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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

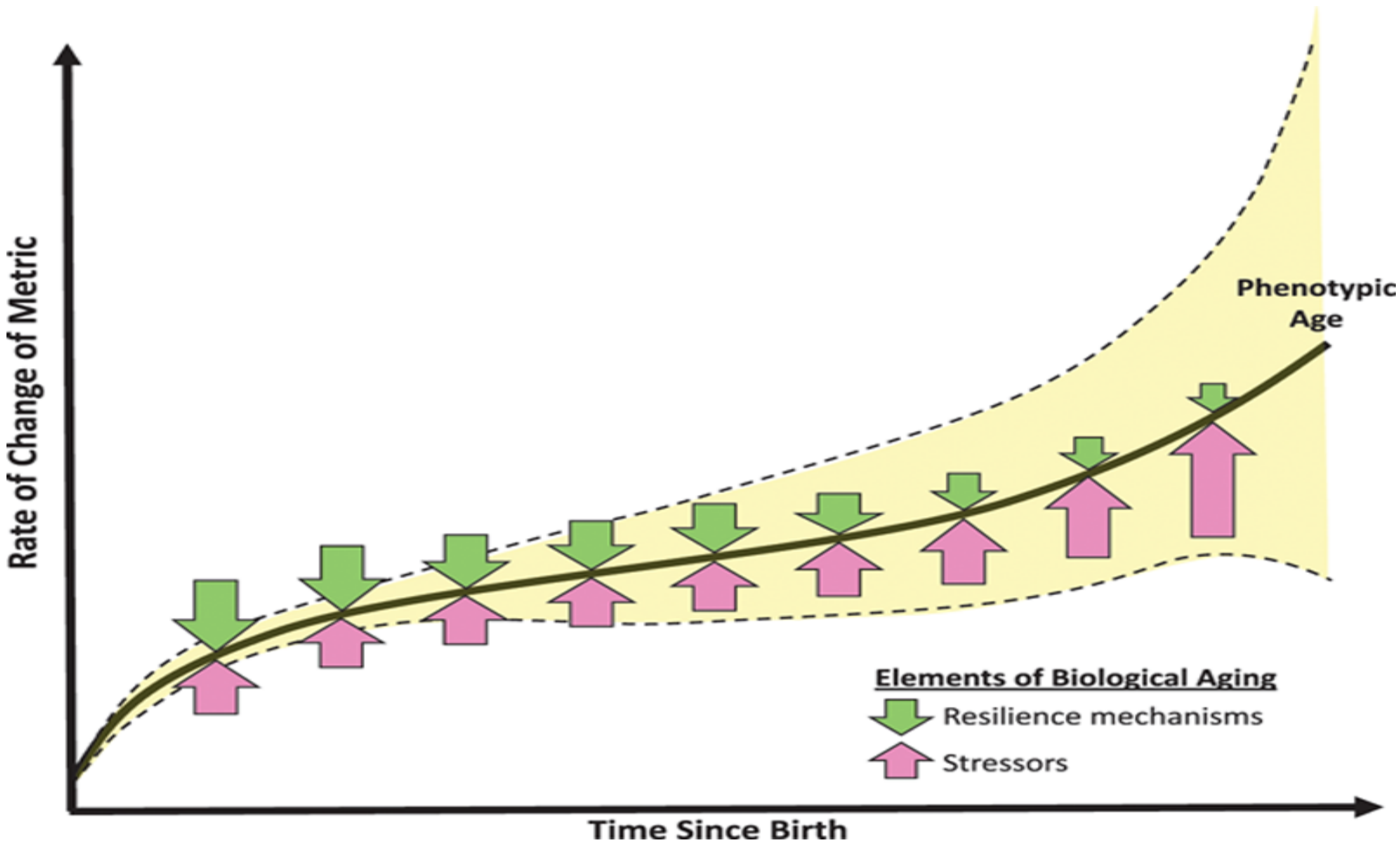
Phenotypic Aging (phenotypes that change)

- Body Composition
- Energetics
- Homeostatic Mechanisms
- Brain health

Biological Aging (root mechanisms)

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

Time and the Metrics of Aging, Volume: 123, Issue: 7, Pages: 740-744, DOI: (10.1161/CIRCRESAHA.118.312816)



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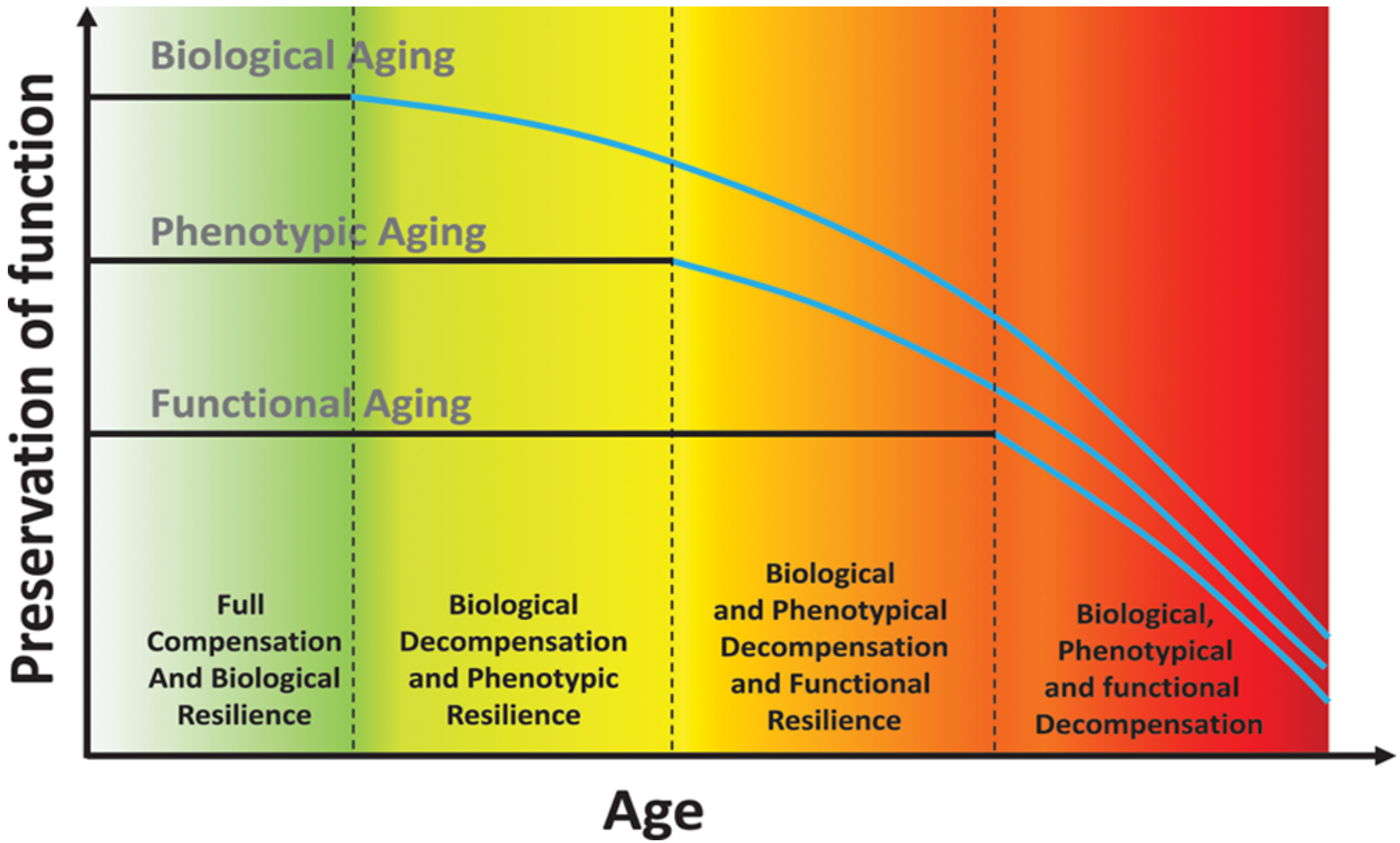

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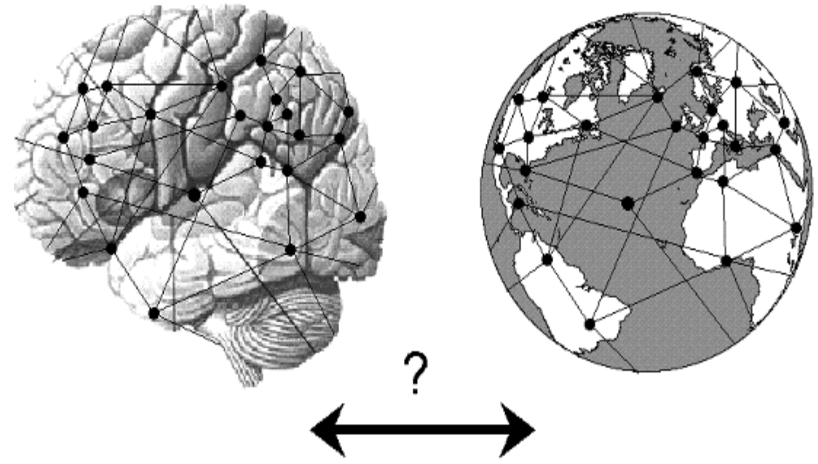
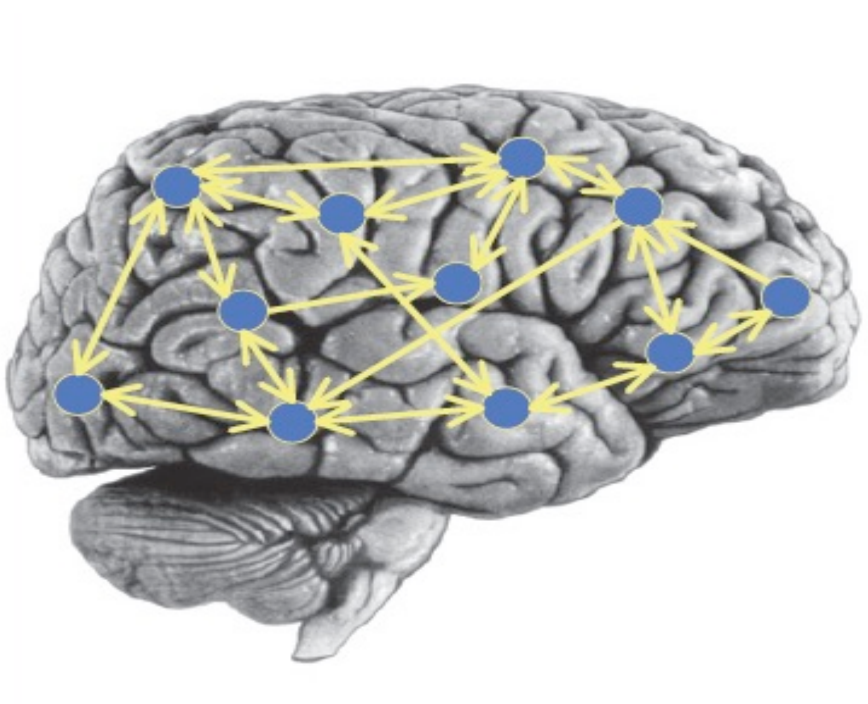
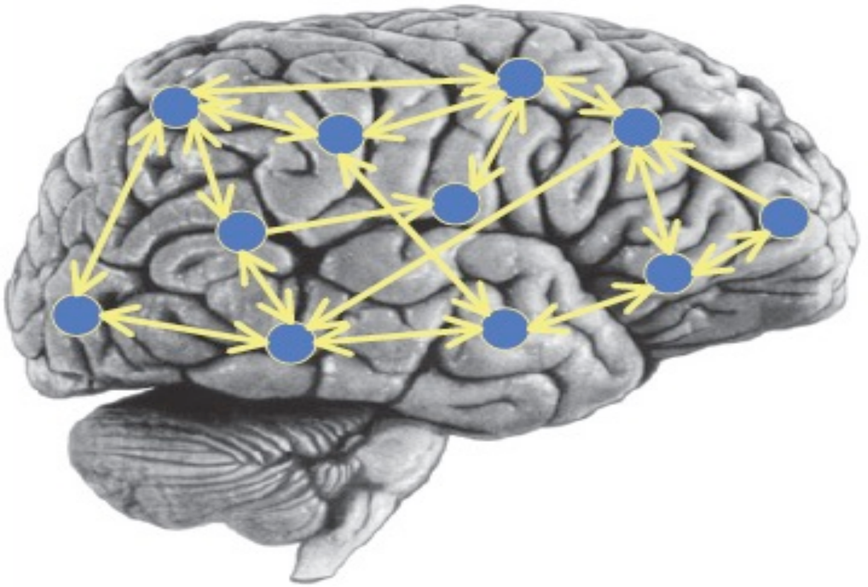
TWO CLASSES OF BRAIN NETWORKS



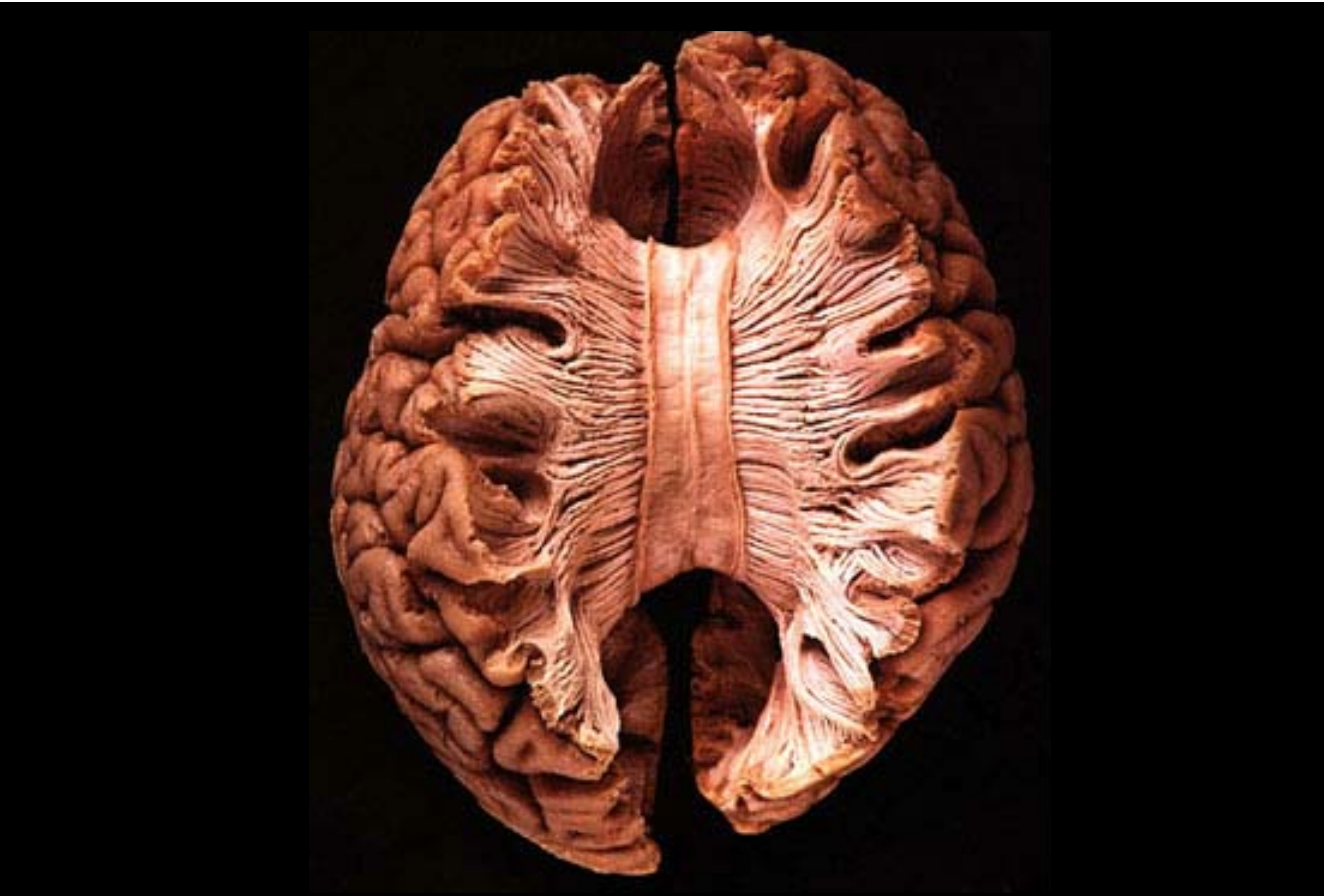


TWO CLASSES OF BRAIN NETWORKS

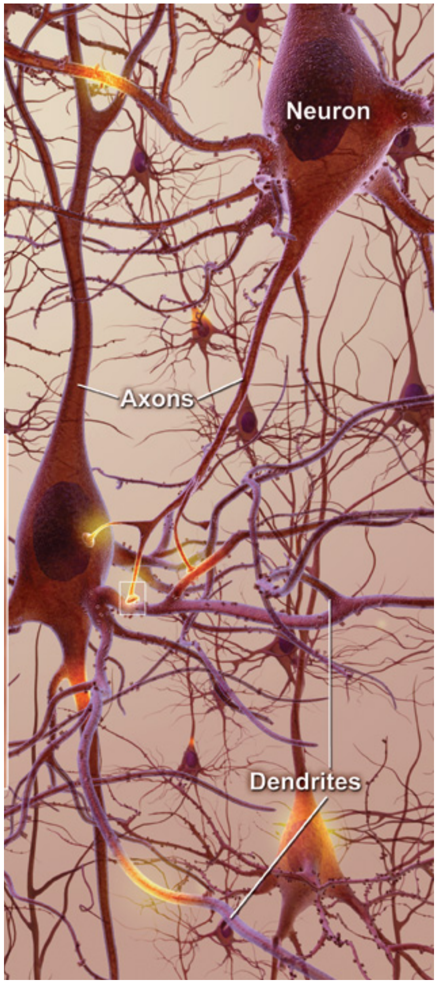


- ✓ Structural (anatomical) connectivity
- ✓ Functional connectivity
- ✓ Effective connectivity

