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# Physiological aging in brain networks

International Summer Institute on Network Physiology, Como 2019

# Summary

- Hierarchical metrics of aging
- Brain partition using structure-function
- Macro scale physiological brain aging
- Chronological and brain connectome age
- The fronto-striato-thalamic (FST) circuit

# Hierarchical Model of the Metrics of Aging (Ferrucci et al., Circulation Research. 2018;123)



# The Metrics of Aging

## Functional Aging (impact on daily life)

- Cognitive Function
- Physical Function
- Mood
- Mental Health



## Phenotypic Aging (phenotypes that change)

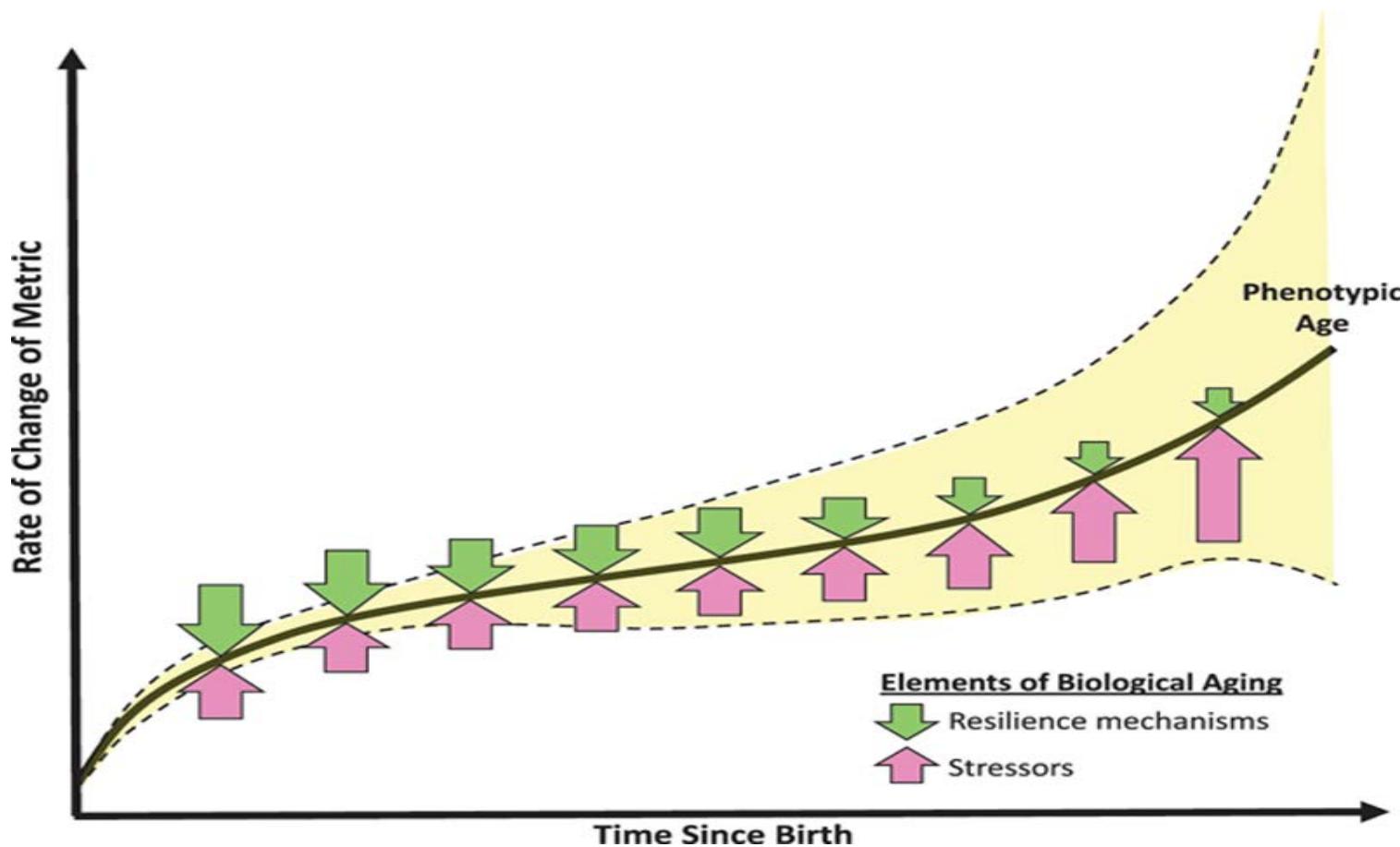
- Body Composition
- Energetics
- Homeostatic Mechanisms
- Brain health

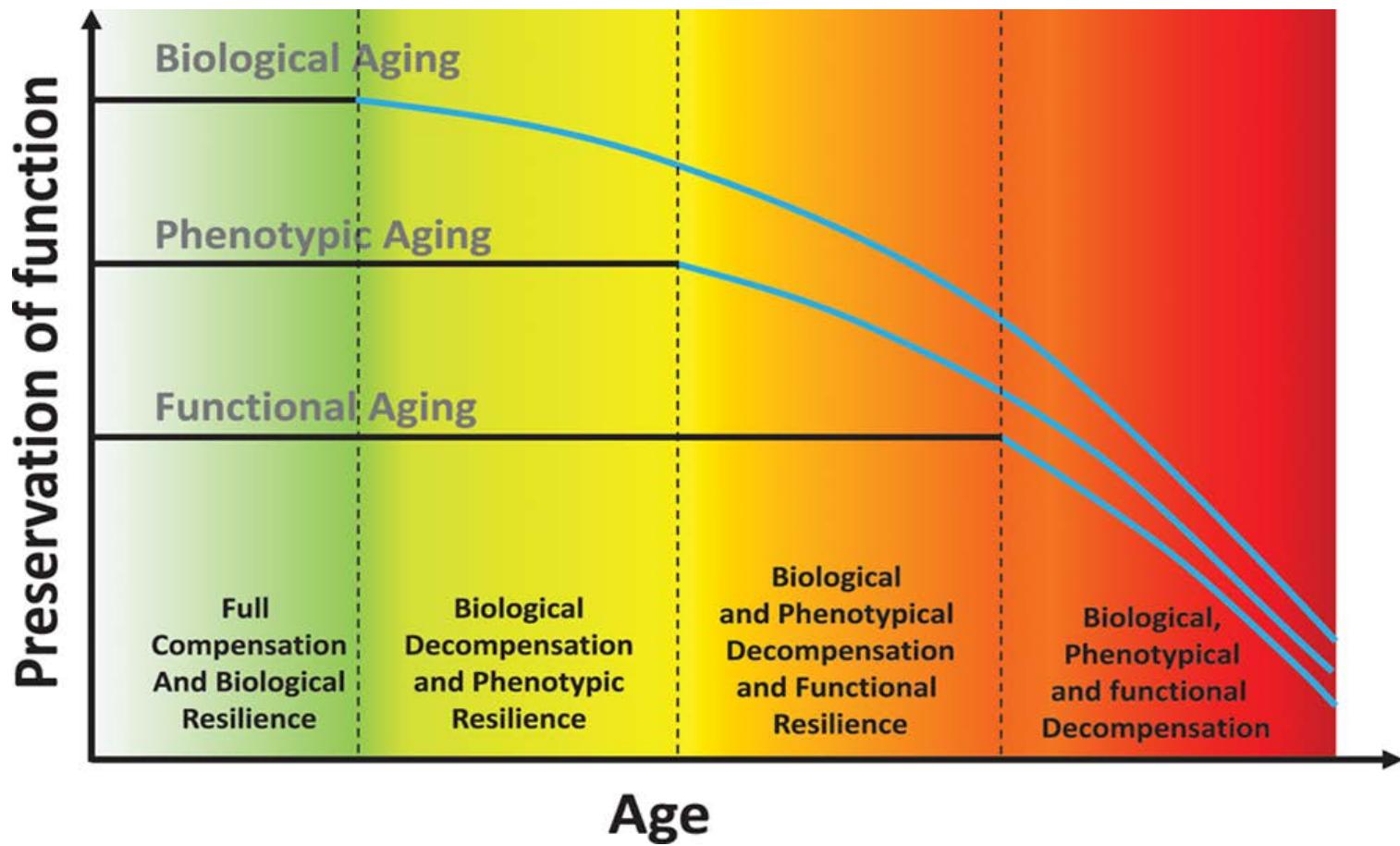


## Biological Aging (root mechanisms)

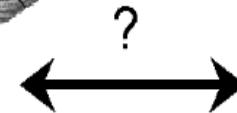
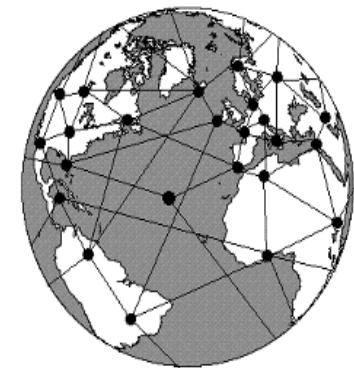
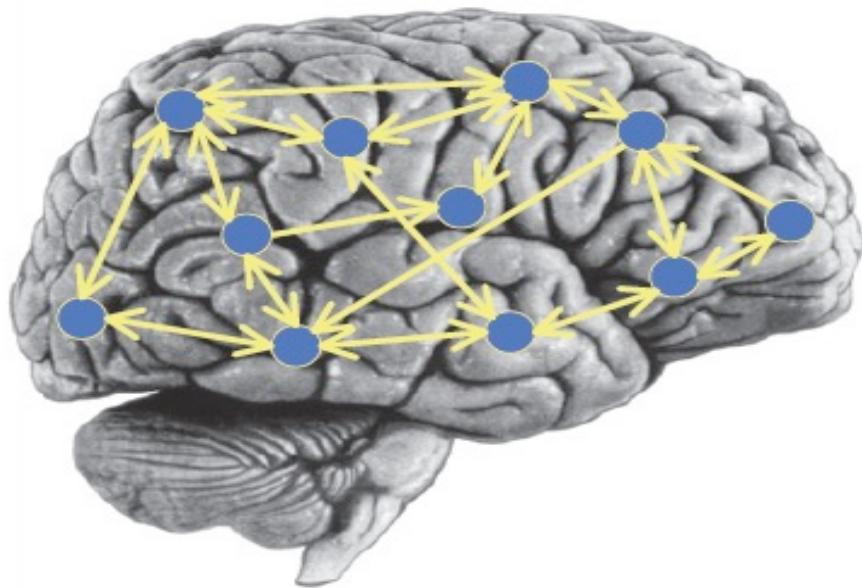
- Molecular Damage
- Defective Repair
- Energy Exhaustion
- Signal/Noise Reduction



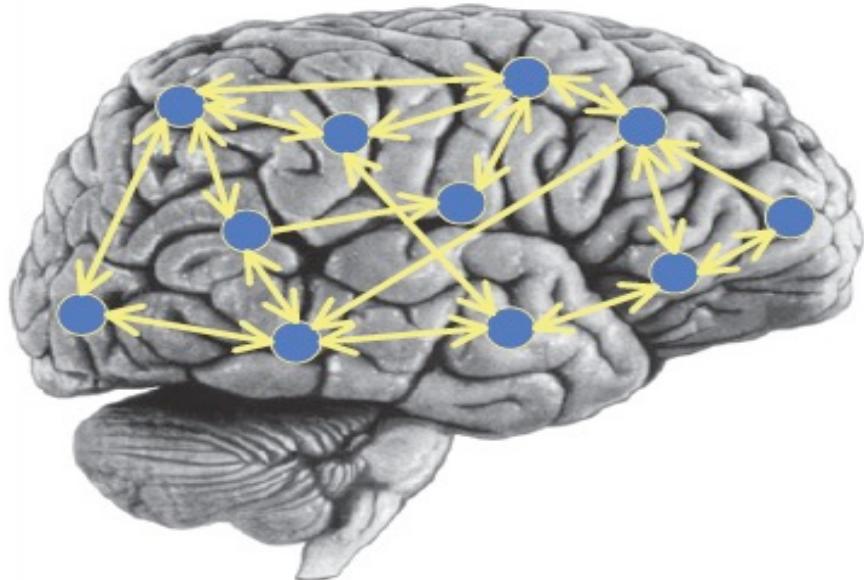




## TWO CLASSES OF BRAIN NETWORKS

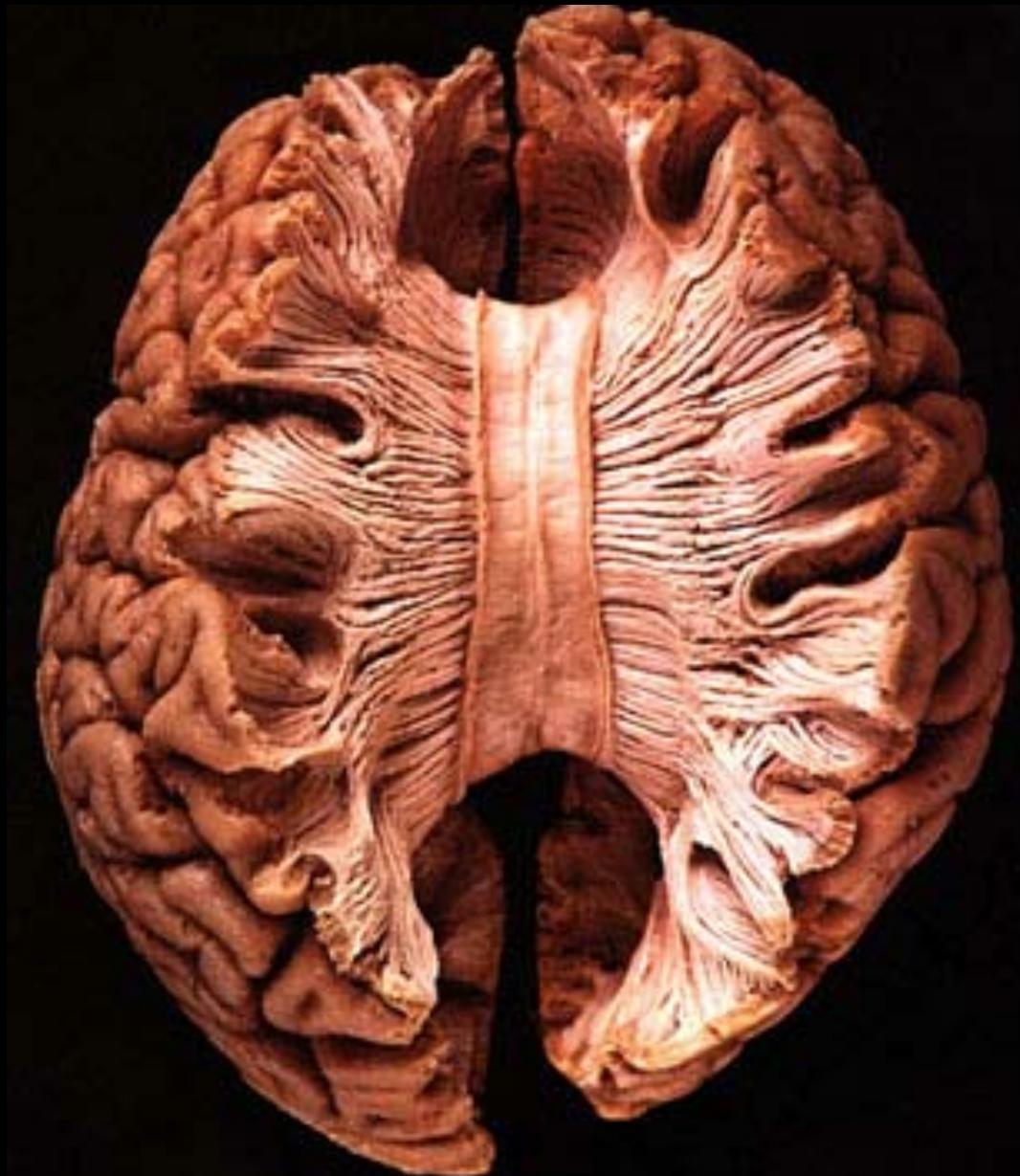


## TWO CLASSES OF BRAIN NETWORKS

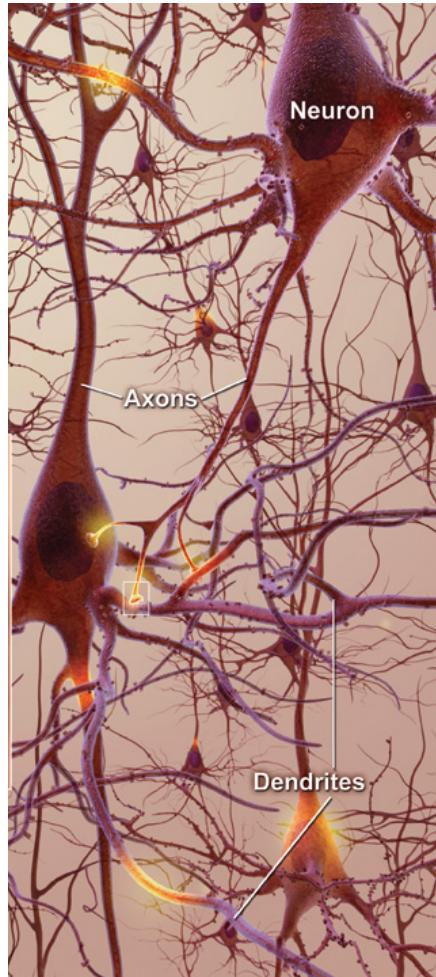


- ✓ Structural (anatomical) connectivity
- ✓ Functional connectivity
- ✓ Effective connectivity

