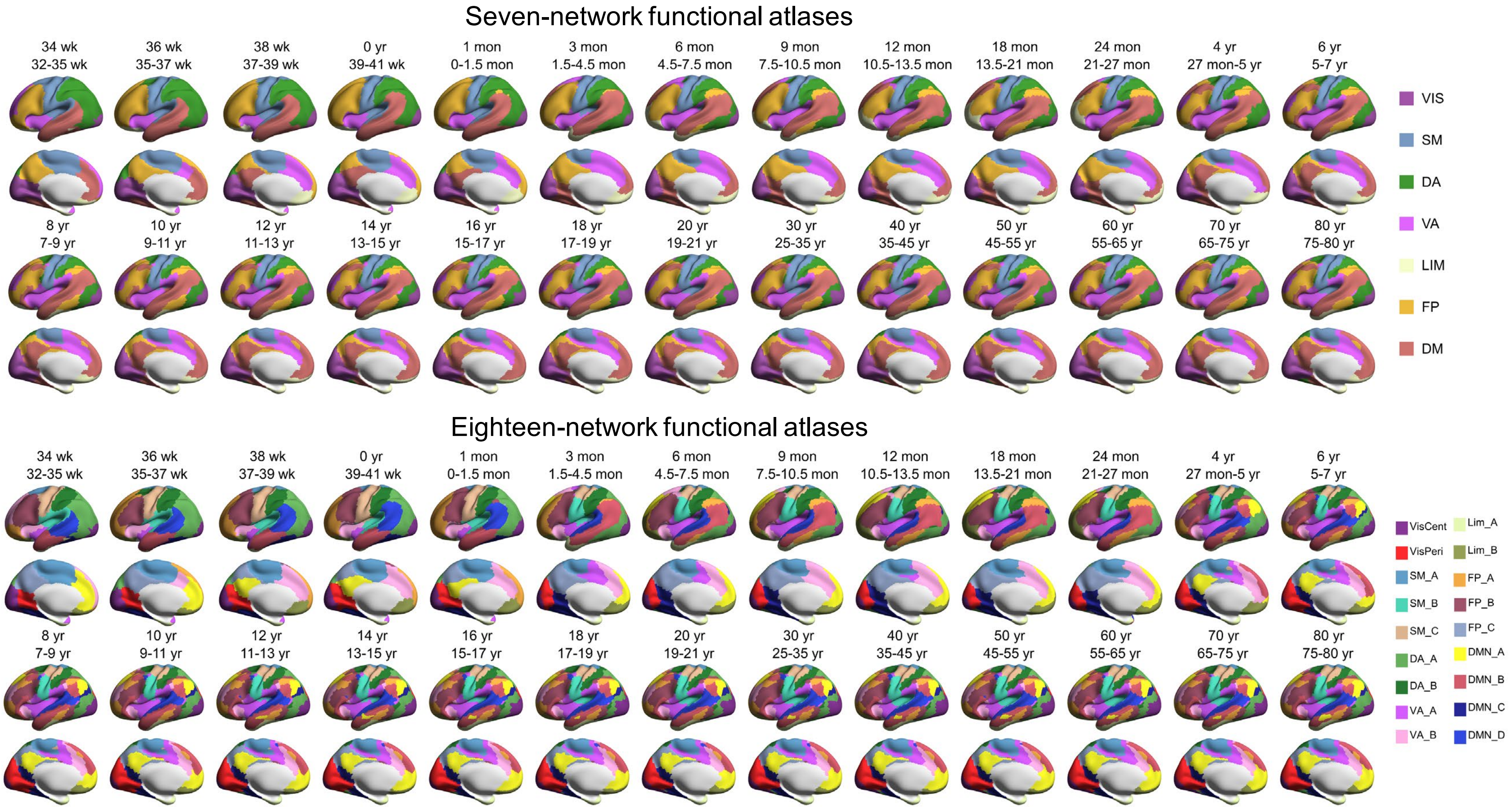
Wang *et al* (2015) *Nat Neurosci*

Constructing population-based and individual-based functional atlas