STRUCTURAL CONNECTIVITY



STRUCTURAL CONNECTIVITY

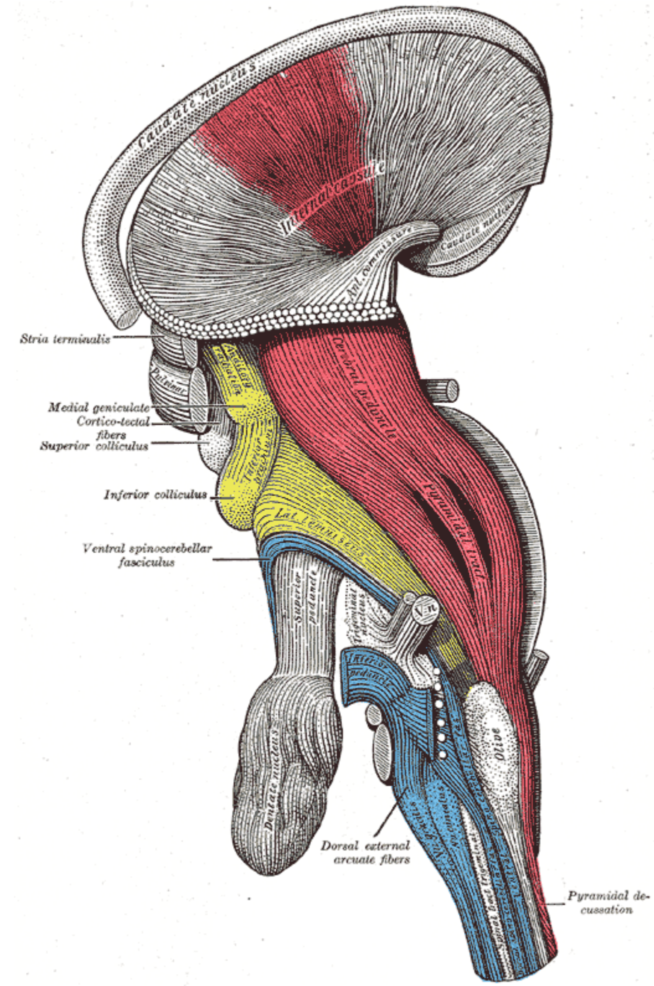


From the National Institute on Aging

Axons measure ~µm in width

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

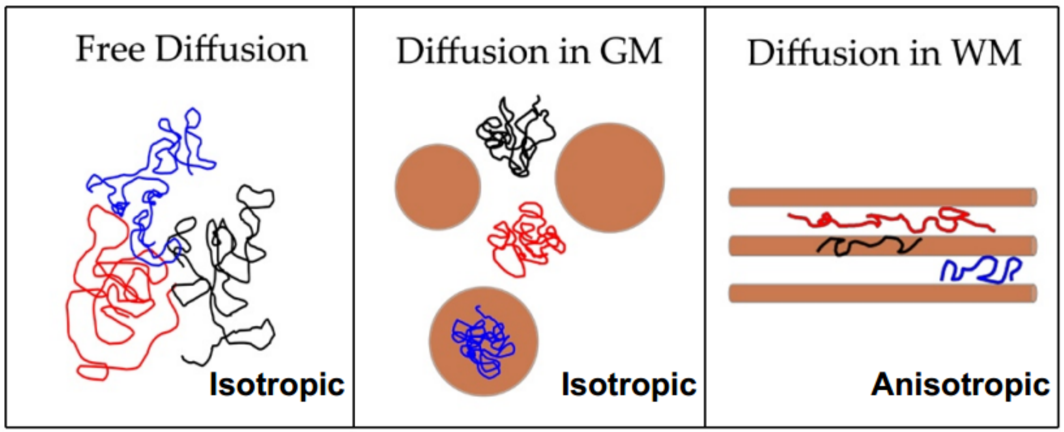
We cannot image individual axons but we can image bundles with diffusion MRI

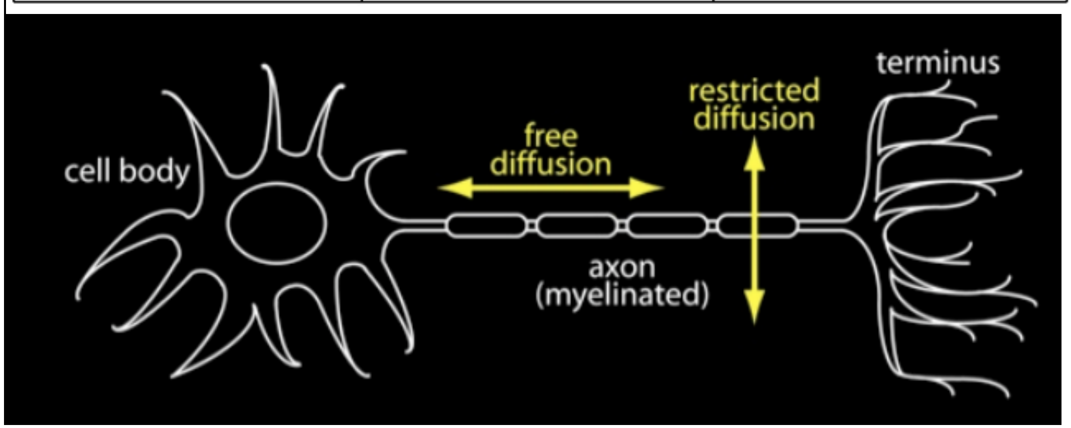


From *Gray's Anatomy: IX. Neurology*

STRUCTURAL CONNECTIVITY

Water diffuses differently across different brain tissues





$$< x^2 > = 2nDt$$

mean squared displacement

time

Diffusion coefficient

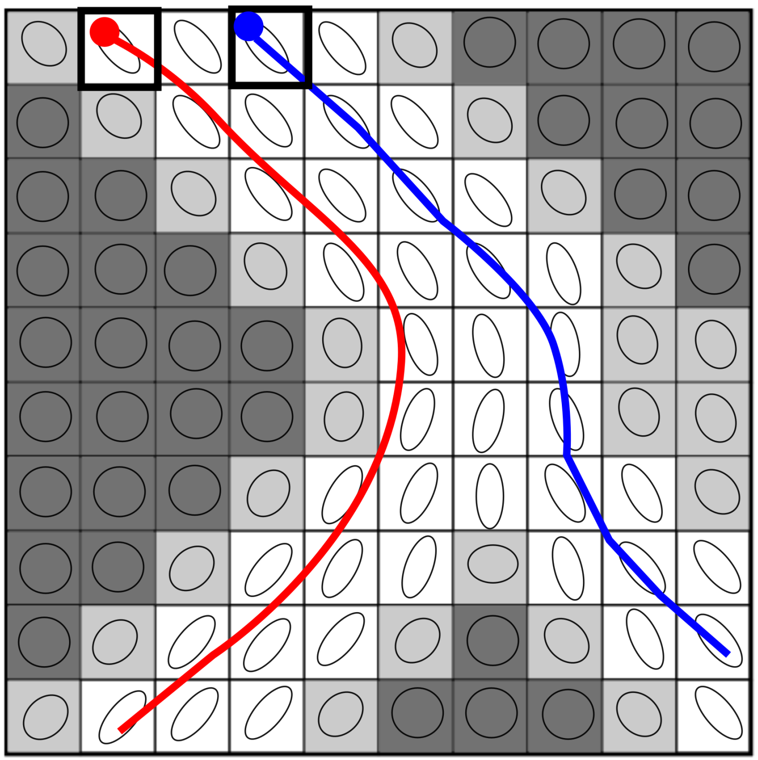
D ~ 2.4 μm²/ms
t~50ms

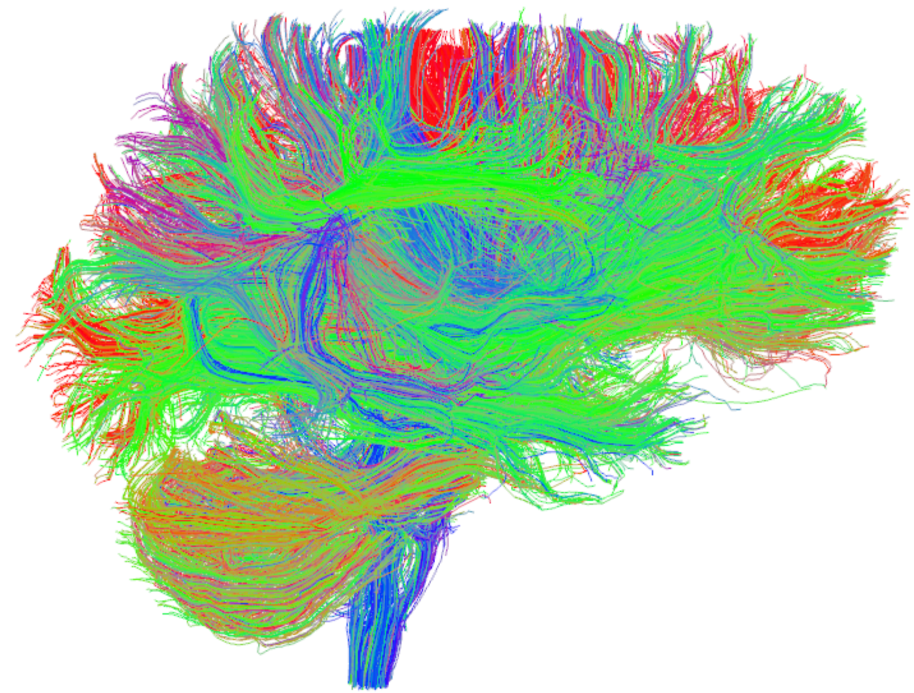
➡ $x=\sqrt{6Dt}$ ~27μm

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

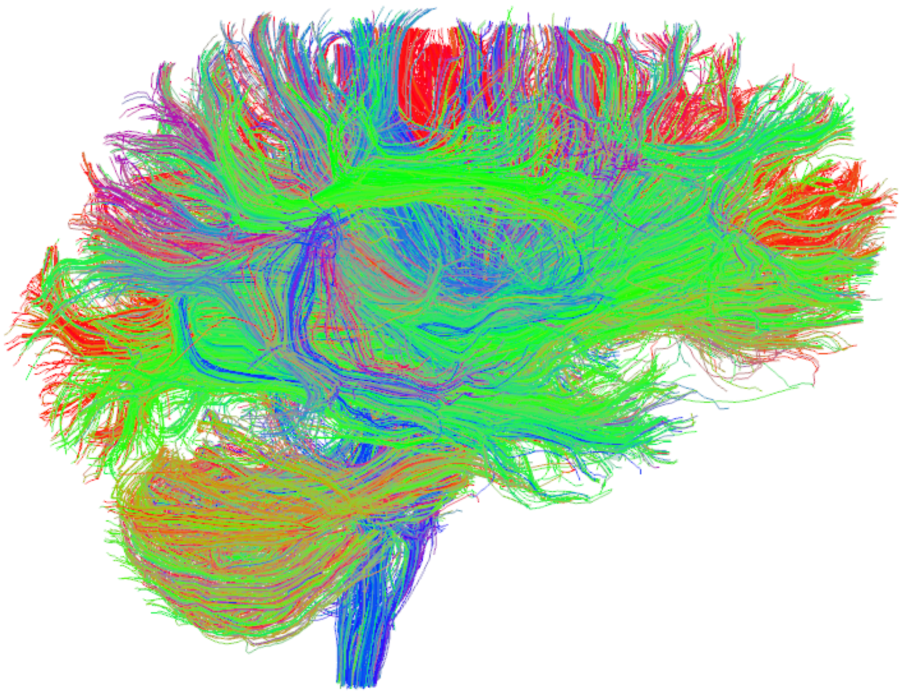
STRUCTURAL CONNECTIVITY

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





STRUCTURAL CONNECTIVITY

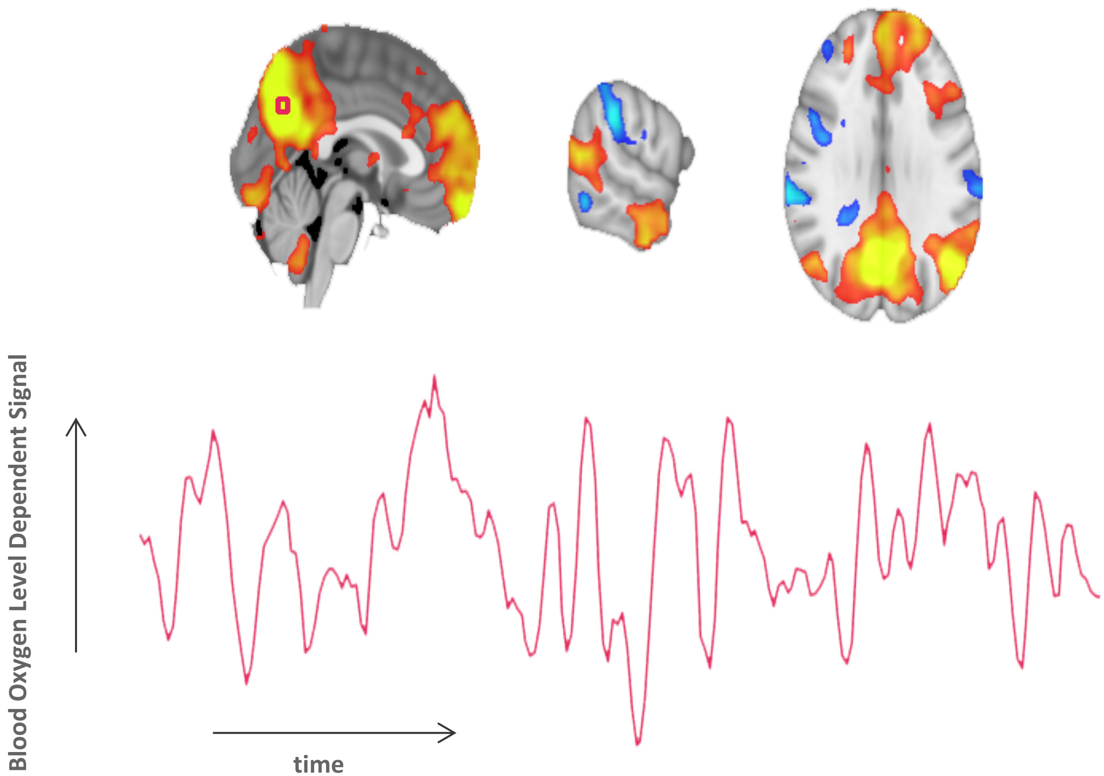


Measures providing SC

- ✓ 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



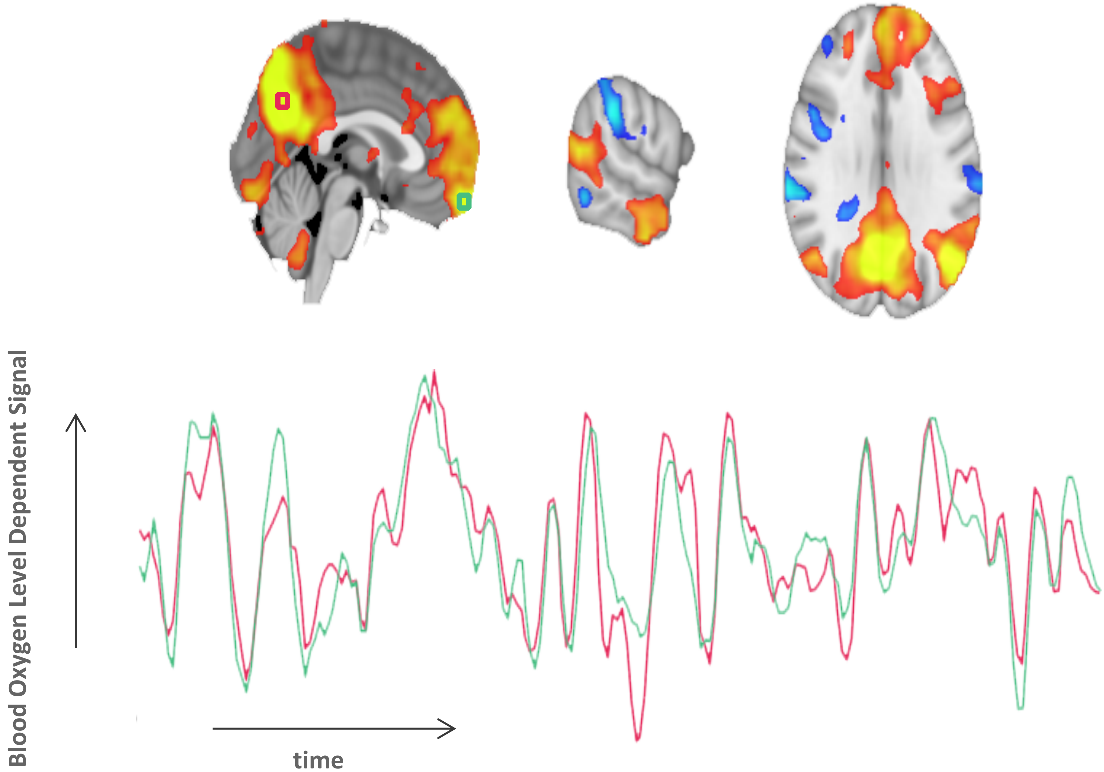
Measures providing FC:

- ✓ 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)



