Network Analysis

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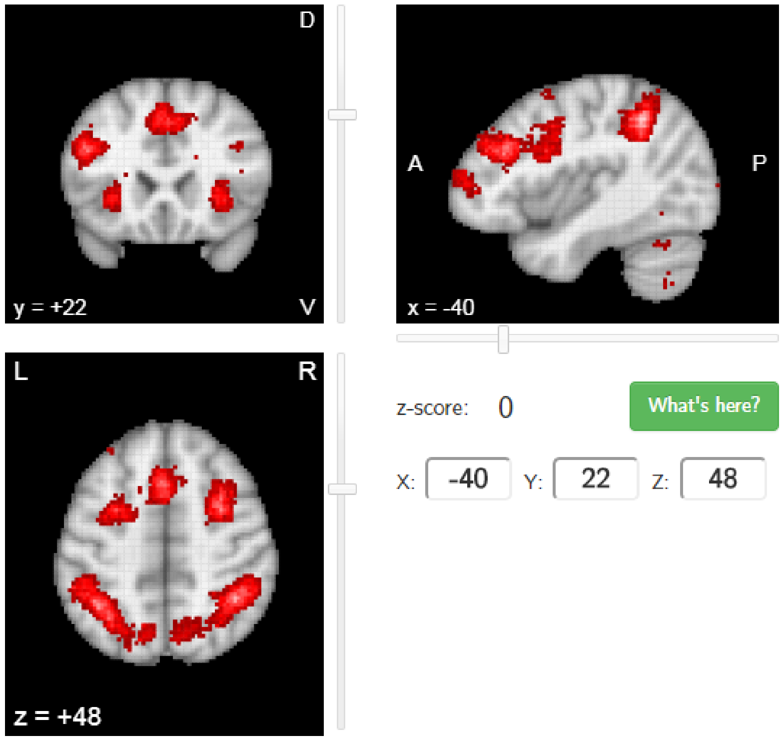
From brain regions to brain graphs

Neurosynth – *"working memory"* → **Network organization of brain areas**

Automated meta-analysis of 901 studies



The Graph-theoretic Approach

- enables characterization of the brain's connectivity structure
- derives measures that assess **global** and **local** features that may be important for network function

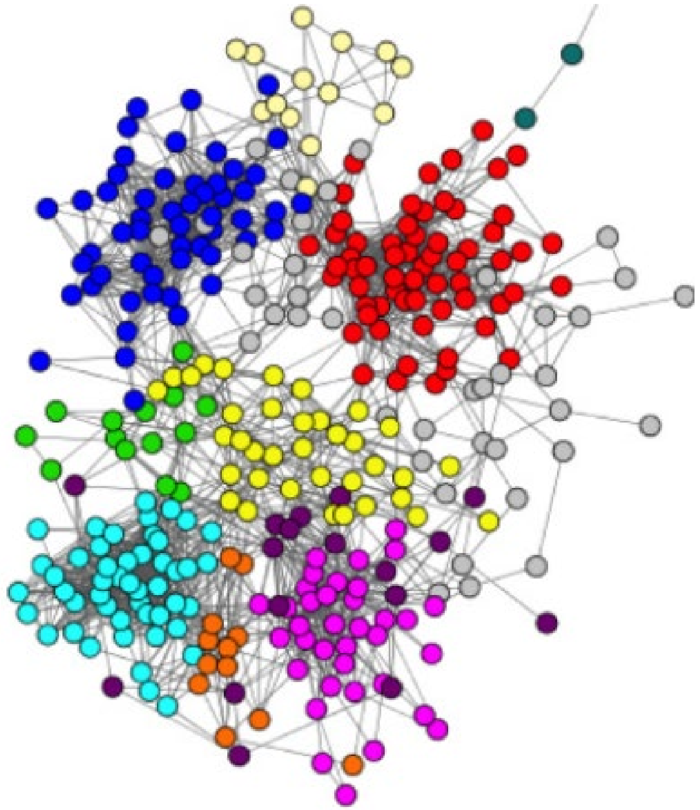
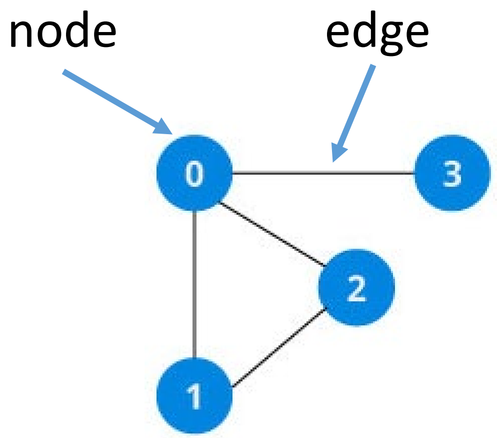


Image: Wig, 2017

What is a graph?



adjacency matrix

	0	1	2	3
0	0	1	1	1
1	1	0	1	0
2	1	1	0	0
3	1	0	0	0

- undirected graph –> symmetric matrix
- unweighted graph –> binary matrix
- diagonal is zero

➢ Any network can be represented as a collection of nodes connected by edges.