Functional homogeneity

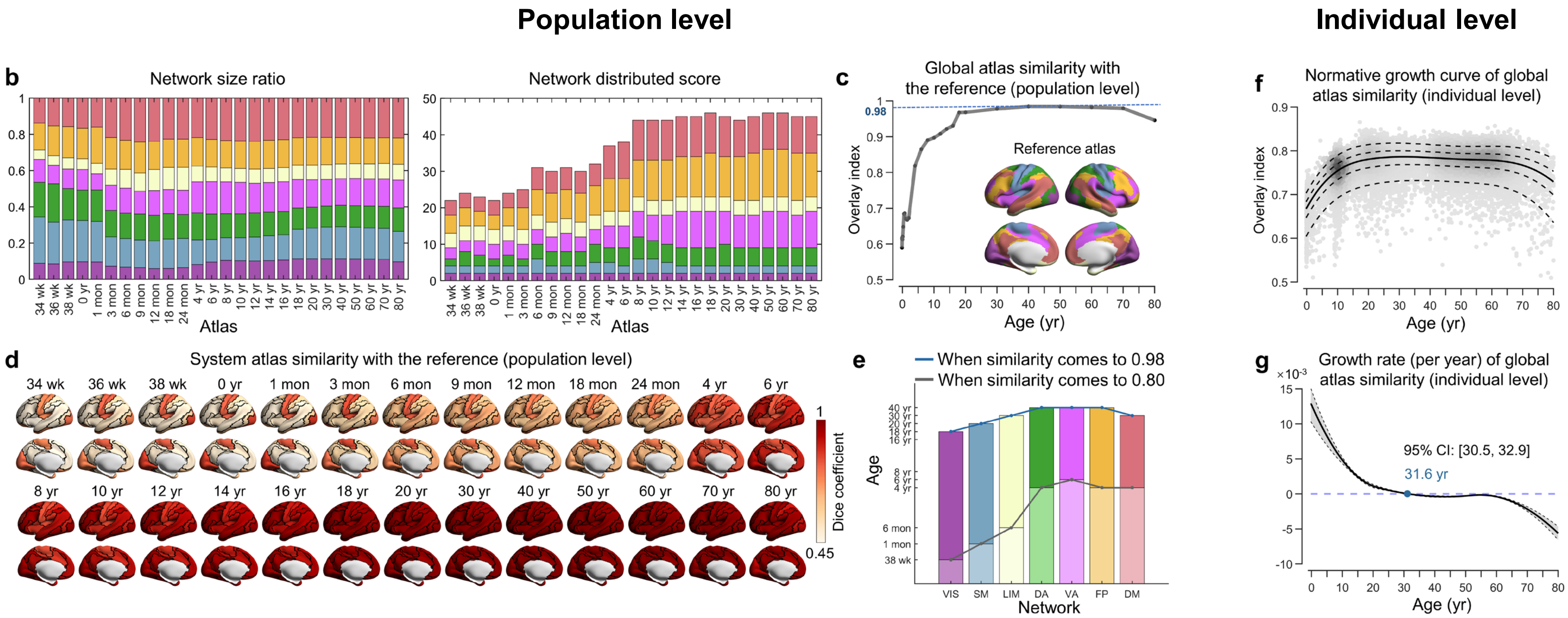
Individual-specific atlas >
Age-specific group atlas >
Adult-based group atlas (all $p < 10^{-8}$)