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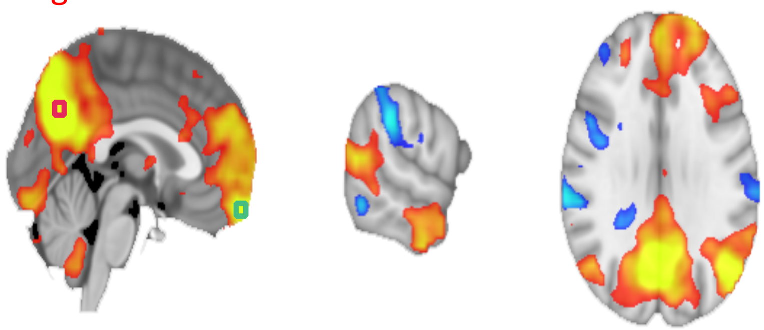
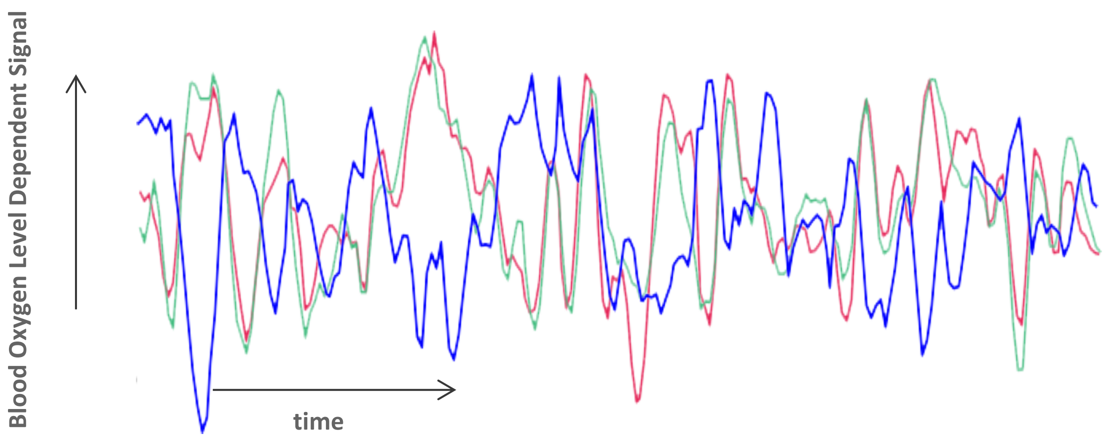
FUNCTIONAL CONNECTIVITY

Similarity between time series of different regions (also distant ones)
Symmetric (in general)
Highly dynamical (unlike SC)
Positive and negative values





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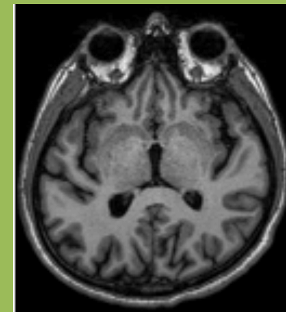
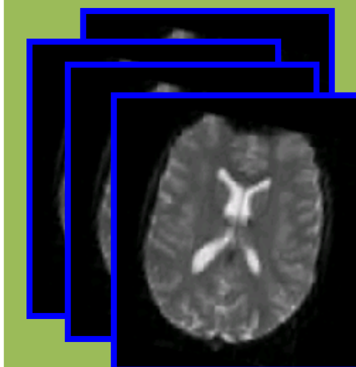
Triple Acquisition



T1 -3D (Anatomical)

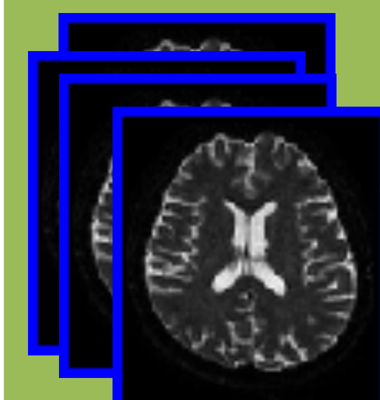
4 min



fMRI Sequence (raw EPI)

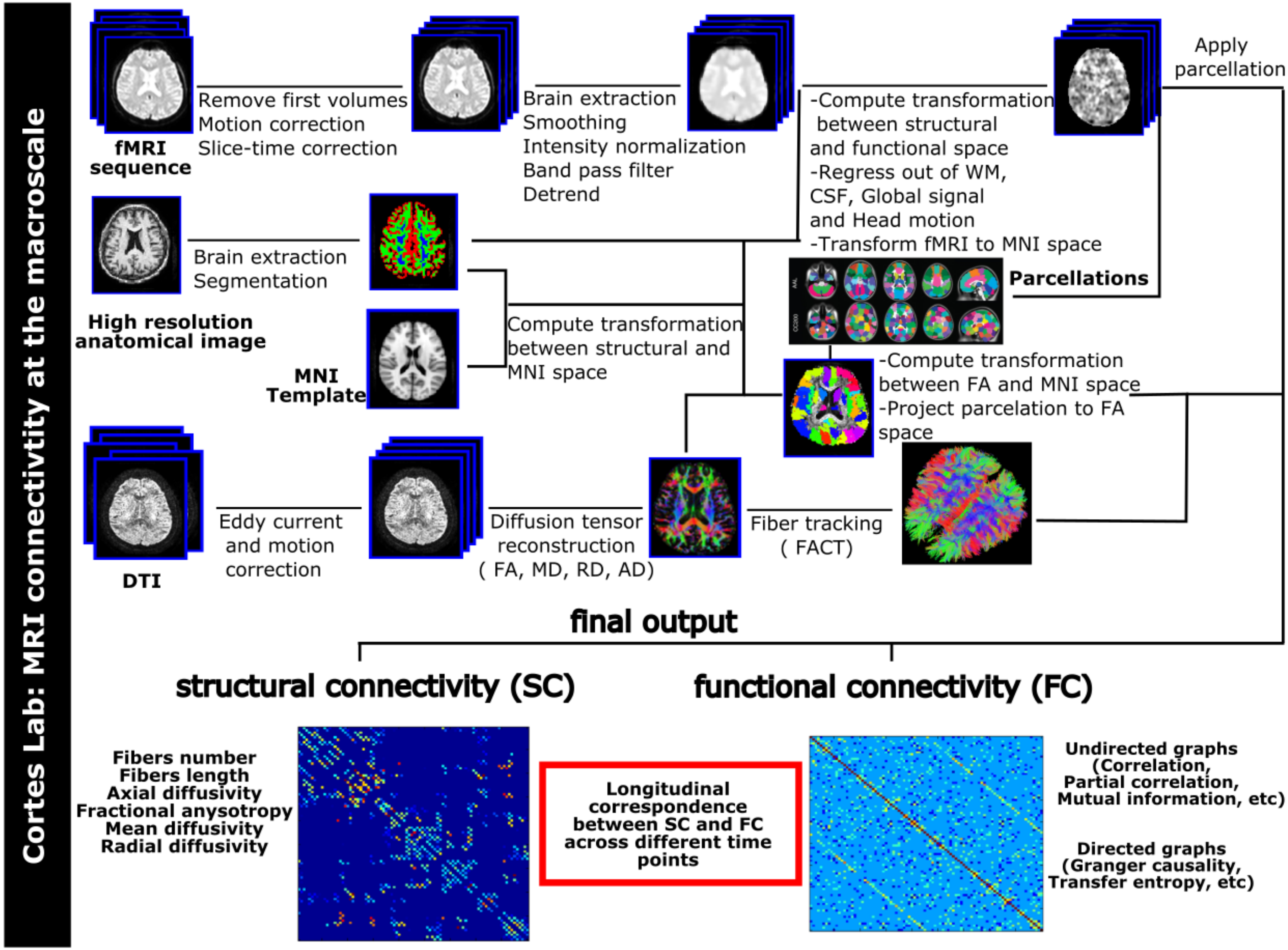
8 min

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



DTI Sequence (raw EPI)

18 min (32 gradients)



Cortes Lab: MRI connectivtity at the macroscale
fMRI sequence
Remove first volumes
Motion correction
Slice-time correction
Brain extraction
Smoothing
Intensity normalization
Band pass filter
Detrend
-Compute transformation between structural and functional space
-Regress out of WM, CSF, Global signal and Head motion
-Transform fMRI to MNI space
Apply parcellation
High resolution anatomical image
Brain extraction
Segmentation
MNI Template
Compute transformation between structural and MNI space
Parcellations
-Compute transformation between FA and MNI space
-Project parcelation to FA space
DTI
Eddy current and motion correction
Diffusion tensor reconstruction (FA, MD, RD, AD)
Fiber tracking (FACT)
final output
structural connectivity (SC)
functional connectivity (FC)
Fibers number
Fibers length
Axial diffusivity
Fractional anysotropy
Mean diffusivity
Radial diffusivity
Longitudinal correspondence between SC and FC across different time points
Undirected graphs (Correlation, Partial correlation, Mutual information, etc)
Directed graphs (Granger causality, Transfer entropy, etc)

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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[1,*], Paolo Bonifazi[2,*], Iñaki Escudero[1,3], Beatriz Mateos[1,3], Miguel A. Muñoz[4], Sebastiano Stramaglia[1,5,6,†] & Jesus M Cortes[1,6,7]

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).

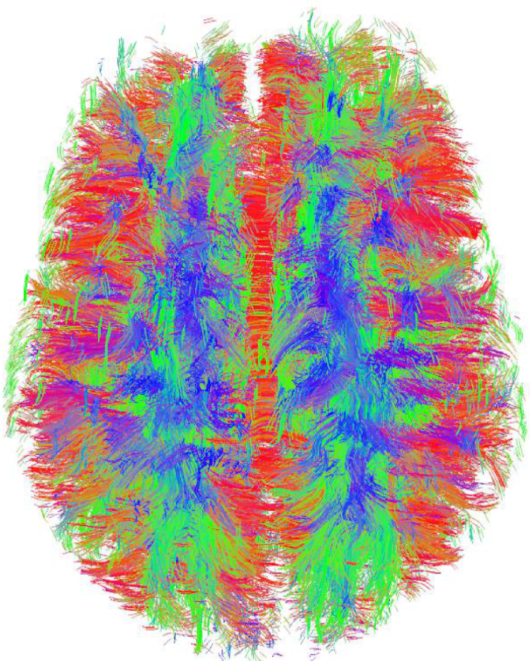
This Project contains the following files:

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

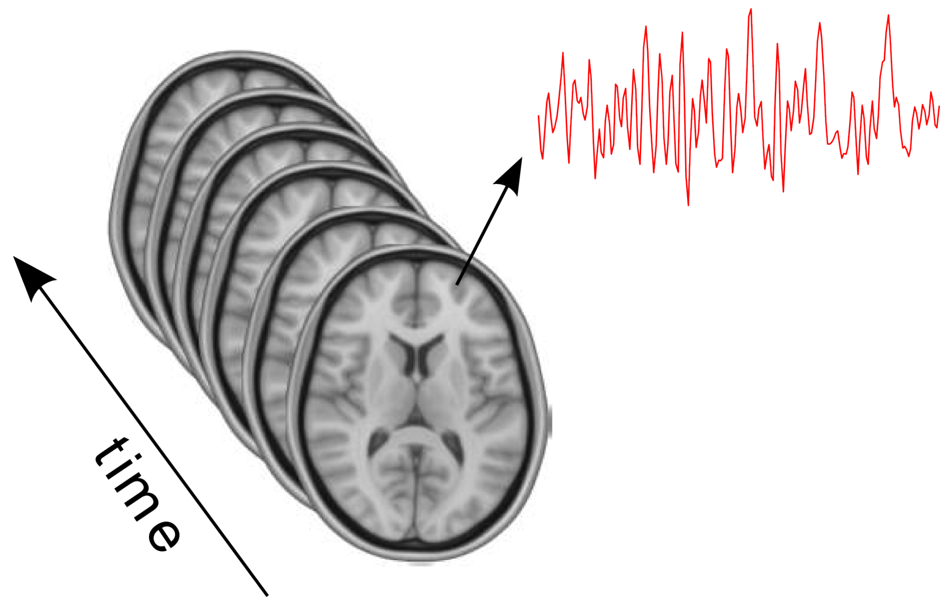
-functional.zip/structural.zip: Zip files containing the functional/structural atlas for all the stages in the hierarchical tree, from M=1 to 2514 ROIs

-test_crosmodularity.m: Code example on how to compute crosmodularity. It needs crossmodularity.m and modularity_index.m

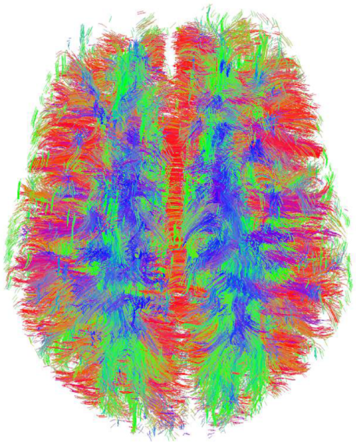
STRUCTURE
DTI (fibers)



FUNCTION
Resting fMRI (time series)



STRUCTURE
DTI (fibers)



FUNCTION
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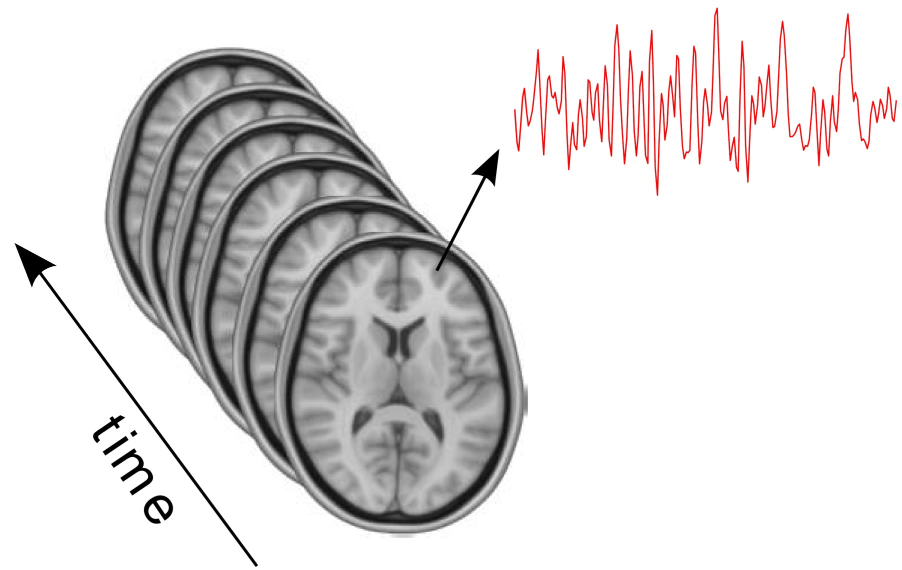


REVIEW SUMMARY

Structural and Functional Brain Networks: From Connections to Cognition

Hae-Jeong Park[1]* and Karl Friston[2]

