Brain Connectivity Development in Childhood and Adolescence : state of the field and challenges

RMN 11 septembre 2025

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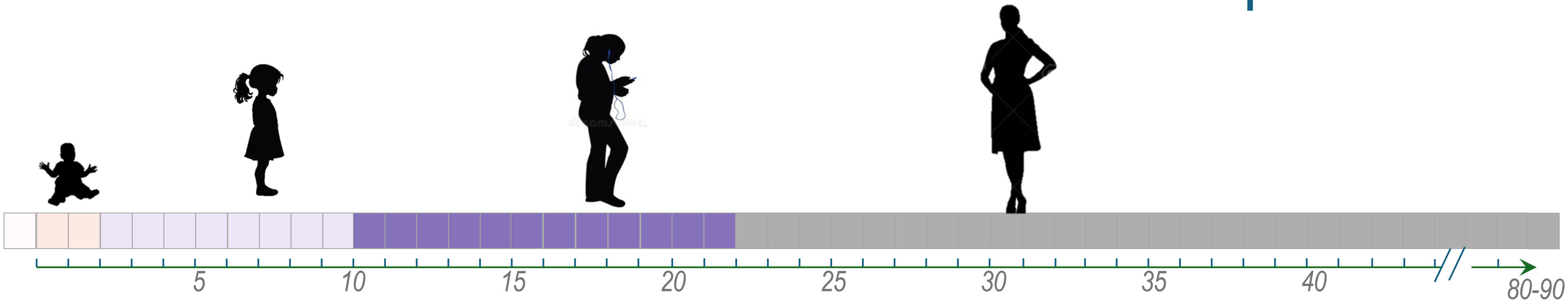
Outline

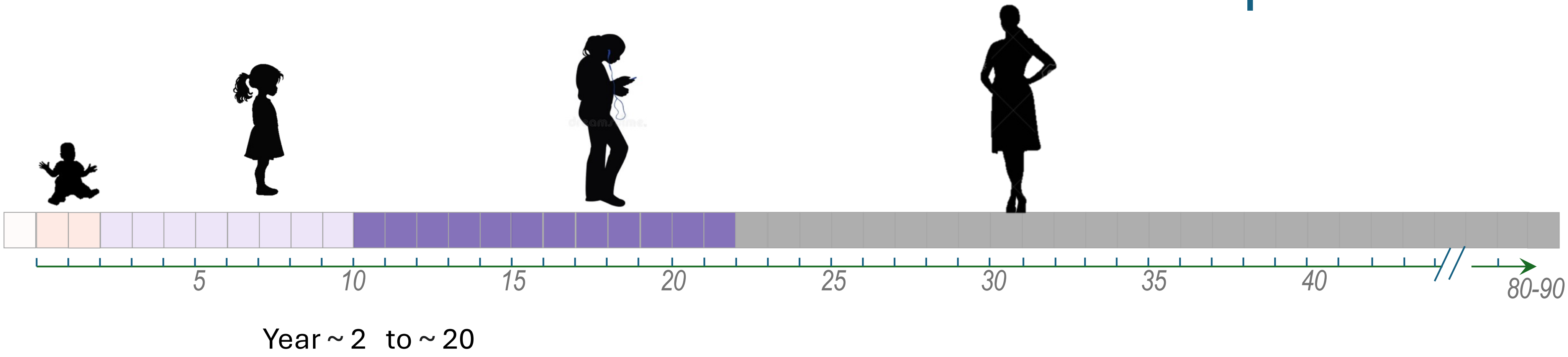
- Context
- Summary of methodologies
- Key findings
- Challenges and future directions

Context: child and adolescent brain development



Year ~ 2 to ~ 20

Context: child and adolescent brain development

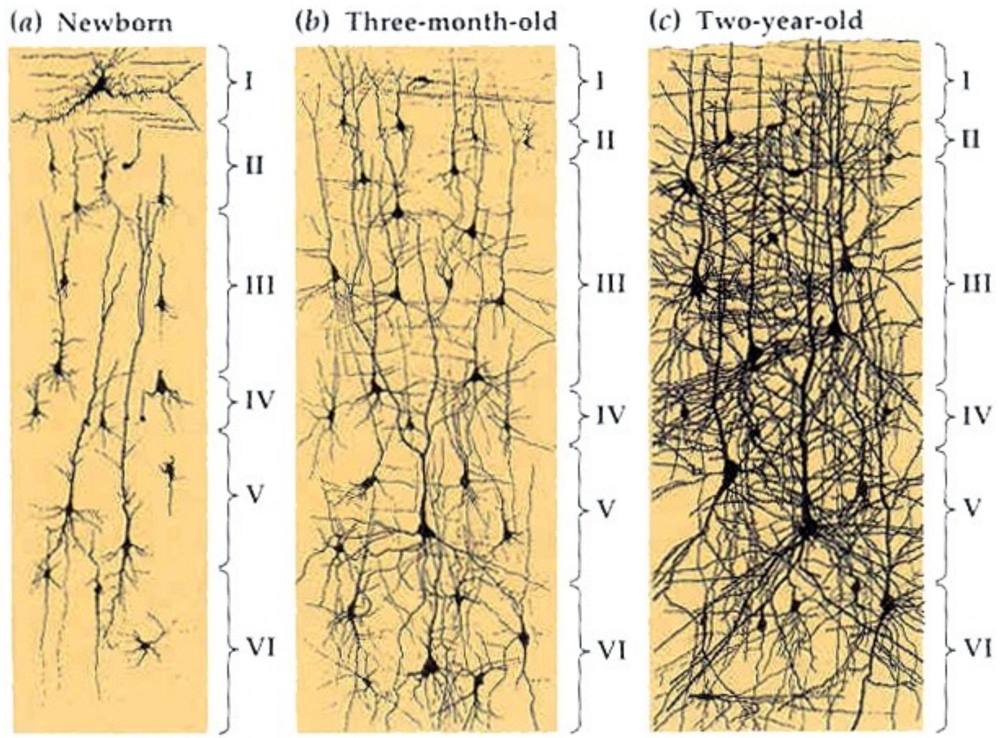


Changes in multiple interacting domains

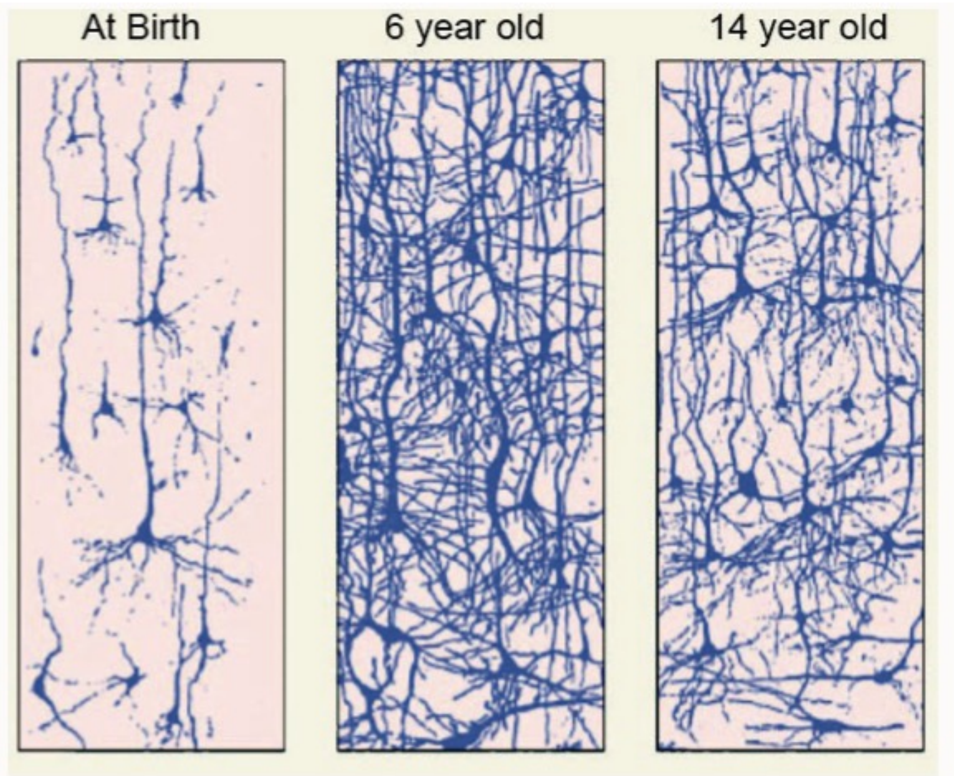
- body shape and size: from a child to an adult
- cognition : concrete – abstract reasoning
- social context : from home to peers and society

Context: child and adolescent brain development

INFANT

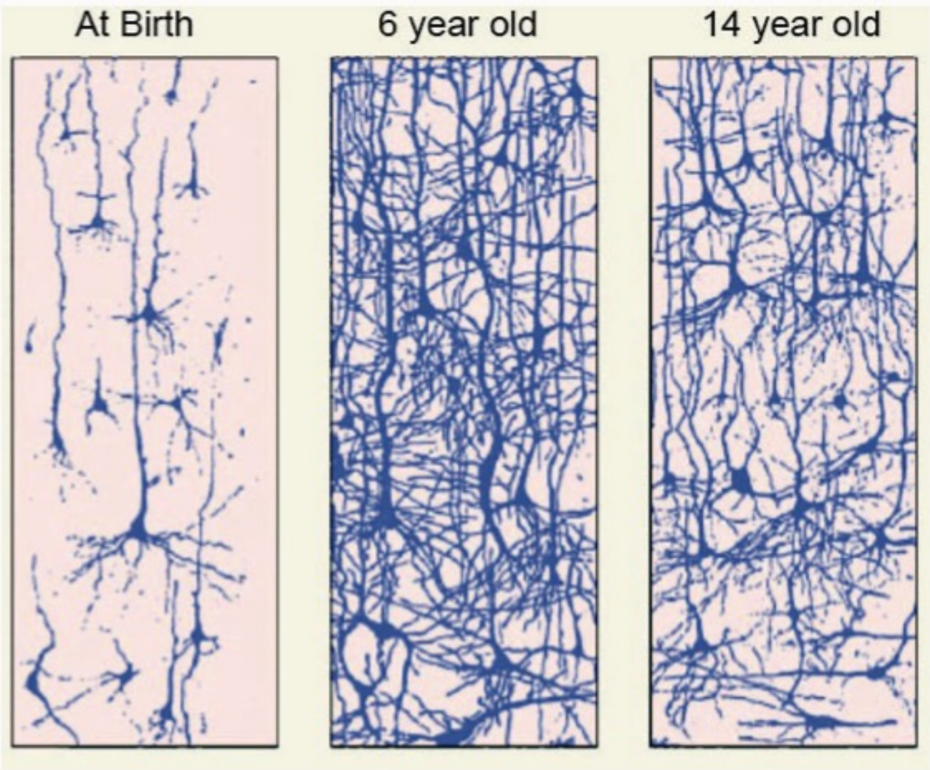


Densité de synapses en fonction de l'âge

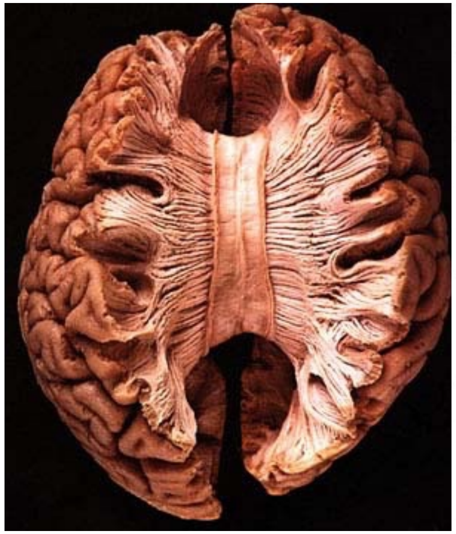


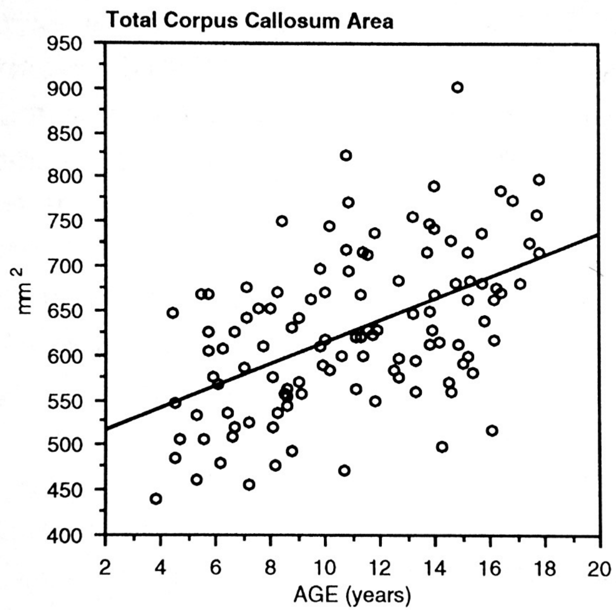
(Chugani, 1997)