image: programiz.com

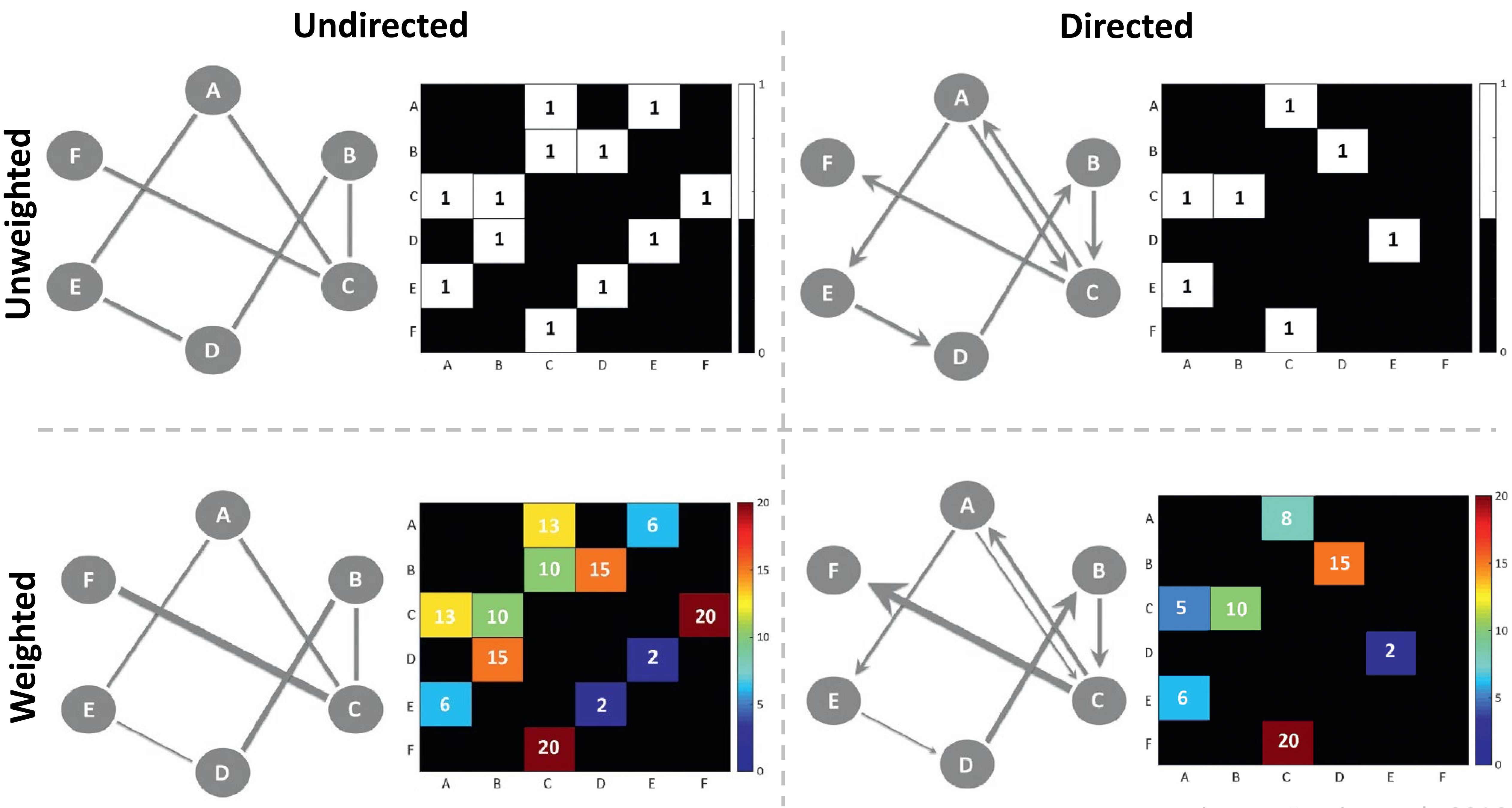
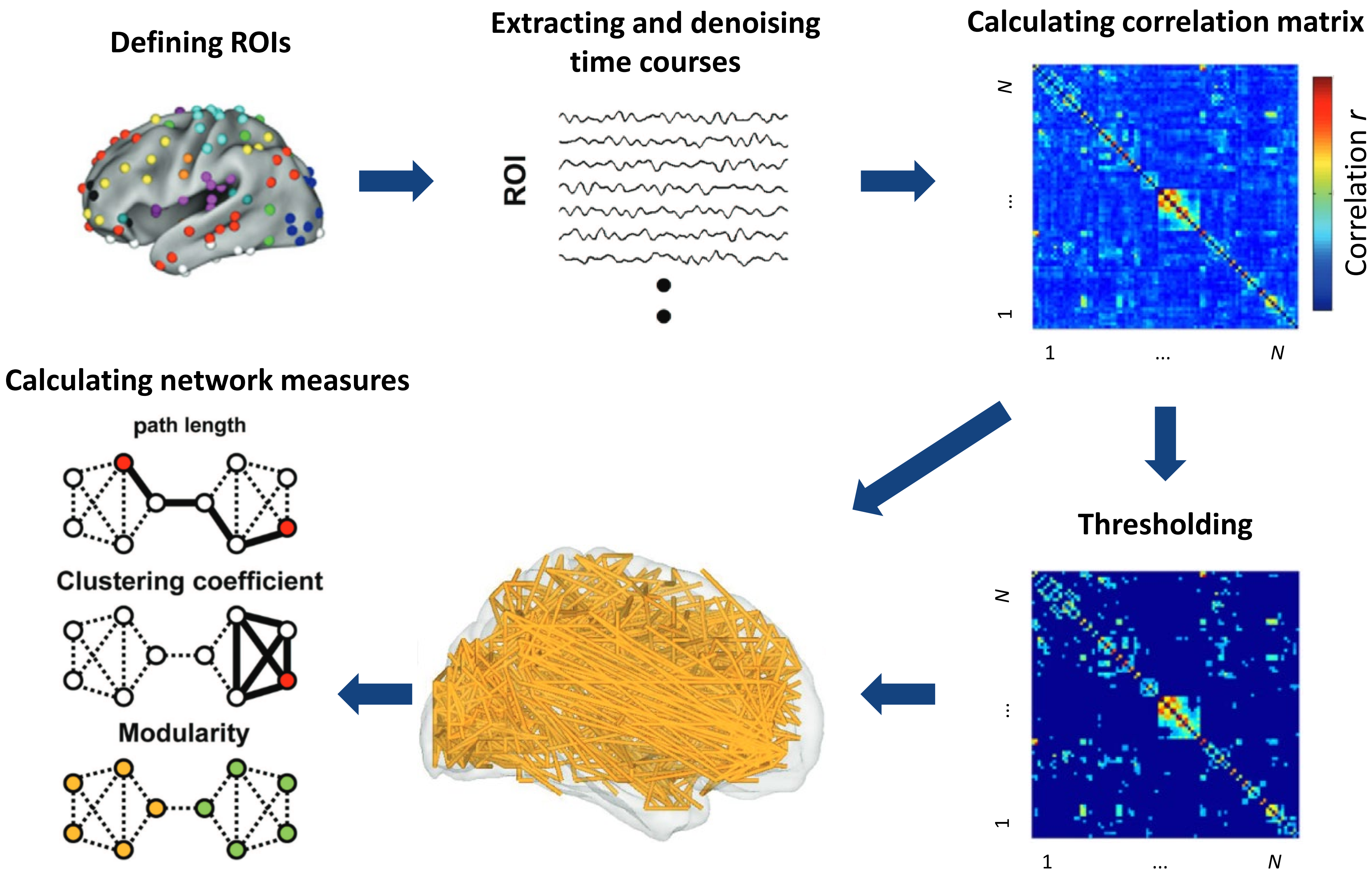


image: Fornito et al., 2016

Procedure

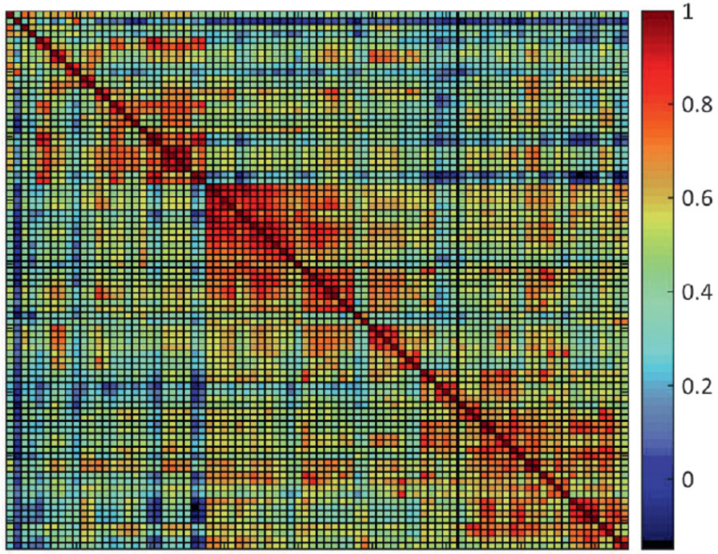


images: Uehara et al., 2013; Taya et al., 2016; Power et al., 2013

Thresholding and binarizing an adjacency matrix

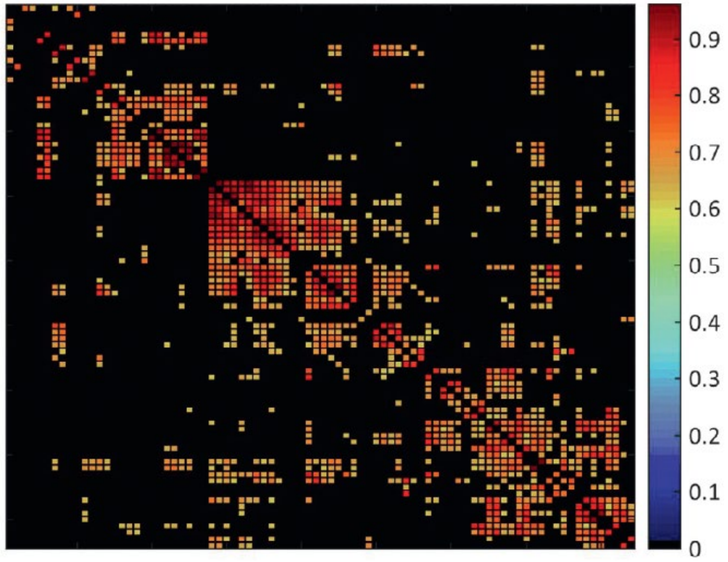
E.g., functional connectivity connectivity data

Unthresholded



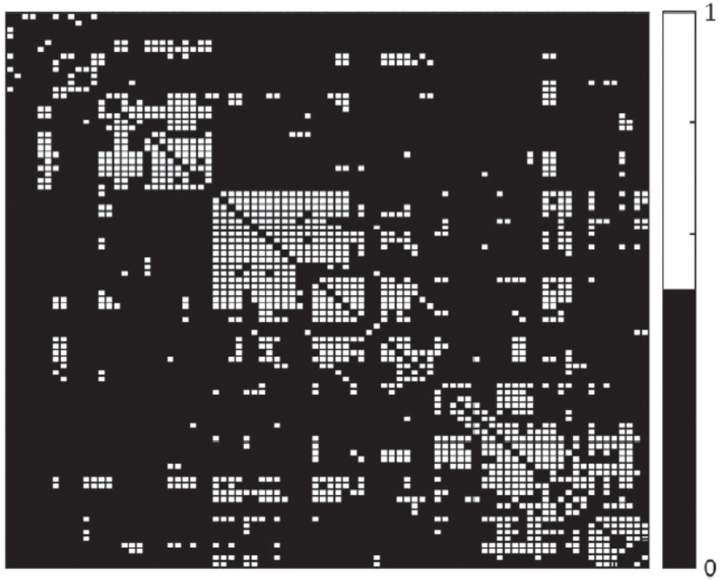
$$C_{ij} = \begin{bmatrix} C_{11} & C_{12} & \cdots & C_{1N} \\ C_{21} & C_{22} & & C_{2N} \\ \vdots & & \ddots & \vdots \\ C_{N1} & C_{N2} & \cdots & C_{NN} \end{bmatrix}$$