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

Emergent complex neural dynamics

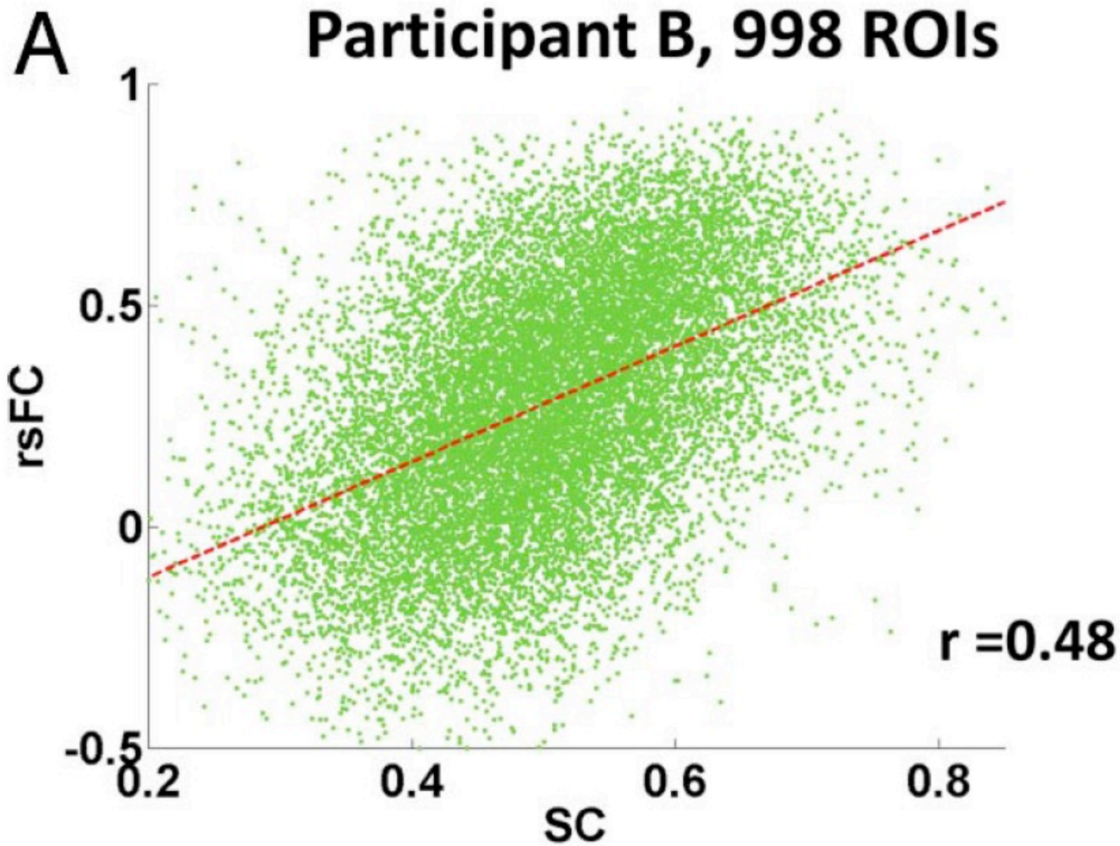
Dante R. Chialvo[1,2]*

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

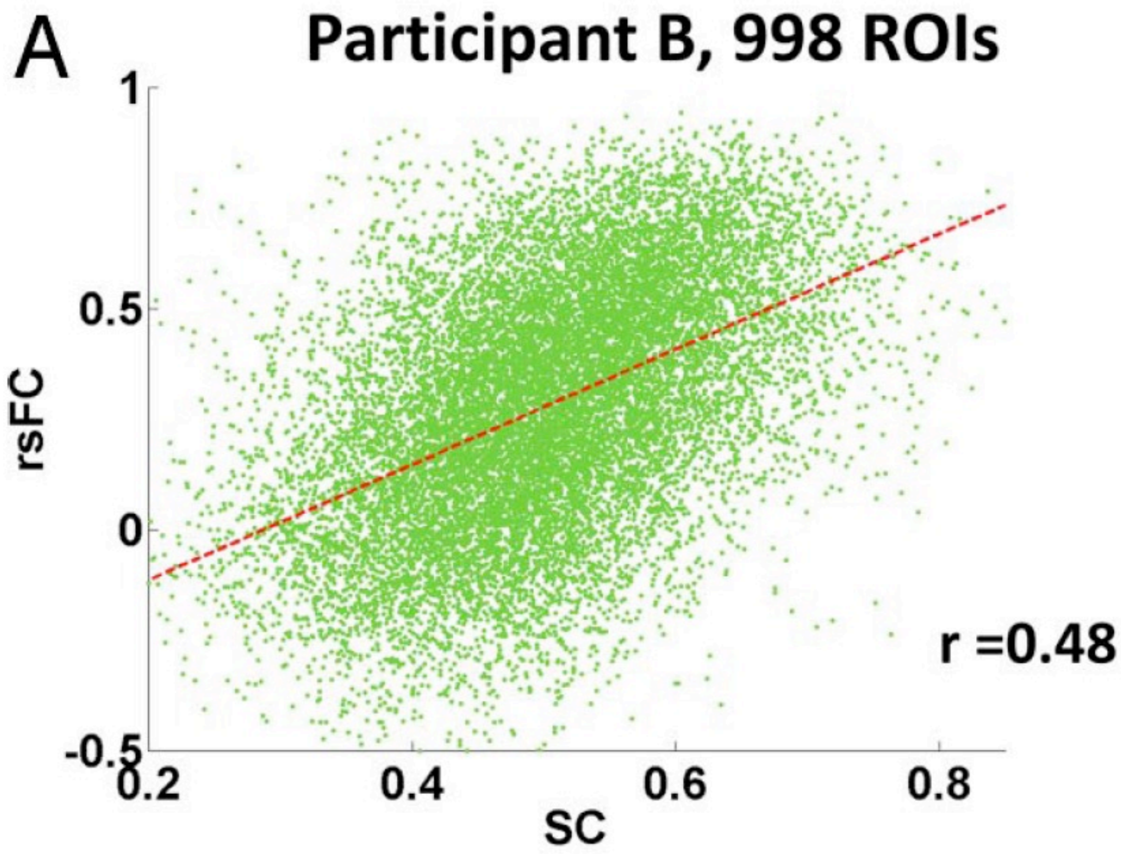
After Gaussianization

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



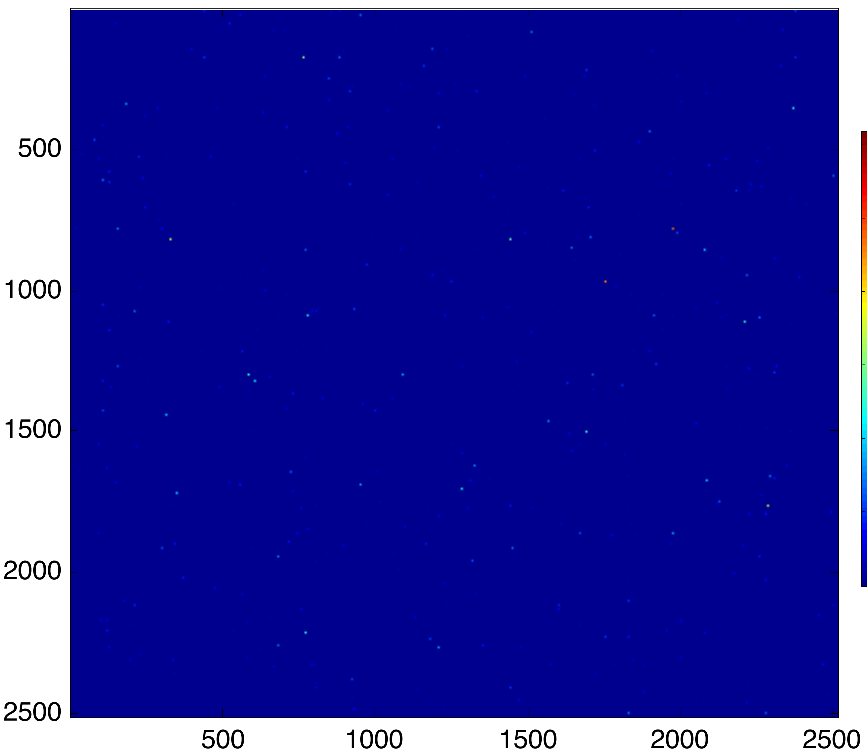
(Honey et al, PNAS, 2009)

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

SUBJECT 1

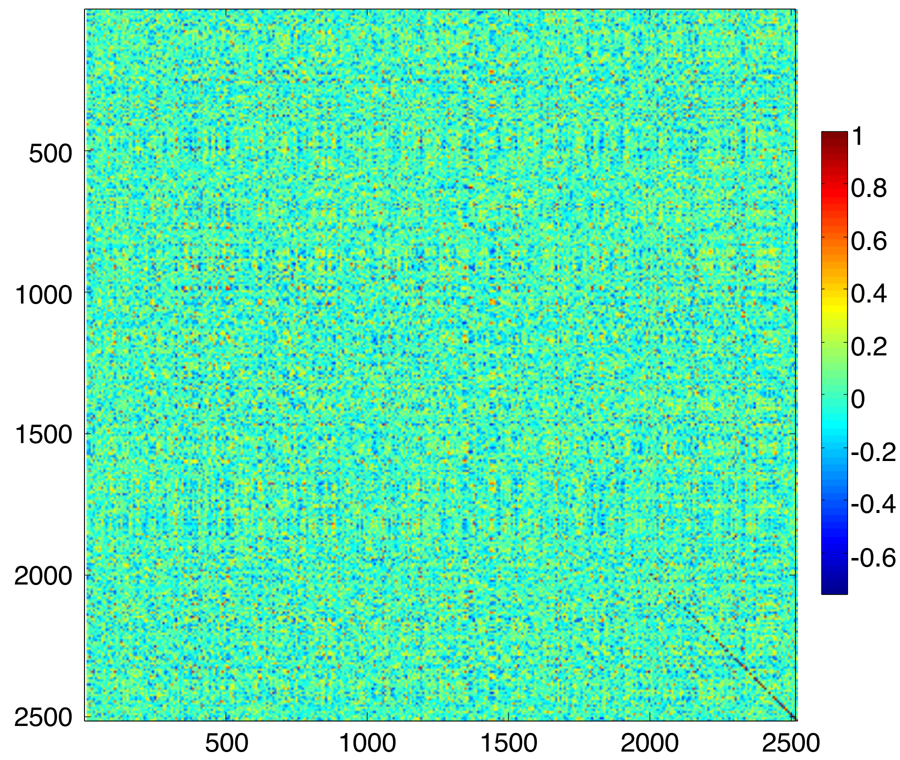
Structural connectivity (SC)

DTI – number of fibers



Functional connectivity (FC)

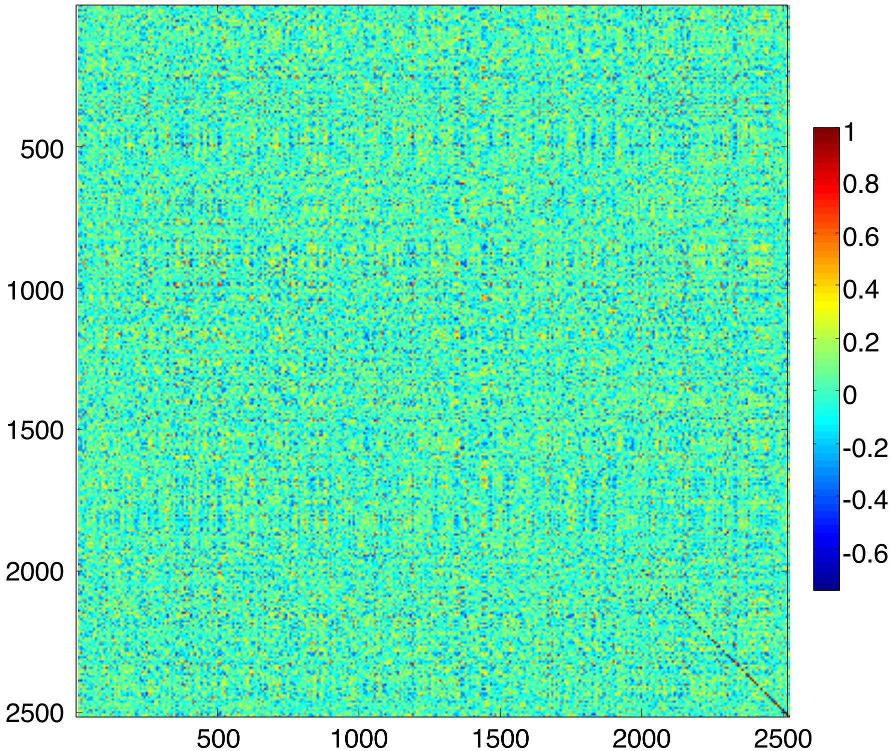
Rs-fMRI – Pearson correlation



SUBJECT 1

Brain modularity: segregation and integration

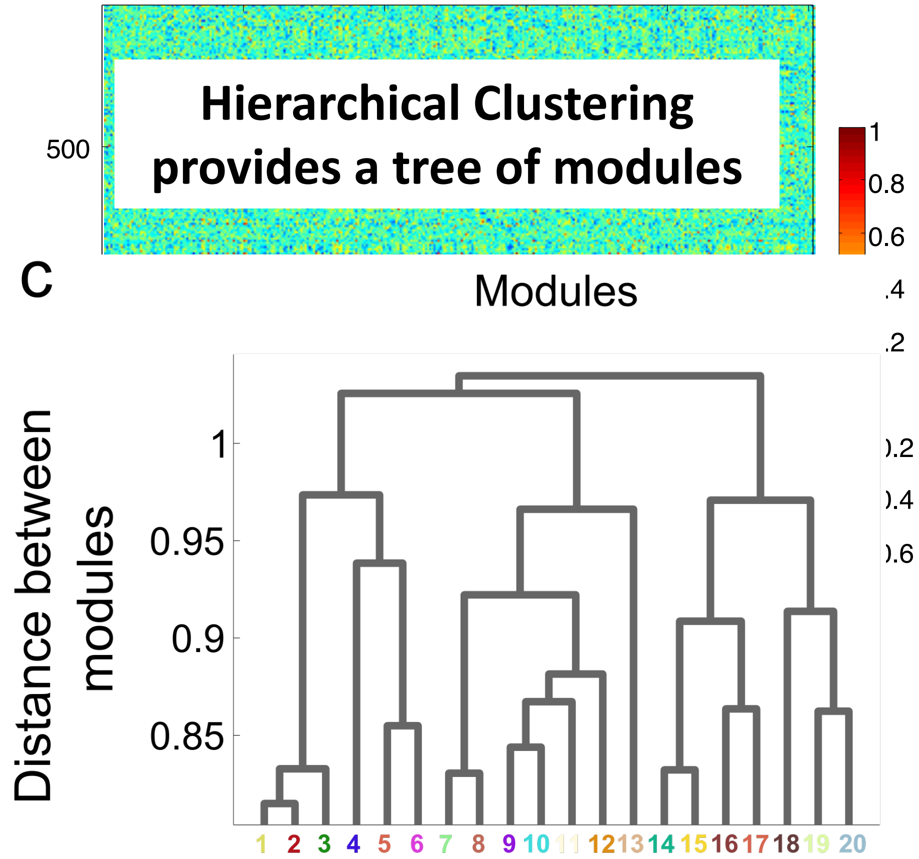
(Tononi, et al., PNAS, 2009)

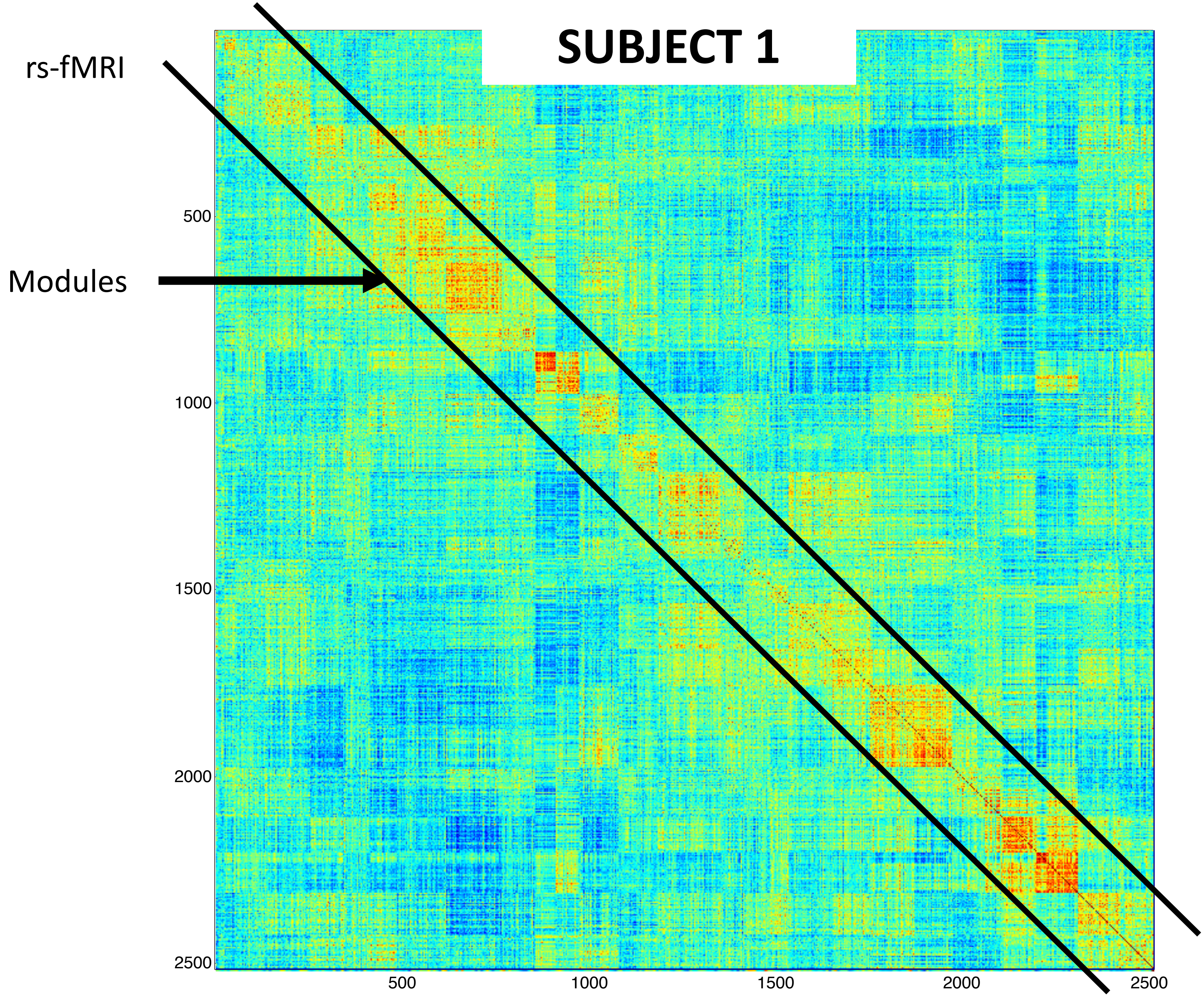


SUBJECT 1

<u>Brain modularity: segregation and integration</u>

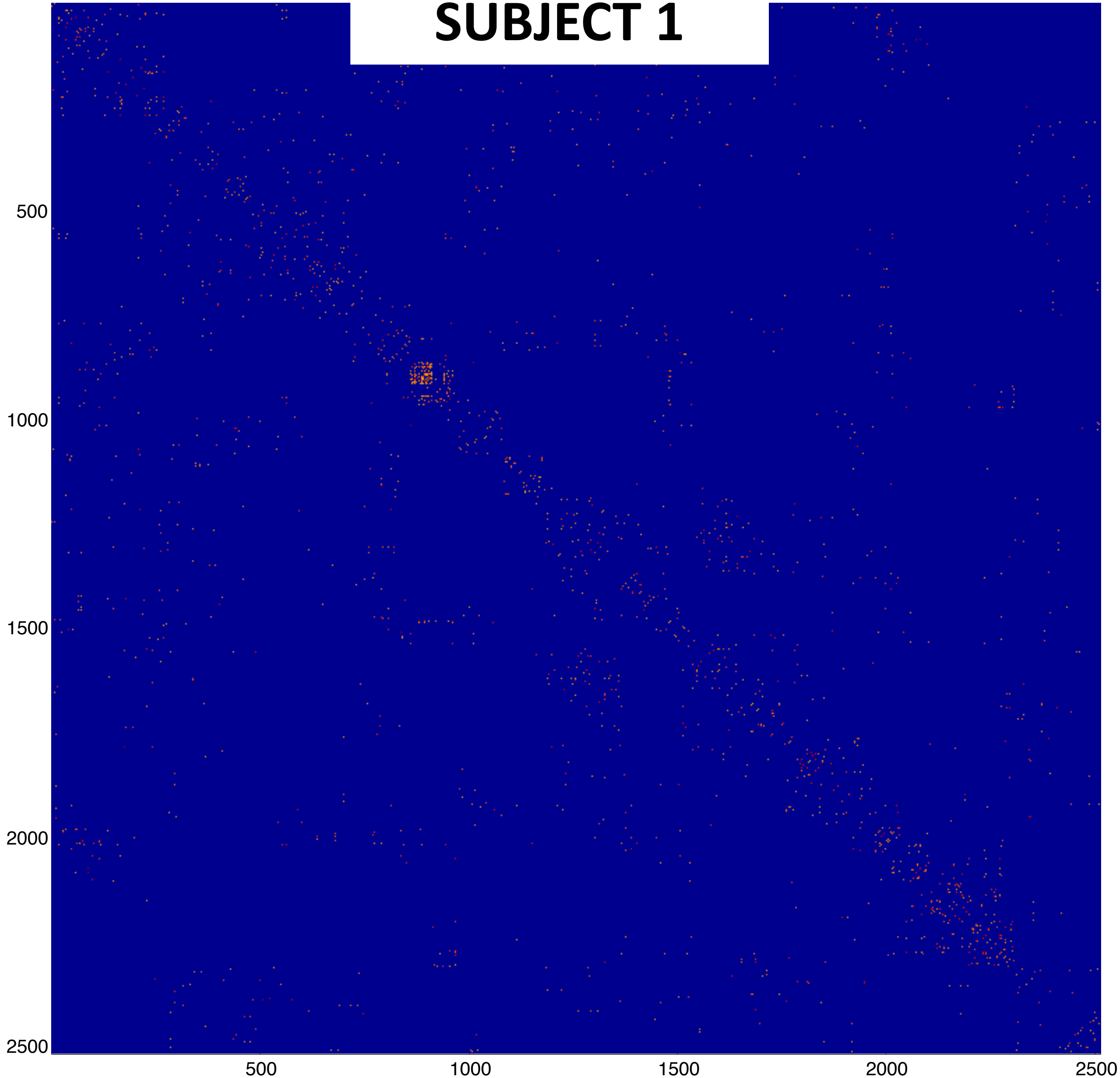
(Tononi, et al., PNAS, 2009)