# STRUCTURAL CONNECTIVITY



# STRUCTURAL CONNECTIVITY

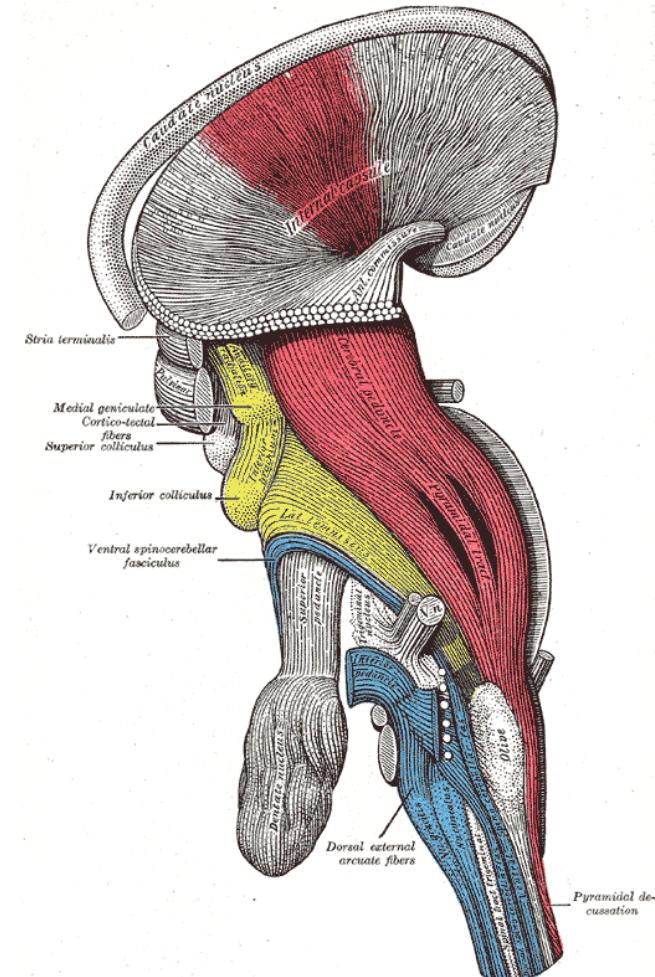


From the National Institute on Aging

Axons measure  $\sim \mu\text{m}$  in width

They group together in bundles that traverse the white matter, mm scale

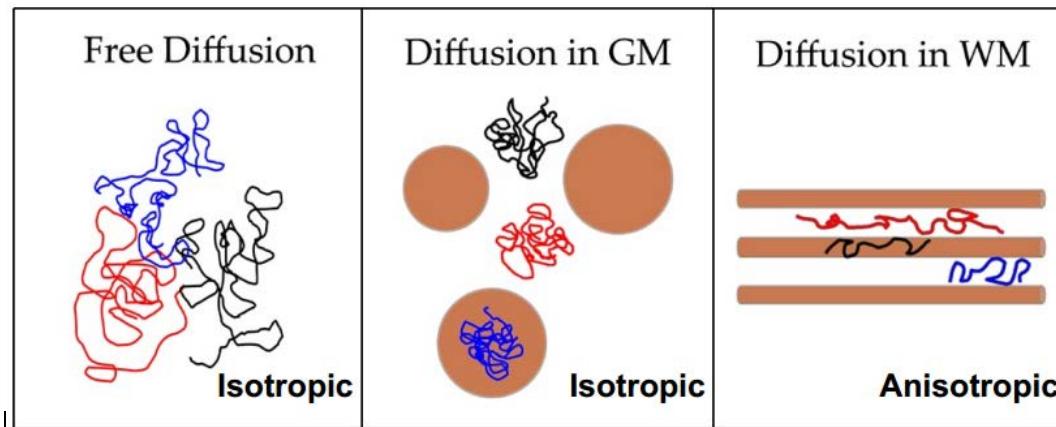
We cannot image individual axons but we can image bundles with diffusion MRI



From Gray's Anatomy: IX. Neurology

# STRUCTURAL CONNECTIVITY

Water diffuses differently across different brain tissues

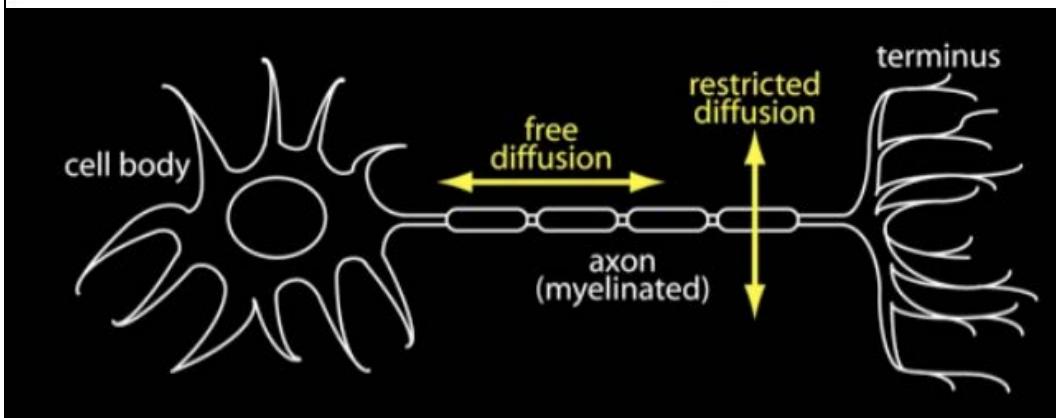


$$\langle x^2 \rangle = 2nDt$$

mean squared displacement      time  
Diffusion coefficient

$$D \sim 2.4 \mu\text{m}^2/\text{ms}$$
$$t \sim 50\text{ ms}$$

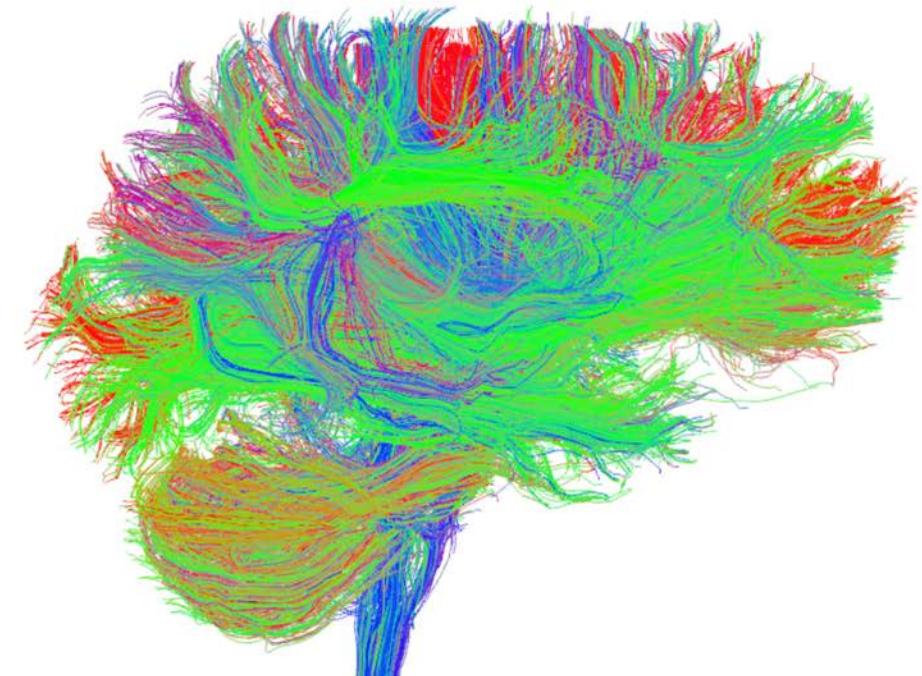
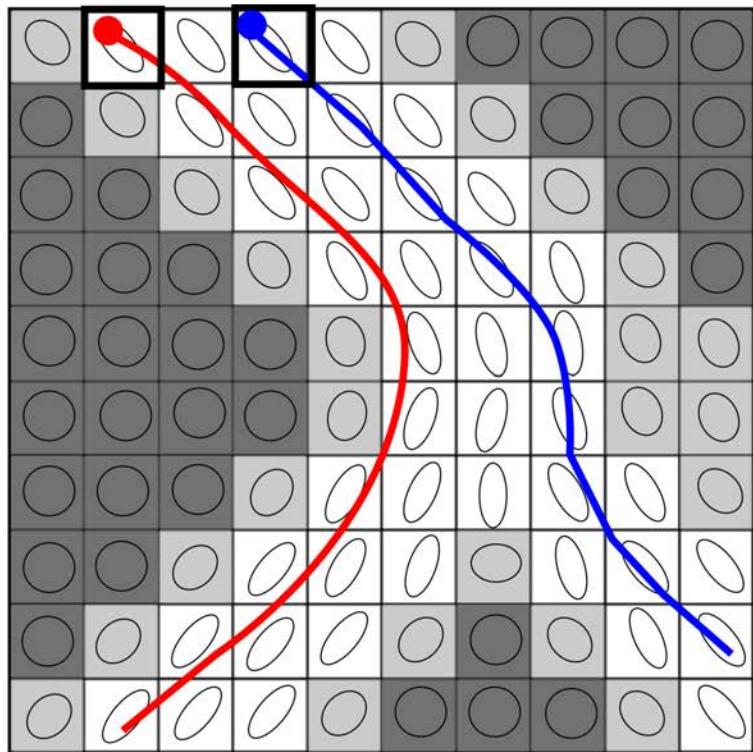
$$\rightarrow x = \sqrt{6Dt} \sim 27\mu\text{m}$$



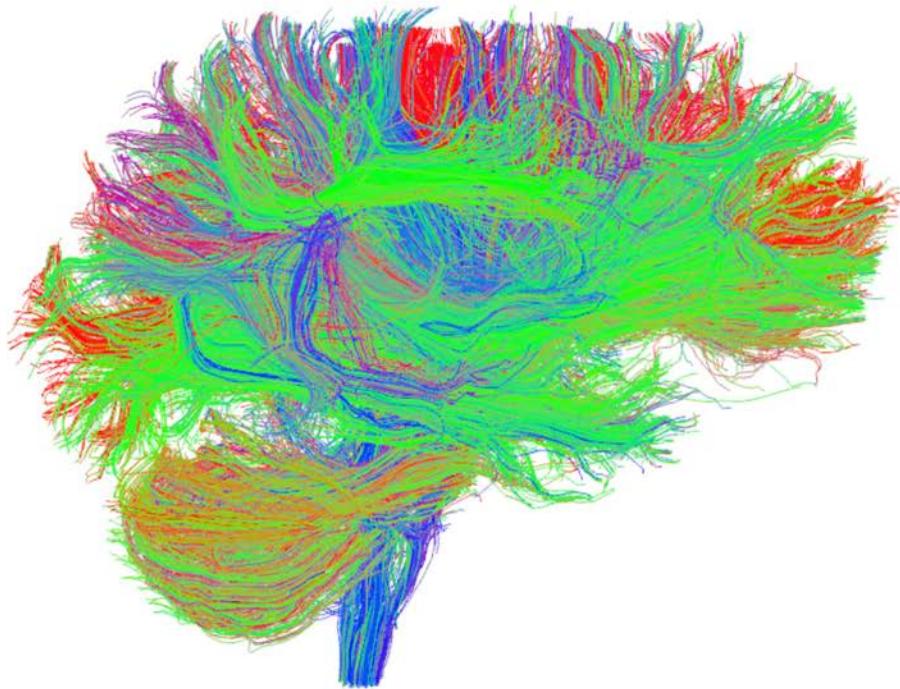
$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

# STRUCTURAL CONNECTIVITY

Use local diffusion orientation at each voxel to determine pathway between regions, a.k.a. tractography



# STRUCTURAL CONNECTIVITY

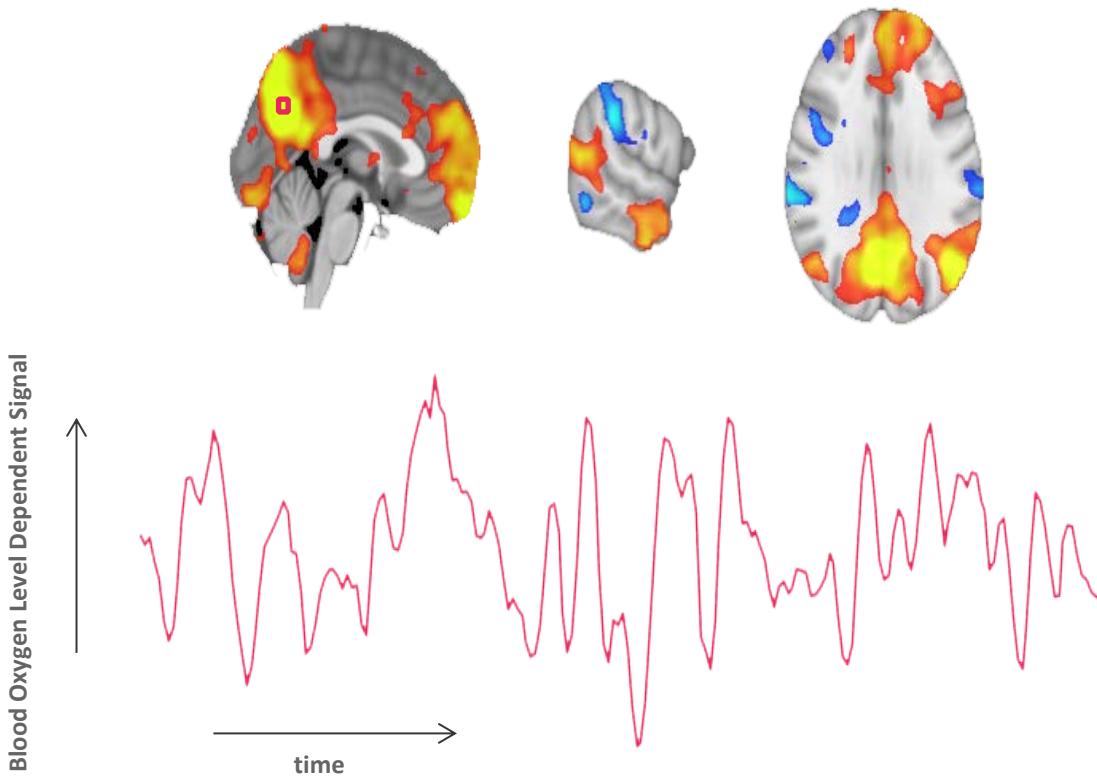


## Measures providing SC

- ✓ Number of fiber
- ✓ Volume
- ✓ Density
- ✓ Fiber length
- ✓ Fractional Anisotropy
- ✓ Mean Diffusivity
- ✓ Radial Diffusivity
- ✓ Axial Diffusivity

Bonifaxi.... et al Cortes, Human Brain Mapping 2018; Diez... and Cortes, Network Neuroscience 2017; Diez I, ... , and Cortes JM, Sci Rep, 2015; Alonso-Montes C, ... , and Cortes JM, Front Psychol, 2015; Erramuzpe A, ... , and Cortes JM, J Neural Eng, 2015; Erramuzpe A, ... , and Cortes JM, F1000 Res, 2015 ; Diez I, ... , and Cortes JM, Brain Conn, 2015; Maki-Marttunen V, ... , Cortes JM, ... , and Chialvo DR, Front Neuroinf, 2013

# FUNCTIONAL CONNECTIVITY



## Measures providing FC:

- ✓ Pearson Correlation
- ✓ Partial Correlation
- ✓ Mutual Information
- ✓ Coherence
- ✓ Phase synchronization

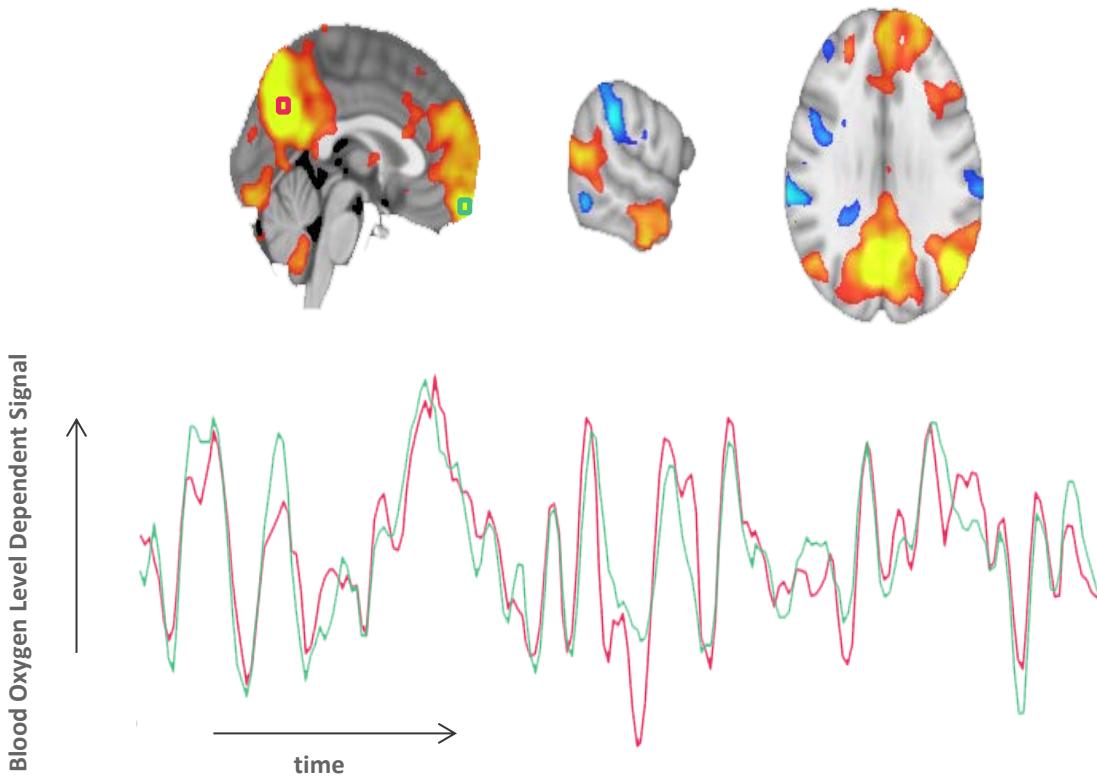
Bonifaxi.... et al Cortes, Human Brain Mapping 2018; Diez... and Cortes, Network Neuroscience 2017; Diez I, ... , and Cortes JM, Sci Rep, 2015; Alonso-Montes C, ... , and Cortes JM, Front Psychol, 2015; Erramuzpe A, ... , and Cortes JM, J Neural Eng, 2015; Erramuzpe A, ... , and Cortes JM, F1000 Res, 2015 ; Diez I, ... , and Cortes JM, Brain Conn, 2015; Maki-Marttunen V, ... , Cortes JM, ... , and Chialvo DR, Front Neuroinf, 2013

# FUNCTIONAL CONNECTIVITY

Similarity between time series of different regions (also distant ones)

Symmetric (in general)

Highly dynamical (unlike SC)



## Measures providing FC:

- ✓ Pearson Correlation
- ✓ Partial Correlation
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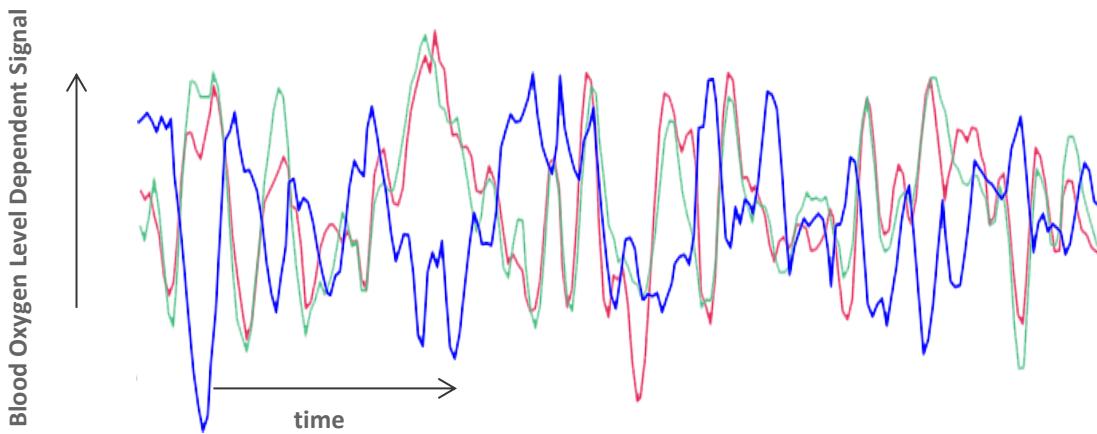
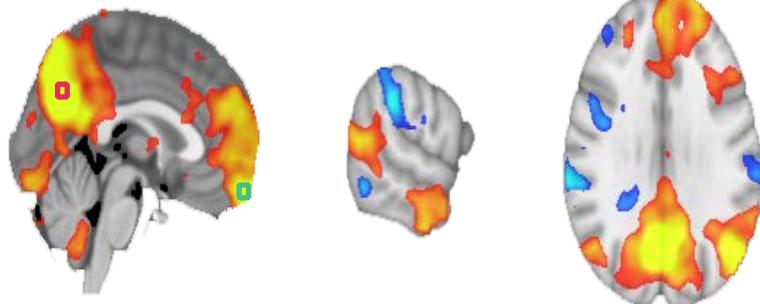
# FUNCTIONAL CONNECTIVITY