Thresholded



$$A_{ij} = \begin{cases} C_{ij} & \text{if } C_{ij} > \tau, \\ 0 & \text{otherwise} \end{cases}.$$

Binarized



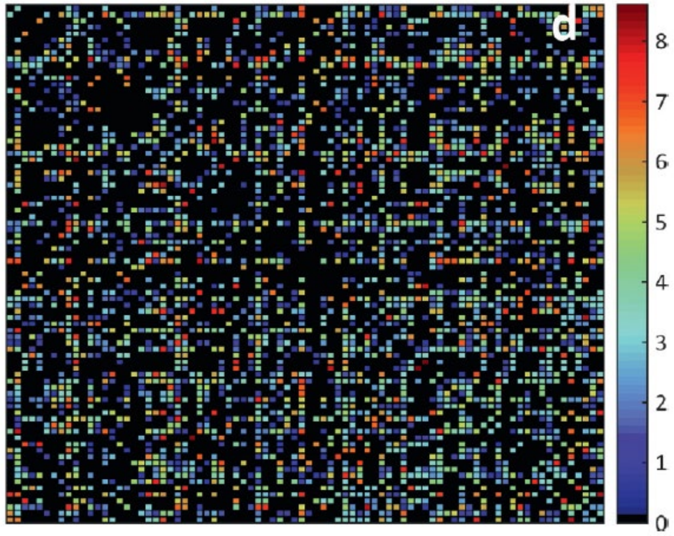
$$A_{ij} = \begin{cases} 1 & \text{if } C_{ij} > \tau, \\ 0 & \text{otherwise} \end{cases}.$$

image: Fornito et al., 2016

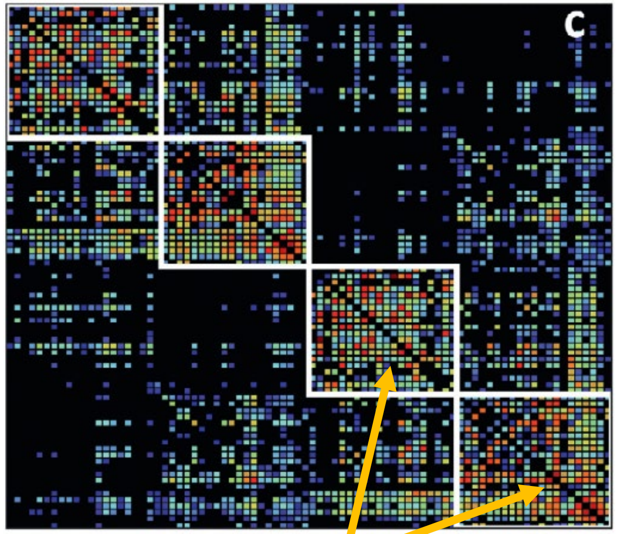
Visualizing adjacency matrices

E.g., structural connectivity data

Random order

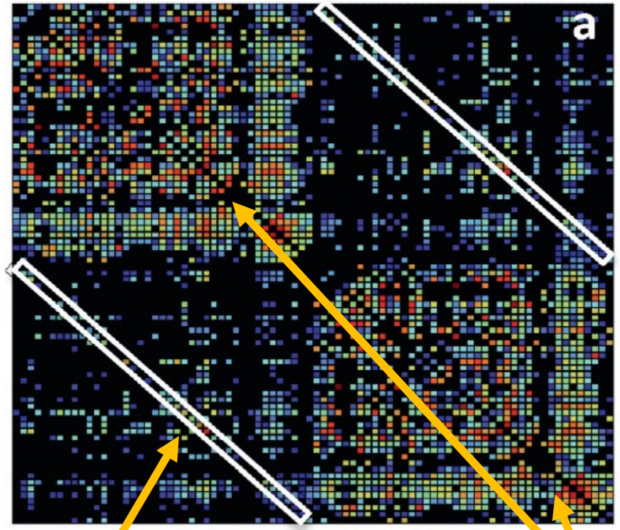


Modular structure



Modules

L vs R hemisphere



Intra-hemispheric connectivity

Connectivity of each region with homologue in the other hemisphere

Anatomical projection

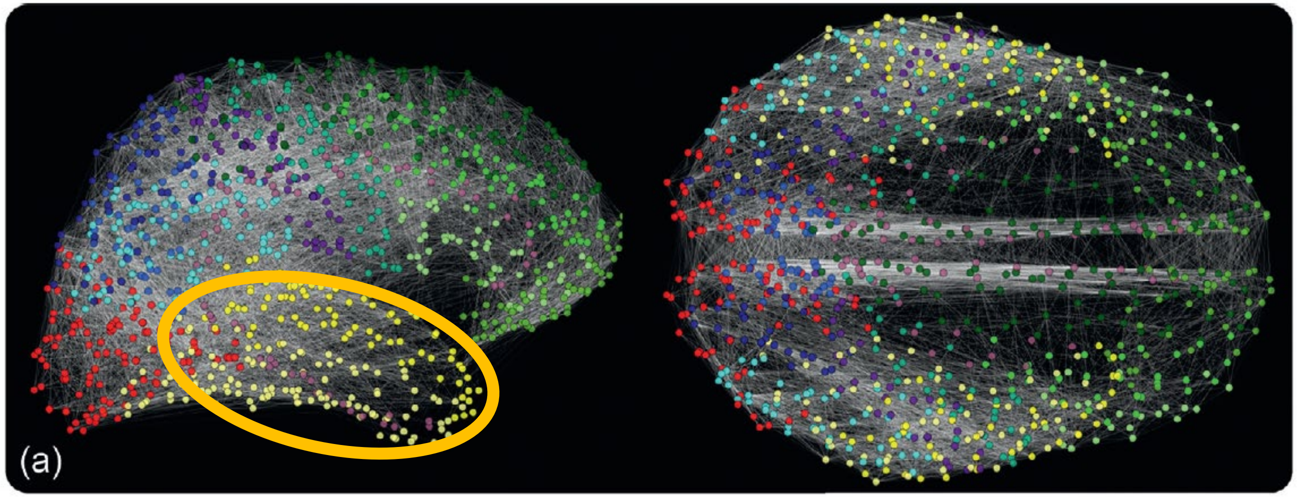
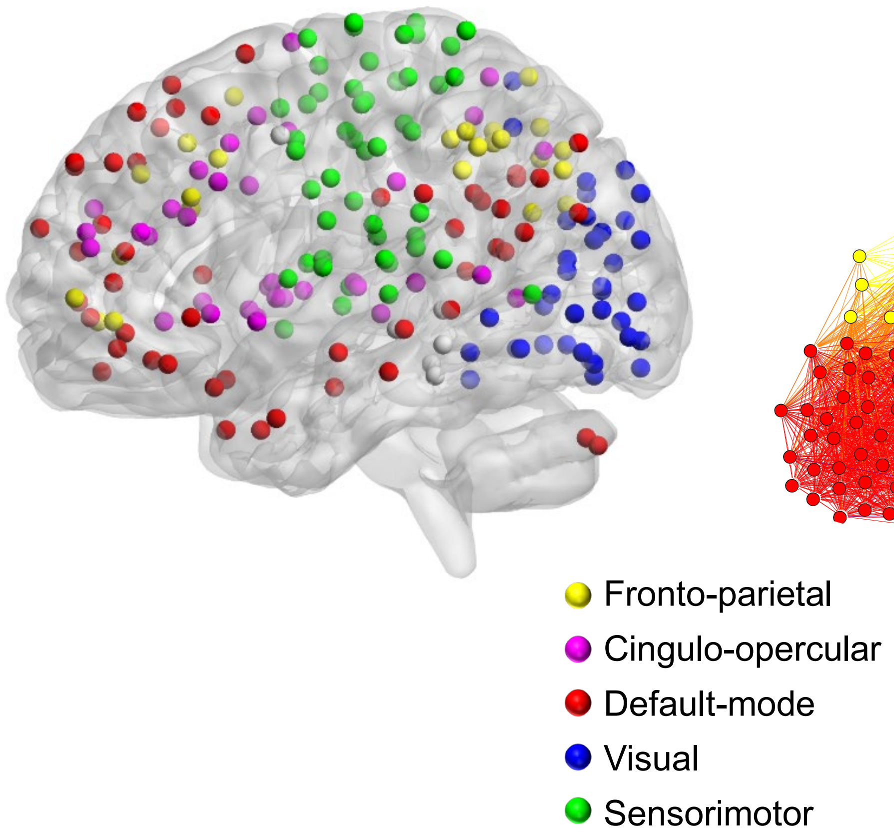