Context: child and adolescent brain development



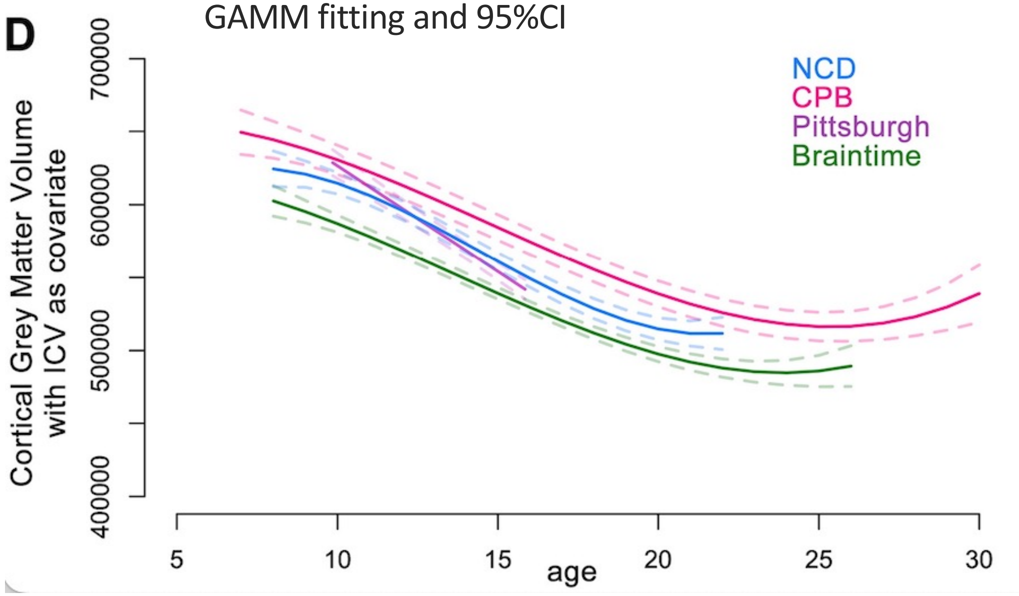
(Chugani, 1997)



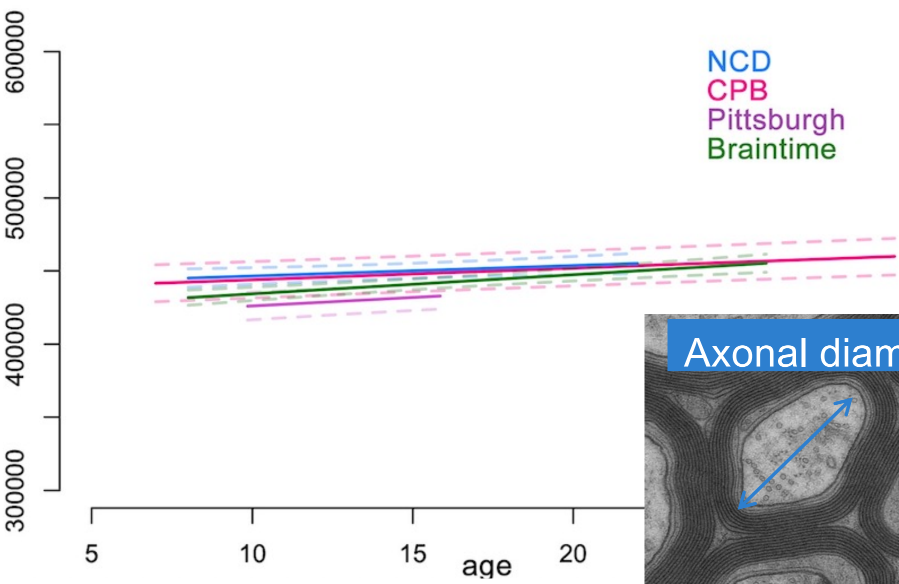


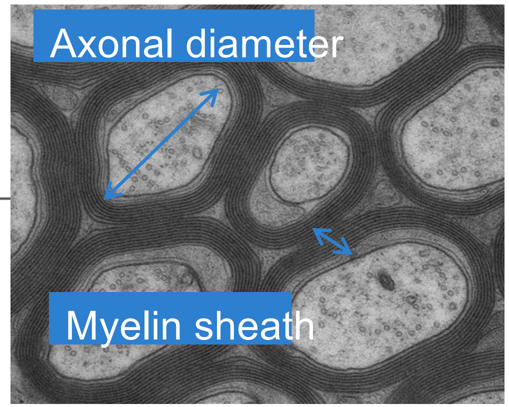
Context: child and adolescent brain development

Grey matter volume



White matter volume



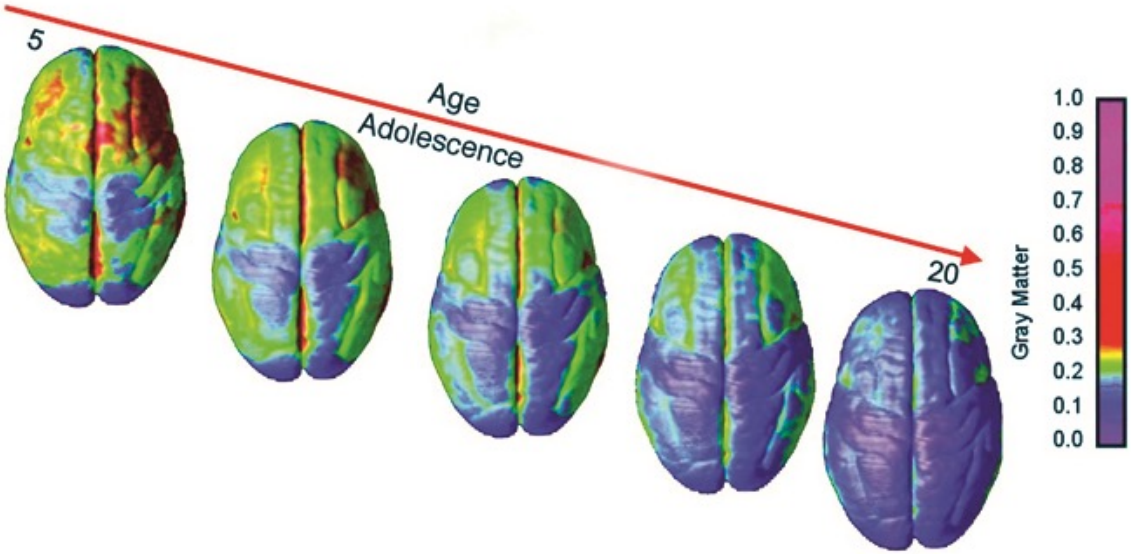


Convergence form 4 longitudinal datasets ; Tamnes 2017; Mills et al 2022

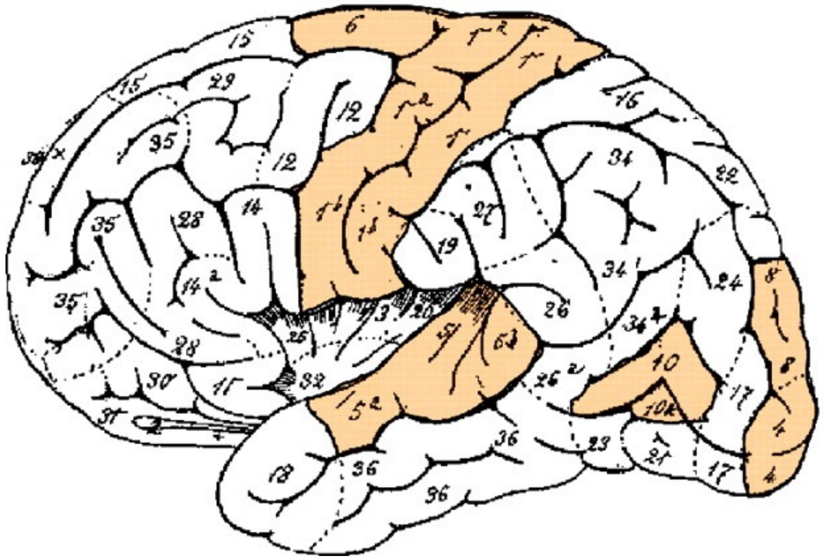
- **Non-monotonic decrease in Grey Matter**
- **Linear increase in White matter volume**

Excl. Cerebellum

Grey matter volume compared to adult



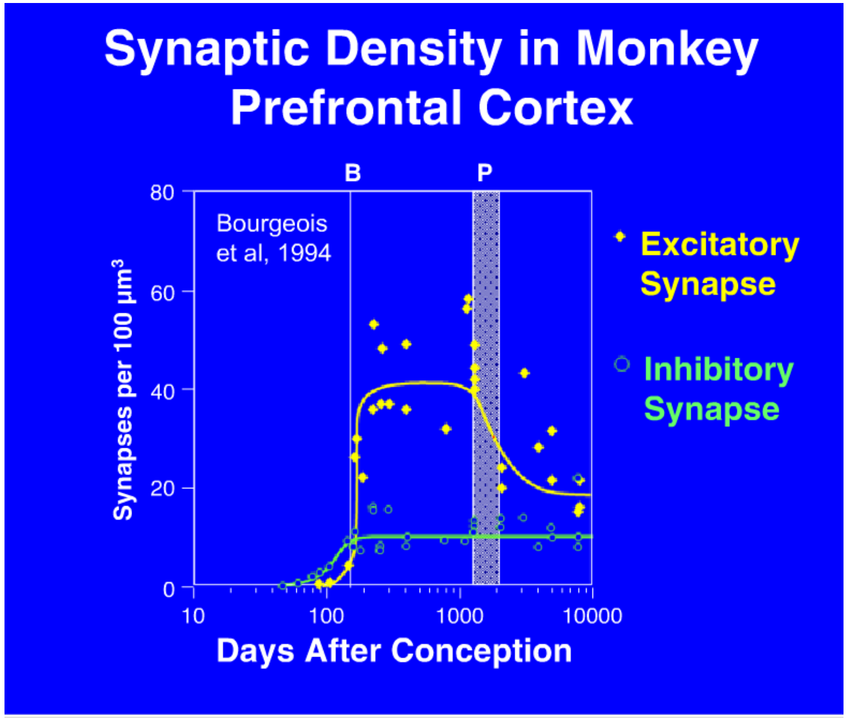
Flechsig's myelogenetic map of human cortex (1901)