Similarity between time series of different regions (also distant ones)

Symmetric (in general)

Highly dynamical (unlike SC)

Positive and negative values

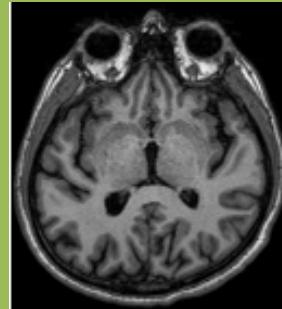


## Measures providing FC:

- ✓ Pearson Correlation
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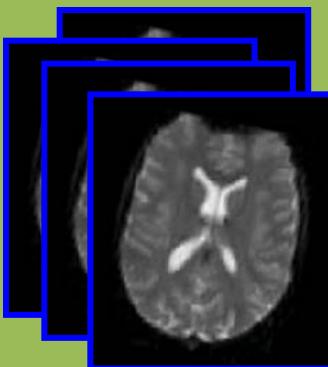
Bonifaxi.... et al Cortes, Human Brain Mapping 2018; Diez... and Cortes, Network Neuroscience 2017; Diez I, ... , and Cortes JM, Sci Rep, 2015; Alonso-Montes C, ... , and Cortes JM, Front Psychol, 2015; Erramuzpe A, ... , and Cortes JM, J Neural Eng, 2015; Erramuzpe A, ... , and Cortes JM, F1000 Res, 2015 ; Diez I, ... , and Cortes JM, Brain Conn, 2015; Maki-Marttunen V, ... , Cortes JM, ... , and Chialvo DR, Front Neuroinf, 2013

# Triple Acquisition



T1 -3D  
(Anatomical)

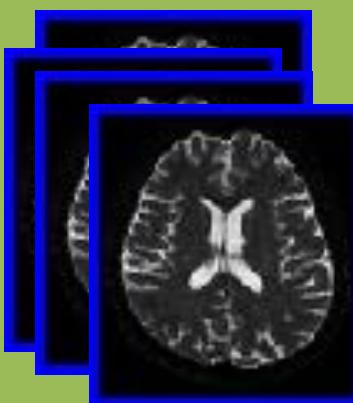
4 min



fMRI Sequence  
(raw EPI)

8 min

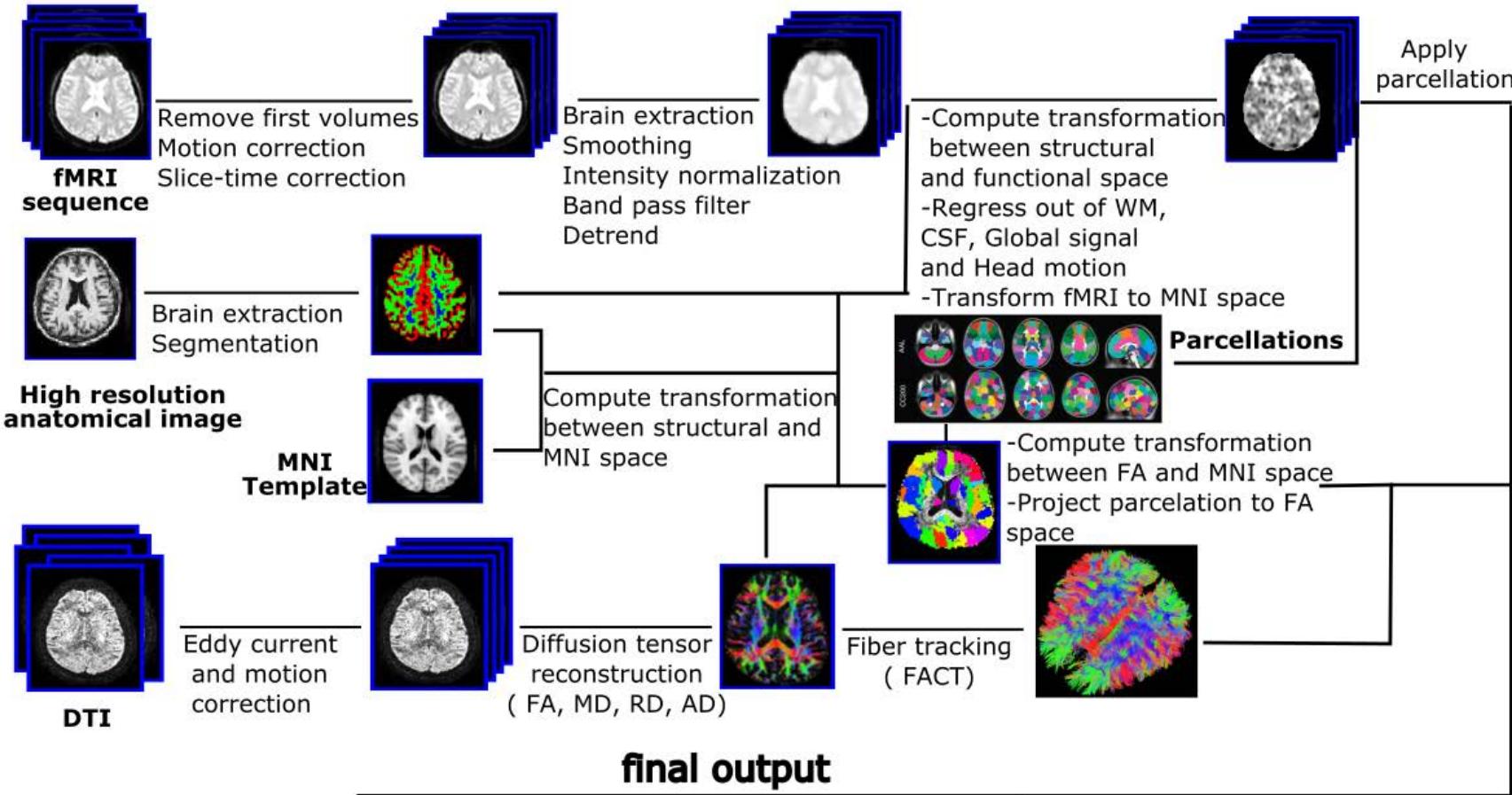
TR: 2.2  
Slices: 30  
Volumes: 200  
Flip Angle: 90°



DTI Sequence  
(raw EPI)

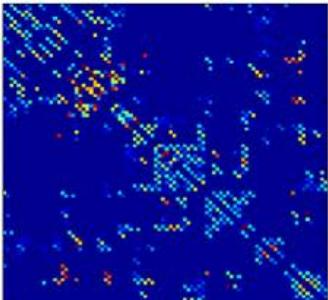
18 min (32 gradients)

# Cortes Lab: MRI connectivity at the macroscale



## structural connectivity (SC)

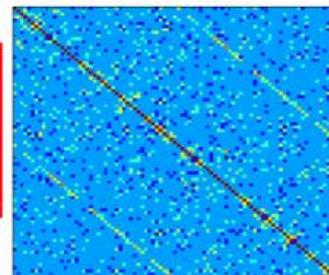
Fibers number  
Fibers length  
Axial diffusivity  
Fractional anisotropy  
Mean diffusivity  
Radial diffusivity



Longitudinal correspondence between SC and FC across different time points

## functional connectivity (FC)

Undirected graphs (Correlation, Partial correlation, Mutual information, etc)



Directed graphs (Granger causality, Transfer entropy, etc)

# SCIENTIFIC REPORTS



OPEN

## A novel brain partition highlights the modular skeleton shared by structure and function

Received: 28 November 2014

Accepted: 23 April 2015

Published: 03 June 2015

Ibai Diez<sup>1,\*</sup>, Paolo Bonifazi<sup>2,\*</sup>, Iñaki Escudero<sup>1,3</sup>, Beatriz Mateos<sup>1,3</sup>, Miguel A. Muñoz<sup>4</sup>,  
Sebastiano Stramaglia<sup>1,5,6,†</sup> & Jesus M Cortes<sup>1,6,7</sup>



## NITRC Wins 2015 HHS Innovates Award Check it out!

### Summary

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**Brain Hierarchical Atlas:** A brain atlas where the regions of interest are relevant for both structure and function

This atlas results from a hierarchical clustering approach applied to a combination of functional (resting fMRI) and structural (DTI) datasets. The novelty of the atlas is based on the fact that ROIs are functionally coherent (i.e., the dynamics of voxels within regions have high similarity) and at the same time they are structurally wired (the voxels within regions are highly integrated by white-matter fibers).

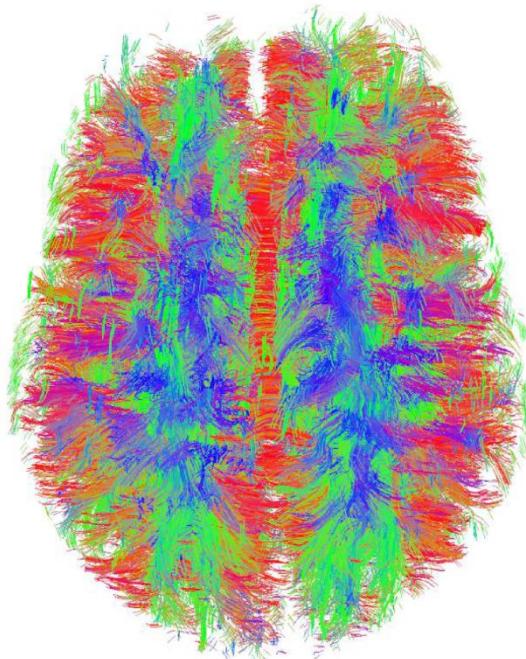
This Project contains the following files:

-average\_networks.mat: The population (N=12) functional and structural matrices, each one with dimensions 2514x2514

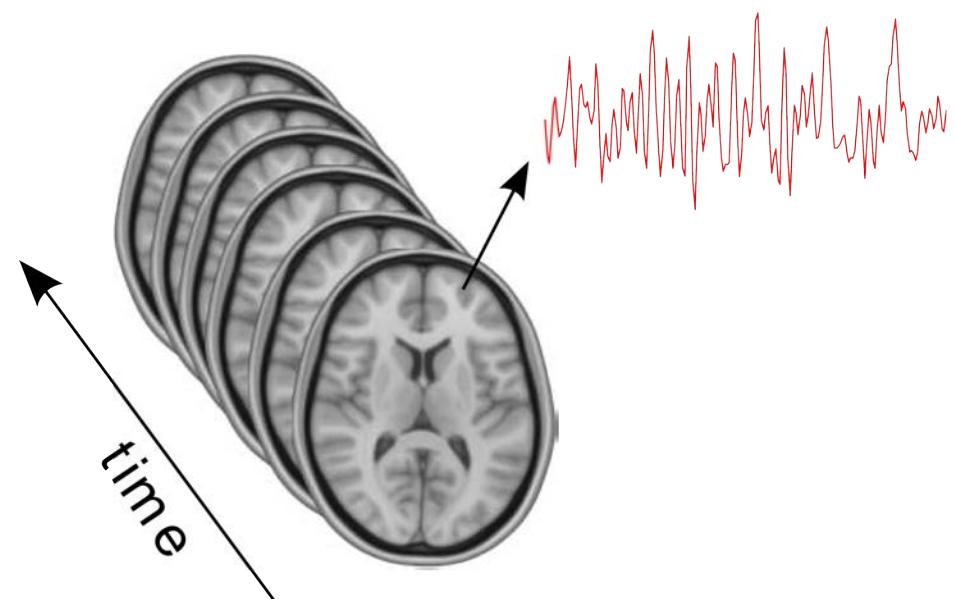
-functional.zip/structural.zip: Zip files containing the functional/structural atlas for all the stages in the hierarchical tree, from M=1 to 2514 ROIs

-test\_crosmodularity.m: Code example on how to compute crosmodularity. It needs crossmodularity.m and modularity\_index.m

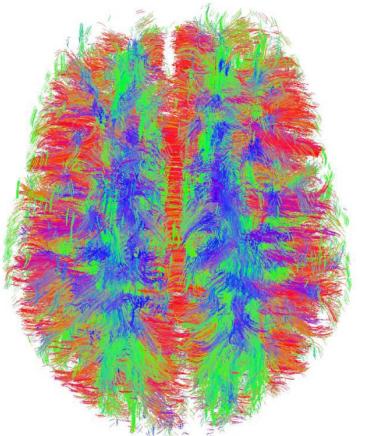
**STRUCTURE**  
DTI (fibers)



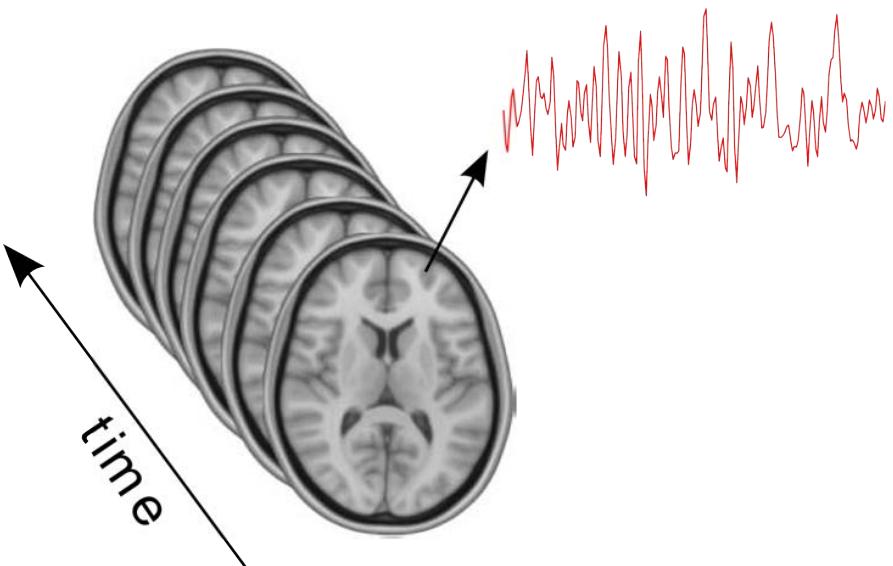
**FUNCTION**  
Resting fMRI (time series)



## STRUCTURE DTI (fibers)



## FUNCTION Resting fMRI (time series)



## REVIEW SUMMARY

# Structural and Functional Brain Networks: From Connections to Cognition

Hae-Jeong Park<sup>1\*</sup> and Karl Friston<sup>2</sup>

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**Background:** The human brain presents a puzzling and challenging paradox: Despite a fixed anatomy, characterized by its connectivity, its functional repertoire is vast, enabling action, perception, and cognition. This contrasts with organs like the heart that have a dynamic anatomy but just one function. The resolution of this paradox may reside in the brain's network architecture, which organizes local interactions to cope with diverse environmental demands—ensuring adaptability, robustness, resilience to damage, efficient message passing, and diverse functionality from a fixed structure. This review asks how recent advances in understanding brain networks elucidate the brain's many-to-one (degenerate) function-structure relationships. In other words, how does diverse function arise from an apparently static neuronal architecture? We conclude that the emergence of dynamic functional connectivity, from static structural connections, calls for formal (computational) approaches to neuronal information processing that may resolve the dialectic between structure and function.

(Park and Friston, Science, 2013)

## The conjecture of the brain at criticality

REVIEW ARTICLES | INSIGHT

PUBLISHED ONLINE: 1 OCTOBER 2010 | DOI: 10.1038/NPHYS1803

nature  
physics

# Emergent complex neural dynamics

Dante R. Chialvo<sup>1,2\*</sup>

A large repertoire of spatiotemporal activity patterns in the brain is the basis for adaptive behaviour. Understanding the mechanism by which the brain's hundred billion neurons and hundred trillion synapses manage to produce such a range of cortical configurations in a flexible manner remains a fundamental problem in neuroscience. One plausible solution is the involvement of universal mechanisms of emergent complex phenomena evident in dynamical systems poised near a critical point of a second-order phase transition. We review recent theoretical and empirical results supporting the notion that the brain is naturally poised near criticality, as well as its implications for better understanding of the brain.

Chialvo D.R. and Bak P. (1999)

Bak P and Chialvo D.R. (2001)

Eguíluz V.M., Chialvo D.R., Cecchi G., Baliki M, and Apkarian AV. (2004)

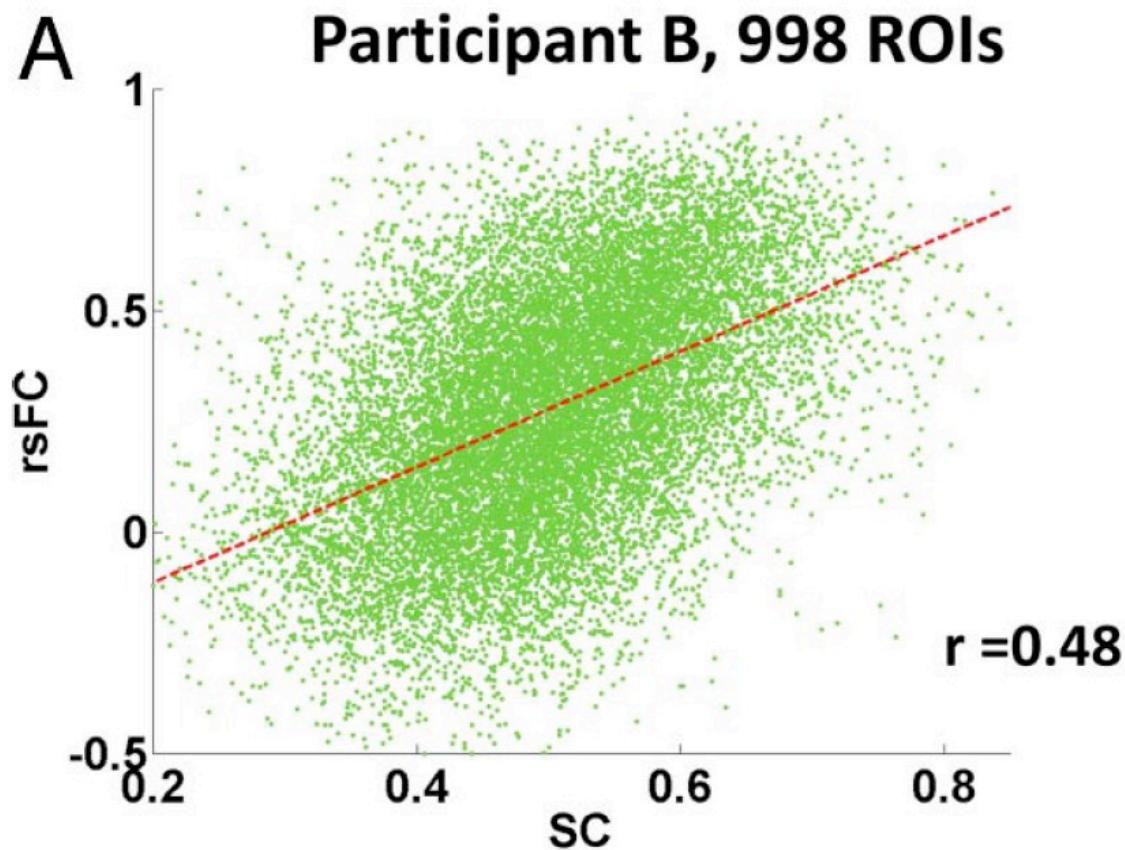
Chialvo, D. R. (2004)