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



https://github.com/sunlianglong/BrainChart-FC-Lifespan

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

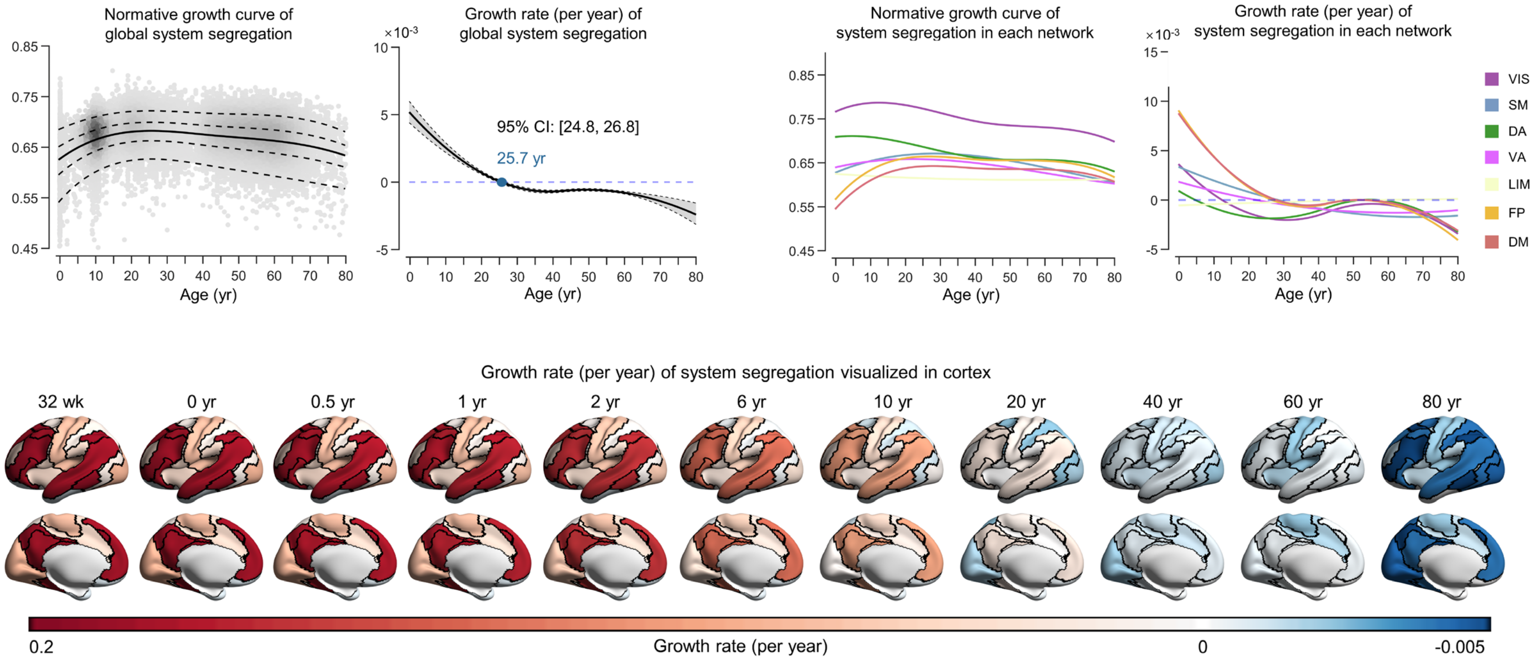


- (Population level) The overall similarity of the whole-cortical atlas exhibited a rapid increase during the first two decades of life, followed by a plateau, and a subsequent slight decrease with age.
- (Individual level) The global similarity of the individualized atlas to the reference increased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

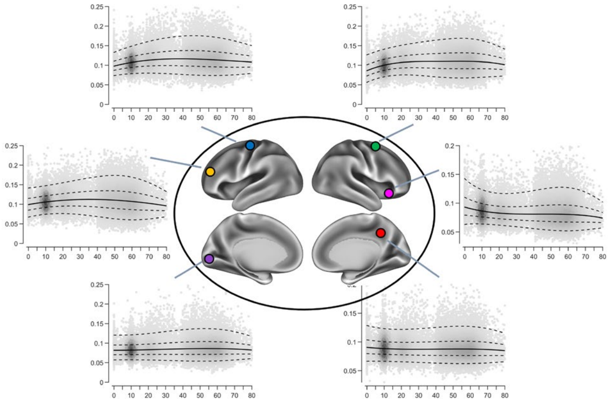
Lifespan growth of system-specific functional segregation

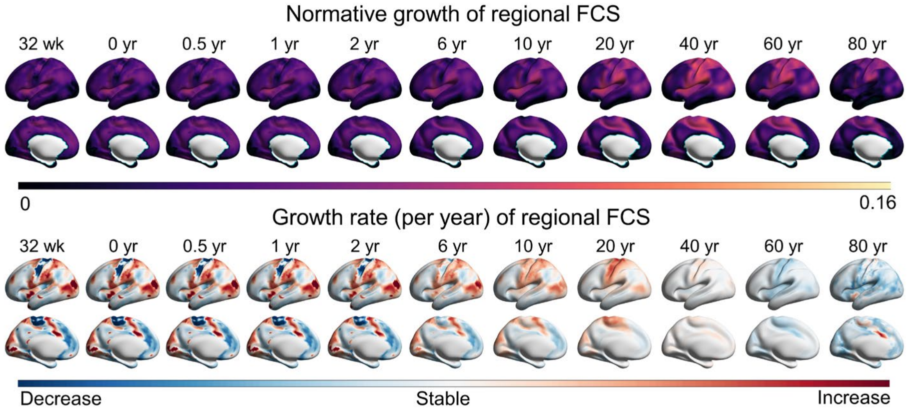
System segregation = $\frac{FC_w - FC_b}{FC_w}$