Primordial regions (coloured) are myelinated at birth
Numbers represent order of myelination

- **Heterosynchronous changes amongst brain areas**
- **Sensory to association gradient**

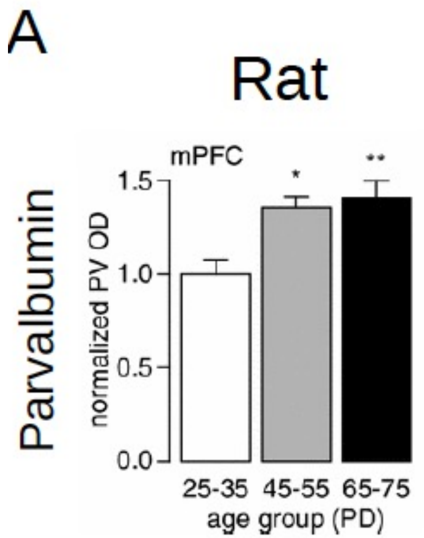
Changes in neurotransmission



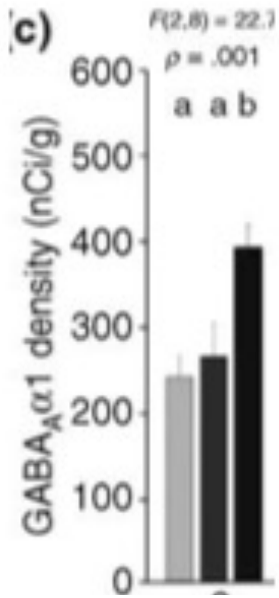
Rakic & Bourgeois 1994)

ROSENBERG AND LEWIS (1995)

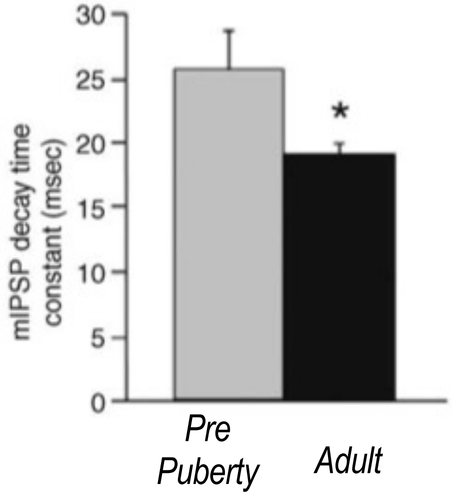
Density of parvalbumin neurons in mPFC



Alpha1_ subunit of GABA receptor



Decay time of GABA IPSP



Caballero et al., 2014

=> Change in number as well as properties of synapses

Context: child and adolescent brain development

- **Grey matter and white matter change along different trajectories**
- **Different brain regions change along different timelines**
- **Synaptic properties change along different space and timeline**

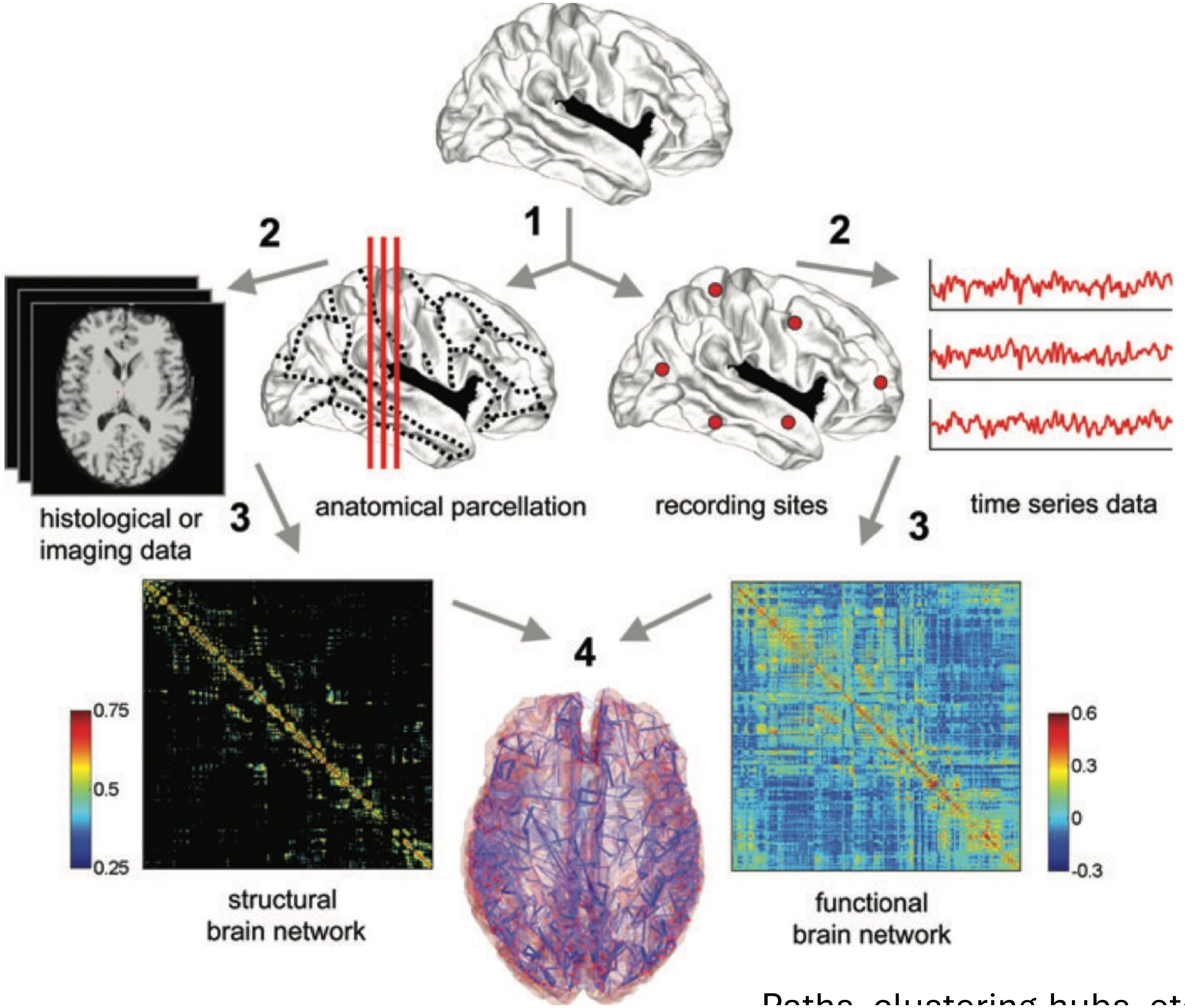
=> local and long-range pattern of structural and functional connectivity will change

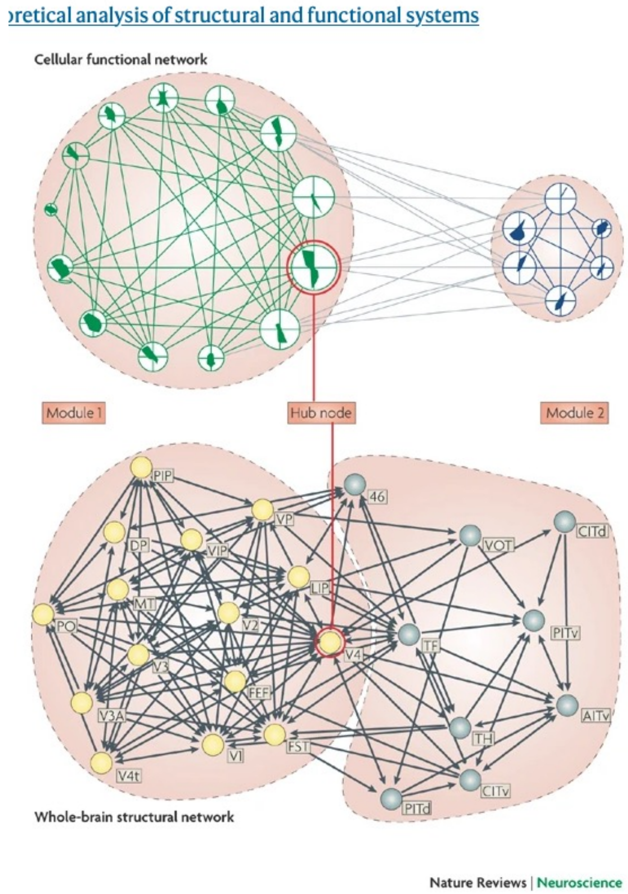
Different types of “connectivity”

- **Anatomical structural) Connectivity**:
  Refers to the physical links—synapses, axon fiber tracts, and white matter pathways—connecting neurons or brain regions.
  - relatively stable ("wiring diagram" of the brain) at the global level
  - Local changes in structure.
- **Functional Connectivity**:
  Represents statistical relationships between neural activities in different brain areas.
  - temporal correlation, covariance, or coherence between patterns of activity, regardless of direct anatomical connection.
  - dynamic and can fluctuate within different timescales.
- **Effective Connectivity**:
  Refers to the directed (causal) influences one neural system exerts on another.
  - integrates aspects of both structural and functional connectivity
  - often inferred from time-series analyses or perturbation studies
  - and is typically associated with causality in neural networks.

Friston, 2012; Sporn, 2007

Different types of "connectivity"