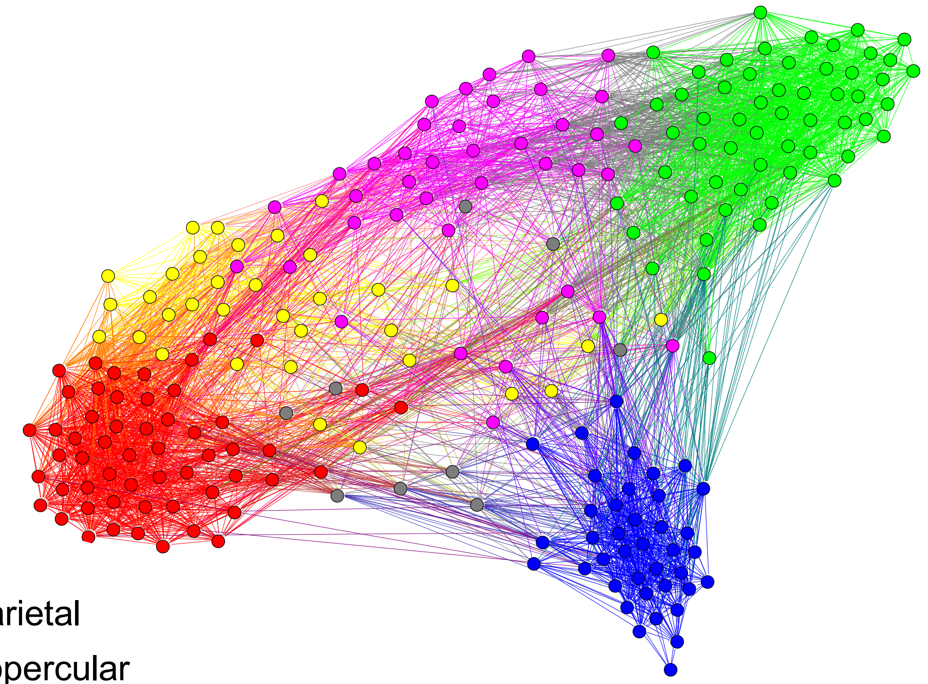
image: Fornito et al., 2016

Common types of visualizations

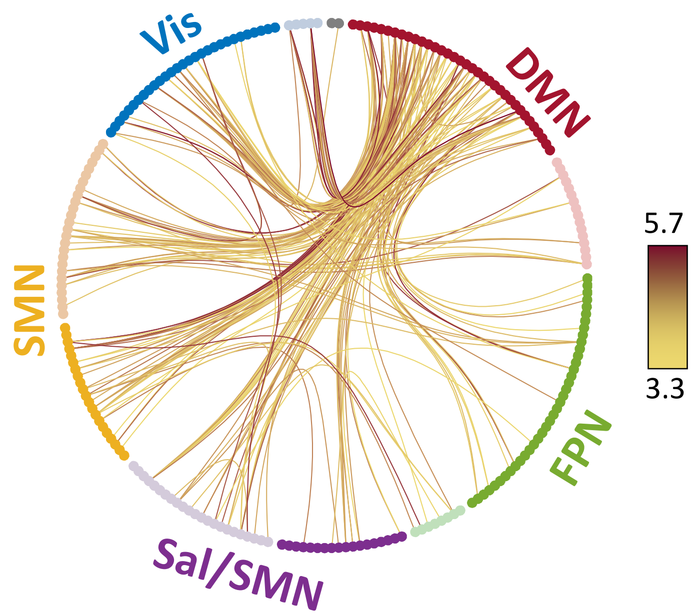
Anatomical projection



Force-directed projection



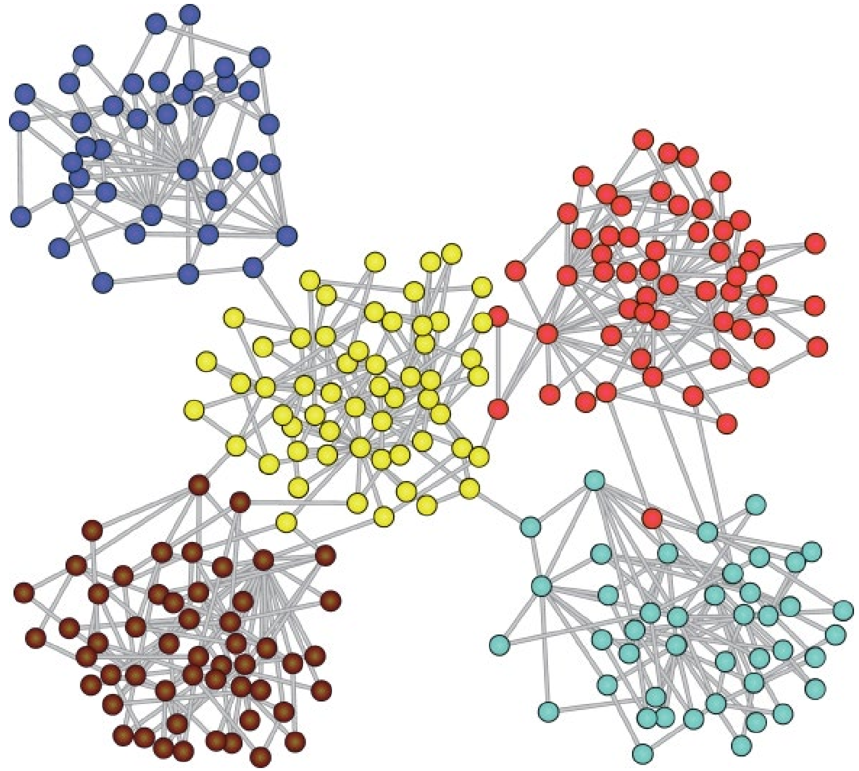
Circular projection/ connectogram



Modularity – Key topological property

Description (Newman & Girvan, 2004)

- Nodes cluster into highly cohesive modules.
- Degree of intramodule connectivity is greater than expected by chance (i.e., in a random network).



Quantification – *Modularity Index*

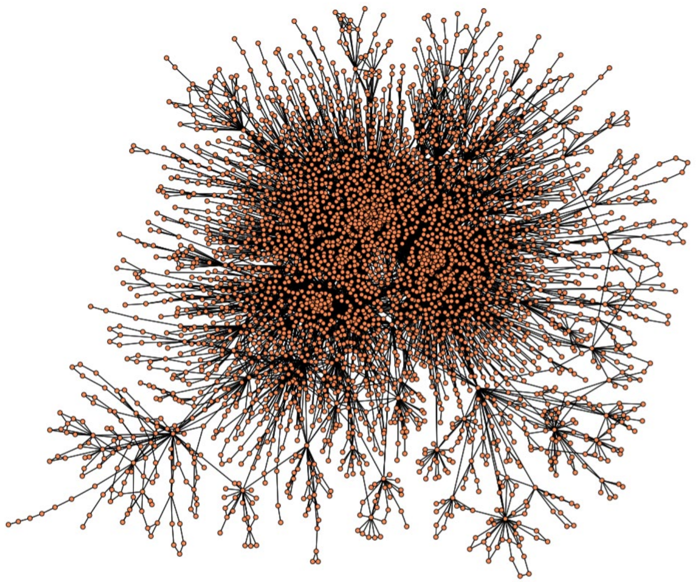
$$Q = \frac{1}{2E}\sum_{ij}[A_{ij} - \gamma e_{ij}]\delta(m_i, m_j)$$