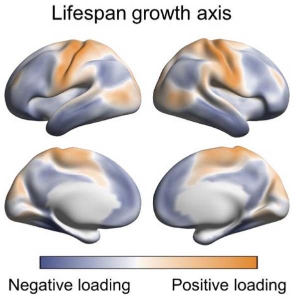
Chan *et al* (2014) PNAS
Chan *et al* (2021) Nat Aging
Wig *et al* (2017) *Trends Cogn Sci*

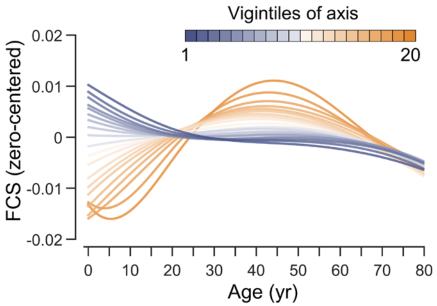


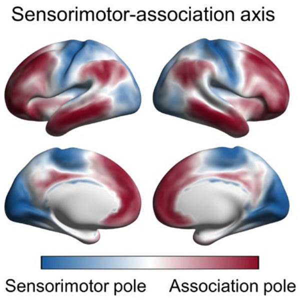
Lifespan growth of regional level functional connectivity

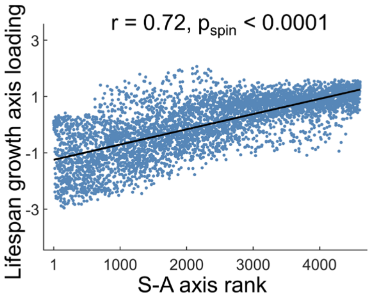










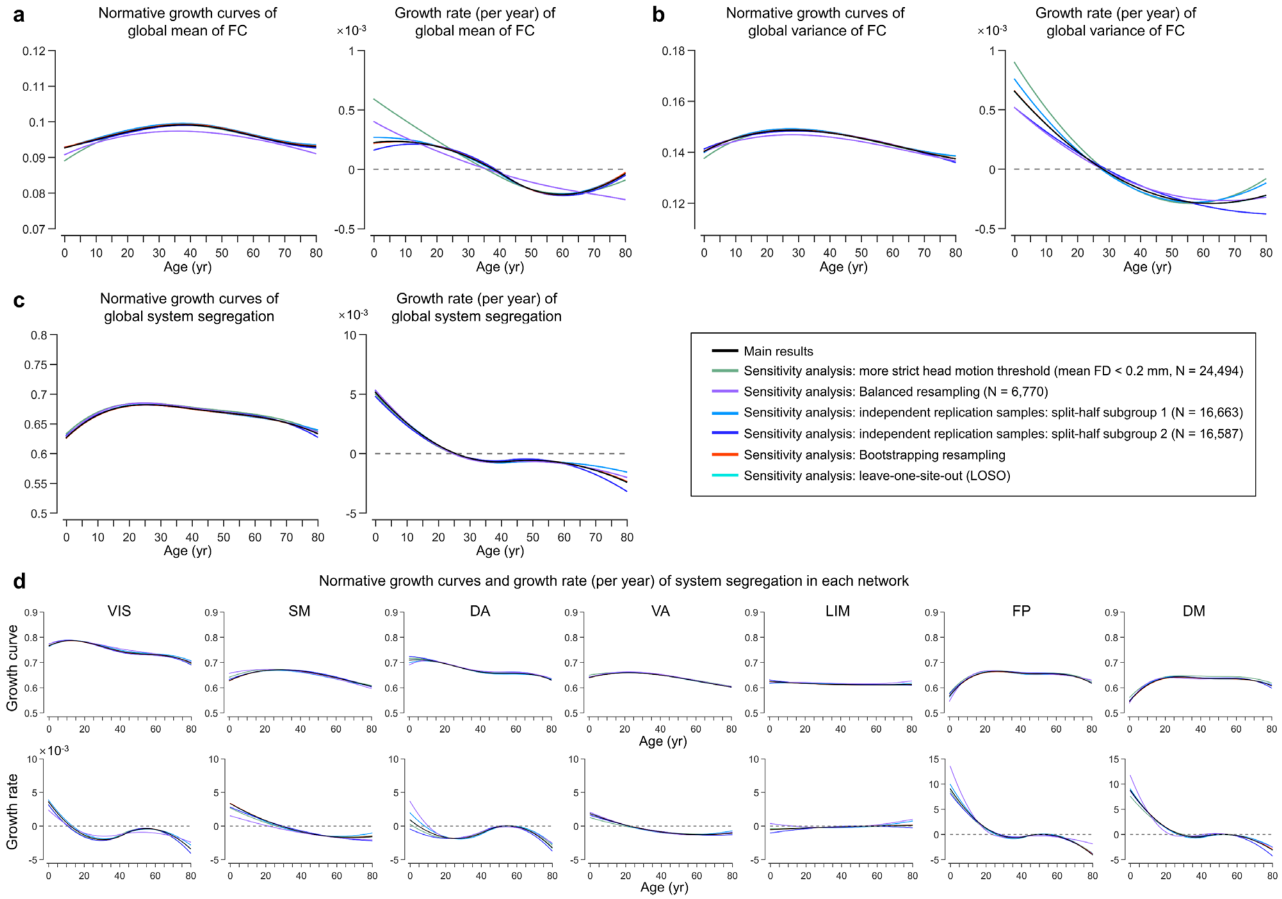


Sydnor *et al* (2021) *Neuron*