SUBJECT 1
rs-fMRI
Modules
500
1000
1500
2000
2500
500
1000
1500
2000
2500

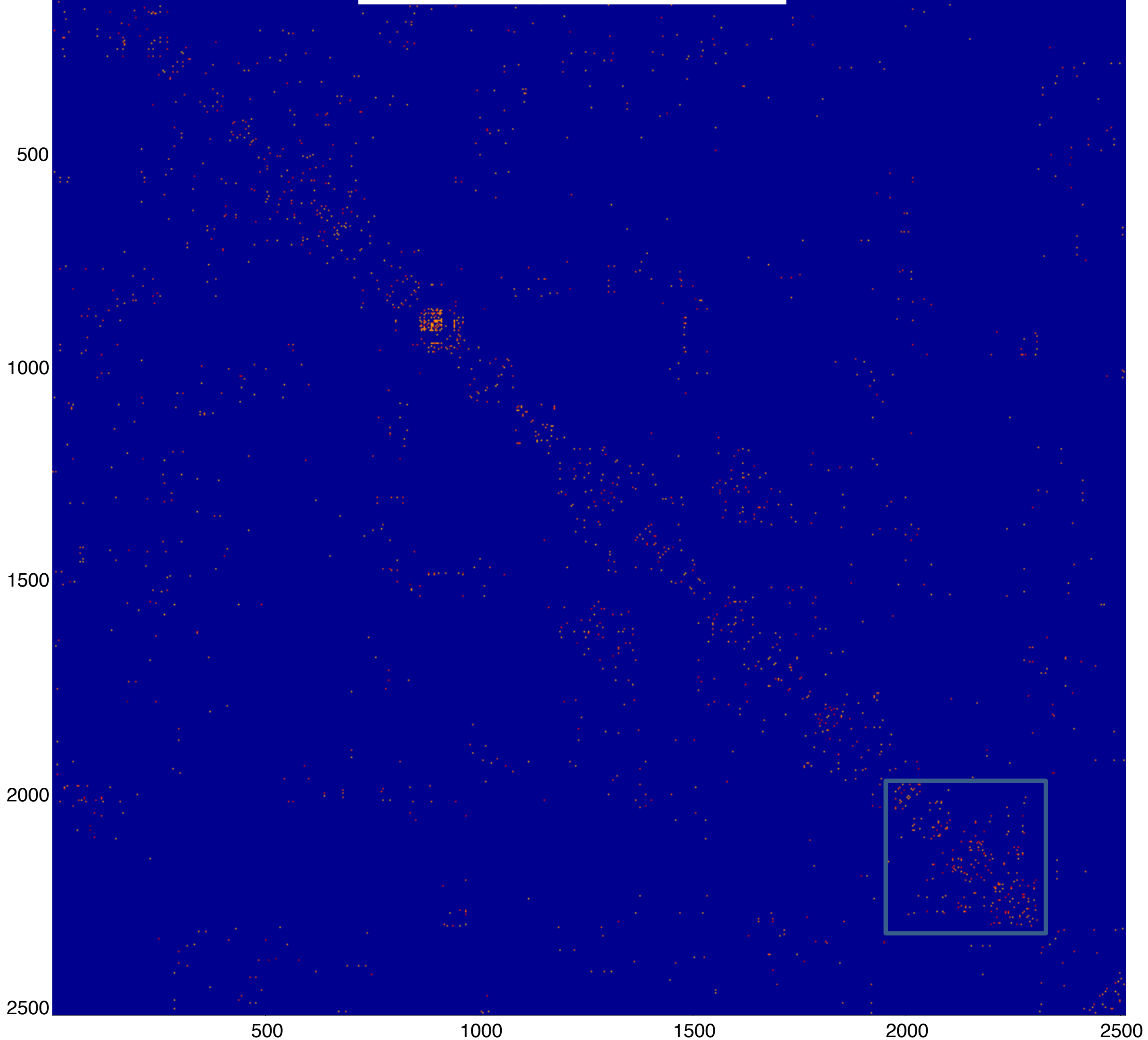
DTI

SUBJECT 1



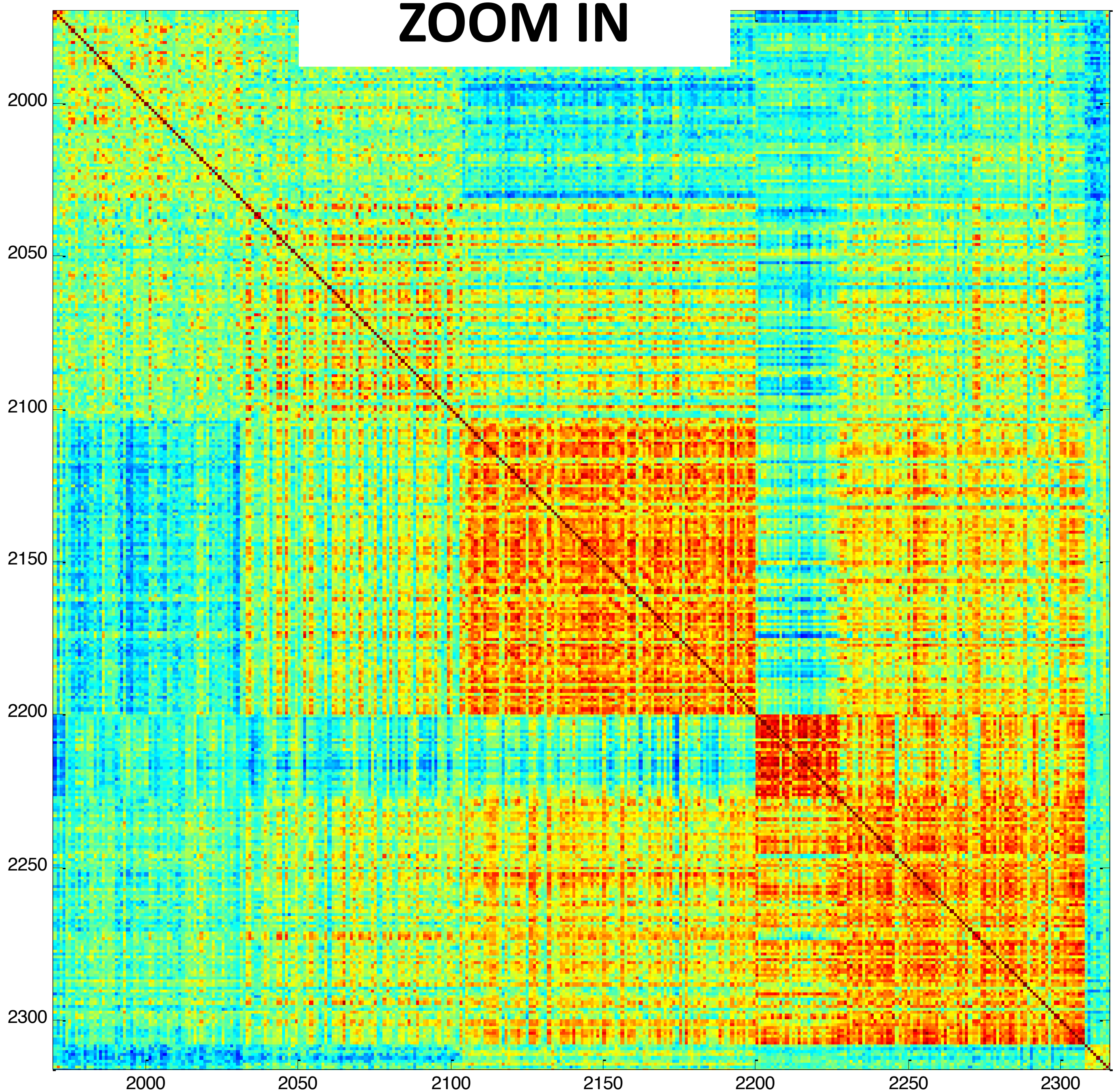
DTI

SUBJECT 1

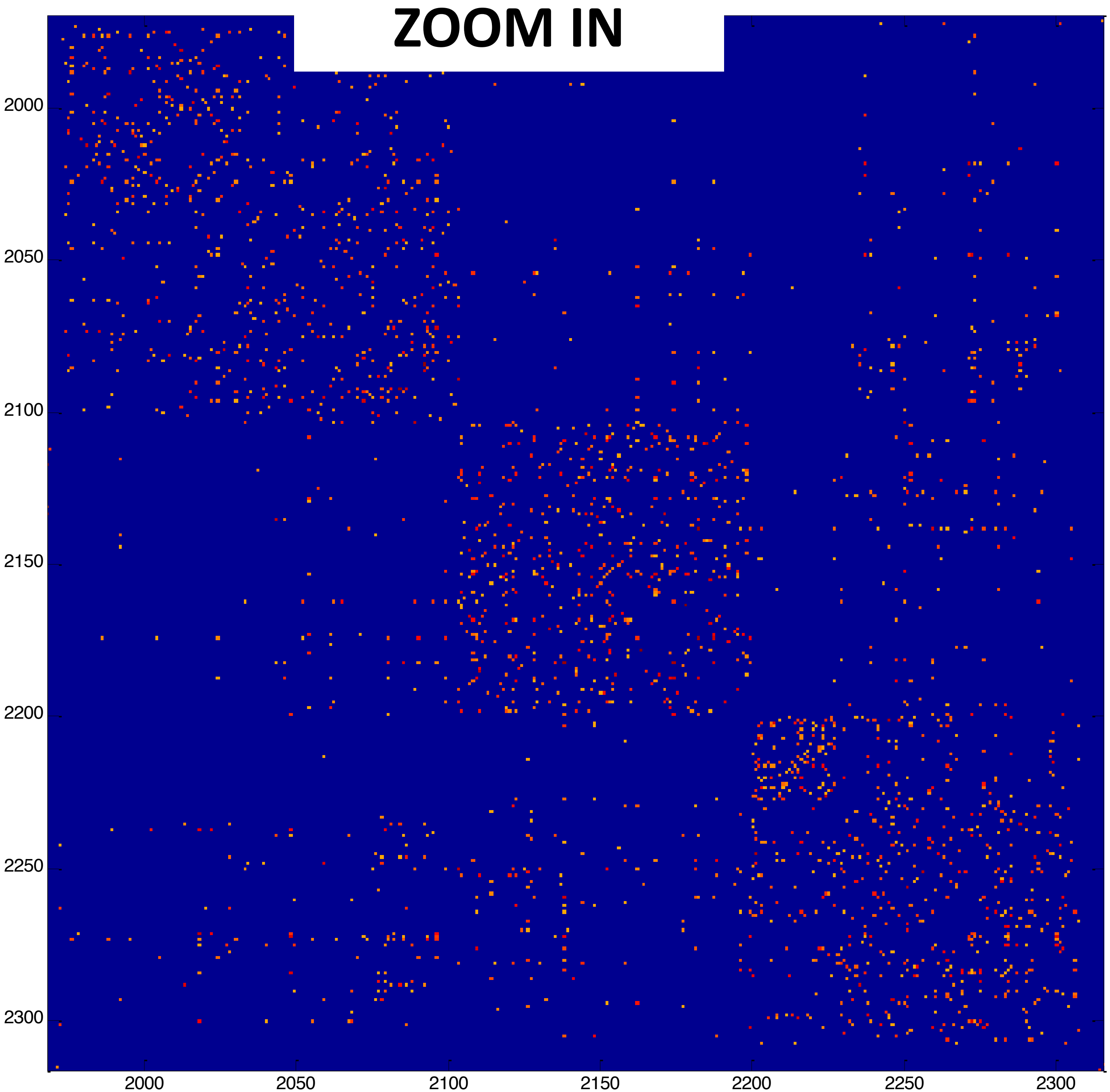


rs-fMRI

ZOOM IN



DTI


ZOOM IN
2000
2050
2100
2150
2200
2250
2300
2000
2050
2100
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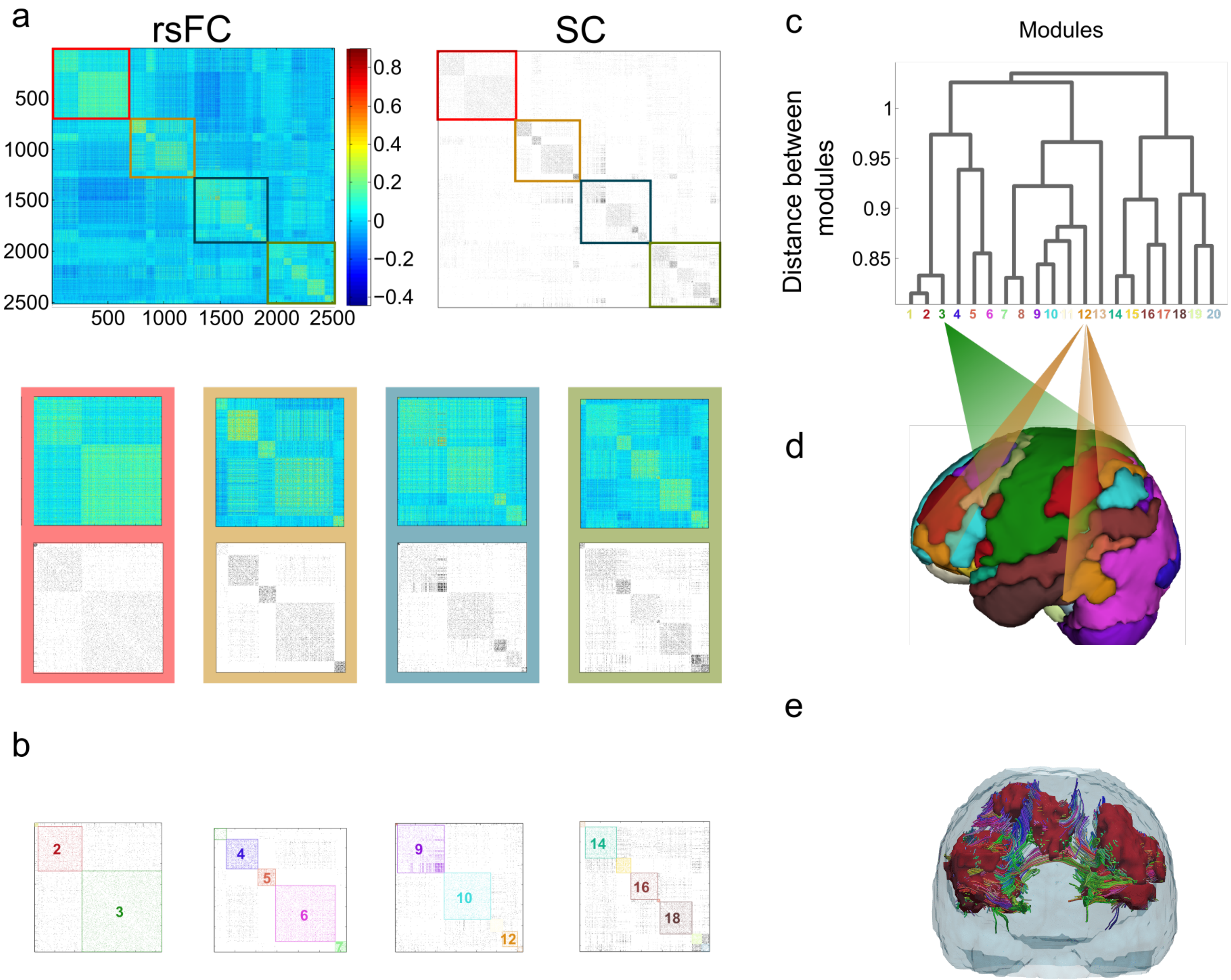
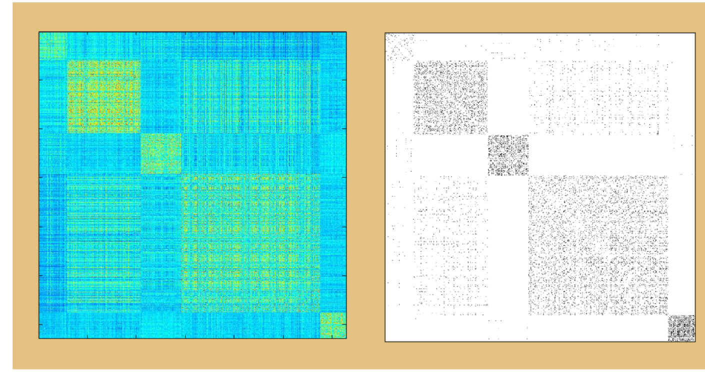
2250
2300