D. Fraiman, P. Balenzuela, J. Foss and D. R. Chialvo (2004)

D. R. Chialvo (2010)

# Pioneer work by Sporns and collaborators

## Pairwise link-to-link comparison



(Honey et al, PNAS, 2009)

## Pairwise link-to-link comparison

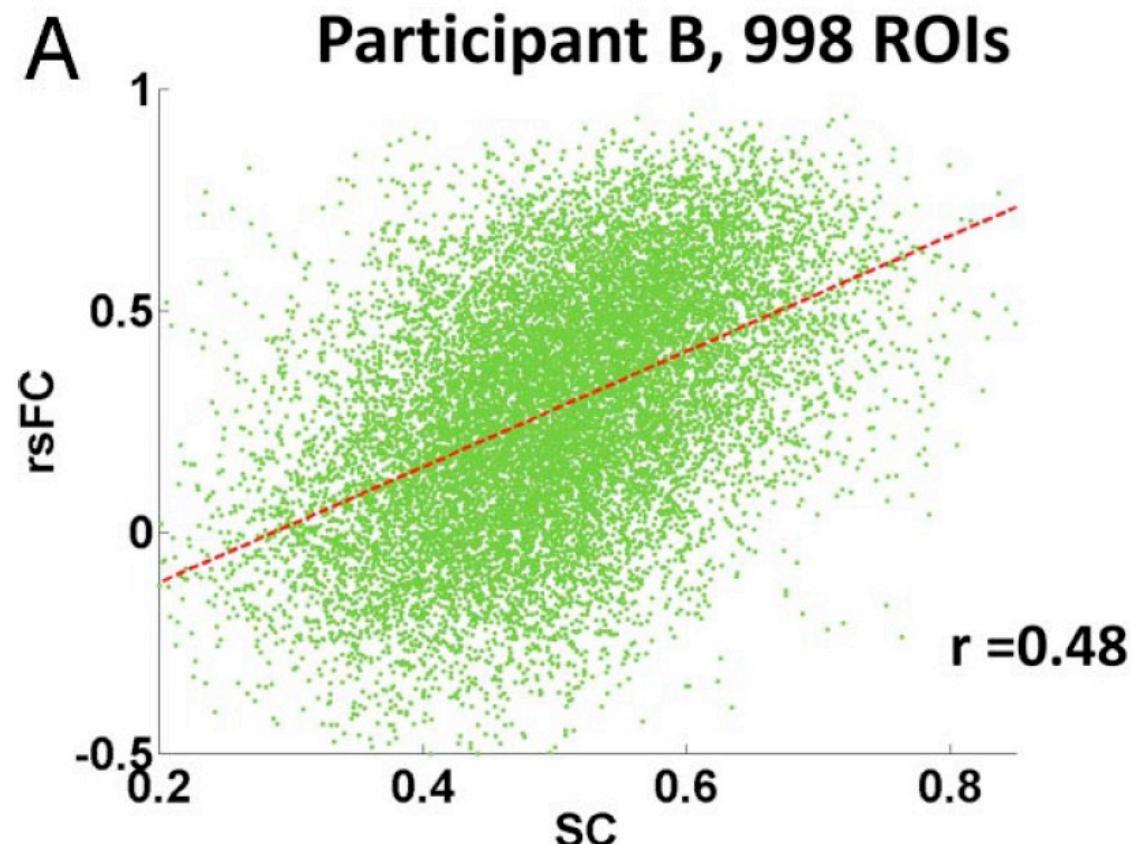
After  
Gaussianization

Only over  
connected pairs

Connected pairs  
are only the 3%  
of the pairs!!!!

Raw data on all  
pairs give  
correlations of  
0.1-0.2

Indirect effects  
make the SC-FC  
matching to be  
hard



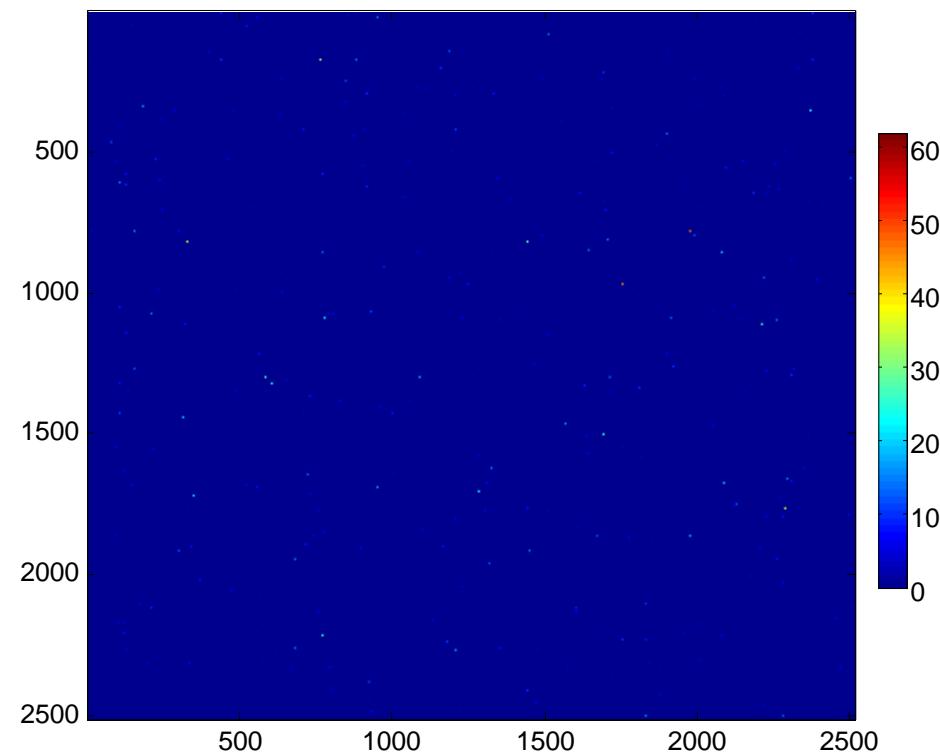
(Honey et al, PNAS, 2009)

Our approach, inspired in this piooner work, makes use of clustering or modularity to search for similarities

# SUBJECT 1

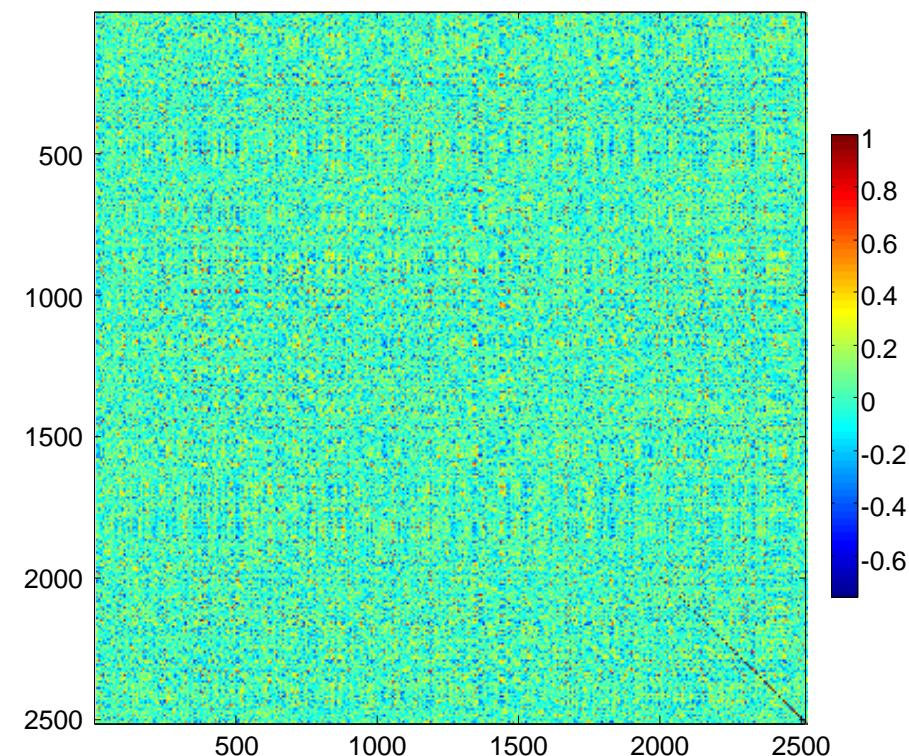
**Structural connectivity (SC)**

DTI – number of fibers



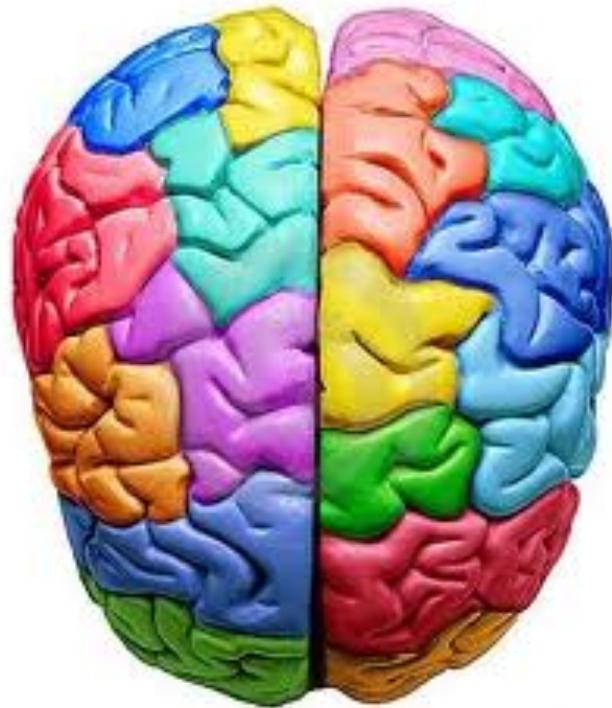
**Functional connectivity (FC)**

Rs-fMRI – Pearson correlation

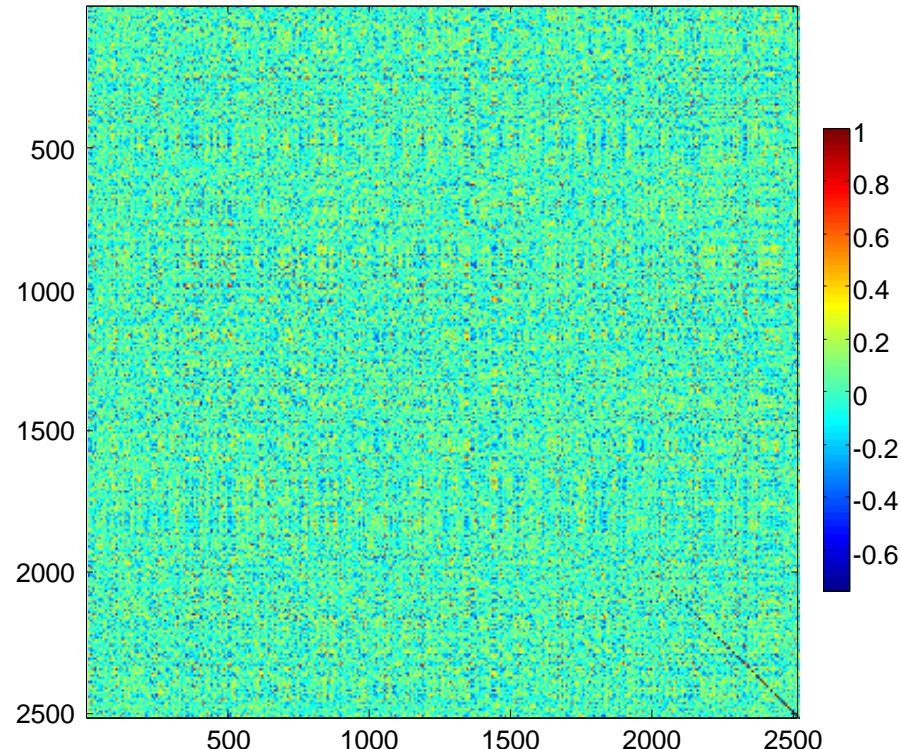


# SUBJECT 1

## Brain modularity: segregation and integration



(Tononi, et al., PNAS, 2009)

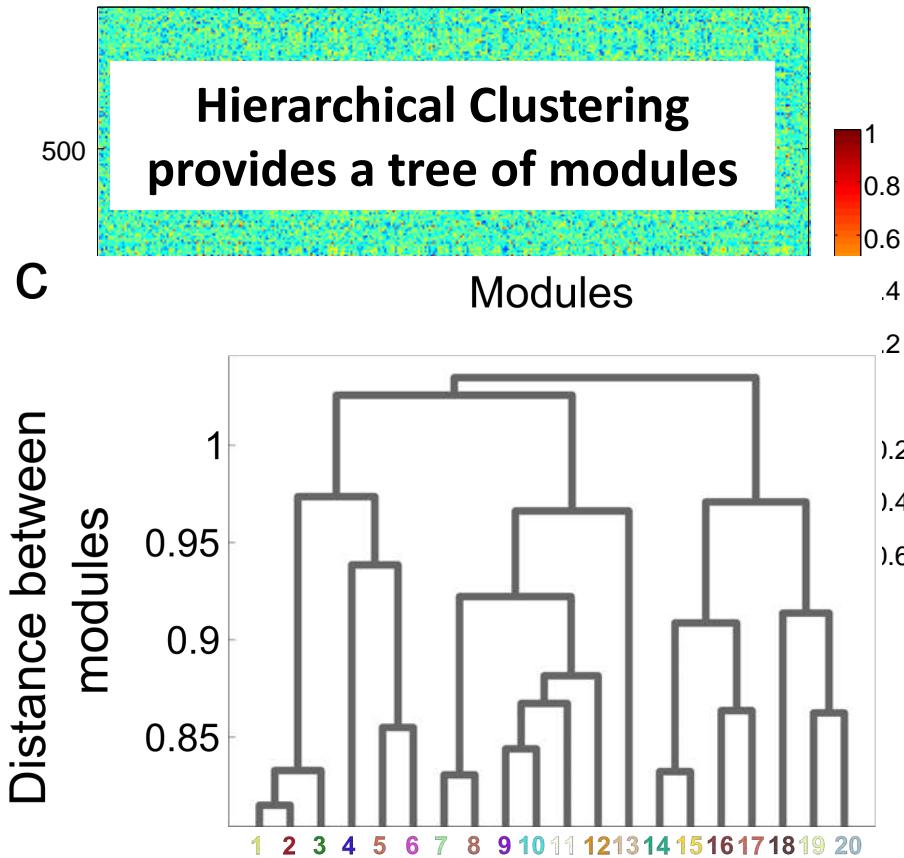


# SUBJECT 1

## Brain modularity: segregation and integration



(Tononi, et al., PNAS, 2009)