- 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

- Analysis with stricter head motion threshold (mean FD < 0.2 mm)
- Balanced resampling analysis
- Split-half replication analysis
- Bootstrap resampling analysis
- Leave-one-study-out analysis



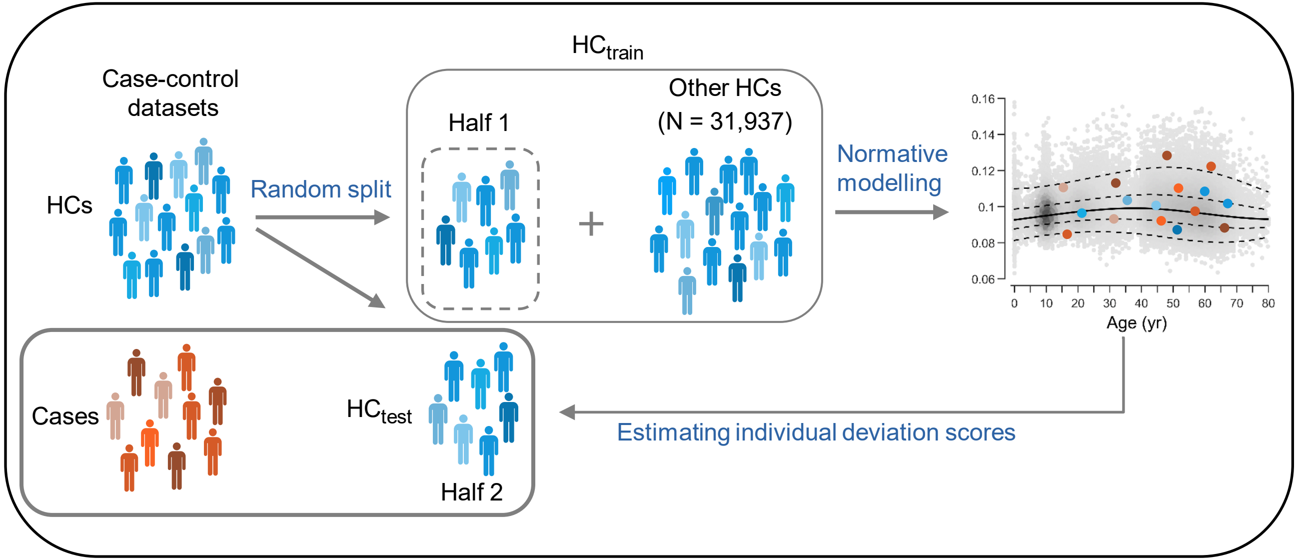
Identifying individual heterogeneity in brain disorders

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.