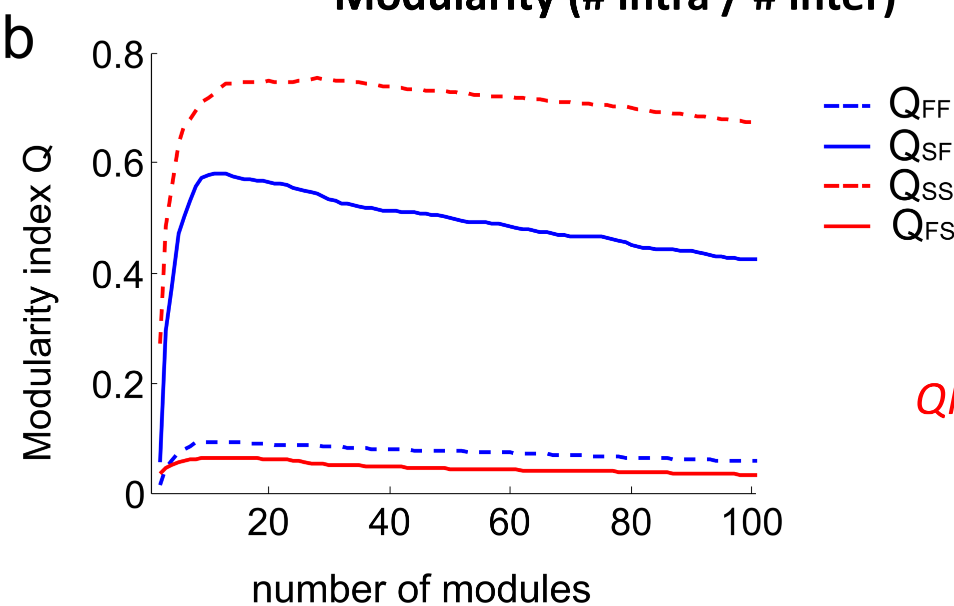

a
rsFC
SC
500
1000
1500
2000
2500
500
1000
1500
2000
2500
0.8
0.6
0.4
0.2
0
−0.2
−0.4
c
Modules
Distance between modules
1
0.95
0.9
0.85
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
d
e
b
2
3
4
5
6
7
9
10
12
14
16
18

Optimal in what sense ?

Cross-modularity sense



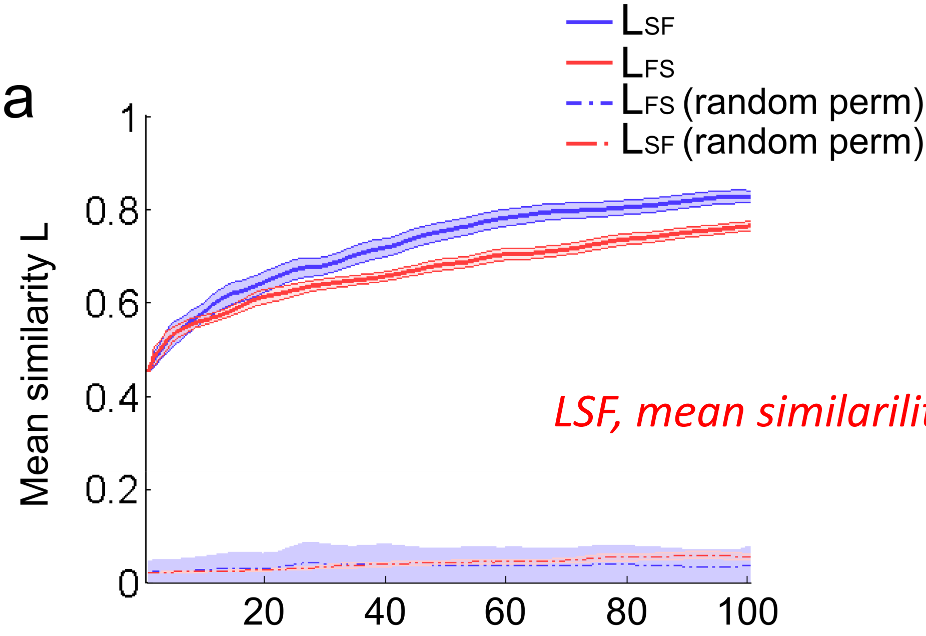
Modularity (# intra / # inter)

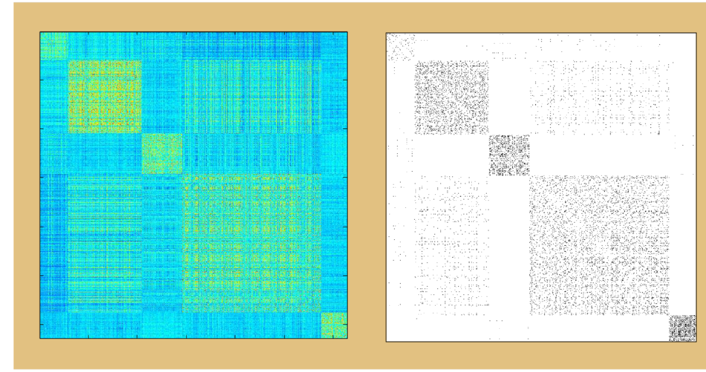


QFS, modularity of F, using the order of S

Similarity between modules (Sorensen index)

a

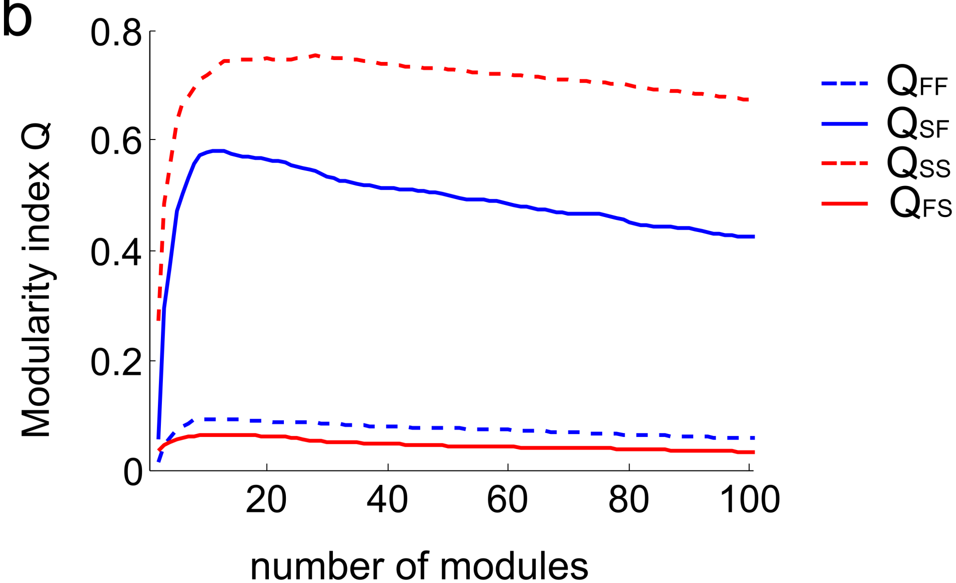




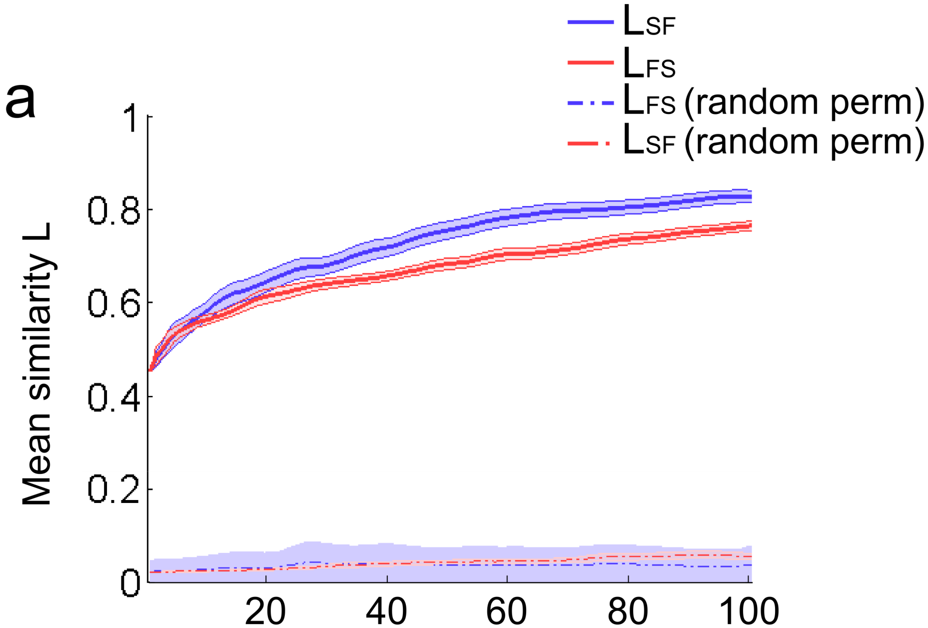
LSF, mean similarility between S anf F, using the order of F

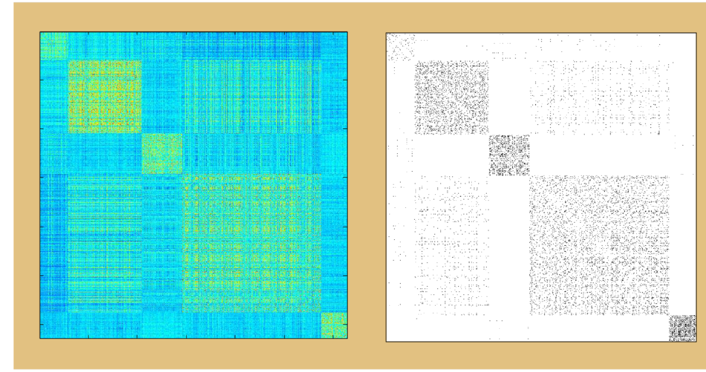
Modularity (# intra / # inter)

b

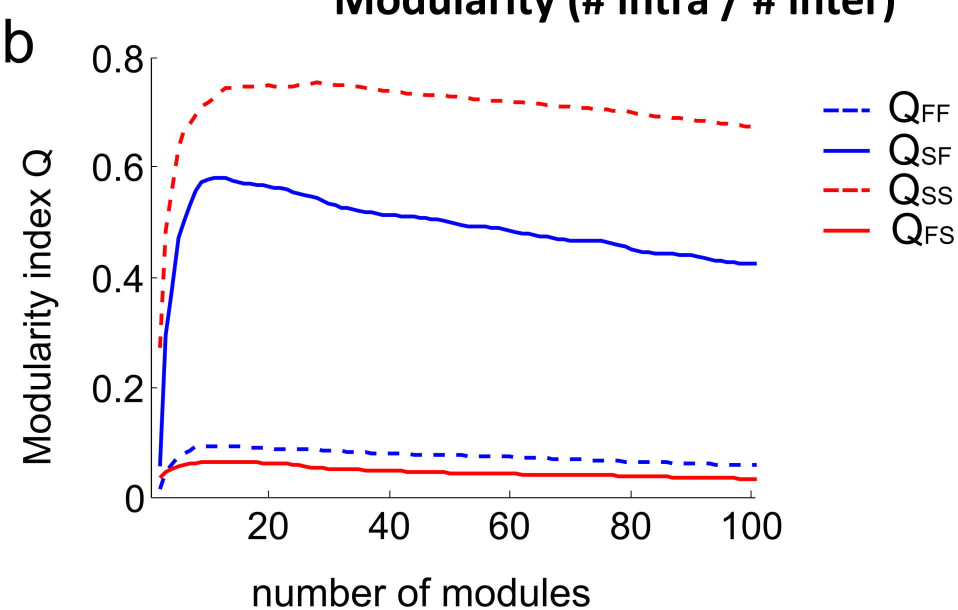


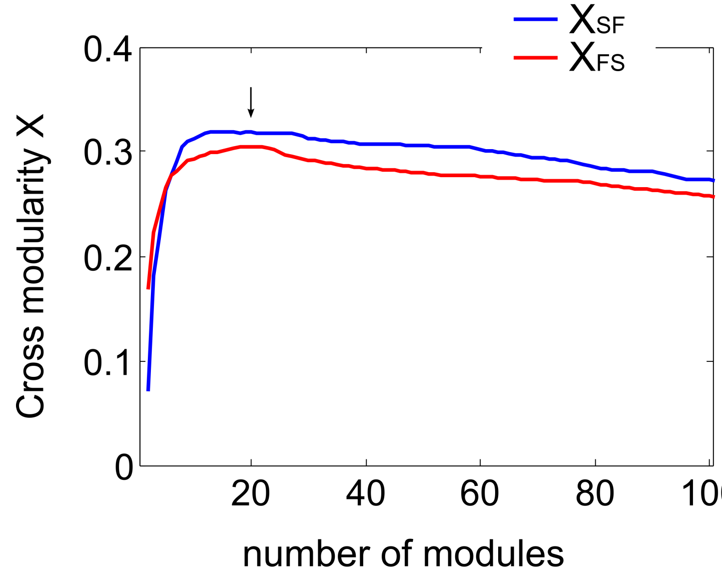
Similarity between modules (Sorensen index)





Modularity (# intra / # inter)

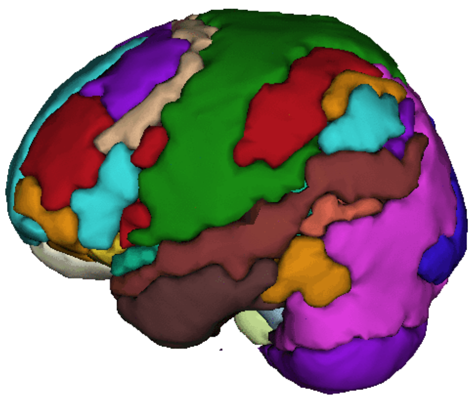




Cross-modularity =
modularity (func) *
modularity (stru) *
similarity (func,struc)

What means high crossmodularity?

Optimal partition with M=20 regions



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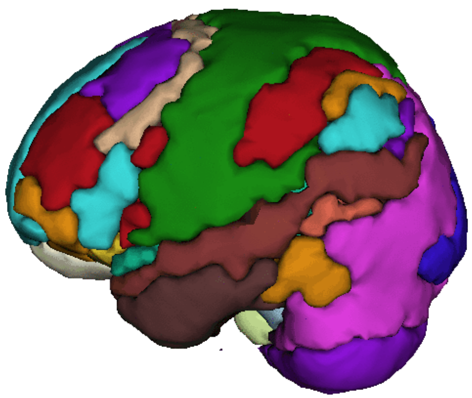
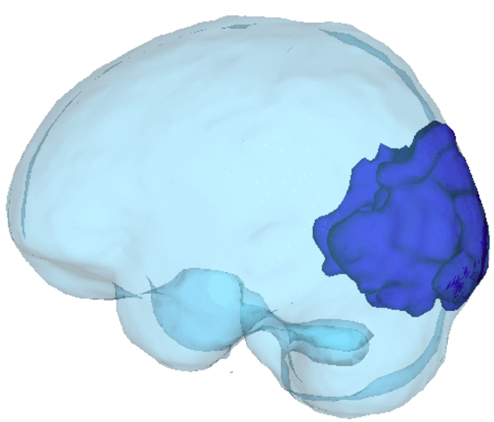
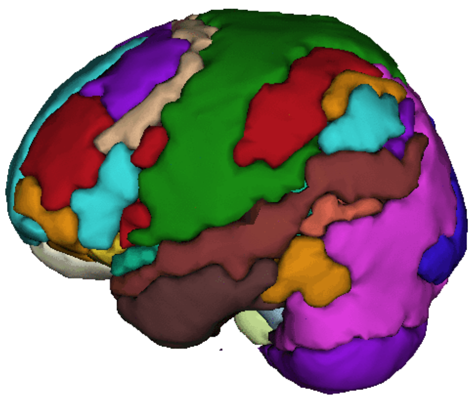