# SUBJECT 1

rs-fMRI

Modules

500

1000

1500

2000

2500

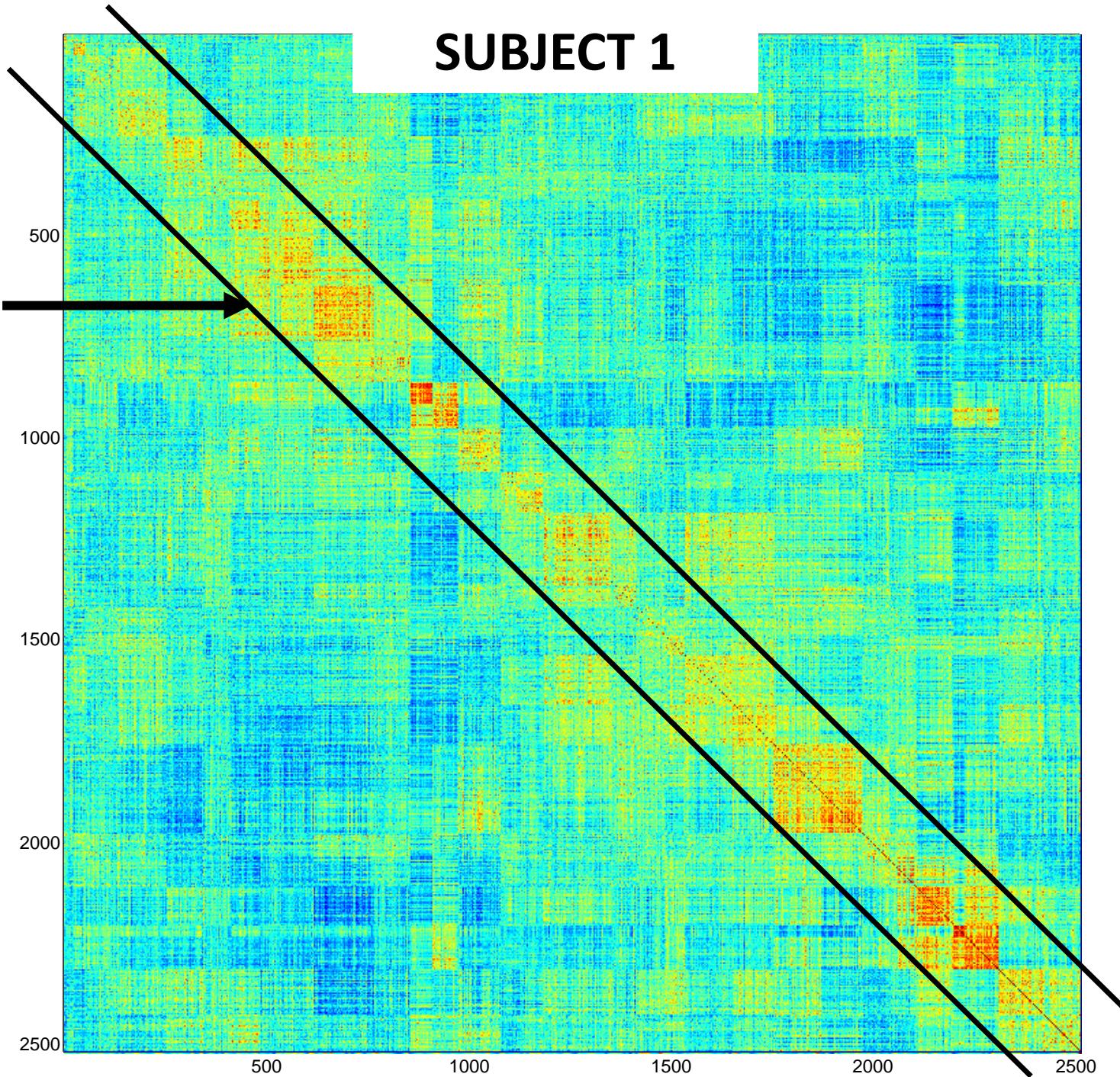
500

1000

1500

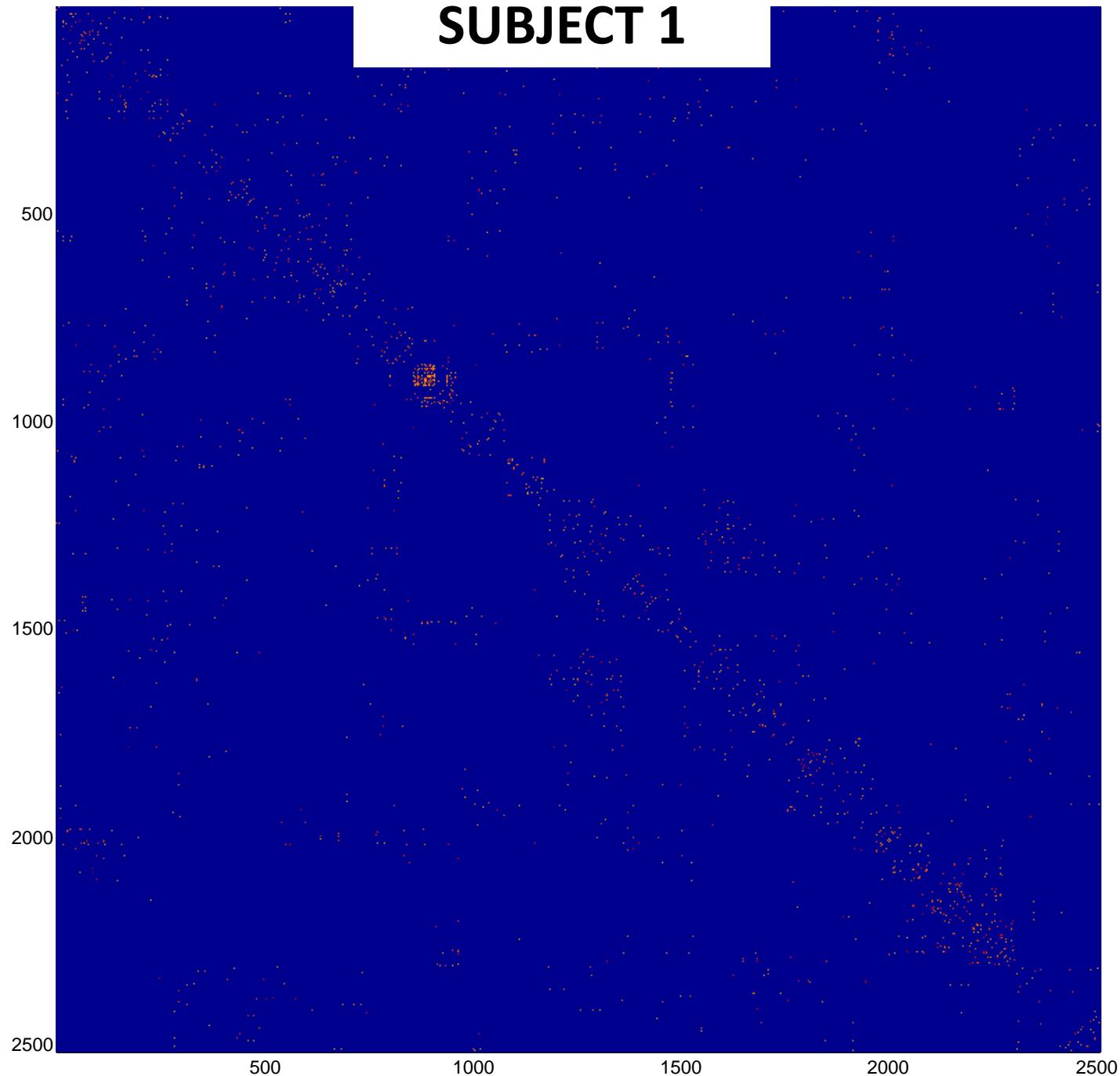
2000

2500



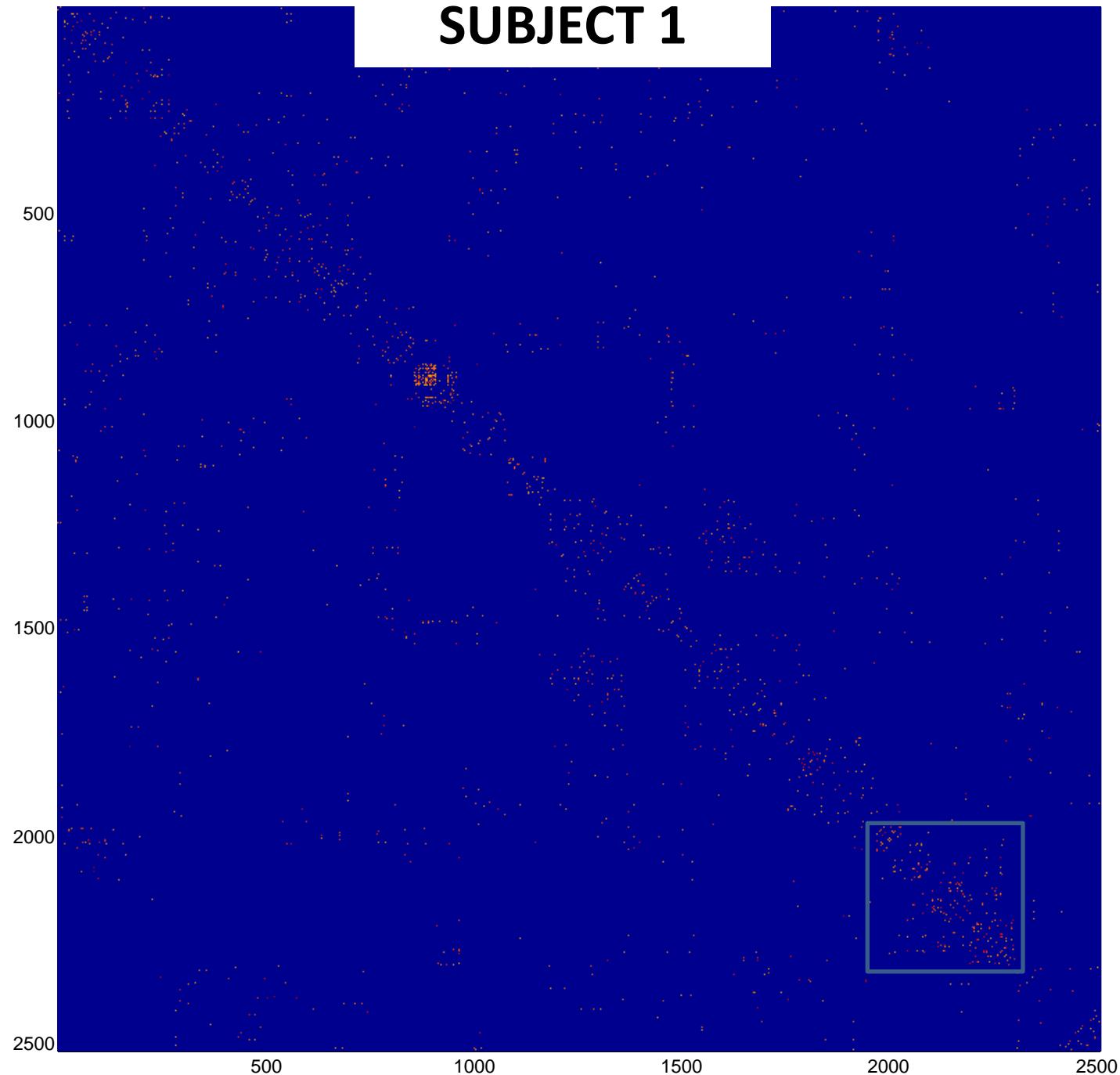
DTI

# SUBJECT 1



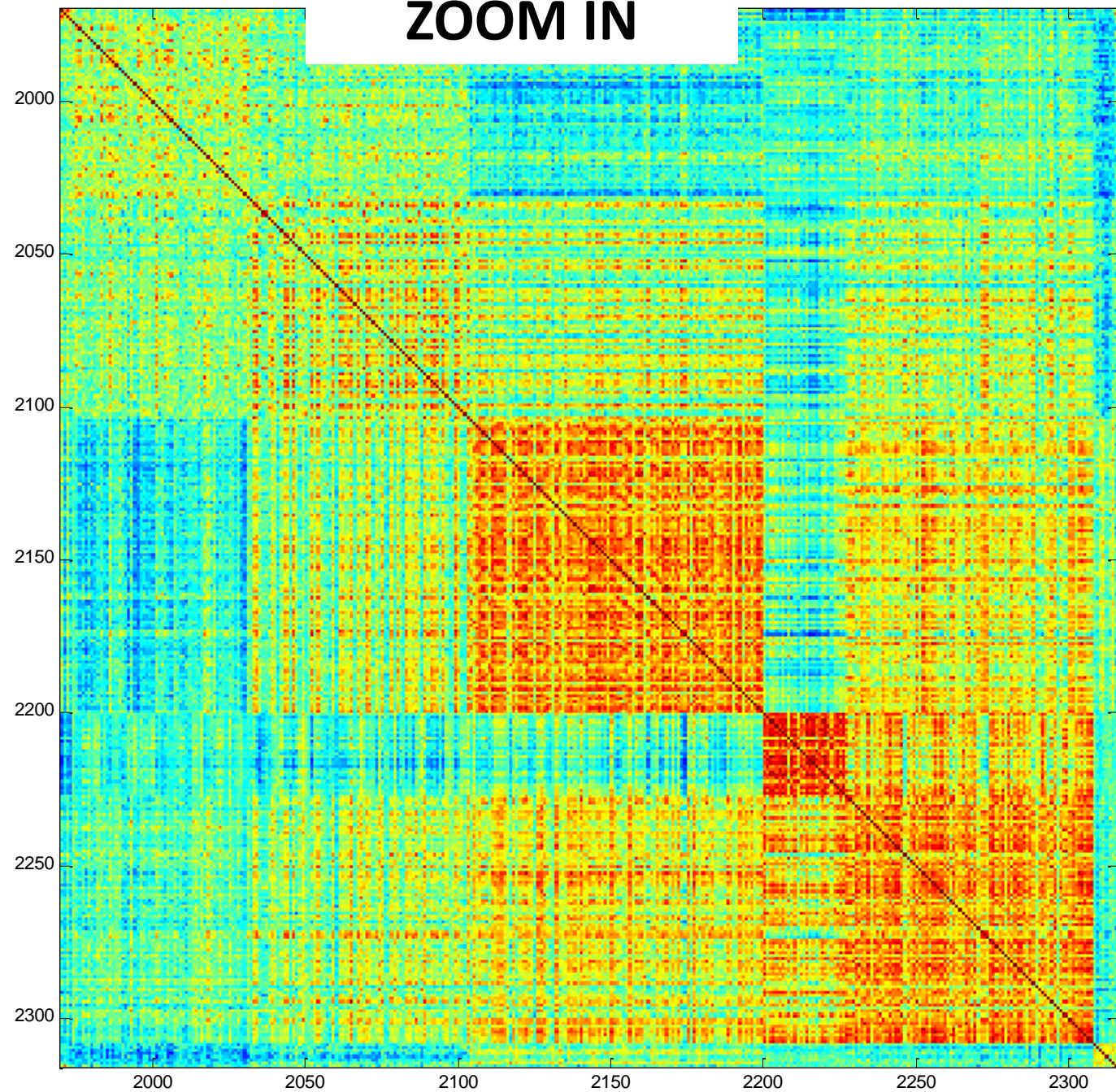
DTI

# SUBJECT 1



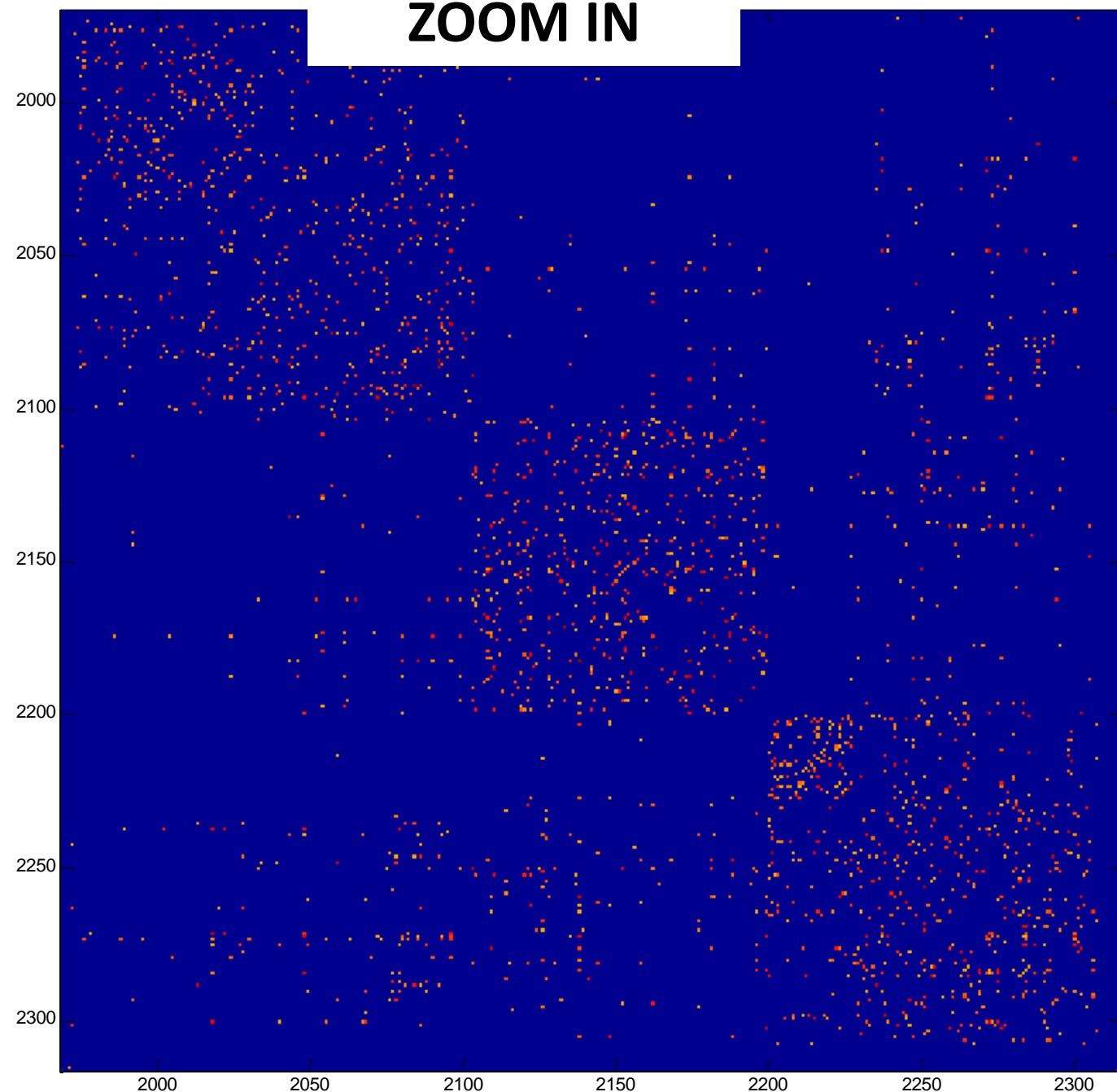
rs-fMRI

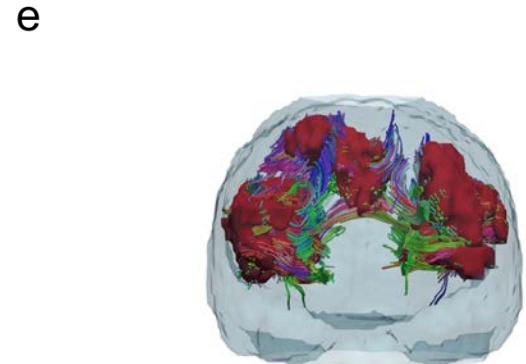
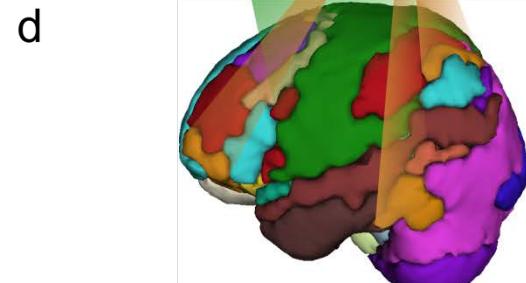
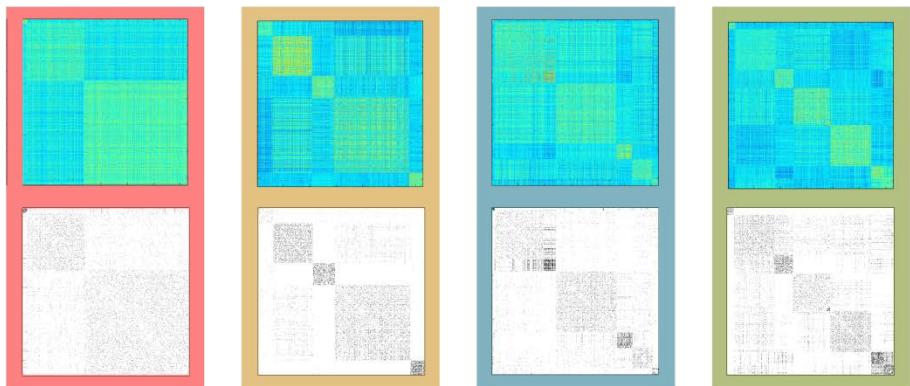
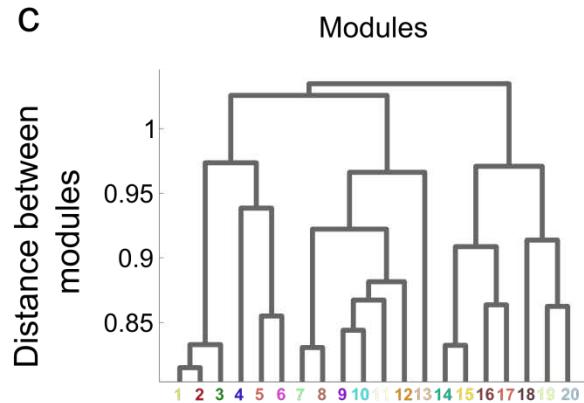
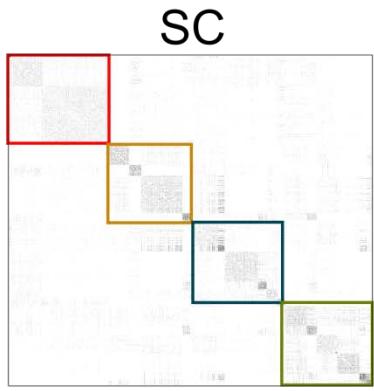
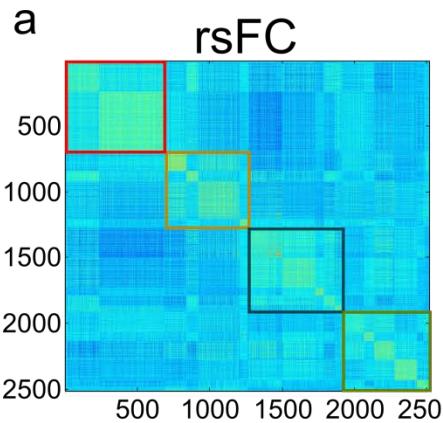
ZOOM IN