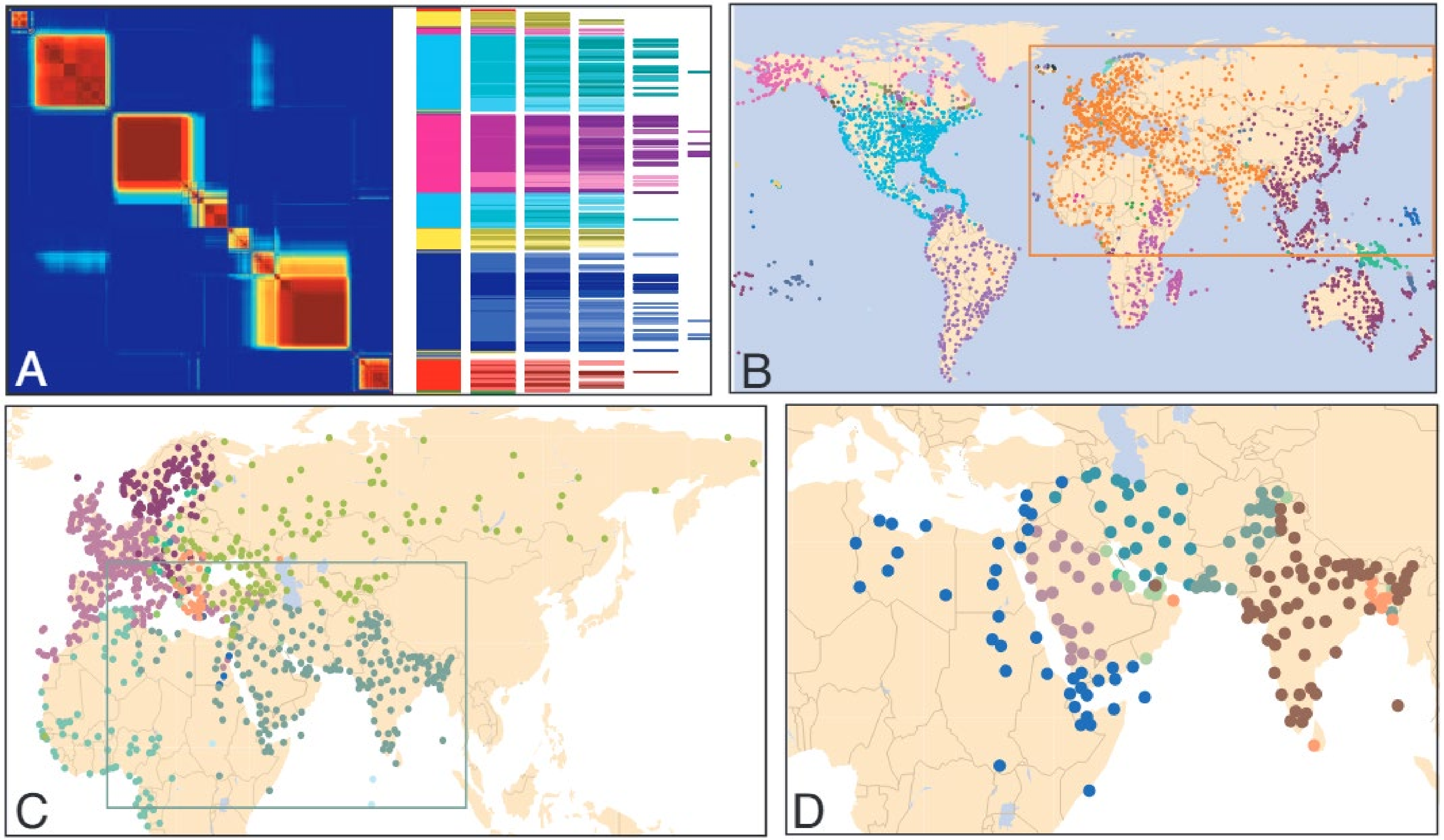
Detection

- community detection algorithms

image: Muller-Linow et al., 2008

Example - Air Transportation Network
(3,618 nodes; 28,287 edges)





Sales-Pardo et al., 2007

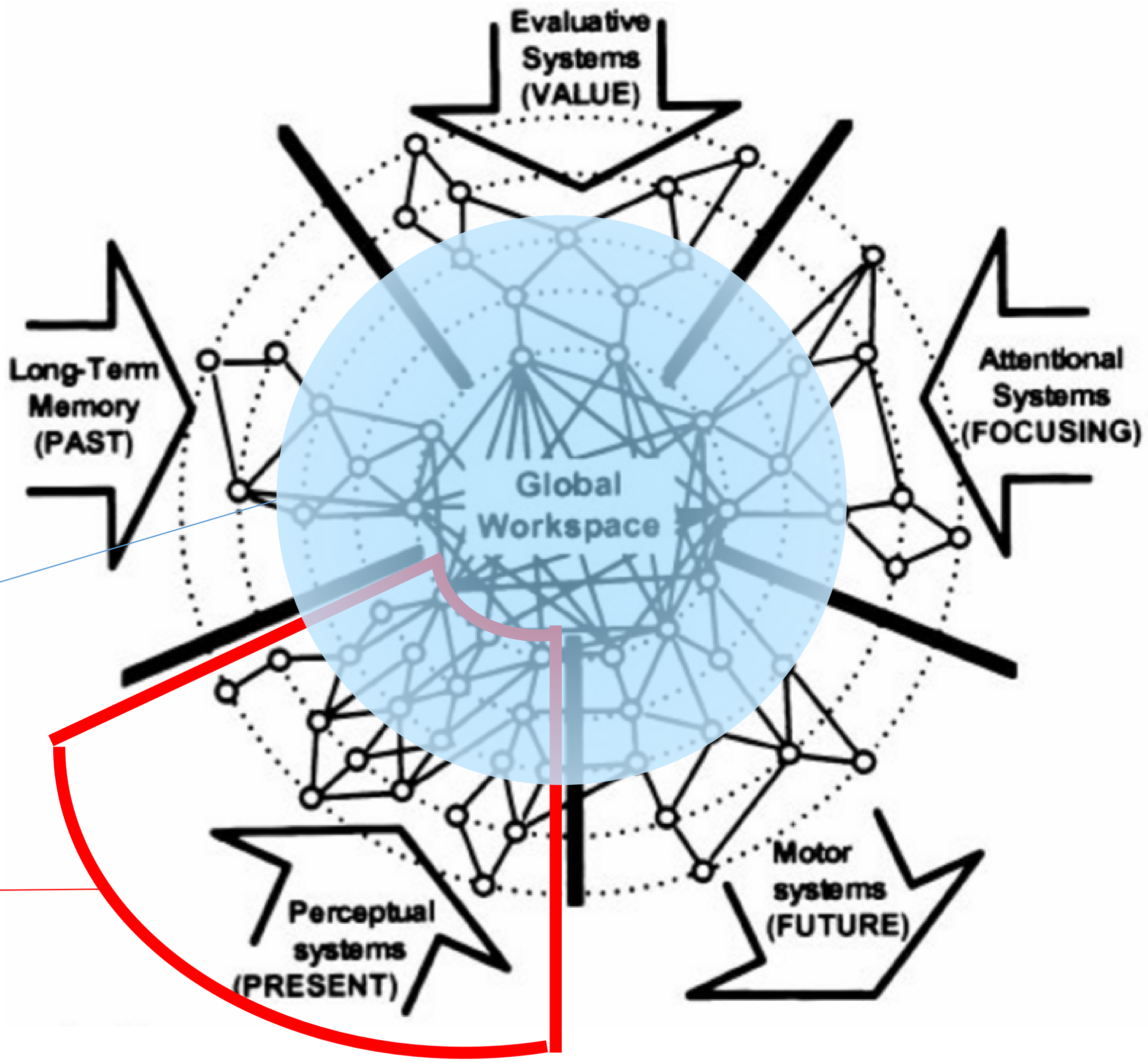
Cognitive modules and global workspace

Modularity of mind (Fodor, 1983)