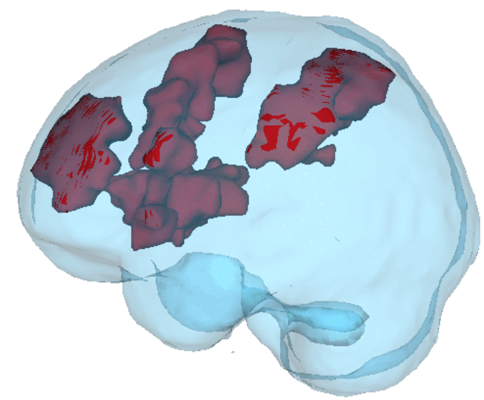
Some regions are compact



Optimal partition with M=20 regions



Some are made of anatomically distinct components



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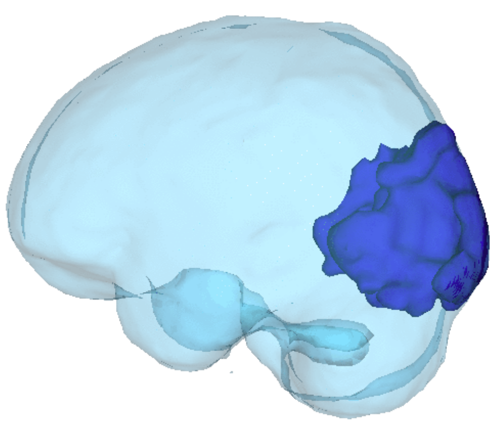
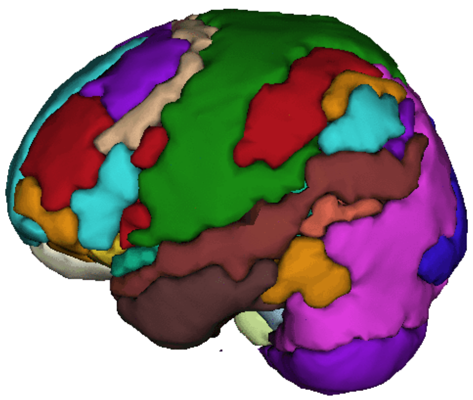


Optimal partition with M=20 regions



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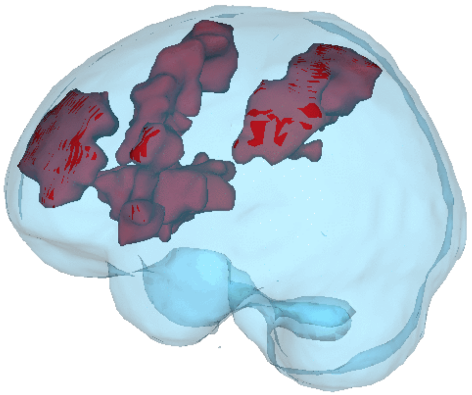
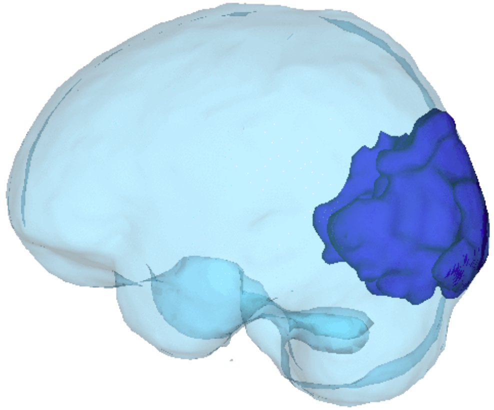
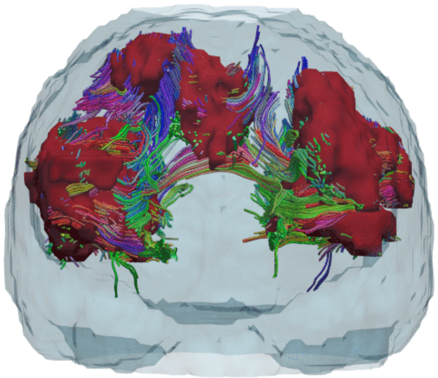


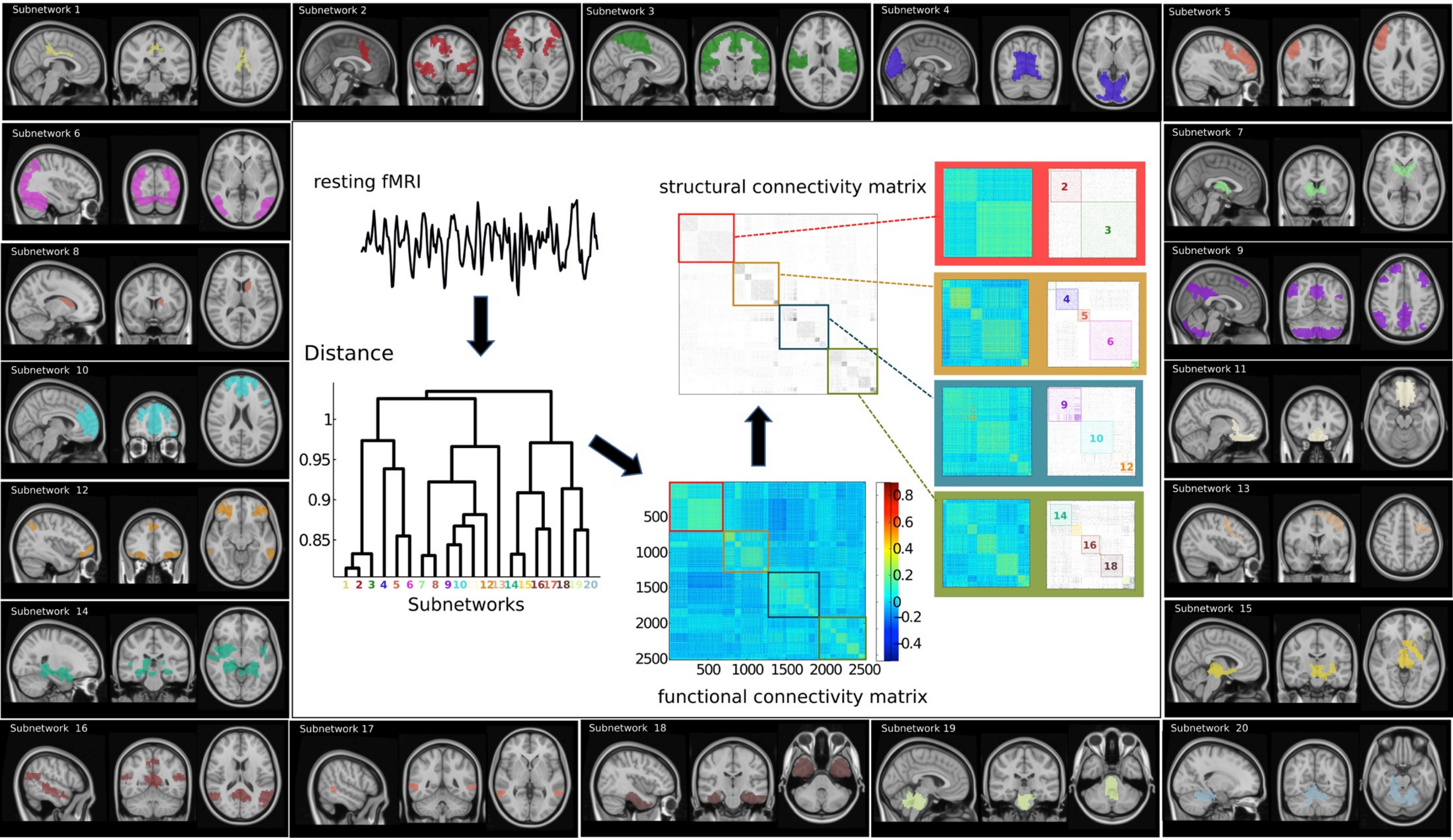
Some regions are compact



Each individual region is structurally wired and functionally similar



Brain Hierarchical Atlas: https://www.nitrc.org/projects/biocr_hcatlas/



http:// www.jesuscortes.info @_jesusmcortes

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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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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If the two are different; which is bigger?

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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

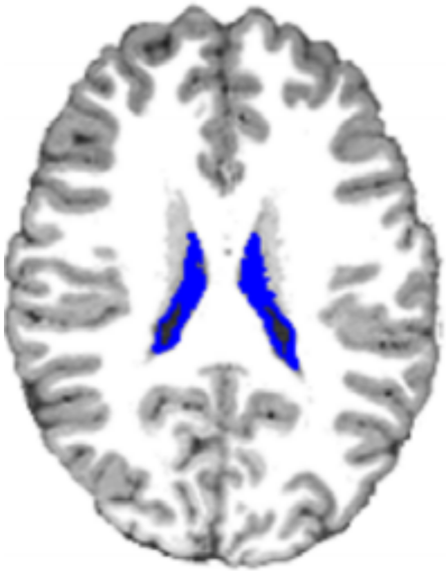
MOTIVATION:

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:

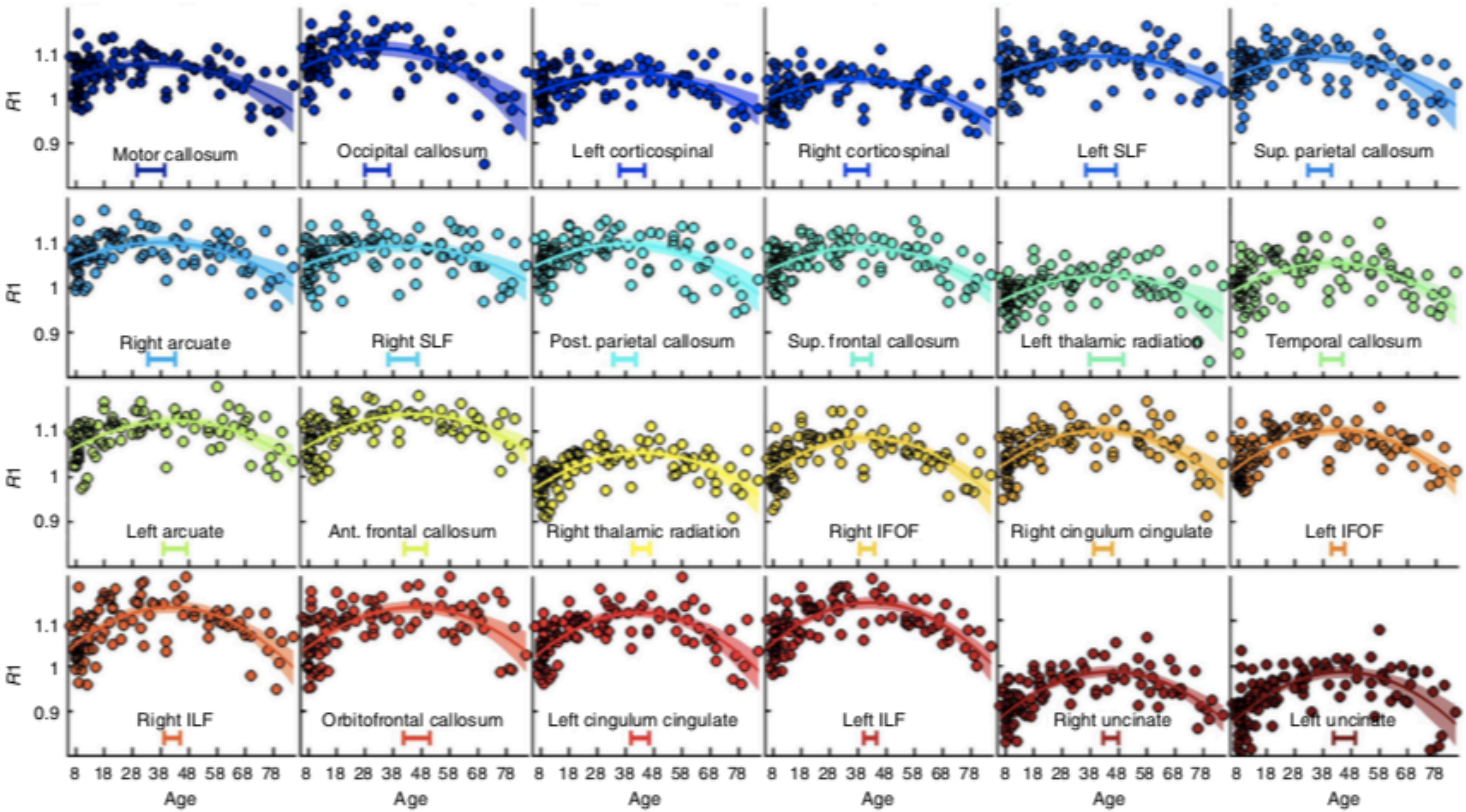


17 yo

72 yo

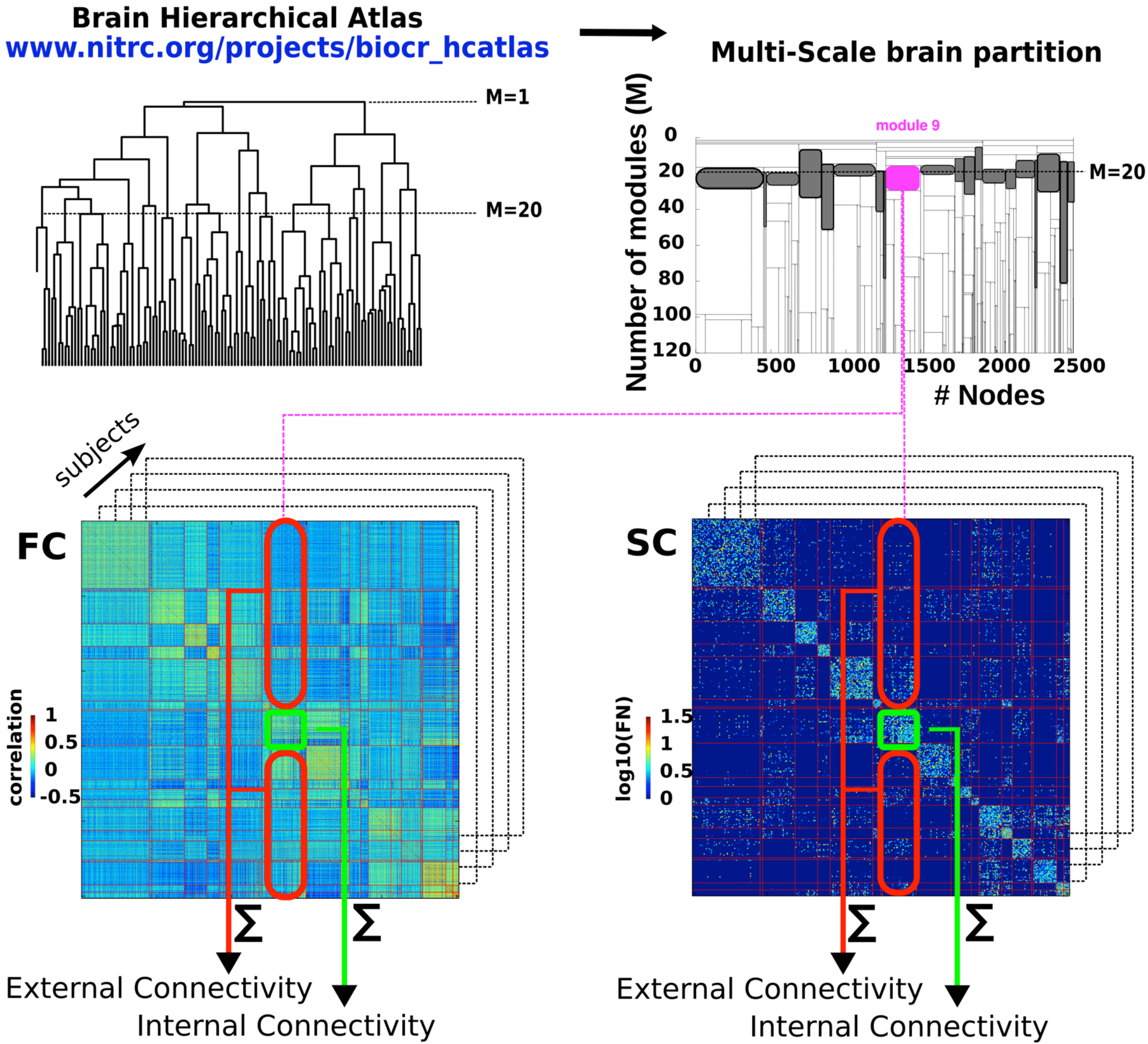
No morphological features were used to predict age

MOTIVATION:



(Yeatman & Mezer, 2014)

METHODS (I)


Brain Hierarchical Atlas
www.nitrc.org/projects/biocr_hcatlas
Multi-Scale brain partition
M=1
M=20
module 9
Number of modules (M)
0
20
40
60
80
100
120
0
500
1000
1500
2000
2500
# Nodes
M=20
subjects
FC
SC
correlation
1
0.5
0
-0.5
log10(FN)
1.5
1
0.5
0
Σ
Σ
Σ
Σ
External Connectivity
Internal Connectivity
External Connectivity
Internal Connectivity

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+…+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