DTI

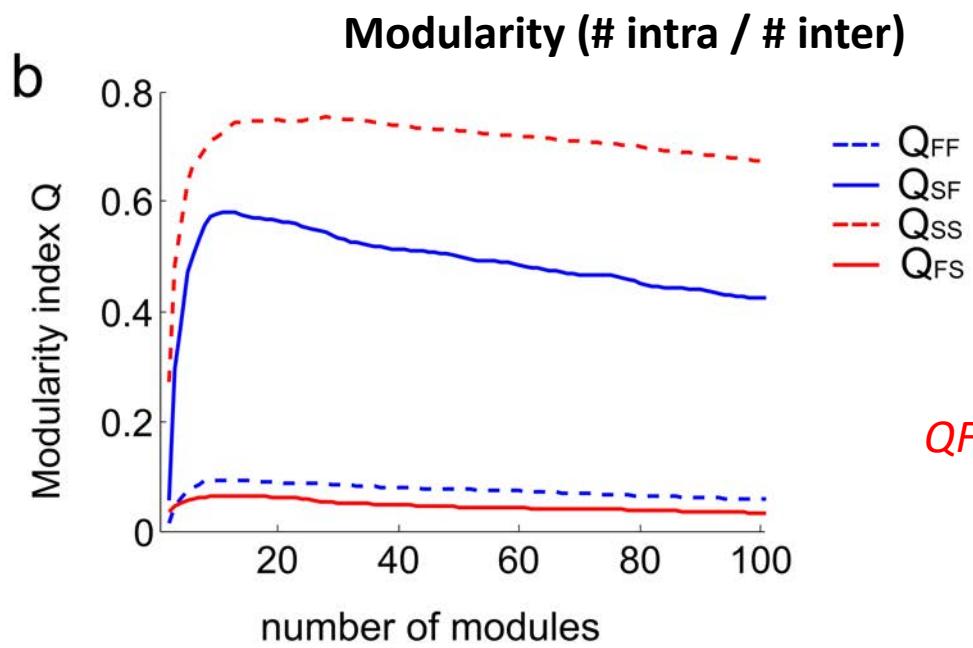
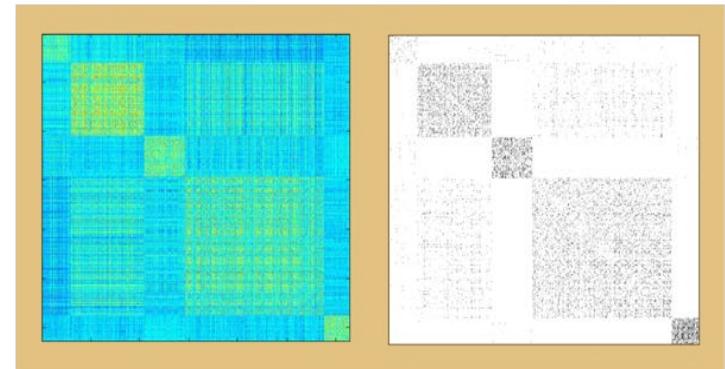
ZOOM IN





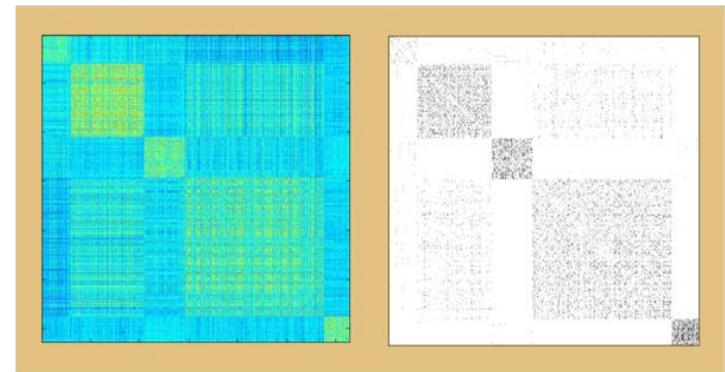
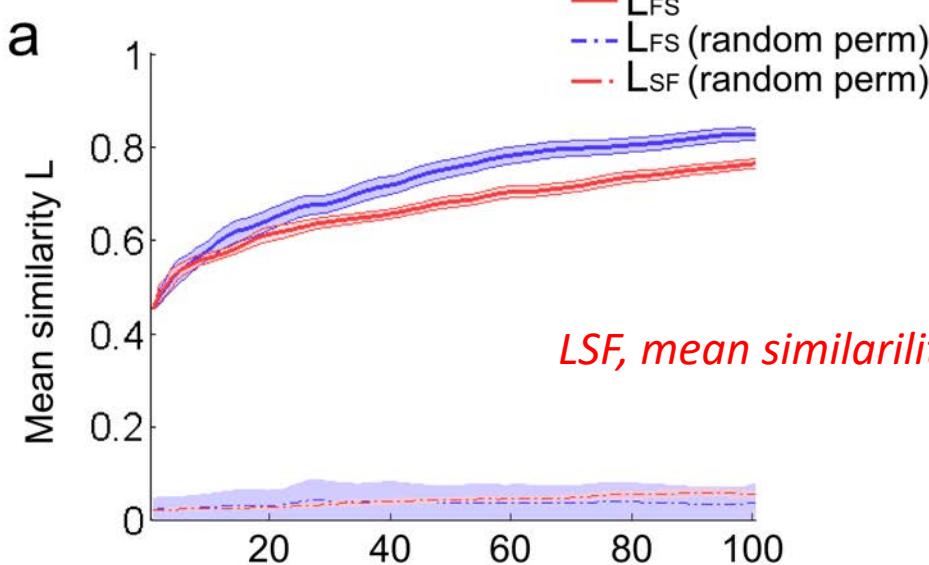
# Optimal in what sense ?

## Cross-modularity sense

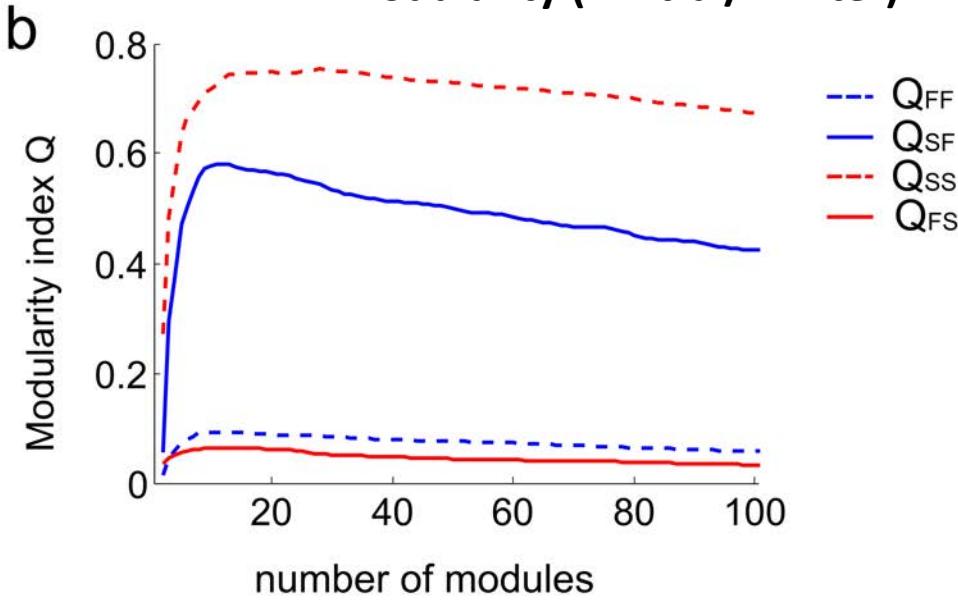


*QFS, modularity of F, using the order of S*

## Similarity between modules (Sorensen index)

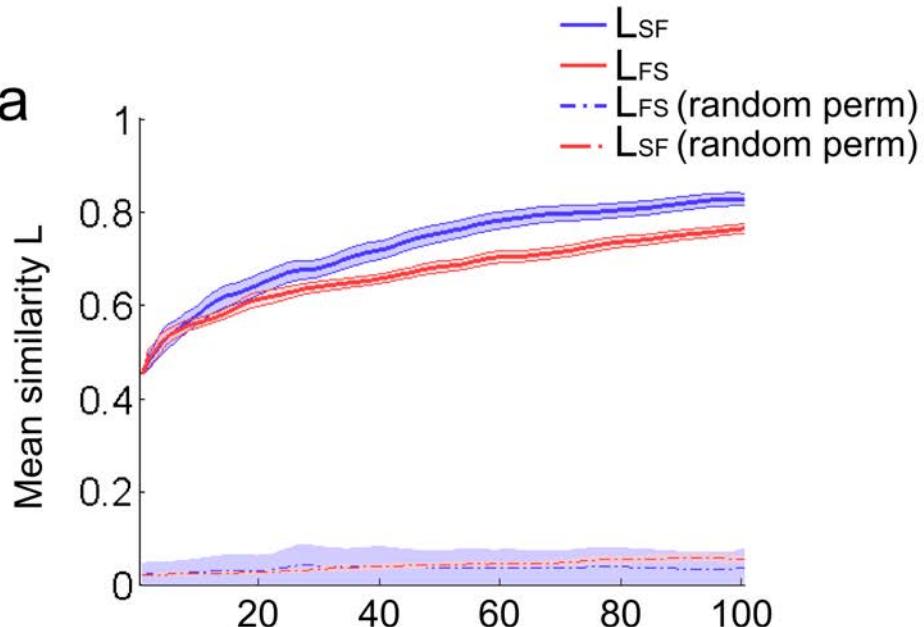


## Modularity (# intra / # inter)

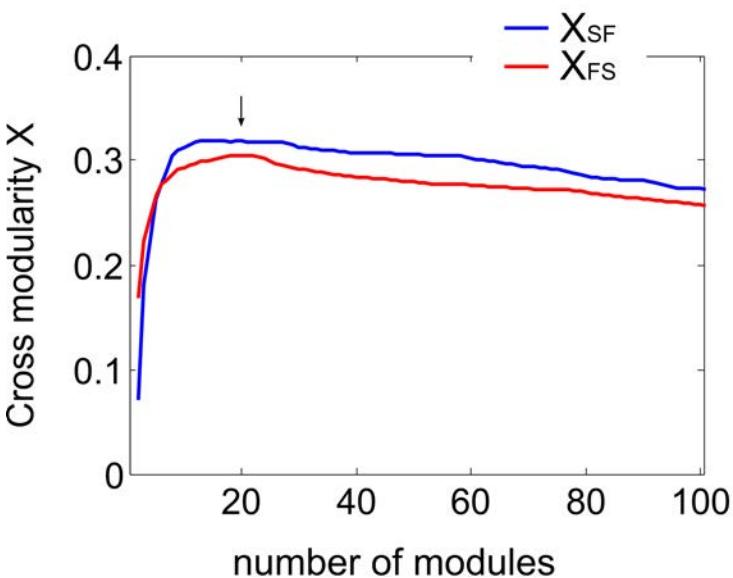
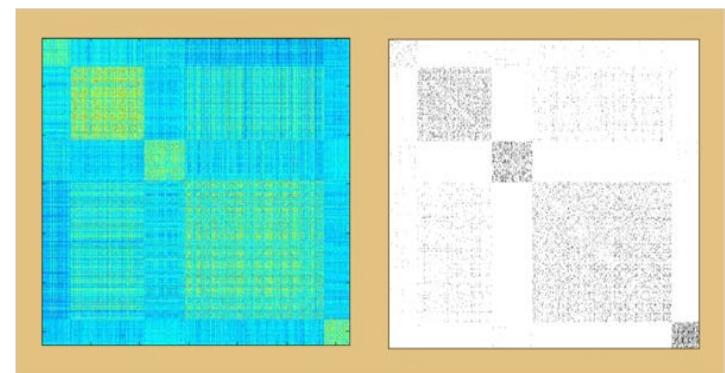
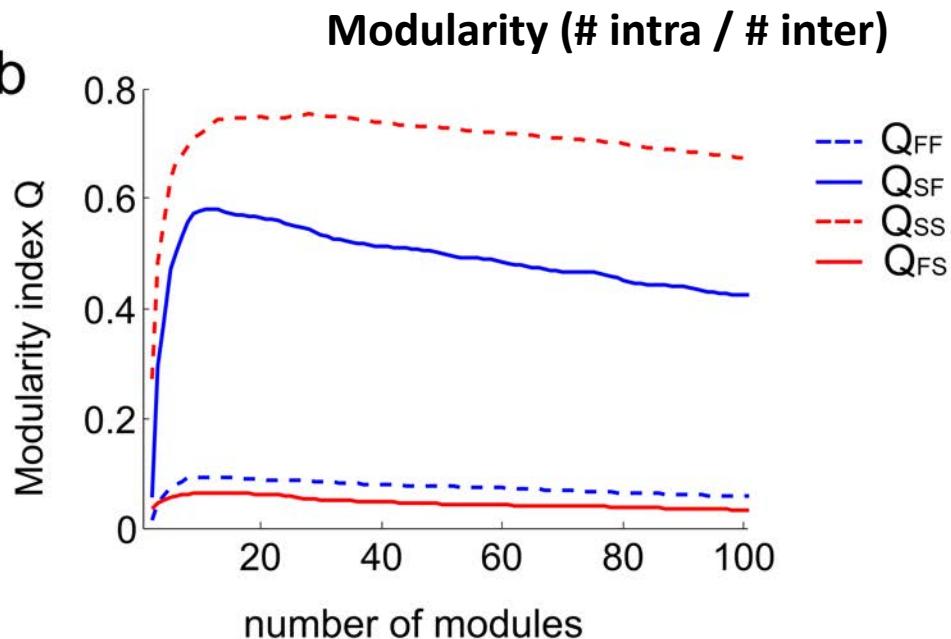


## Similarity between modules (Sorenson index)

a



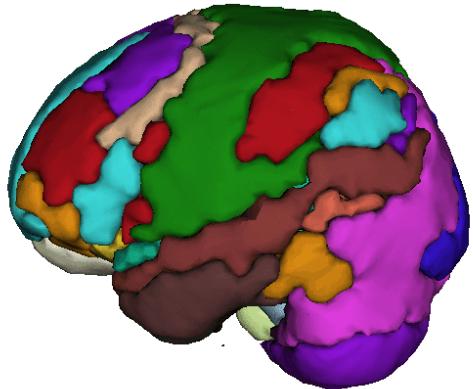
b



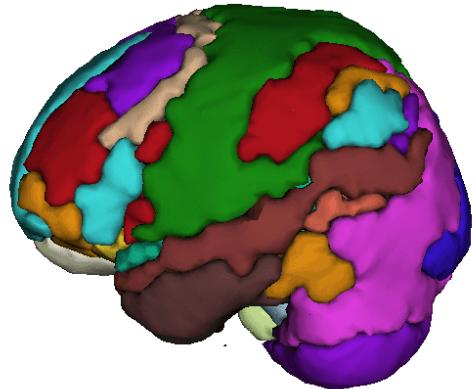
Cross-modularity =  
modularity (func) \*  
modularity (stru) \*  
similarity (func,struc)

# What means high crossmodularity?

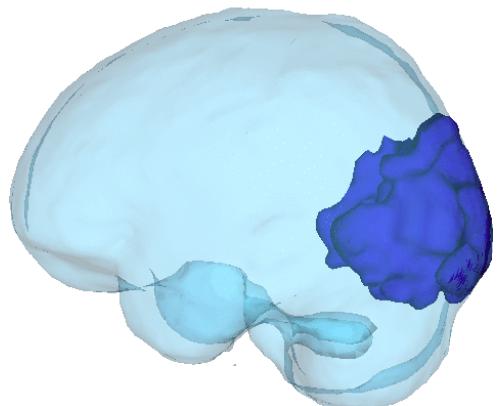
# Optimal partition with M=20 regions



# Optimal partition with M=20 regions

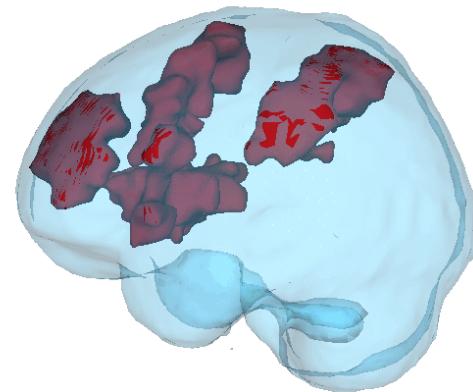
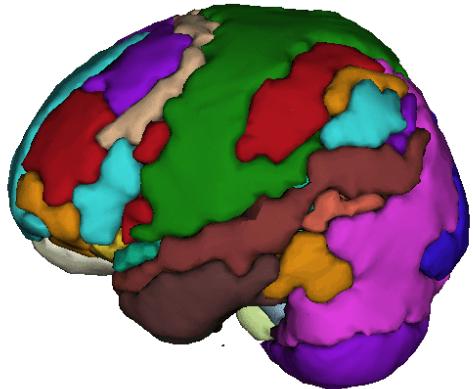


**Some regions are compact**

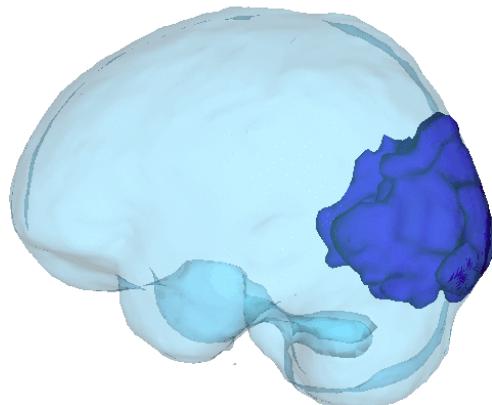


# Optimal partition with M=20 regions

Some are made of anatomically distinct components

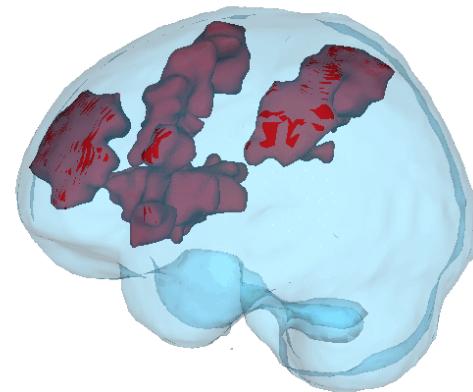
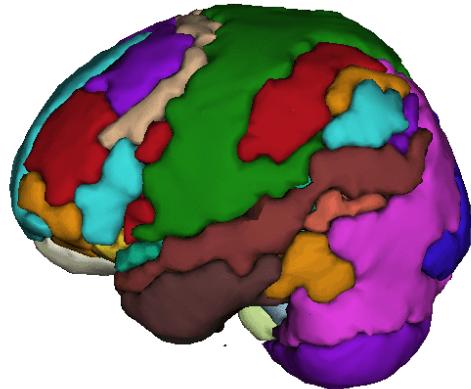


Some regions are compact

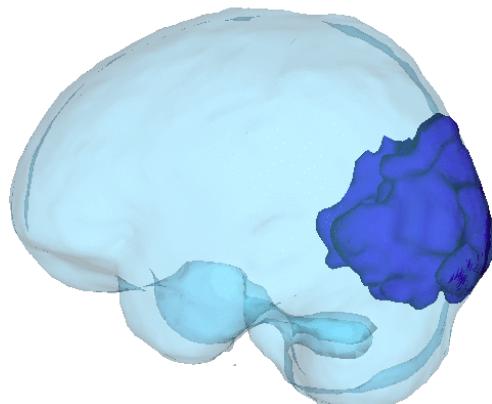


# Optimal partition with M=20 regions

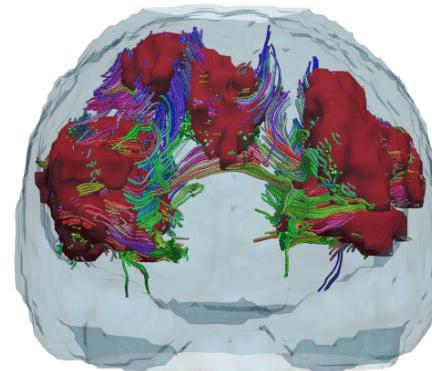
Some are made of anatomically distinct components