Functional segregation & integration

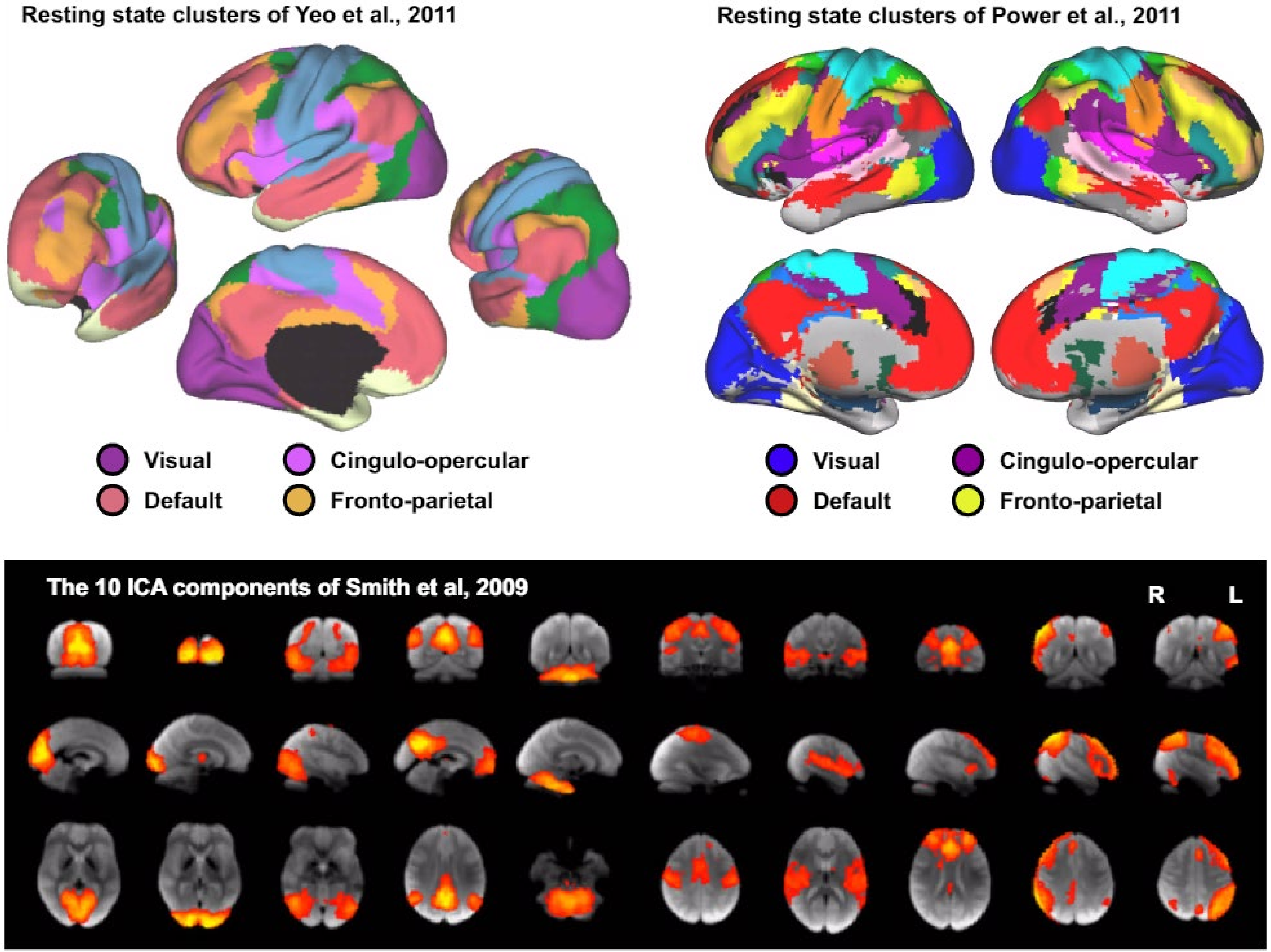
High-level cognitive functions (eg. WM) - rely more on a ***global workspace*** than on segregated modular functions.

Modules - spatially localized and include specialized brain areas (visual, auditory, motor ...)



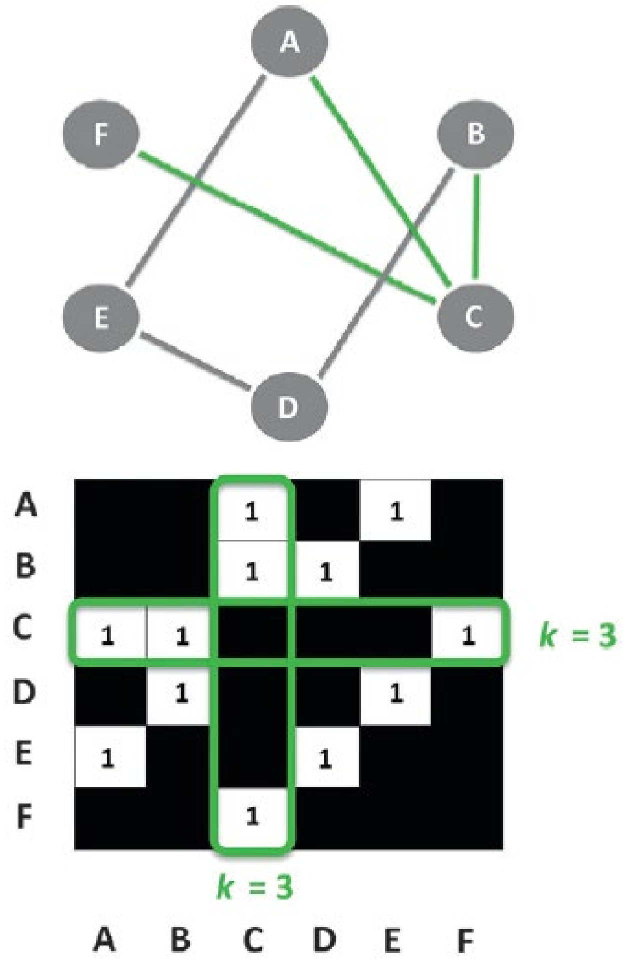
Dehaene et al., 1998

Large-scale functional organization of the brain



Power et al., 2014

Node degree & strength



- Binary undirected network
  - Degree of node i:
    - # of edges connecting node i with all other nodes
  - Mean degree of an undirected network:
    - mean of all node degrees

$$k_i = \sum_{j \neq i} A_{ij}.$$

$$\langle k \rangle = \frac{1}{N} \sum_{i=1}^{N} k_i.$$

- Weighted undirected network
  - Strength of node *i*:
    - sum of weights of edges attached to node *i*
  - Positive vs. negative node strength
    - signed weighted networks (e.g., correlation)

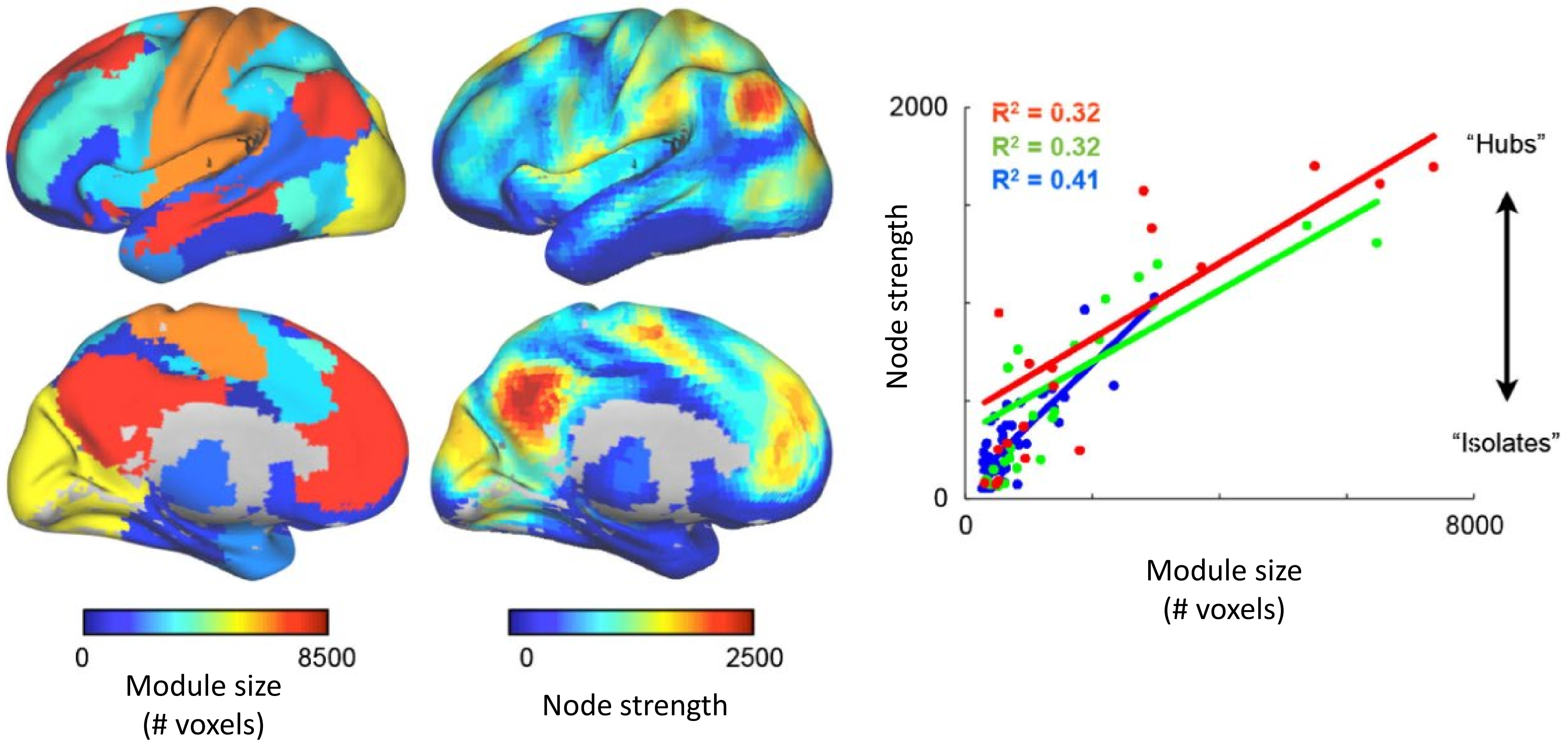
$$s_i = \sum_{j \neq i} w_{ij}$$

$$s_i^+ = \sum_{j \neq i} w_{ij}^+, \quad \text{and} \quad s_i^- = -\sum_{j \neq i} w_{ij}^- .$$