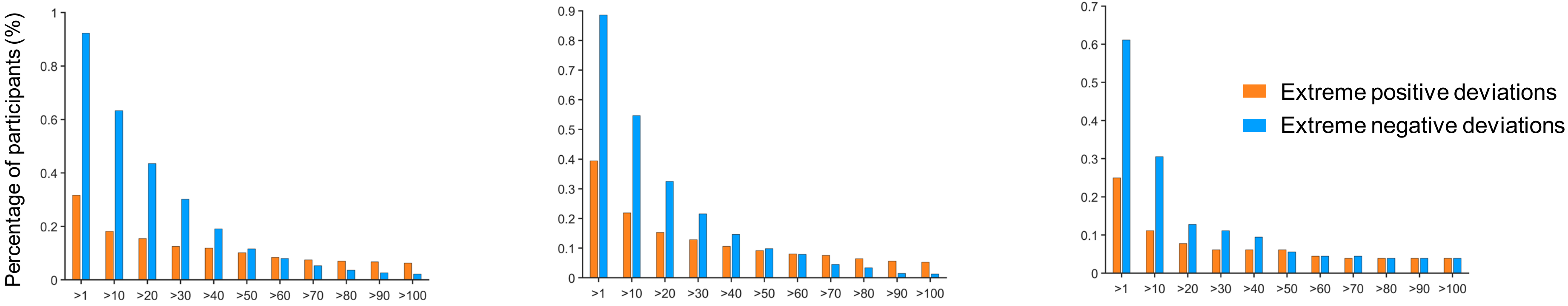
High reproducibility was observed among the 100 repetitions (mean R > 0.95, mean MSE < 0.1 of the growth curves) and the 100 sets of deviation scores (mean R > 0.97, mean MSE < 0.2).

Rutherford *et al* (2022) *Nat Protoc;*
Segal *et al* (2023) *Nat Neurosci*

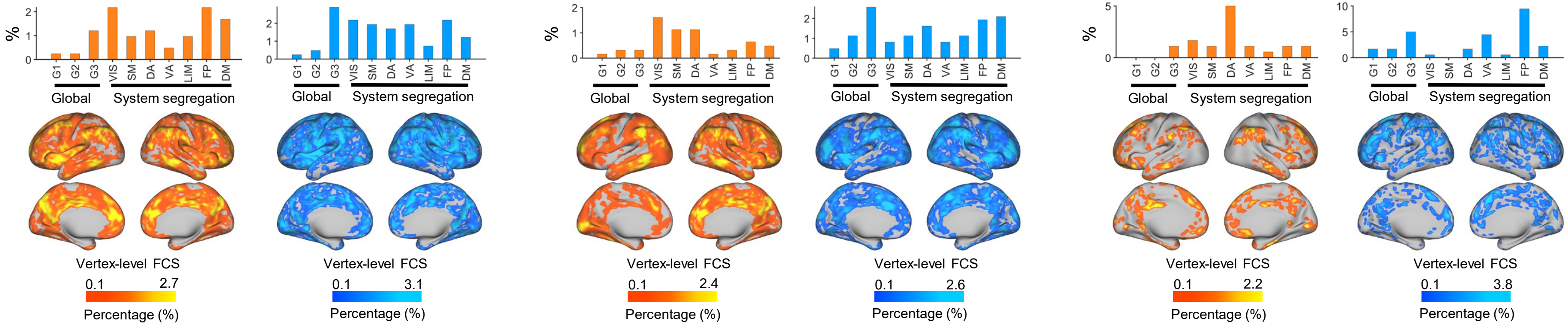
Identifying individual heterogeneity in brain disorders