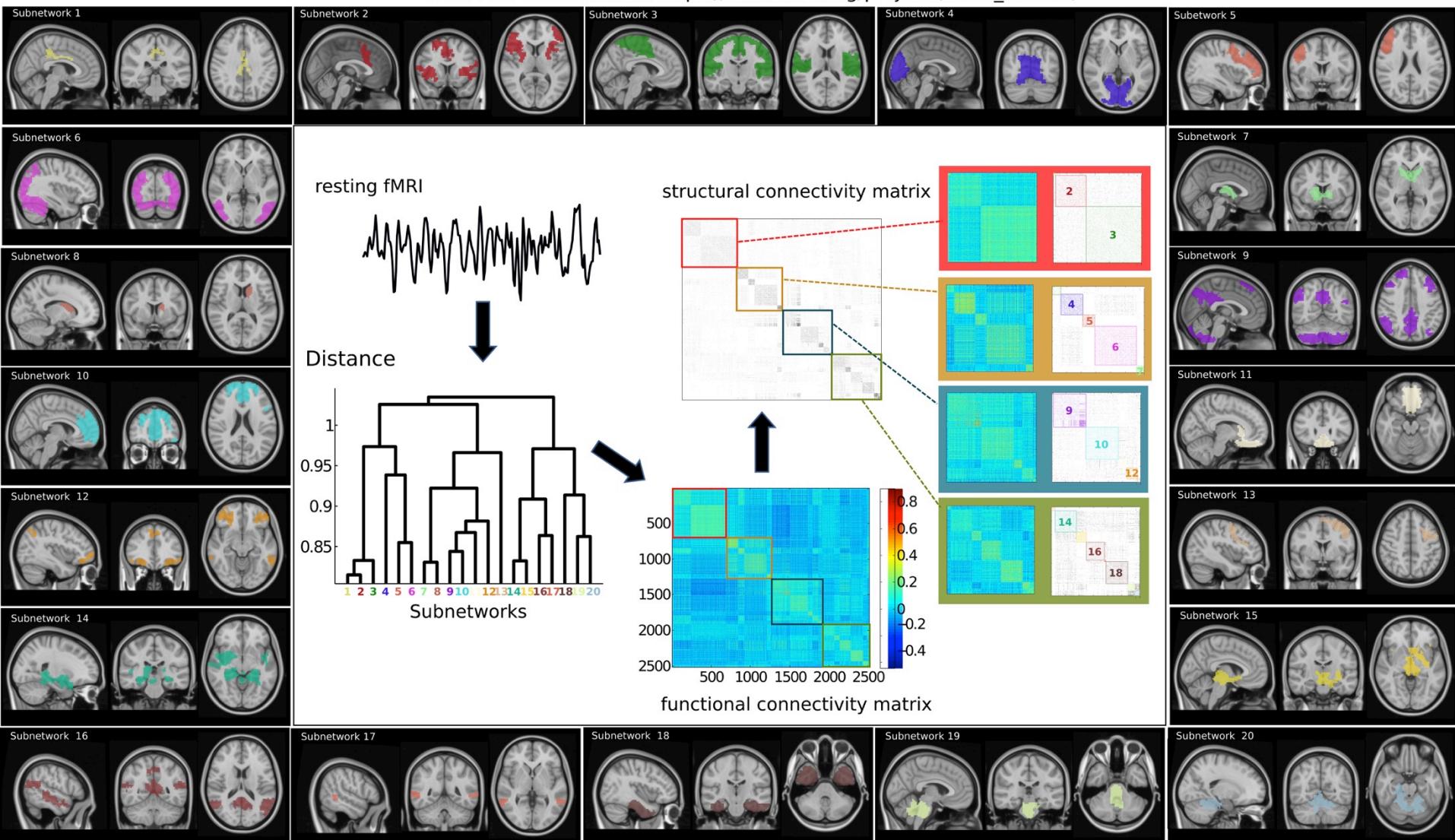
Some regions are compact



Each individual region is structurally wired and functionally similar



Brain Hierarchical Atlas: [https://www.nitrc.org/projects/biocr\\_hcatlas/](https://www.nitrc.org/projects/biocr_hcatlas/)



# HEALTHY (NON-PATHOLOGICAL) BRAIN AGE ?



# HUMAN BRAIN MAPPING 2018

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WILEY

## **RESEARCH ARTICLE**

# **Structure–function multi-scale connectomics reveals a major role of the fronto-striato-thalamic circuit in brain aging**

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Matthieu P. Boisgontier<sup>3</sup> | Lisa Pauwels<sup>3</sup>  | Sebastiano Stramaglia<sup>4</sup> |  
Stephan P. Swinnen<sup>3,5</sup>  | Jesus M. Cortes<sup>1,2,6</sup>**

## MOTIVATION:

**Q1:** Can we use brain connectivity to measure brain maturation?

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Two different concepts: Brain Connectome Age (BCA) vs Chronological Age (CHA)

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Two different concepts: Brain Connectome Age (BCA) vs Chronological Age (CHA)

If the two are different; which is bigger?

For old people, if  $BCA < CHA$  is good

For young people, if  $BCA < CHA$  might indicate neurodevelopmental problems

## MOTIVATION:

**Q2:** Can we alter, e.g. rejuvenate, BCA by a treatment or therapy ? For instance, by increasing the level of physical activity, using a drug or a rehab program



## MOTIVATION:

**Q3:** What are the brain areas whose connectivity predicts age?

The circuit correlates of brain aging



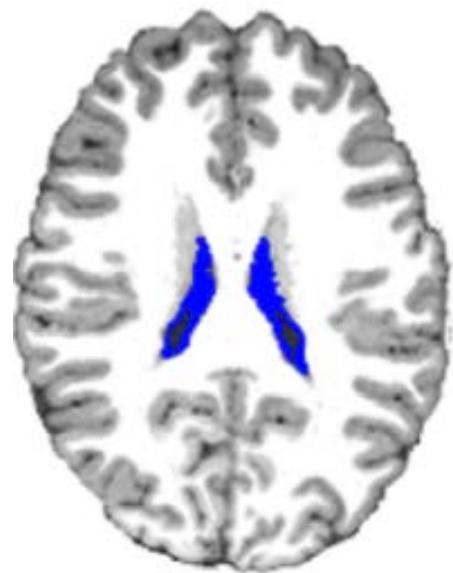
## MOTIVATION:

**Q1:** Can we use brain connectivity to measure brain maturation?

First time on 1973, Reitan introduced the Brain-Age Quotient as a measure for age-related cognitive functioning... However, this was not continued that much

Brain age using morphological features have been assessed before by Cole & Franke and collaborators (Cole et al 2015, 2017a, 2017b, 2017c)

## MOTIVATION:



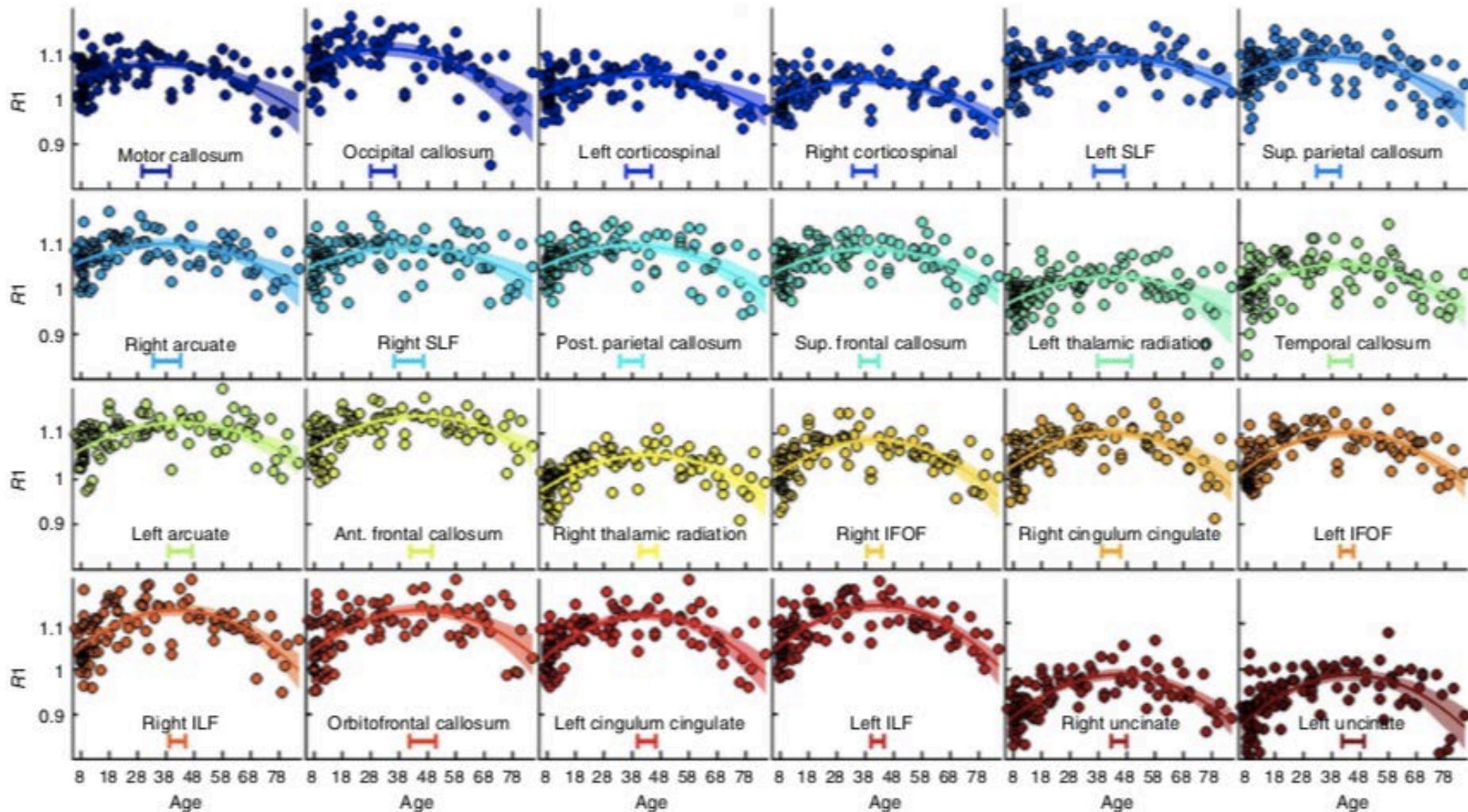
17 yo



72 yo

No morphological features were used to predict age

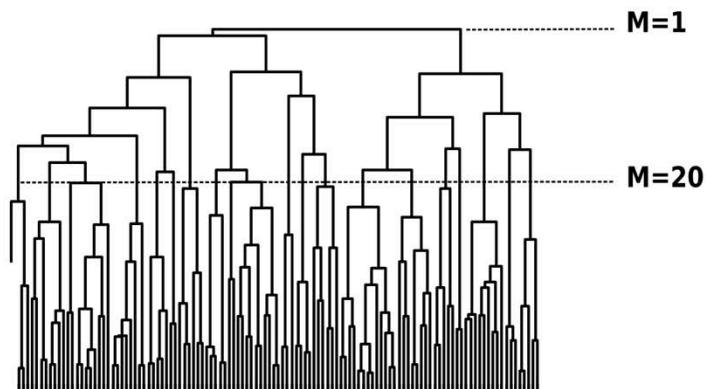
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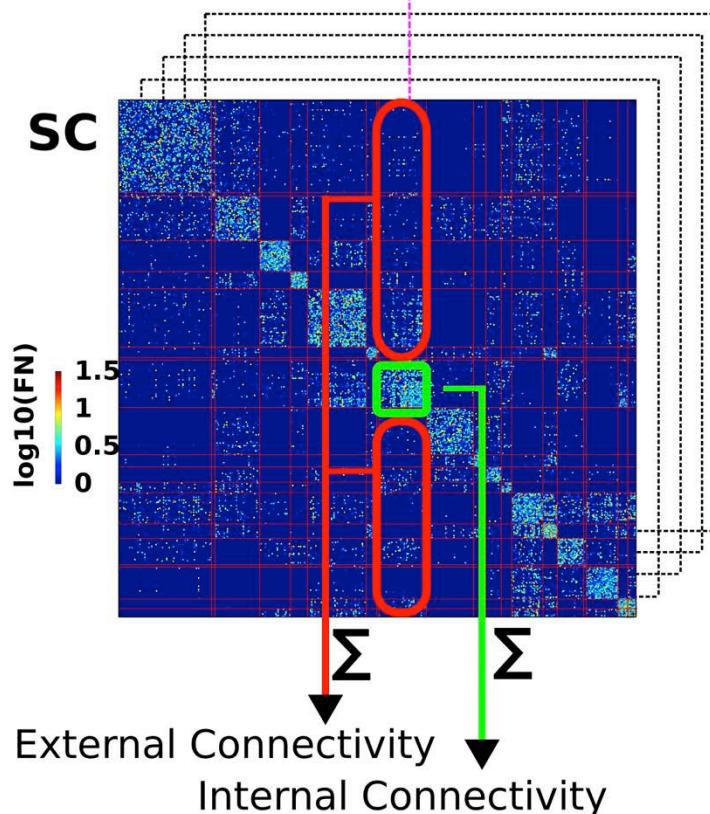
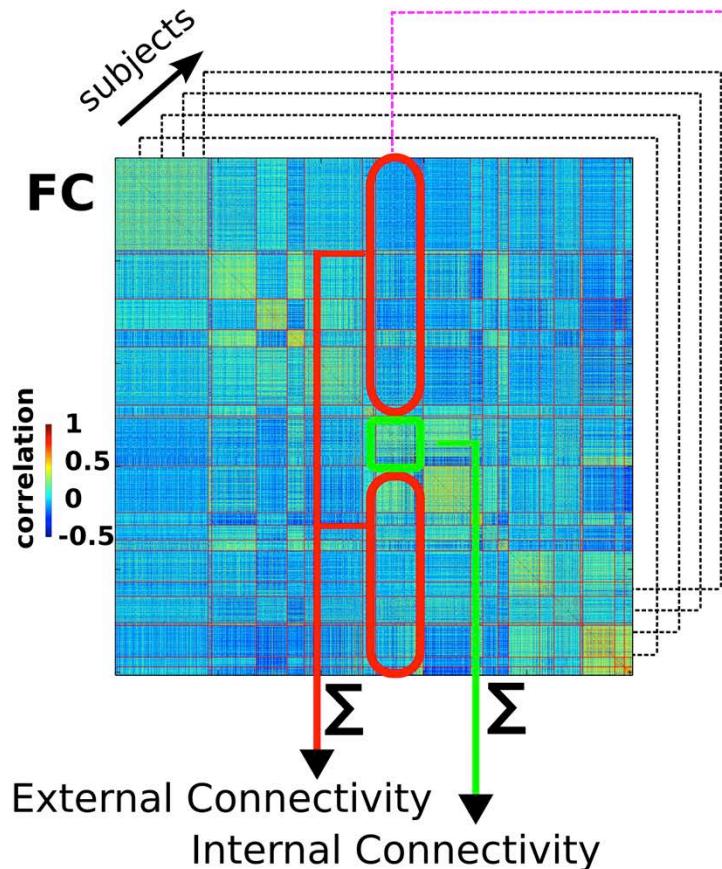
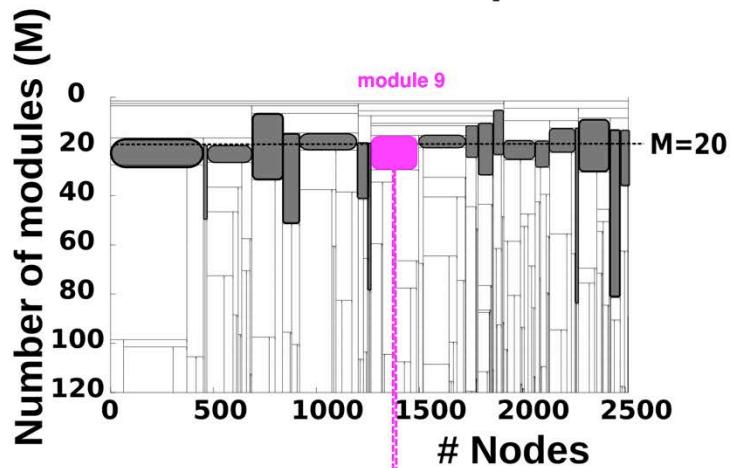
(Yeatman & Mezer, 2014)

# **METHODS (I)**

**Brain Hierarchical Atlas**  
[www.nitrc.org/projects/biocr\\_hcatlas](http://www.nitrc.org/projects/biocr_hcatlas)



**Multi-Scale brain partition**



## METHODS (II)

N=155 subjects

Age ranging between 10 and 80 years (mean = 44, SD = 22)

Triple acquisitions 3T MRI (T1, 64 directions DTI and rs-fMRI)

$4 * (1+2+3+\dots+M) = 2 [M * (M+1)]$  different initial features  
(FIC, FEC, SIC, SEC times dendrogram level)

**Correlo-dendrogram** as a bi-variate Feature selection: Values such that the correlation between CHA and FEC\*SEC or FIC\*SIC are significant, i.e.,  $p_E = \sqrt{p_{FEC} * p_{SEC}}$  ,  $p_I = \sqrt{p_{FIC} * p_{SIC}}$  , which define a structure-function connectivity feature.