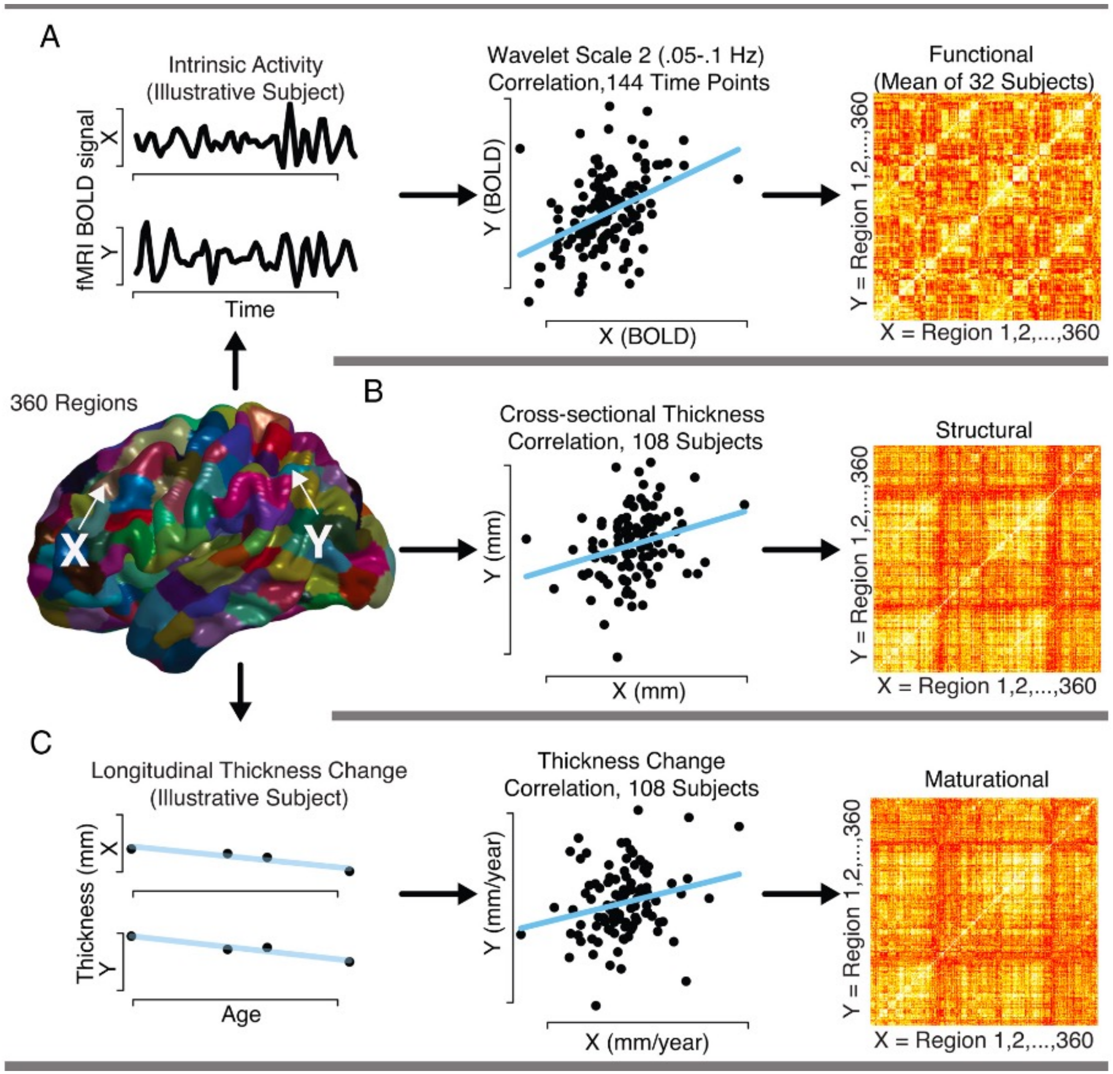


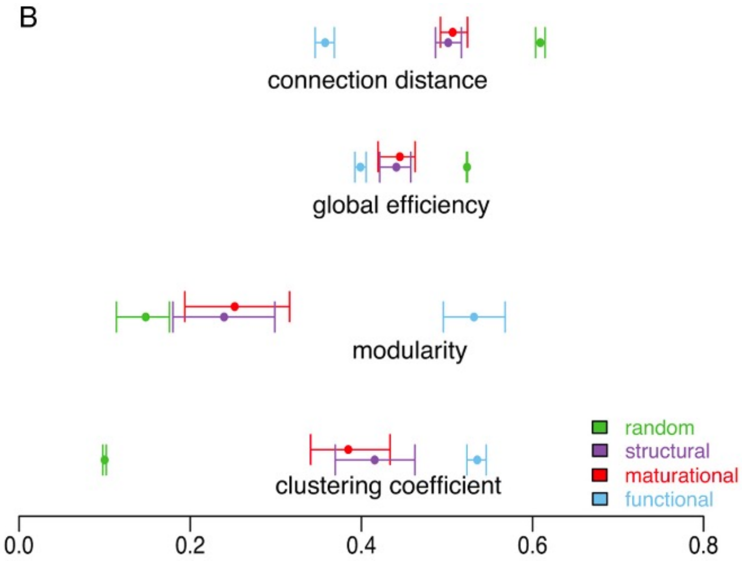


Bullmore et Sporns 2009

Paths, clustering hubs, etc

Different types of “connectivity”





Alexander-bloch et al 2013

Different types of “connectivity” for different questions

- Understanding brain organisation
  - Modularity
  - Identification of systems etc
- Brain-behaviour correlation
  - Do changes in brain organisation support changes in behaviour
- Identifying abnormal organisation and development
  - Biomarkers

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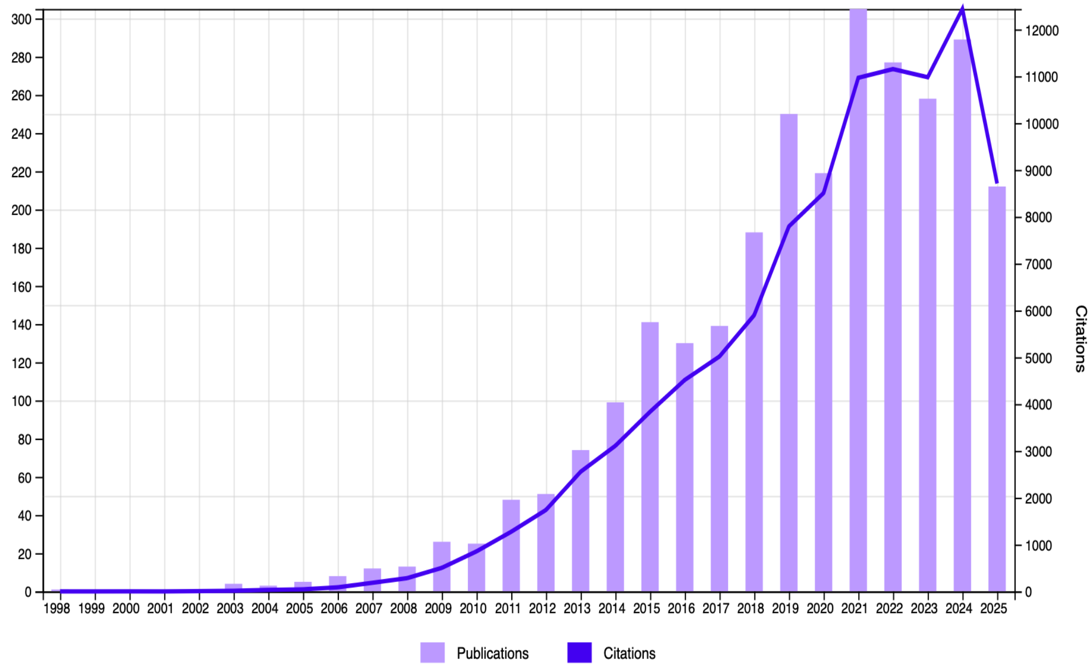
Key findings: available data web of science

Brain connectivity and child or adolescent

2778 → Functional connectivity 1071



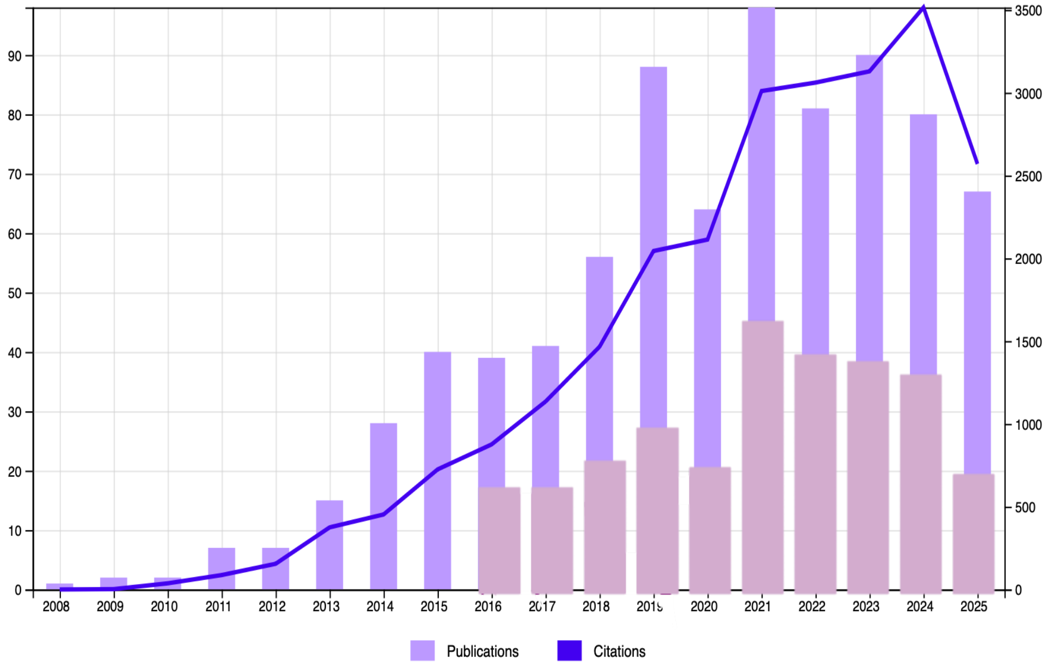
“resting state” and “child or adolescent” Web

788
(66 reviews)

Detailed analysis

Exclude , adults or infants study, methods, non huma

308



Key findings: available data

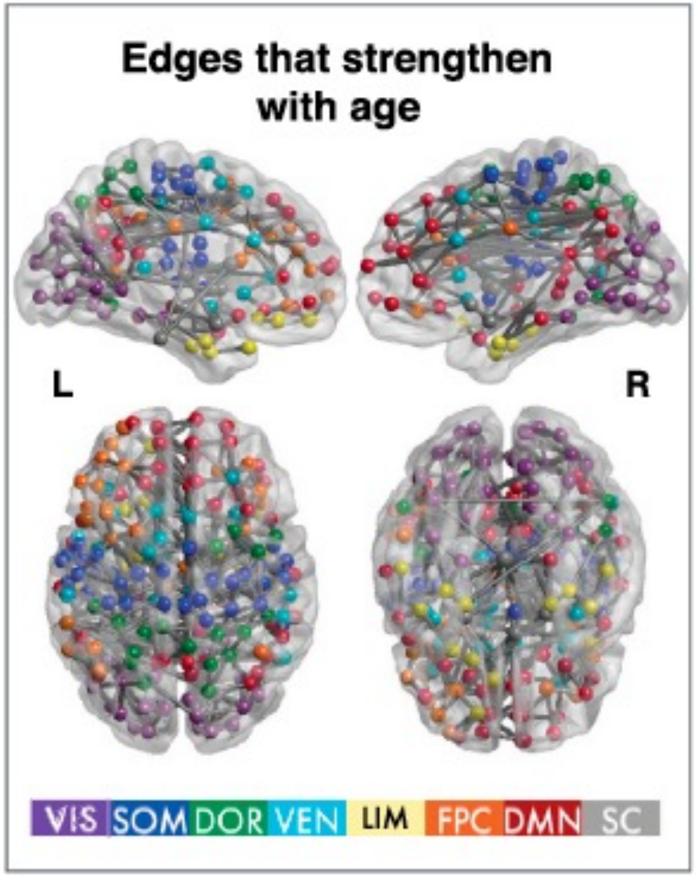
Cohort	Date	age	N with MRI	Modality
Healthy Brain Network (NYC; 3 sites)	2014	8-22	3907 (target10000)	DWI; T1/T2/FLAIR/MT Resting (+ movie) + EEG
Philadelphia Neurodevelopmental Cohort (PNC)	2009	8-21	1601 (404 long.)	T1/T2; DWI; ASL; Task (WM , Emo); RS (6 min)
Nathan Kline Institute-Rockland Sample (NKI-RS)	2010	6-85	1000 (long.)	T1/T2; DWI; RS; Task
ABCD study (US 21 sites)	2018	9-10 at baseline; long	11800	T1/T2; DWI; RS; Task
IMAGEN	2008	14-16-19-22	2000	T1/T2; DWI; RS; Task
Generation R (Netherlands)	2002	Fetal->ado	3000	T1/T2; DWI; RS;