ASD **MDD** **AD**

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



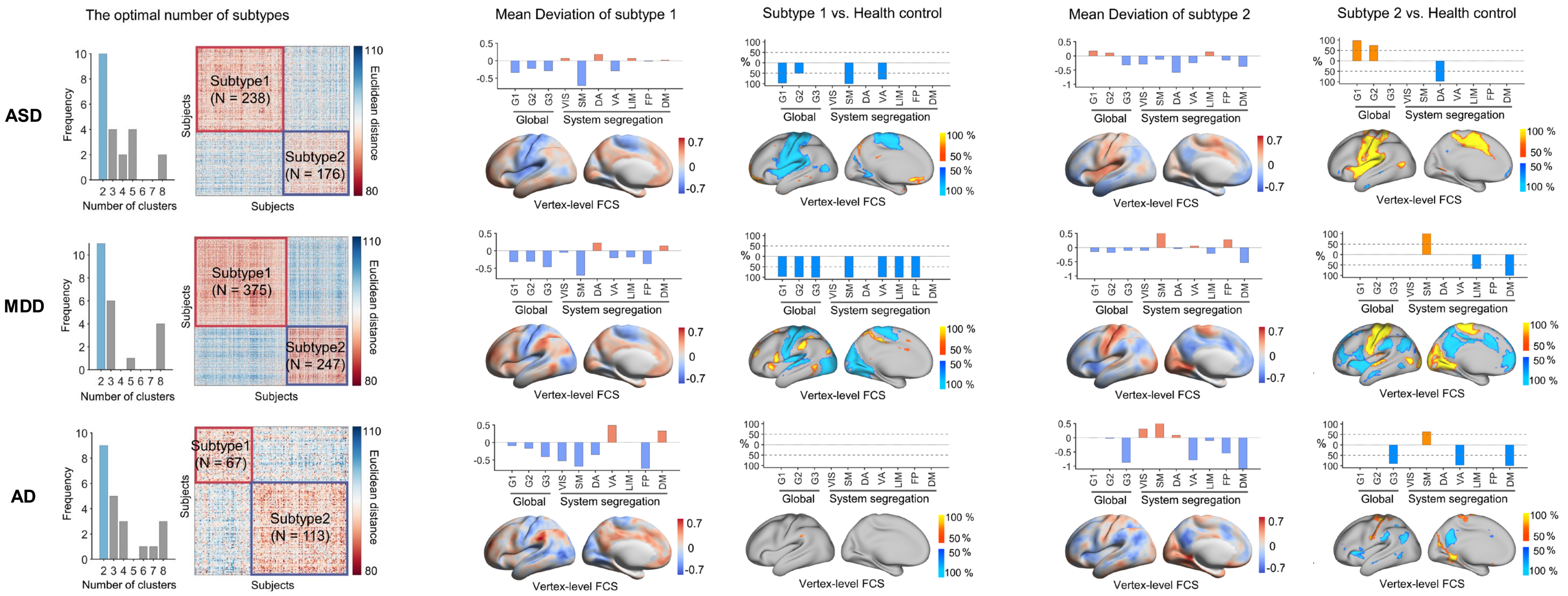
The percentage of extreme FC deviations of global, system, and vertex levels