Fornito et al., 2016

Node roles: Hubs

Caution: Association between node strength and module size in correlation-based FC

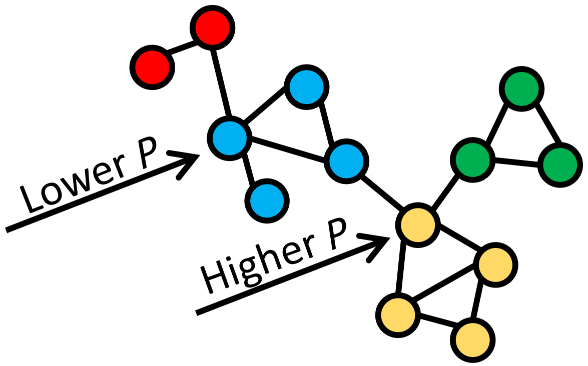


Power et al., 2013

Node roles

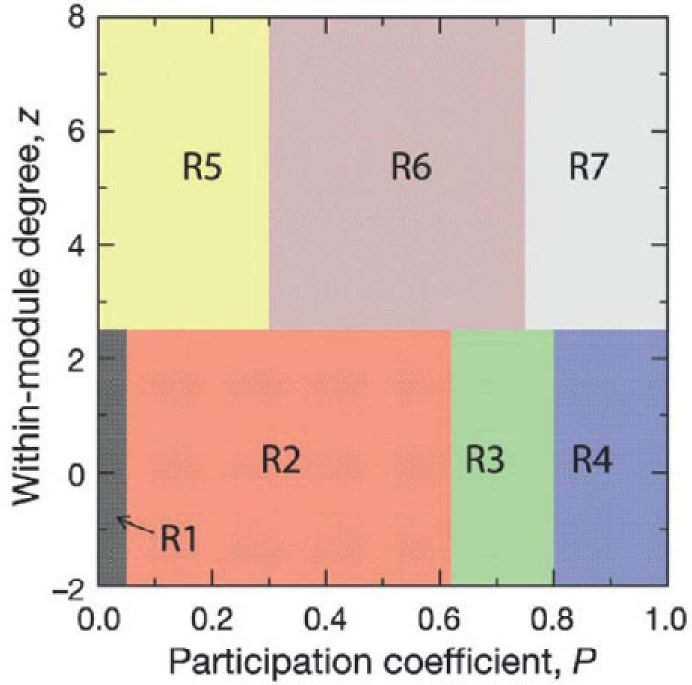
- **Within-module degree z-score** $z_i = \dfrac{k_i(m_i) - \bar{k}(m_i)}{\sigma_{k(m_i)}}$
  - Difference between
    - Within-module degree for node *i* (# connections linking node *i* to other nodes in the same module *m*)
    - Mean within-module degree of nodes in the same module as node *i*
  - Divided by standard deviation of *k*(*m*) values across all nodes in module *m*

- **Participation coefficient** $P_i = 1 - \sum_{m=1}^{M} \left(\dfrac{k_i(m)}{k_i} \right)^2$
  - How a node's links are distributed across different modules