Key findings

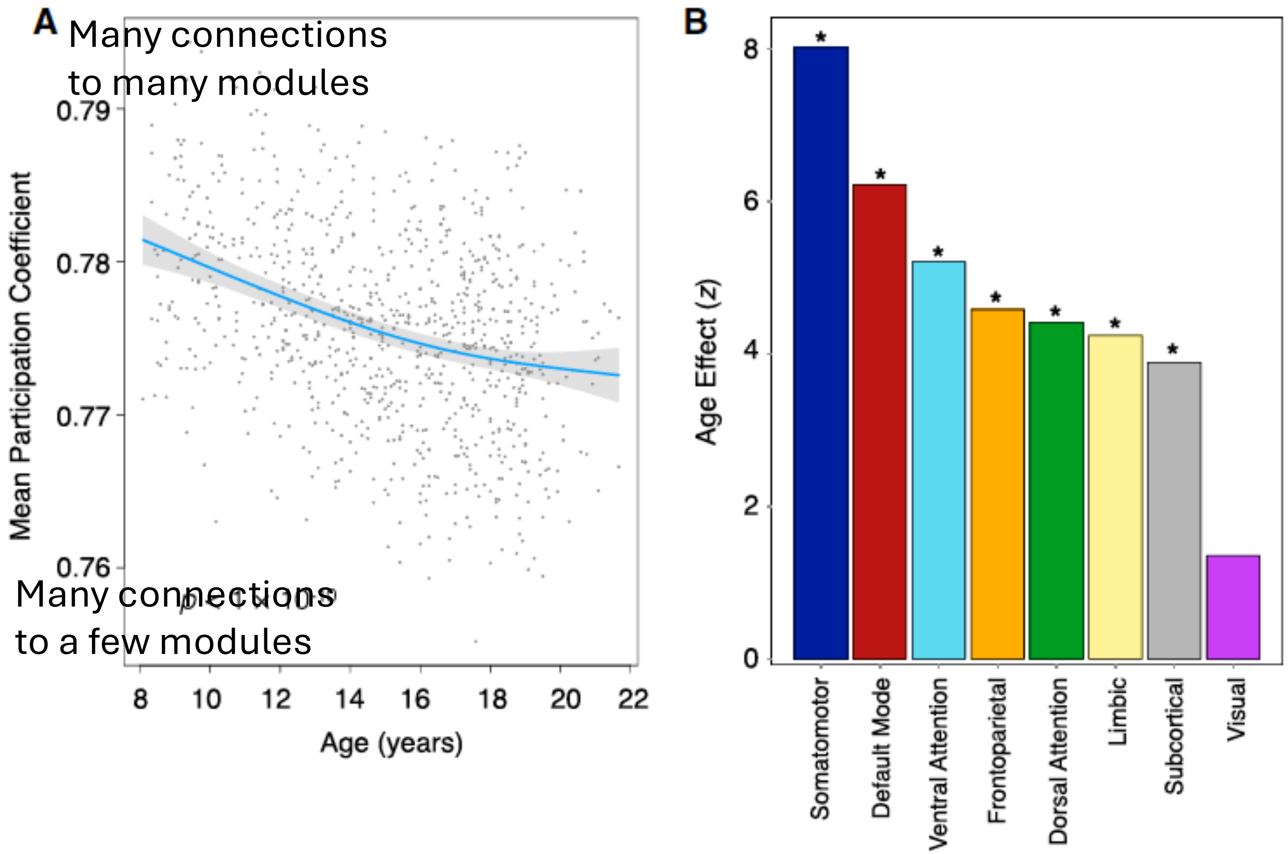
White matter integrity in functionnally defined networks

Probabilistic tractography.
Each parcel attrivuted to one functional module

=> More segregation with age



DWI Baum 2017



White matter integrity in functionnally defined networks

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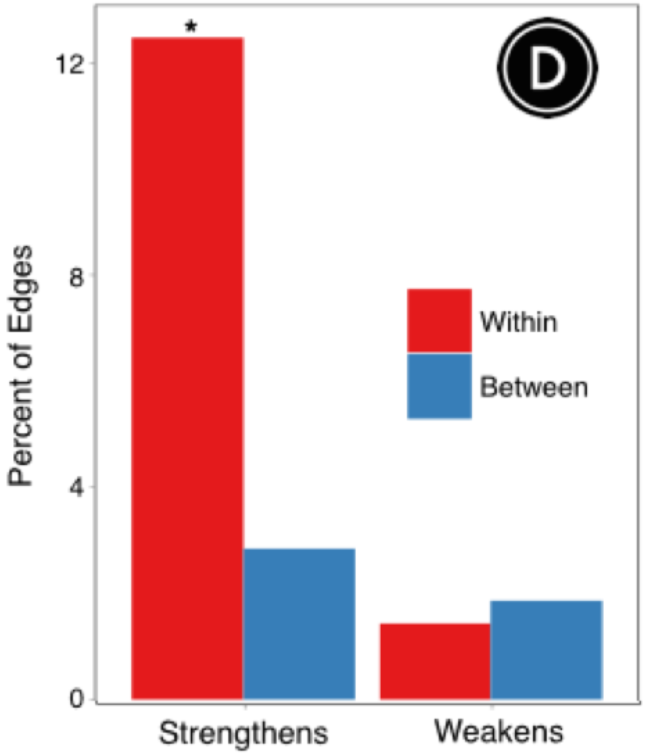
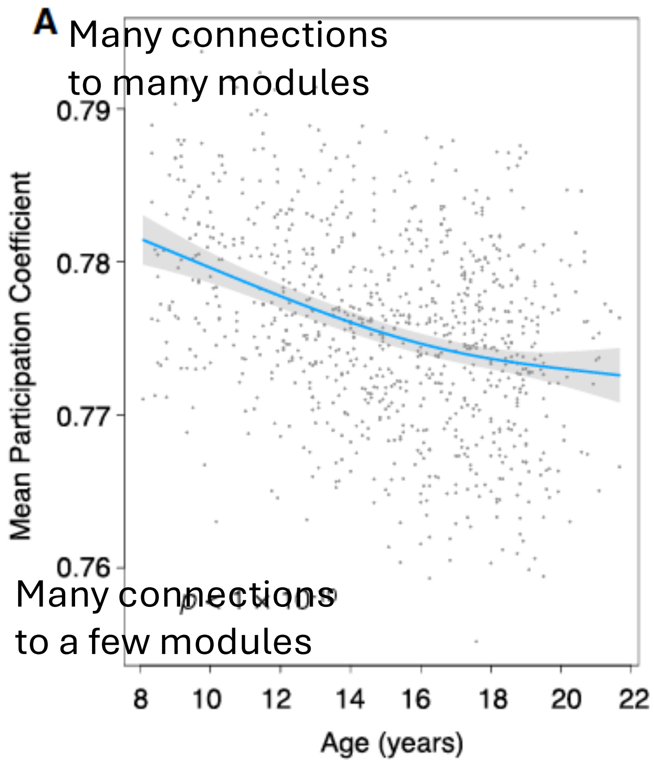
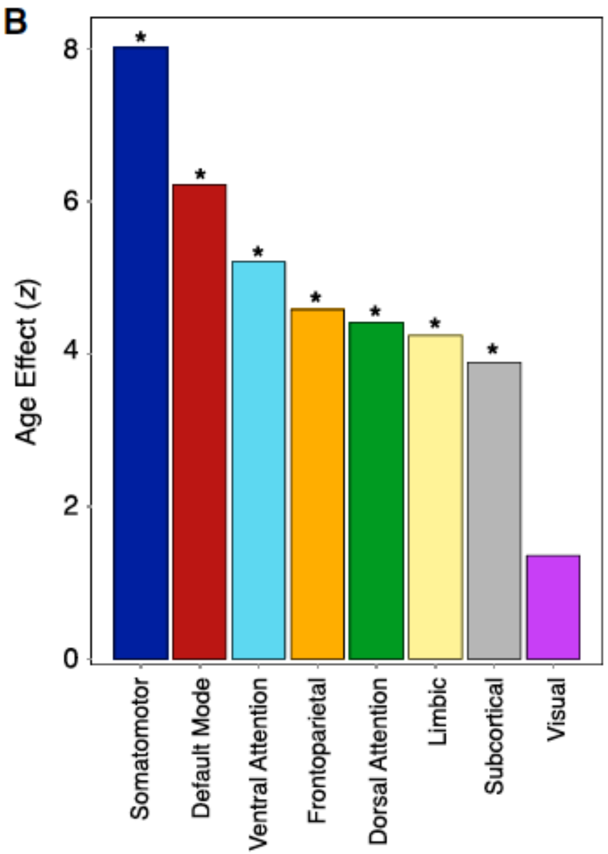
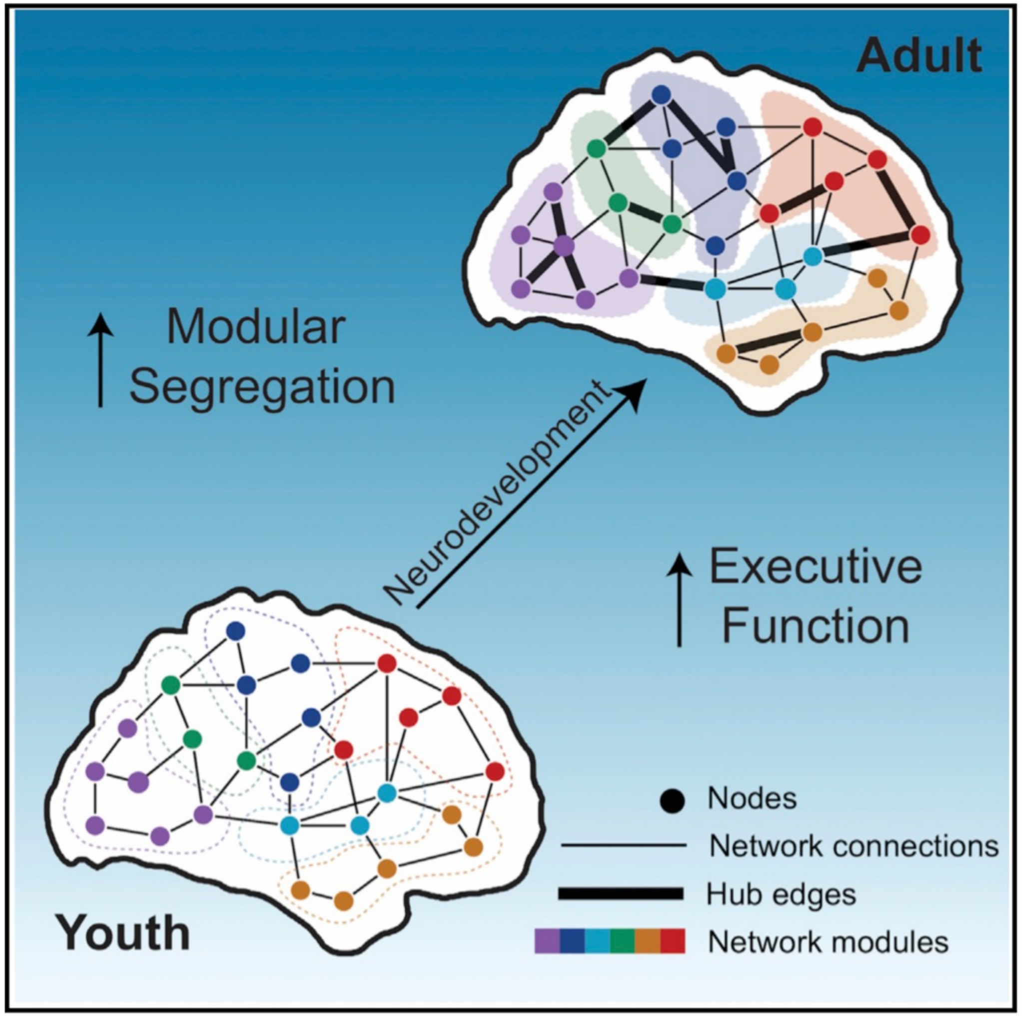