Identifying individual heterogeneity in brain disorders

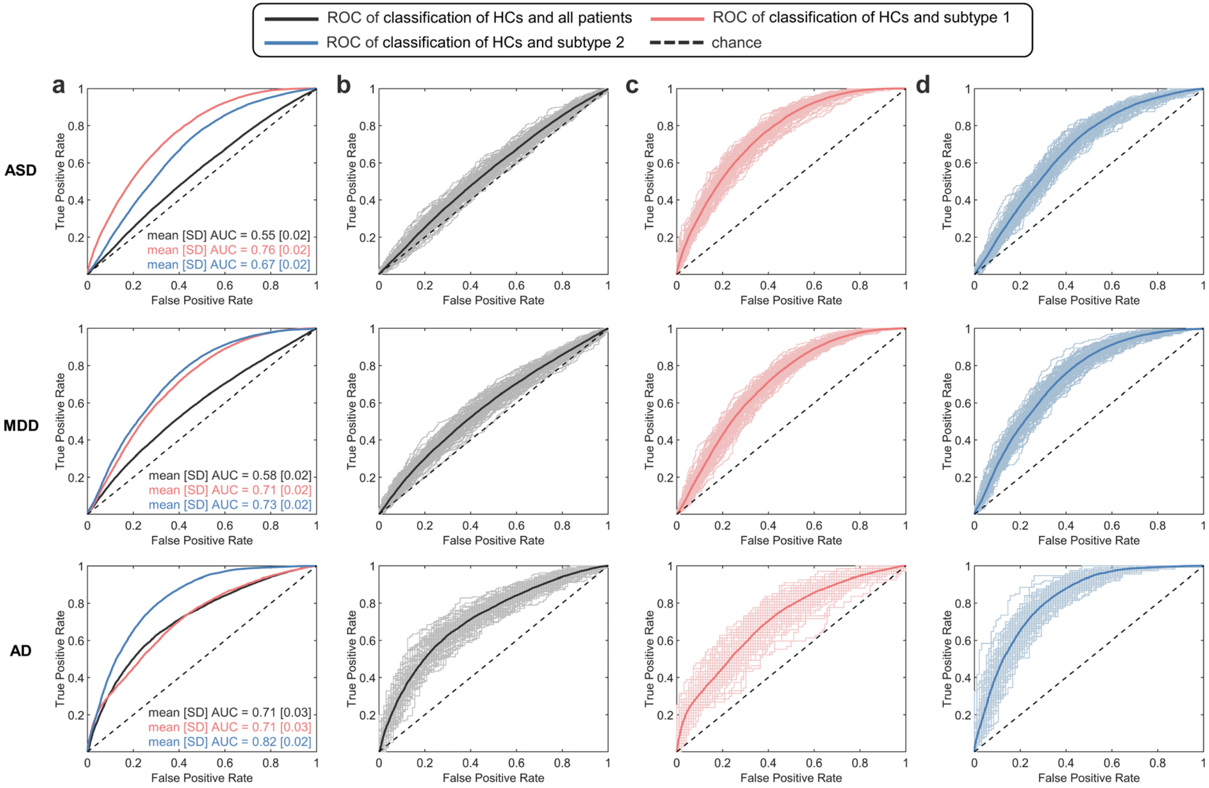
Subtyping analysis

- 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



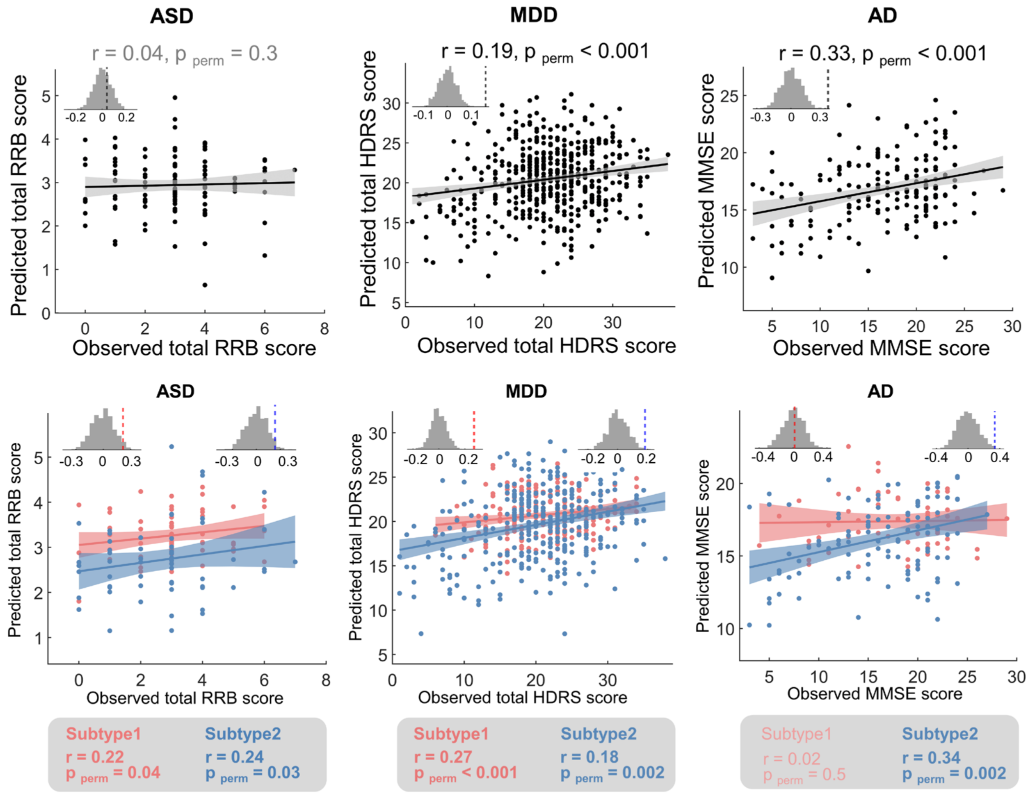
- The mean AUCs for ASD subtypes 1 and 2 were 0.76 and 0.67, respectively, but 0.55 without subtyping.
- The mean AUCs for MDD subtypes 1 and 2 were 0.71 and 0.73, respectively, but 0.58 without subtyping.
- The mean AUCs for AD subtypes 1 and 2 were 0.71 and 0.82, respectively, but 0.71 without subtyping.

Identifying clinical relevance in brain disorders

Prediction analysis

Without subtyping

With subtyping



Summary

- The global mean and variance of functional connectome 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 functional connectivity 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 of this study, please refer to the preprint available at:
https://www.biorxiv.org/content/10.1101/2023.09.12.557193v3

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]

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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,

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Pre-print