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

with design matrix defined as

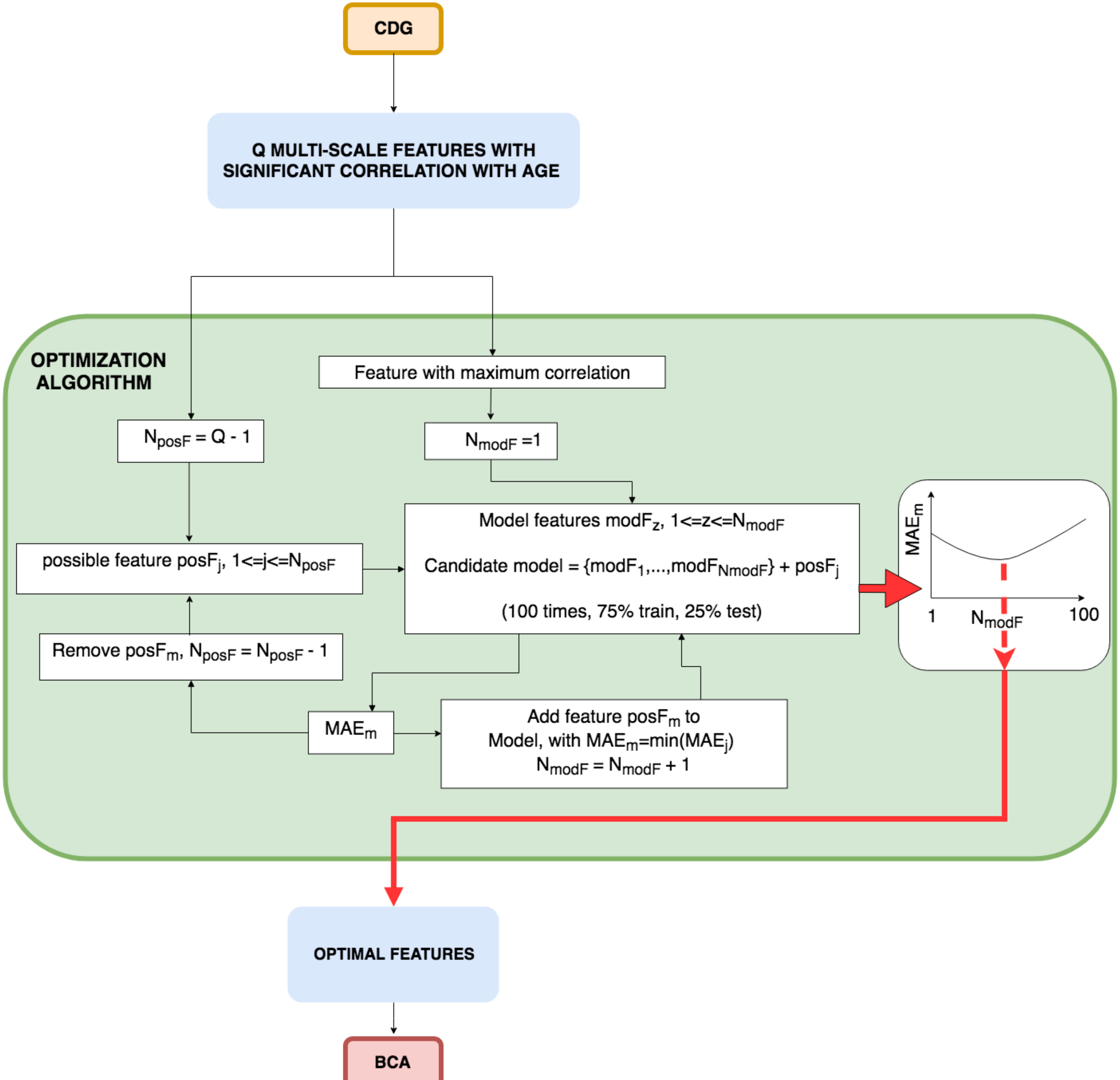
$$\varphi \equiv \begin{pmatrix} 1 x_1^1 x_2^1 \cdots x_{K-1}^1 \\ 1 x_1^2 x_2^2 \cdots x_{K-1}^2 \\ \vdots \\ 1 x_1^P x_2^P \cdots x_{K-1}^P \end{pmatrix}$$

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

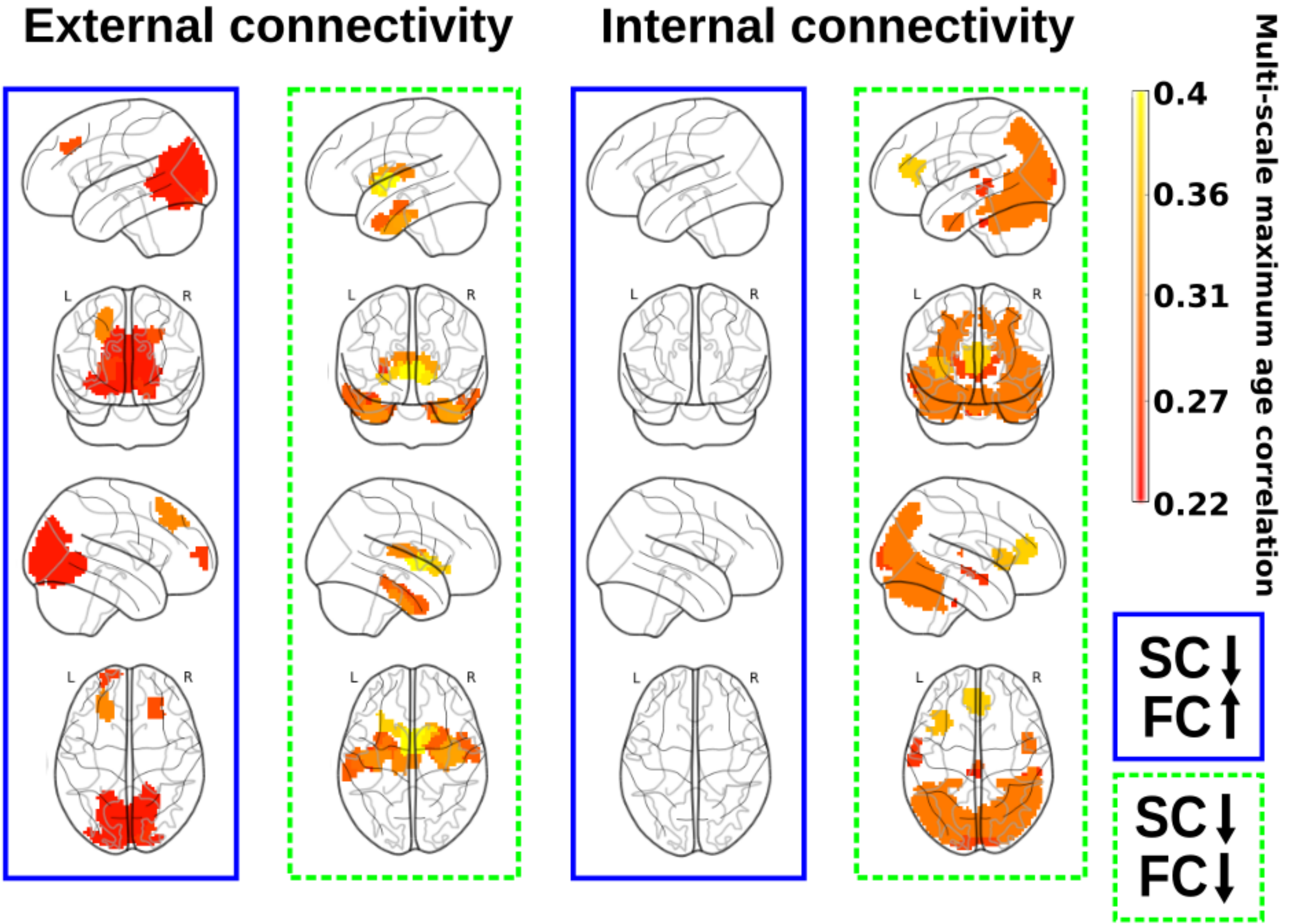
with N_1 = 115 (75%) for training and N_2=38 (25%) for testing

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

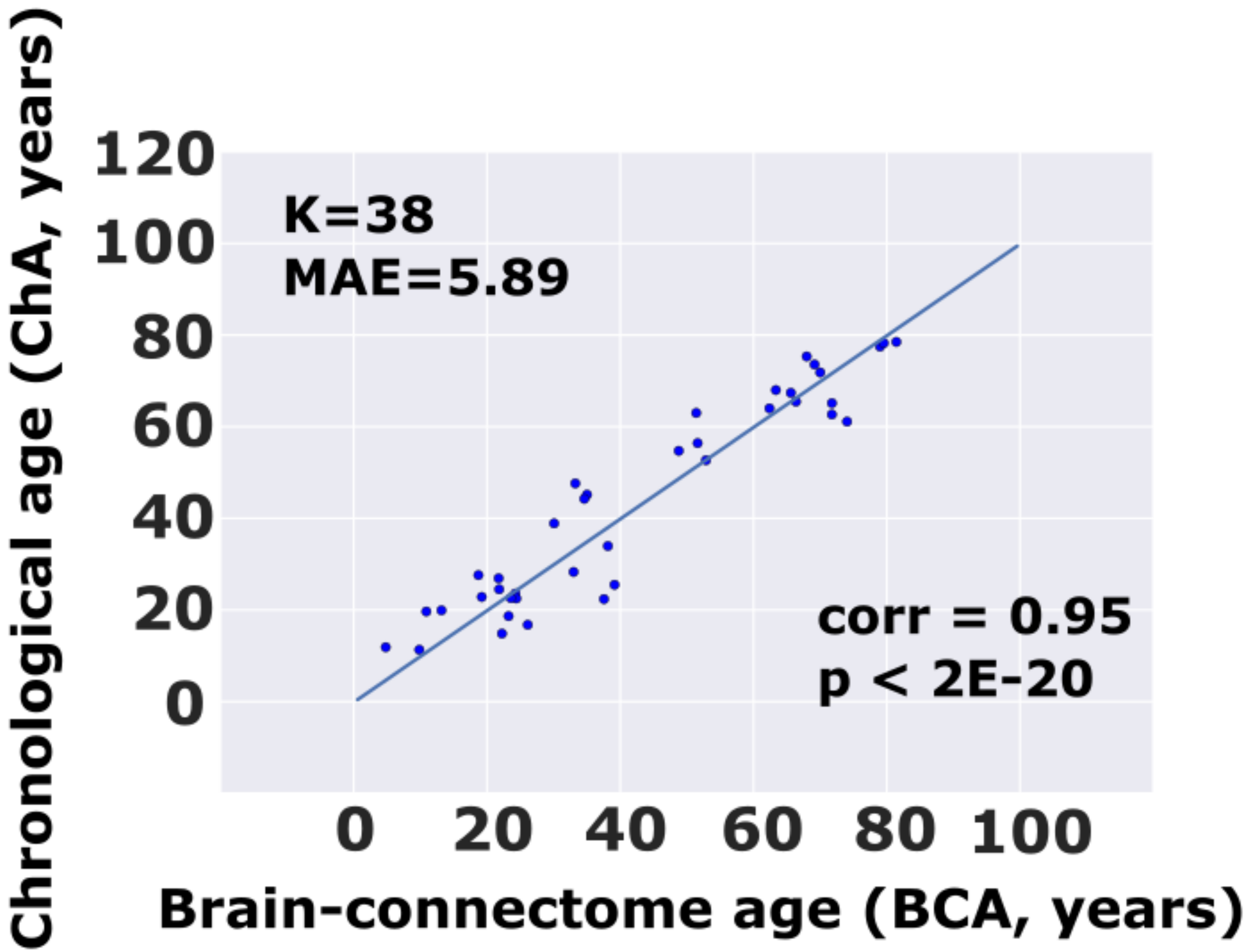
Brain connectome age depends on K


CDG
Q MULTI-SCALE FEATURES WITH SIGNIFICANT CORRELATION WITH AGE
OPTIMIZATION ALGORITHM
Feature with maximum correlation
N_{posF} = Q - 1
N_{modF} =1
Model features $modF_z$, 1<=z<=N_{modF}
Candidate model = {$modF_1$,...,$modF_{NmodF}$} + $posF_j$
(100 times, 75% train, 25% test)
possible feature $posF_j$, 1<=j<=N_{posF}
Remove $posF_m$, N_{posF} = N_{posF} - 1
MAE_m
Add feature $posF_m$ to Model, with MAE_m=min(MAE_j)
N_{modF} = N_{modF} + 1
MAE_m
1
N_{modF}
100
OPTIMAL FEATURES
BCA

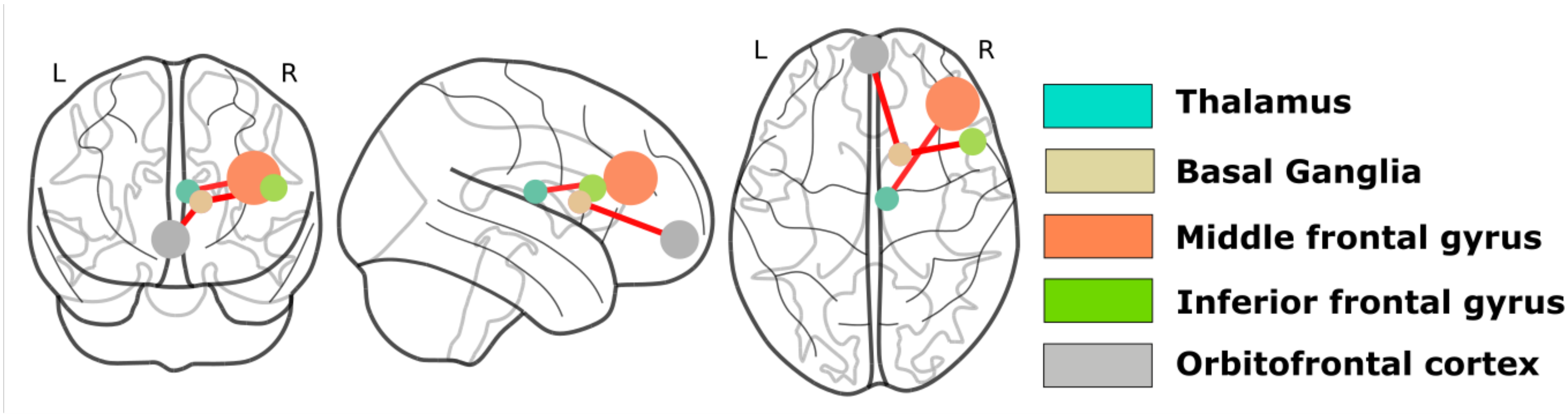
RESULTS

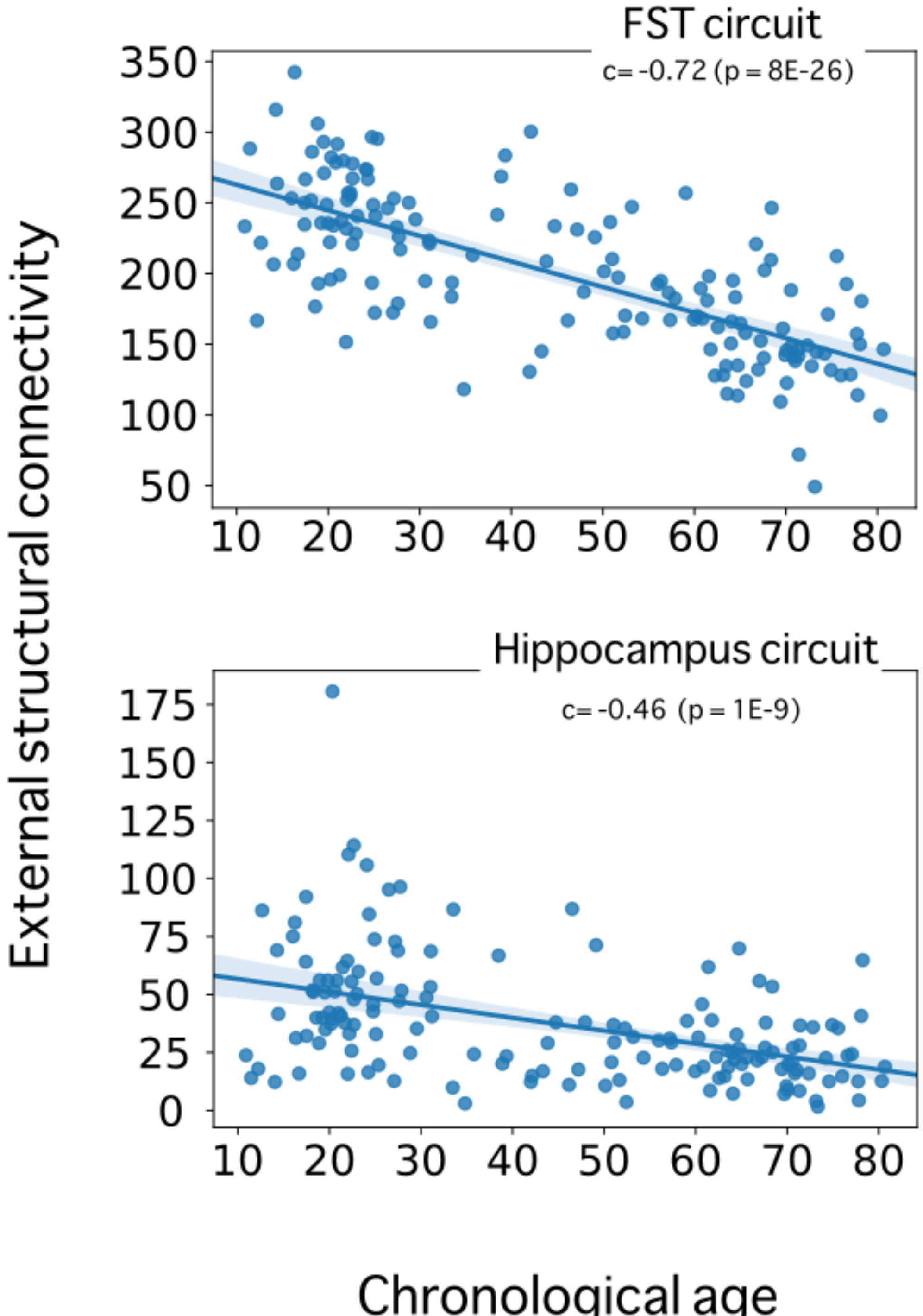


External connectivity
Internal connectivity
L
R
0.4
0.36
0.31
0.27
0.22
Multi-scale maximum age correlation
SC↓
FC↑
SC↓
FC↓


K=38
MAE=5.89
corr = 0.95
p < 2E-20
Chronological age (ChA, years)
Brain-connectome age (BCA, years)
120
100
80
60
40
20
0
0
20
40
60
80
100

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





FST circuit
c= -0.72 (p = 8E-26)
350
300
250
200
150
100
50
10
20
30
40
50
60
70
80
Hippocampus circuit
c= -0.46 (p = 1E-9)
175
150
125
100
75
50
25
0
10
20
30
40
50
60
70
80
External structural connectivity
Chronological age

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

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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