DWI Baum 2017

Graphical Abstract



Authors

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Correspondence

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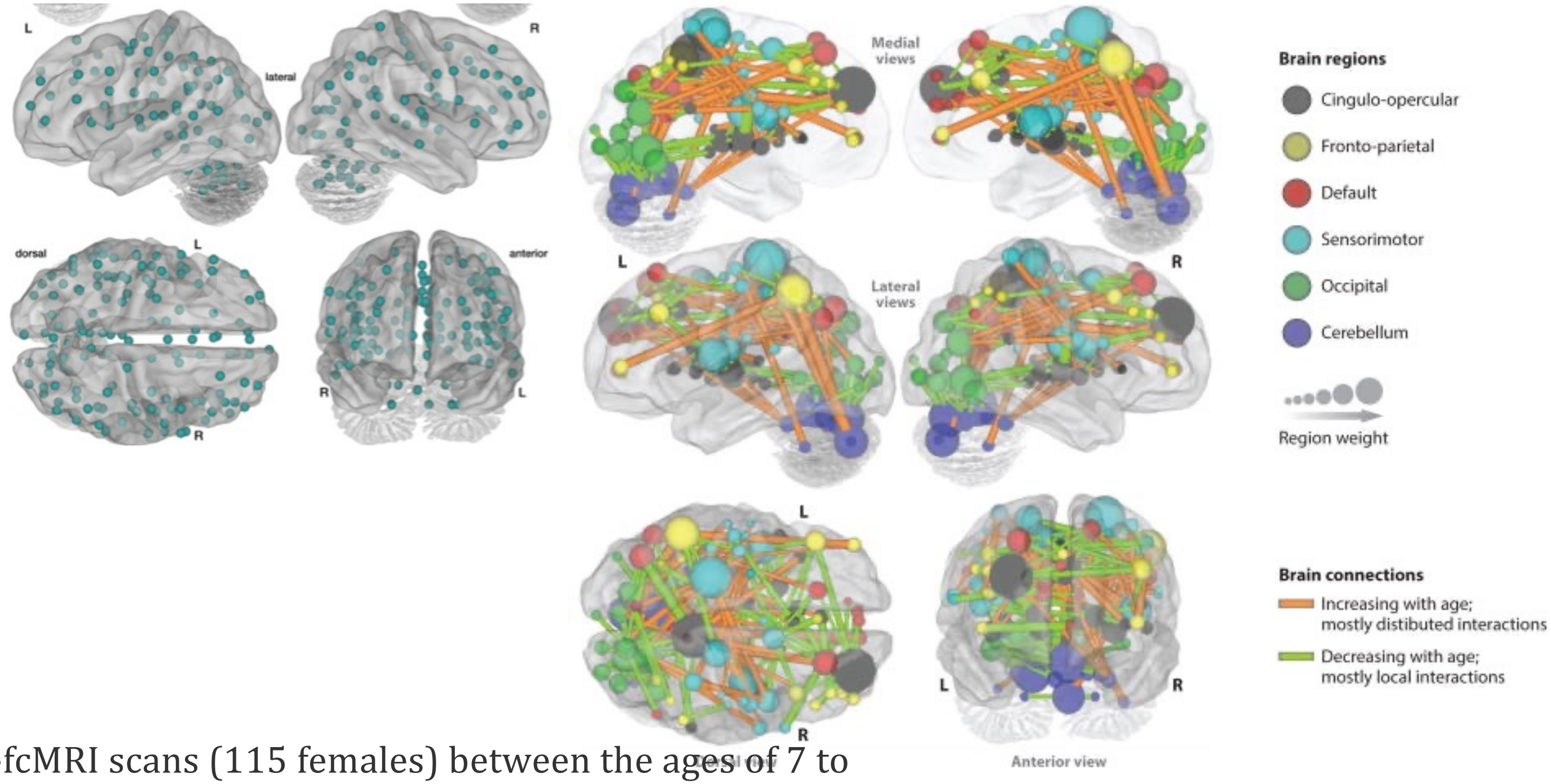
In Brief

Baum et al. apply network analytic techniques to demonstrate that human white matter networks become increasingly modular during adolescent development. Furthermore, targeted strengthening of hub connections facilitates global network integration. This process of network evolution mediates improvements in executive functioning during youth.

Baum 2017

See also Genc etal 2024 (Cardiff, n=88 8-19

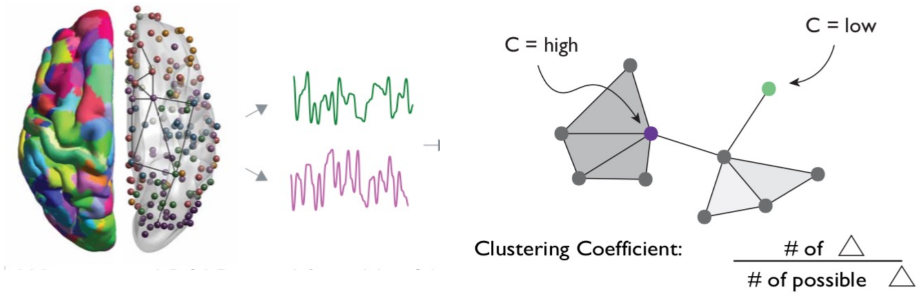
Development regional resting-state functional connectivity

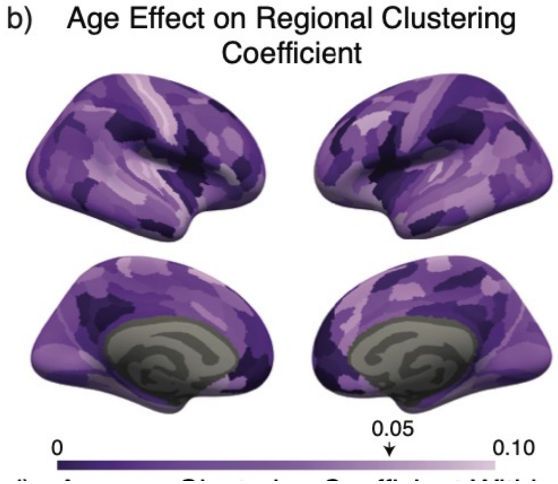


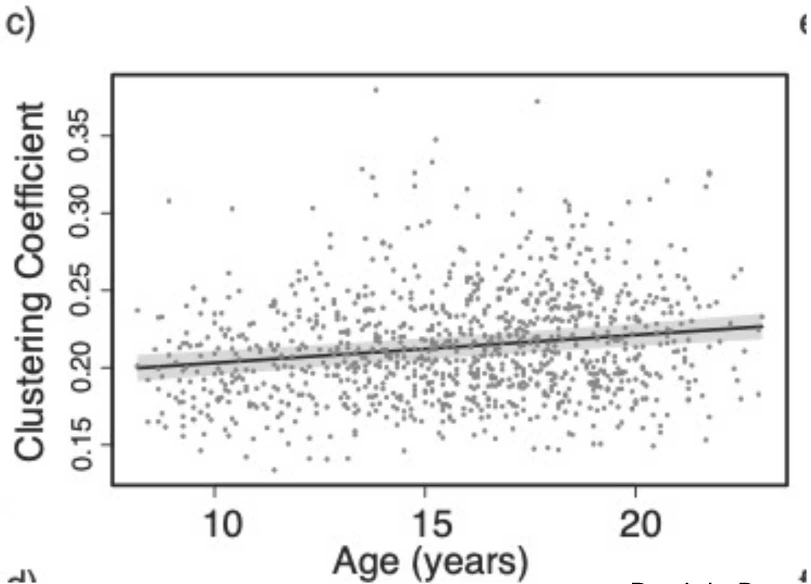
238 rs-fcMRI scans (115 females) between the ages of 7 to 30 years.

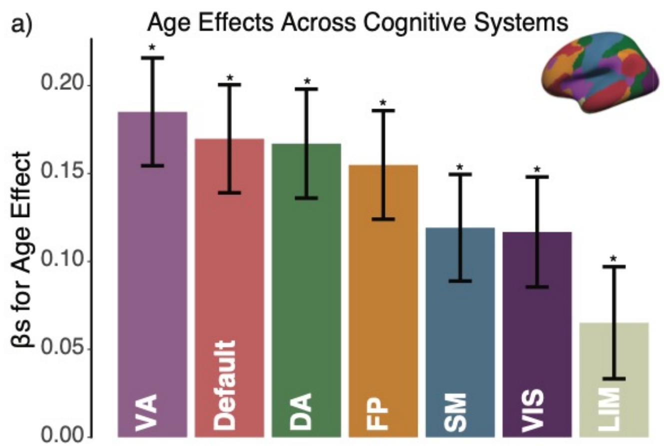
Dosenbach 2010

Local measure of network segregation



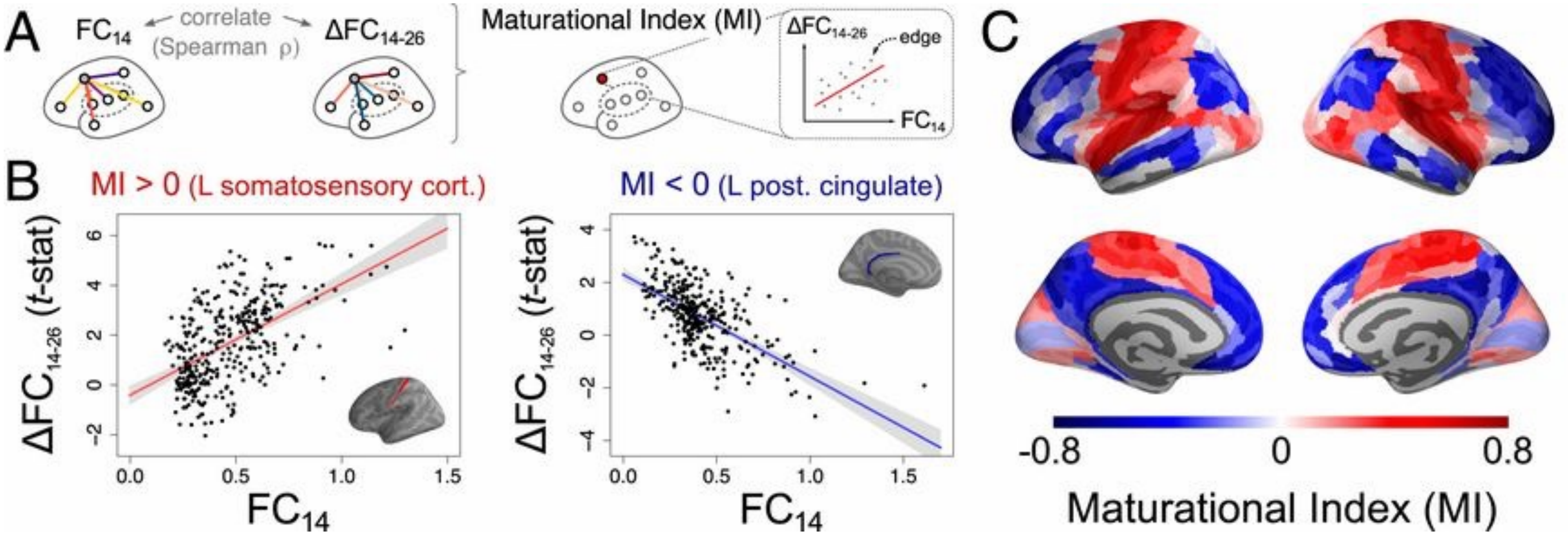






Daniele Bassett, Keynote; Ursula Tooley, Lifespan Development; session; poster T454