**Bonferroni correction** : For each new dendrogram level M, only two modules are new with respect to the M-1 level, eg. starting at M=20 and finishing at M=1000 ,  
 $p$  threshold =  $0.05 / [20 + (1000-20)* 2]$

## METHODS (III)

$$t_n = \omega_0 + \sum_{j=1}^{K-1} \omega_j x_j^n + \epsilon_n$$

Estimated age for participant n,  $x_j$  structure-function connectivity feature

$$E(\omega) = \frac{1}{2} \sum_{n=1}^P \left\{ t_n - \omega_0 - \sum_{j=1}^{K-1} \omega_j x_j^n \right\}^2$$

Error for P different subjects

$$\omega^{MLE} = (\varphi^T \varphi)^{-1} \varphi^T t$$

with design matrix defined as

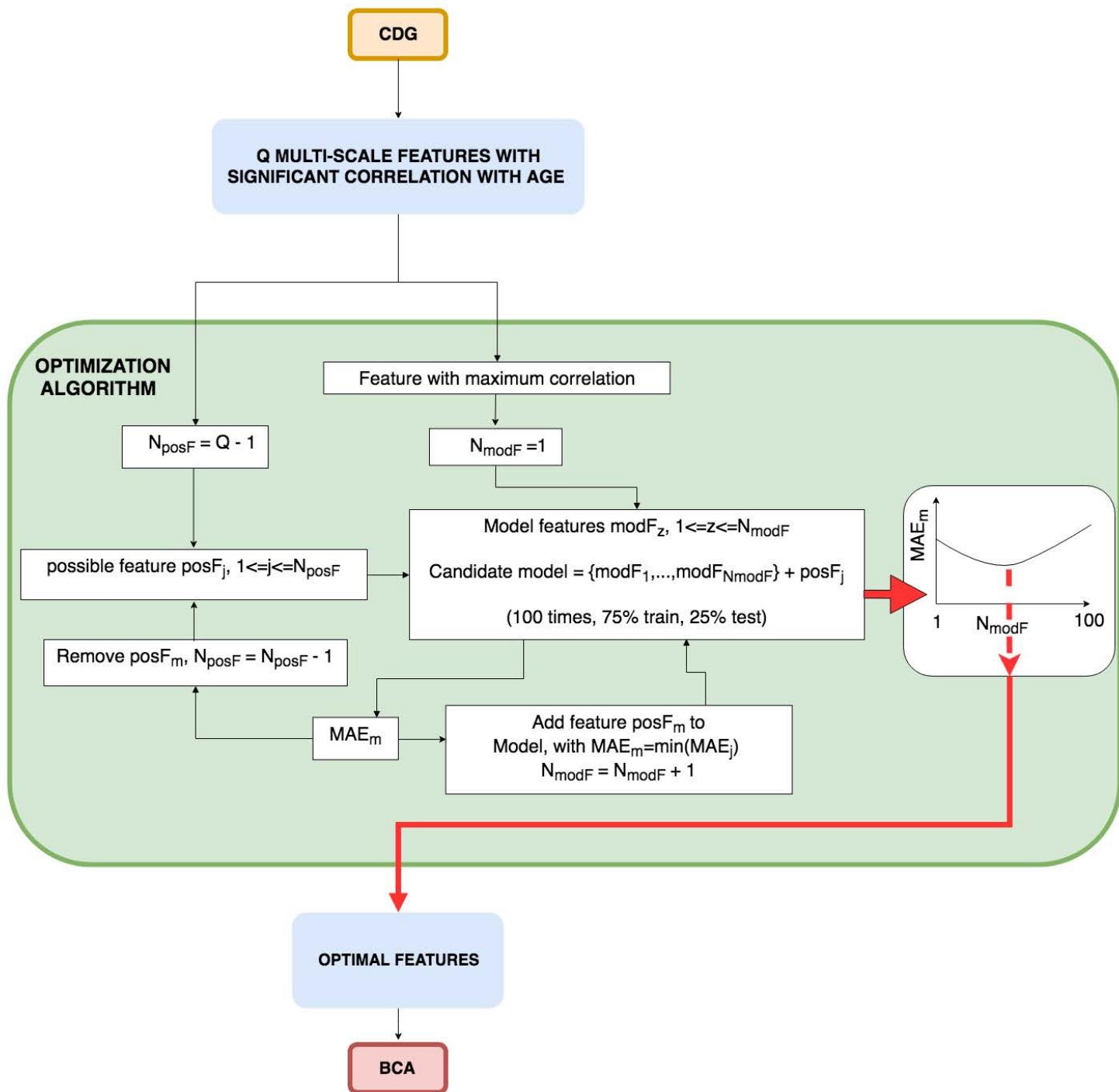
$$\varphi \equiv \begin{pmatrix} 1 & x_1^1 x_2^1 \cdots x_{K-1}^1 \\ 1 & x_1^2 x_2^2 \cdots x_{K-1}^2 \\ \vdots & \vdots \\ 1 & x_1^P x_2^P \cdots x_{K-1}^P \end{pmatrix}$$

$$MAE(K) = \frac{1}{N_2} \sum_{n=1}^{N_2} |ChA_n - BCA_n(K)|$$

with  $N_1 = 115$  (75%) for training and  $N_2=38$  (25%) for testing

$$BCA_n(K) \equiv \omega_0^{MLE} + \sum_{j=1}^{K-1} \omega_j^{MLE} x_j^n$$

Brain connectome age depends on K



# **RESULTS**

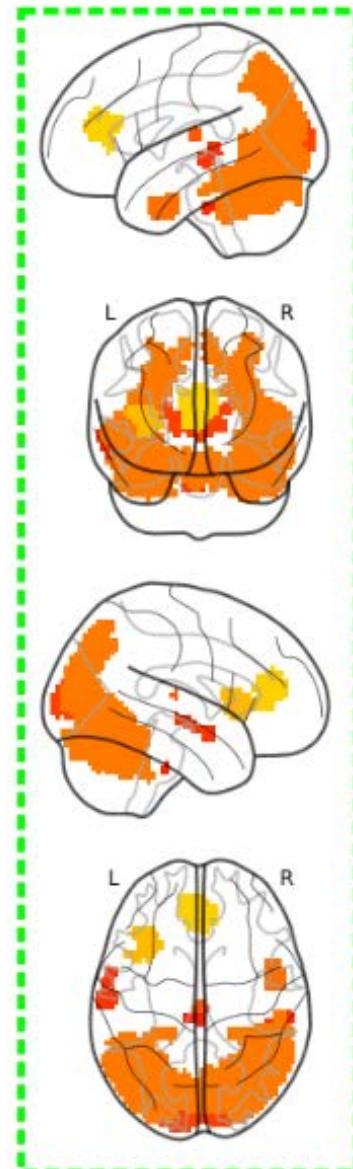
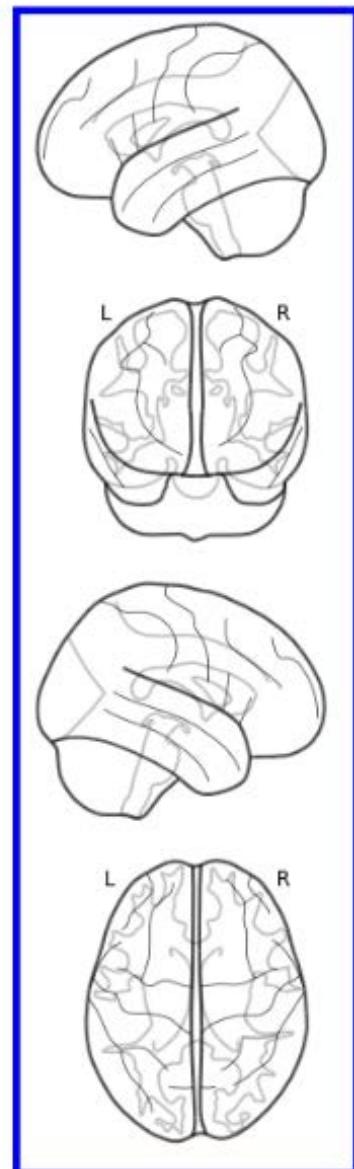
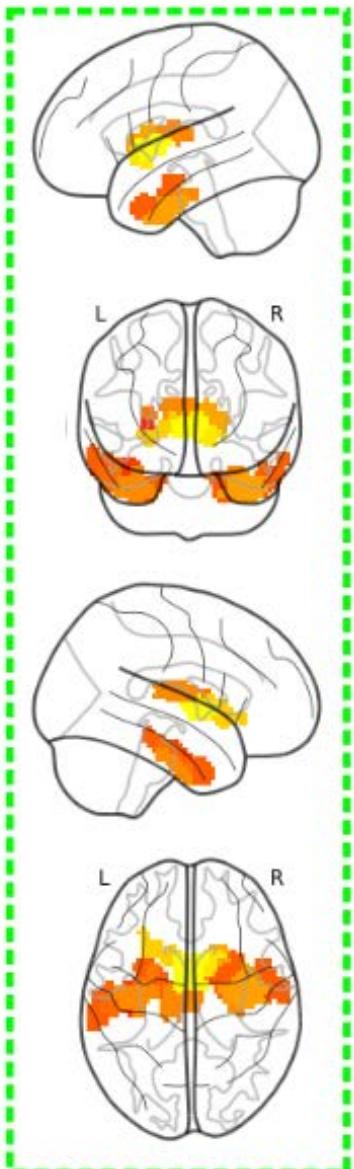
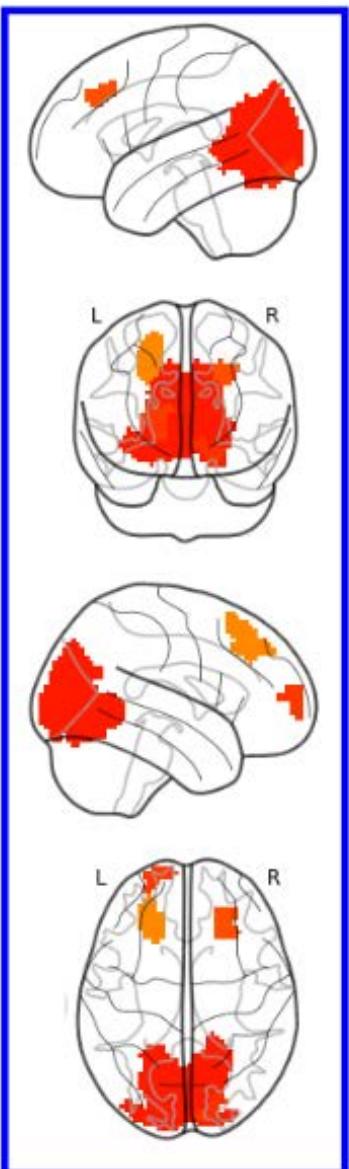
# External connectivity

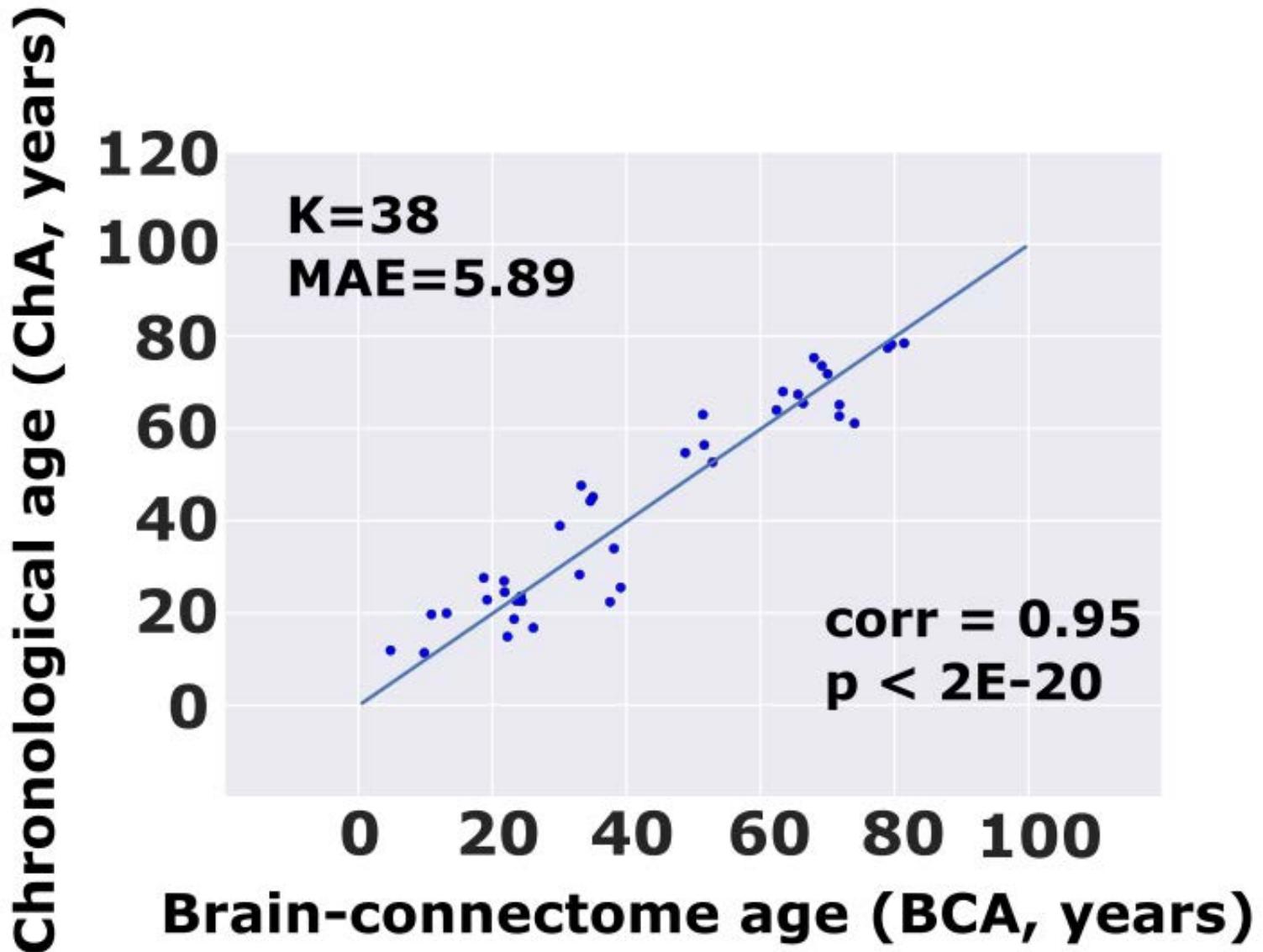
# Internal connectivity



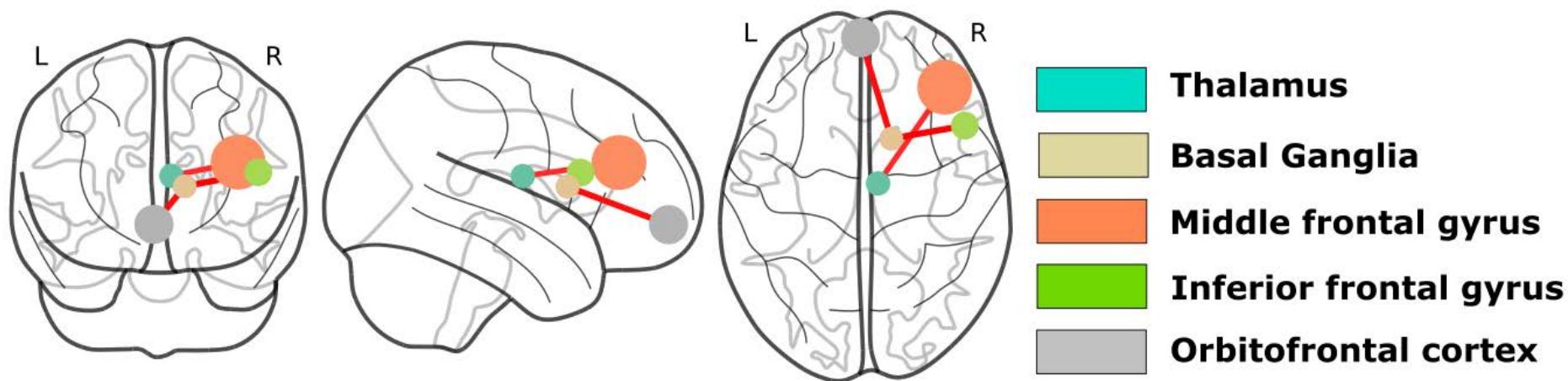
**SC ↓**  
**FC ↑**

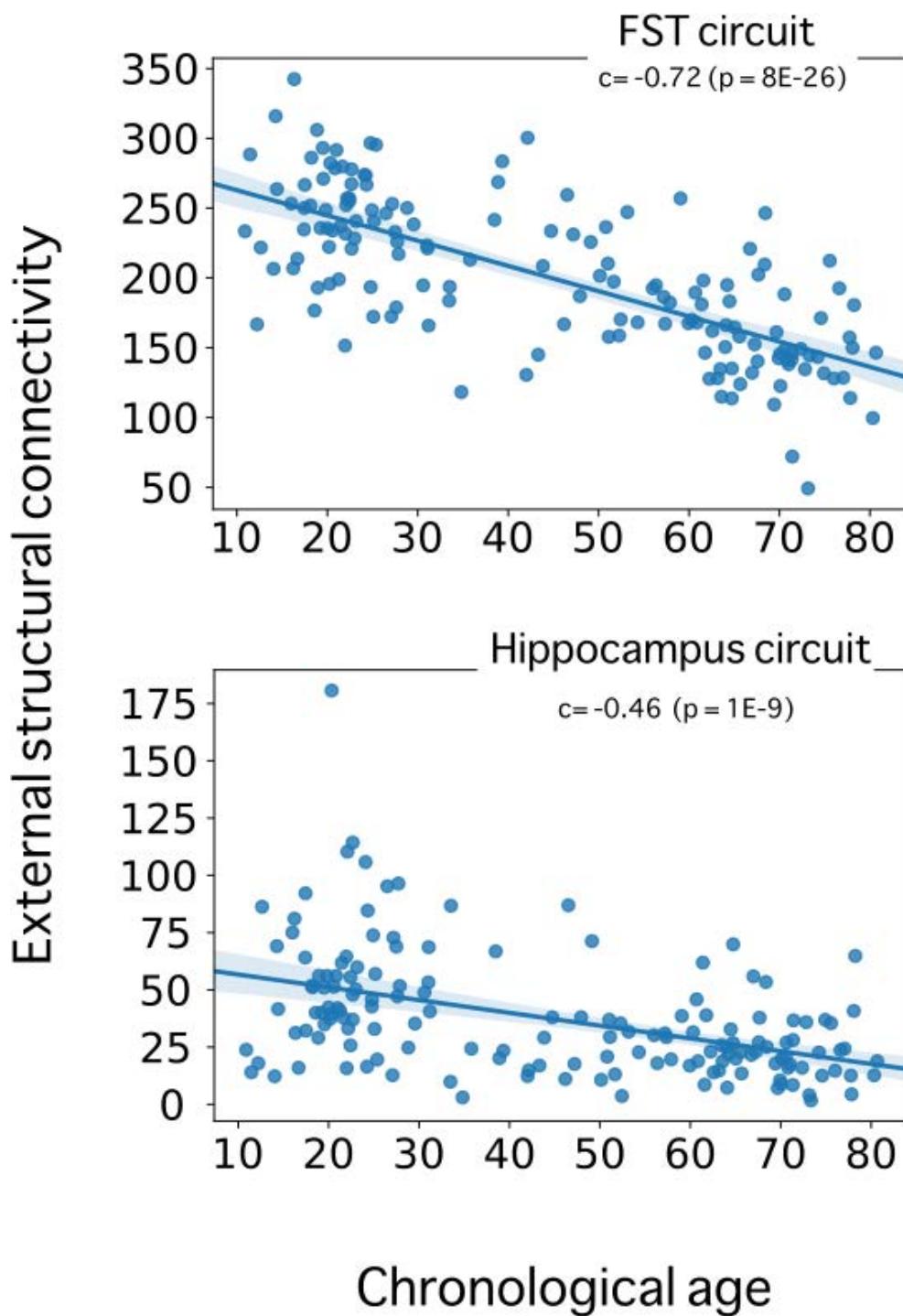
**SC ↓**  
**FC ↓**





# The connectivity descriptors predicting aging the most: The fronto-striato-thalamic (FST) circuit





## **DISCUSSION**

BCA, ie., a multi-scale structure-function estimation of CHA, can work as good as other brain age estimators using morphological descriptors

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Our approach based on BCA reveals that the circuit participating the most in age prediction is FST, in contrast to previous literature majorly reporting the role of the hippocampus circuit. Therefore, we suggest that when studying healthy aging, FST should be taken in consideration; When studying pathological aging, hippocampus circuit has been shown the gold standard in both human and animal studies

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The FST mediates motor skills, cognitive control and executive function, but also regulates dopamine (reward, motivation) and serotonin (mood, emotion) release

The discrepancy between the CHA and BCA might work as a biomarker for quantifying deterioration as a result of disease or improvement after some treatment or therapy, which has unlimited applications

## FUTURE WORK:

The effect of physical activity in brain age