Conservative vs disruptive protracted development



MI >0, conservative mode of developmental change: connections that were already strong at 14 become stronger by the age of 26,
MI<0 disruptive mode of developmental change: connections that were weak at 14 got stronger by the age of 26 (and connections that were strong at baseline became weaker)

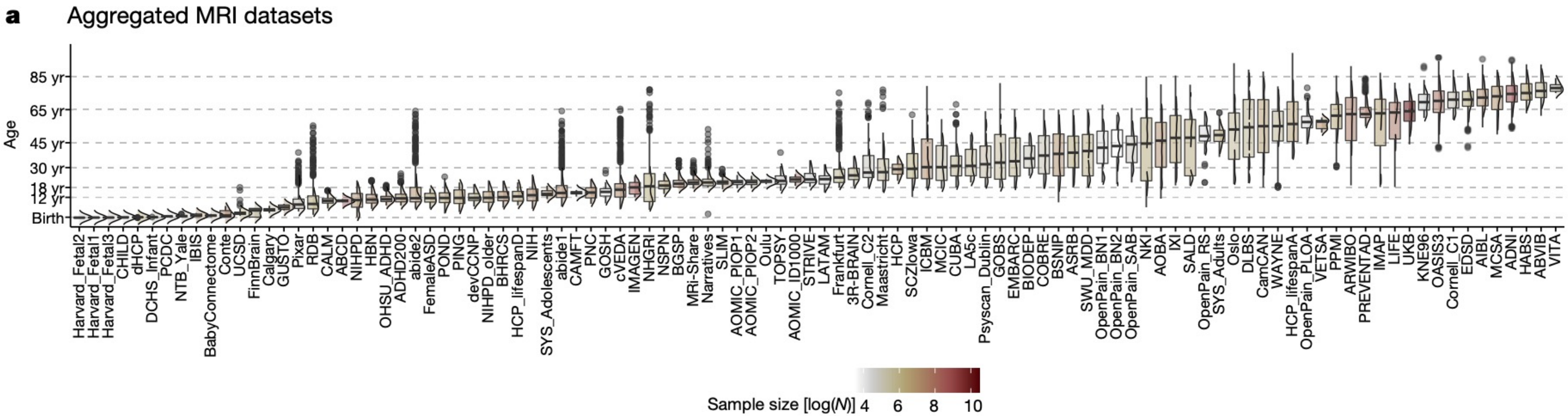
Vasa et al PNAS 2020

Key findings summary

- Continuous changes through childhood and adolescence
- Strengthening of functional networks
  - More segregation and integration
- Later development of association cortices
- Overall convergence between indices and methodologies

Challenges: general

- Overwhelming amount of data, with fast evolving analysis tools



Bethlehem et al **Brain charts for the human lifespan, Nature 2022**

Challenges: general

- Overwhelming amount of data, with fast evolving analysis tools

Challenges: general

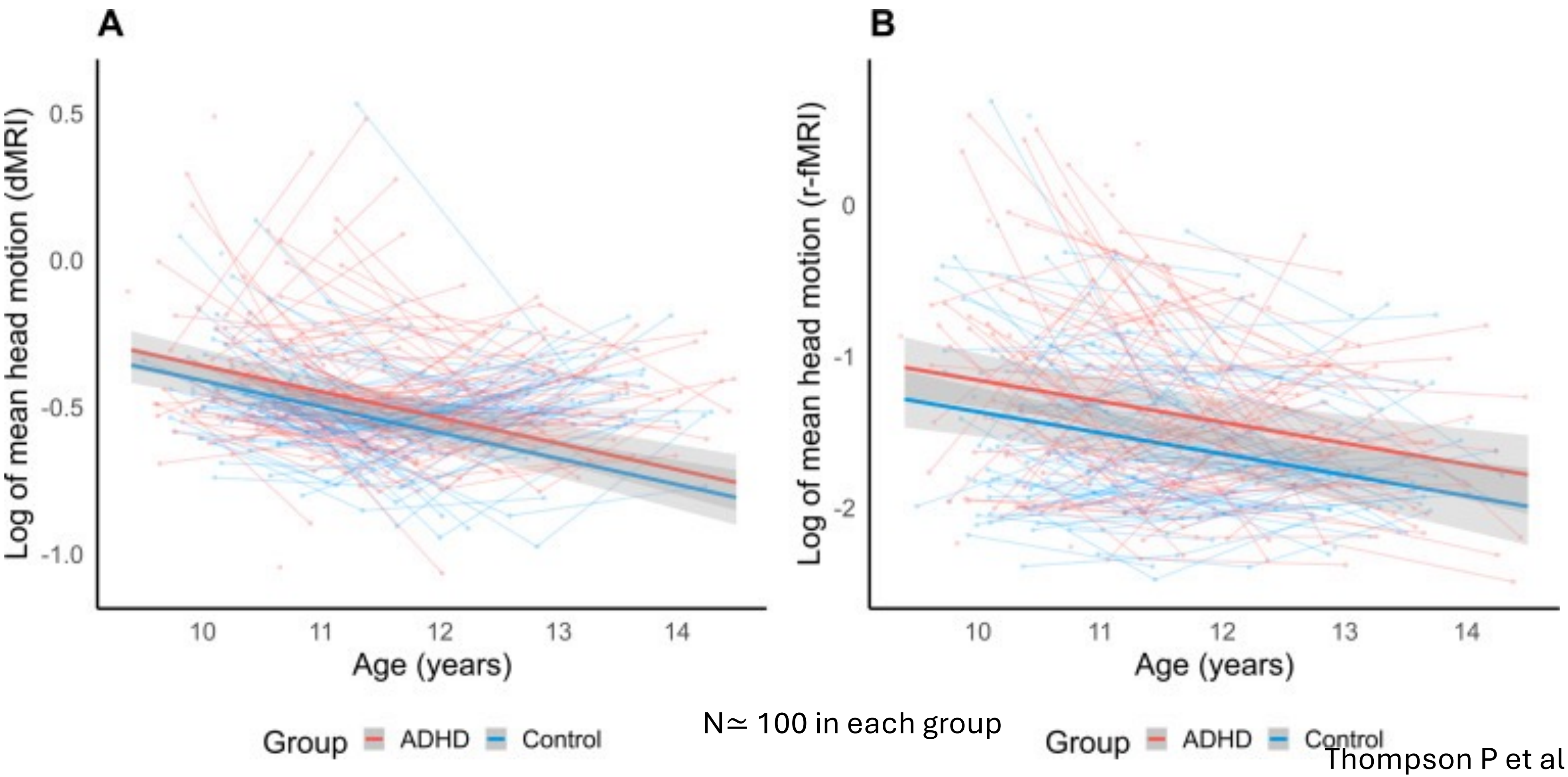
- Overwhelming amount of data, with fast evolving analysis tools
- Link with behaviour
- Highly dimensional data=> more and more sophisticated computational models => tendency to interprete always within the same framework(s)

- Publication biases

Challenges: methodological

- Parameters may change
- Rely on adult model for parcellation (but see Doucet, 2025)
- Motion

Motion



N≃ 100 in each group

Thompson P et al 2024

Motion – ABCD study

TABLE 2 | Correlation of (continuous) study variables with rs-fMRI motion (FD).

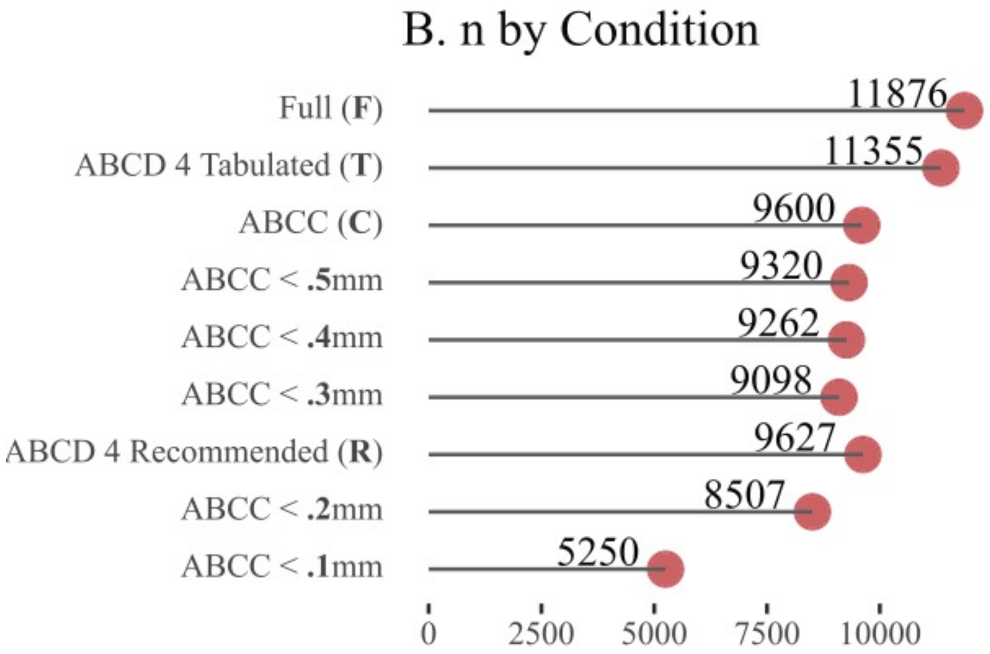
	FD at 0.1		FD at 0.2		FD at 0.3		FD at 0.4		FD at 0.5	
ADI	0.08	***	0.09	***	0.1	***	0.1	***	0.1	***
COI	−0.09	***	−0.11	***	−0.12	***	−0.12	***	−0.12	***
NIHTB flanker	−0.06	***	−0.06	***	−0.06	***	−0.06	***	−0.06	
NIHTB crystallized	−0.07	***	−0.08	***	−0.09	***	−0.09	***	−0.1	***
NIHTB total	−0.11	***	−0.13	***	−0.14	***	−0.14	***	−0.15	***
WISC V matrix	−0.08	***	−0.1	***	−0.11	***	−0.11	***	−0.11	***
P-Factor	0.05	***	0.07	***	0.08	***	0.09	***	0.09	***
Internalizing	−0.04	***	−0.05	***	−0.05	***	−0.05	***	−0.05	***
Externalizing	0		0.01		0.01		0.01		0.01	
Age	−0.09	***	−0.1	***	−0.11	***	−0.11	***	−0.11	***
BMI	0.22	***	0.24	***	0.23	***	0.22	***	0.21	***

***$p < 0.001$ in corresponding bivariate linear model.

Peverill et al Hum Brain Map 2025

Motion – ABCD study

- Nb subjects excluded as a function of criterion



- Non –random repartition : Subject exclusion due to excessive motion is related to
  - High BMI
  - Low executive fct
  - Early puberty
  - Low parental income
  - Low parental education
  - Black and hispanic ethnicity

Peverill et al Hum Brain Map 2025

- Excluding participants corrects for quality artifacts in functional connectivity data but this list-wise deletion also biases statistics because exclusions are not completely at random.
- Biases resulting from exclusions are likely even with relatively liberal standards for acceptable data quality.

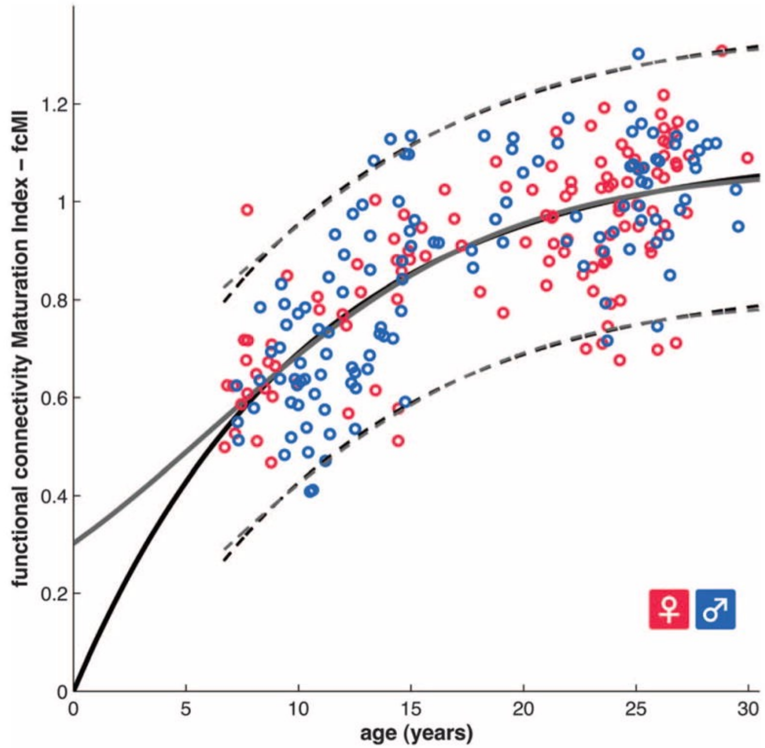
- Missing data handling strategies such as multiple imputation should be used to correct biases from non-random exclusions in functional connectivity analyses.

Interpreting functional connectivity across ages

- Resting-state functional connectivity (rs-FC) widely used as marker of brain activity and used to capture interindividual differences

Support vector machine regression classification based on resting-state measures

Maturation index = predicted age scan relative to adult
200 dimensional weighted index



Dosenbach, et al (2010). Prediction of individual brain maturity using fMRI. *Science , 329*(5997),

Interpreting functional connectivity across ages

- Resting-state functional connectivity (rs-FC) widely used as marker of brain activity and used to capture interindividual differences
- A number of studies show the task-based or task-state FC allows better prediction of behaviour (attention: Rosenberg 2016; general cognition Greene 2018, Elliot 2019; reading comp. Jiang 2020) (debate for movie during resting; Finn 2017)

NeuroImage 270 (2023) 119946

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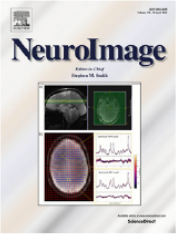
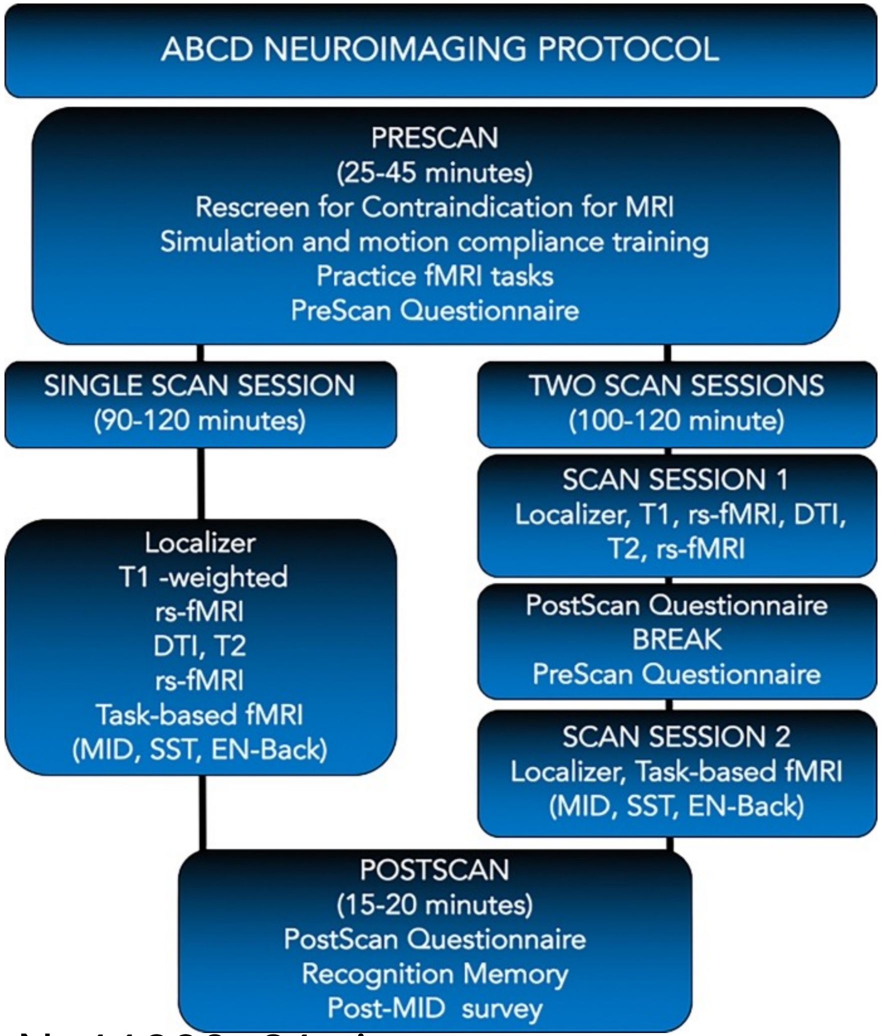


Task fMRI paradigms may capture more behaviorally relevant information than resting-state functional connectivity

Weiqi Zhao[a,c], Carolina Makowski[b,c], Donald J. Hagler[c], Hugh P. Garavan[d], Wesley K. Thompson[e], Deanna J. Greene[a,c], Terry L. Jernigan[a,b,c,f,i], Anders M. Dale[b,g,h,i,*]

See also Greeen et al 2018; Elliott et al 2019)



N=11880- 21 sites

Adolescent Brain Cognitive Development
Teen Brains. Today's Science. Brighter Future.

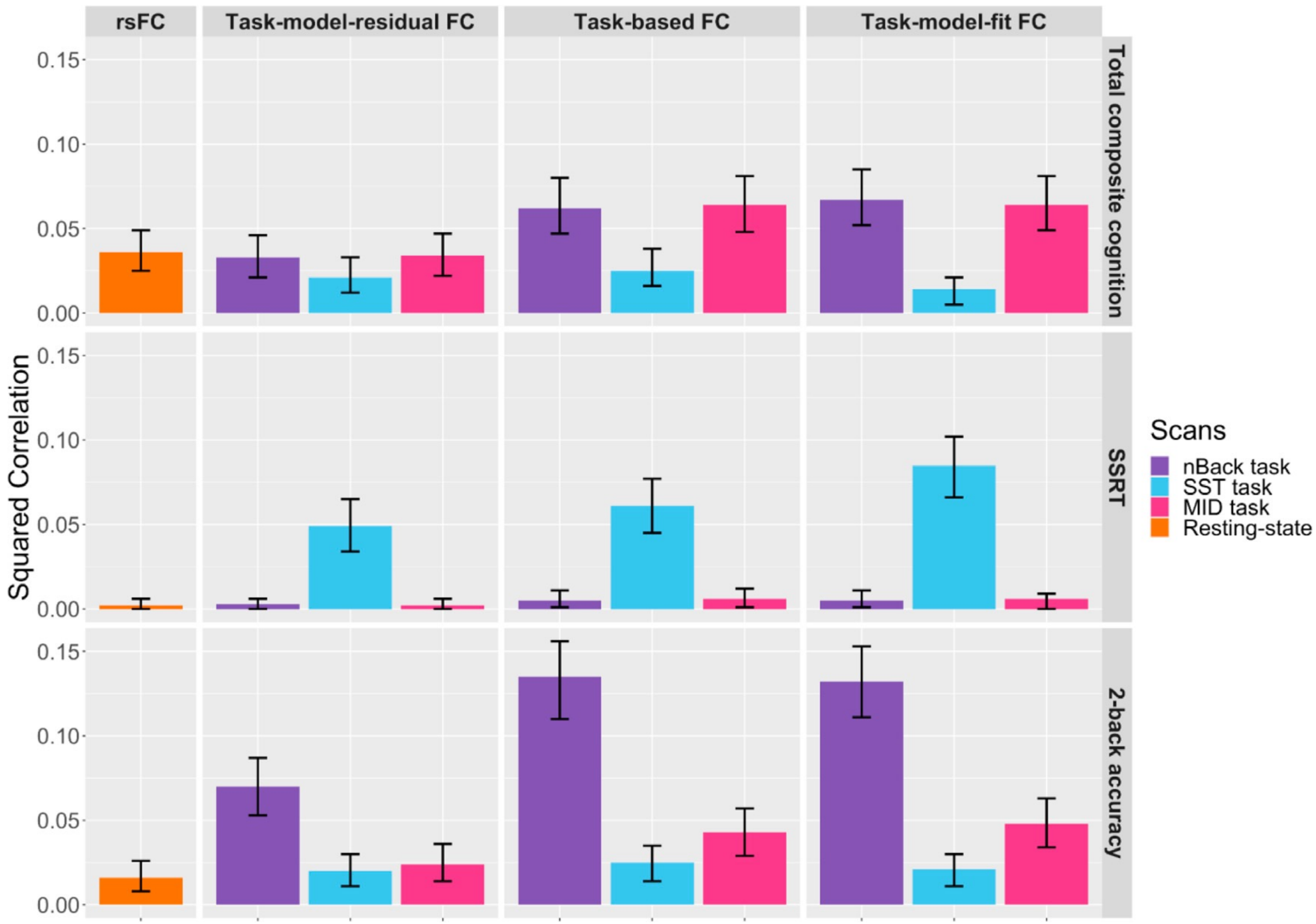
- 3 tasks
  - Emotion N Back
  - Stop Signal
  - Monetary Incentive delay
- 4 x 5 min of rest data over 2 sessions
- Extensive personnal and behavioural (NIH toolbox) data

Prediction of behaviour by FC

FC	*Pairwise correlation of*
Resting-state	fMRI time series at rest
Task-based	complete fMRI time series during task
Task-model-fit	Task design * beta estimates of condition task regressors = time series component explained by the task design
Task-model-residual	task-model-residual time series = task fMRI time series component that cannot be explained by the task design

352 parcels (Gordon 2016)

- Behavioral prediction with nested 10 folds cross validation scheme after Fast-efficient-mixed effects modeling
- Squared correlation between the predicted and the observed behavioral score was used as the metric for out-of-sample behavioral prediction performance of each imaging measure.


rsFC
Task-model-residual FC
Task-based FC
Task-model-fit FC
Total composite cognition
SSRT
2-back accuracy
Squared Correlation
0.15
0.10
0.05
0.00
Scans
nBack task
SST task
MID task
Resting-state

CONCLUSION

- Large worldwide effort to understand evolution of brain organisation from childhood to adulthood
- Demonstrate validity of MRI measures
- Still need to refine conceptual framework to integrate this knowledge
- Promising translational aspect