Topological Roles for Network Nodes

Guimera & Amaral, 2005

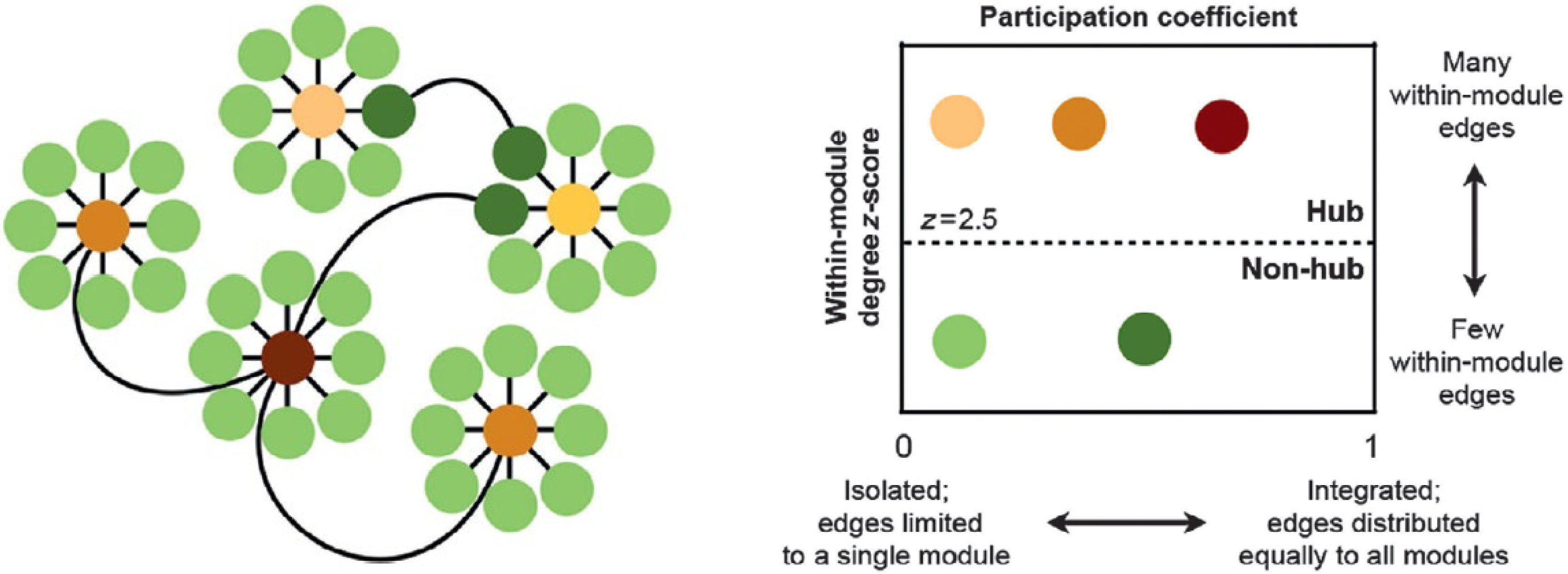


R5, provincial hub
R6, connector hub
R7, kinless hub

R1, ultra-peripheral
R2, peripheral
R3, nonhub connector
R4, nonhub kinless

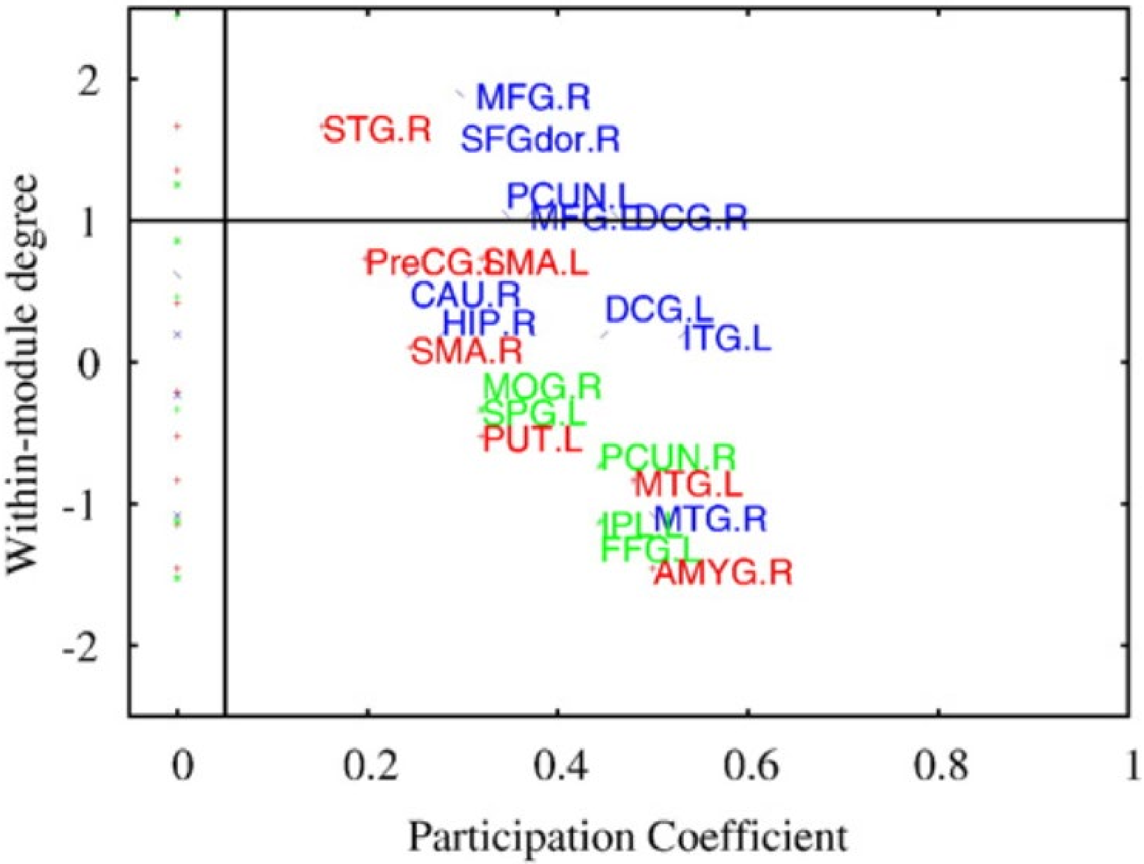
Node role distinctions in brain imaging

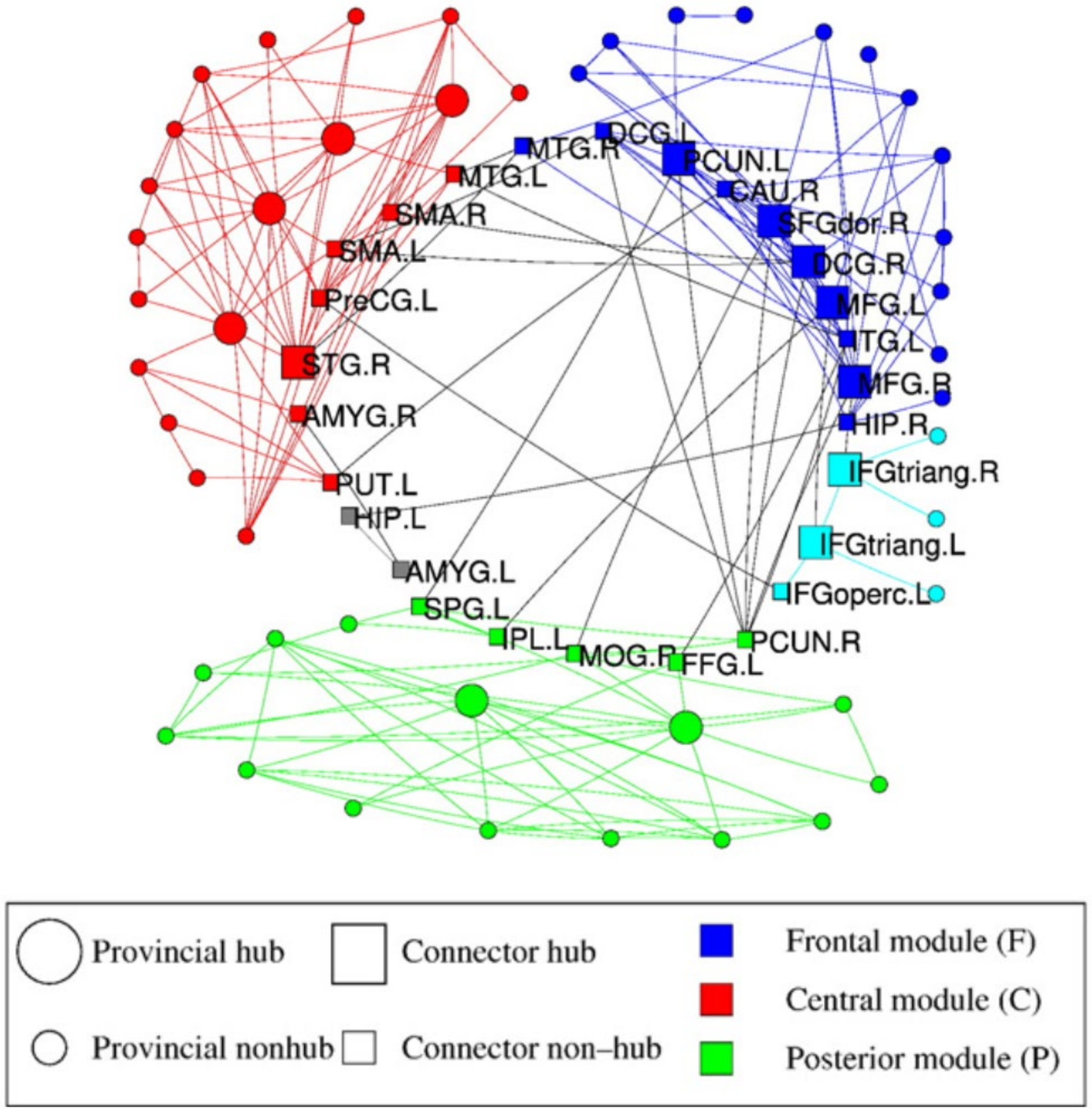
Power et al., 2013



Brain modules and regional node roles

Resting state data, 90 anatomically defined brain regions

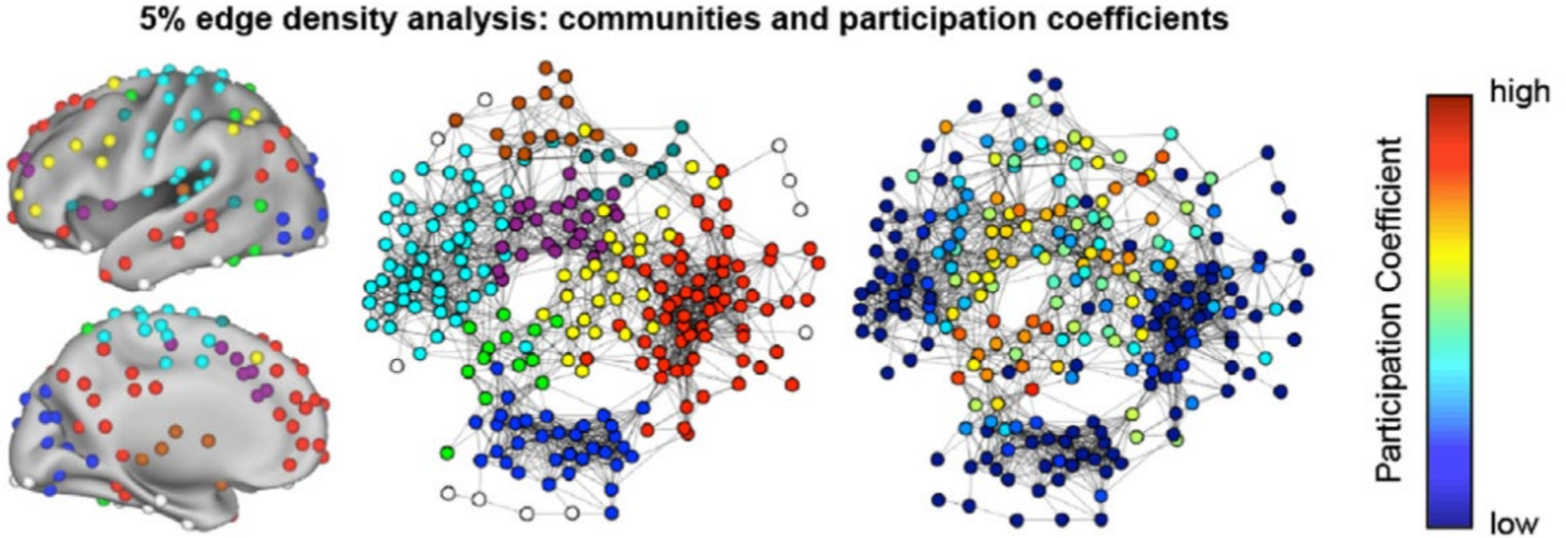




Meunier et al., 2009

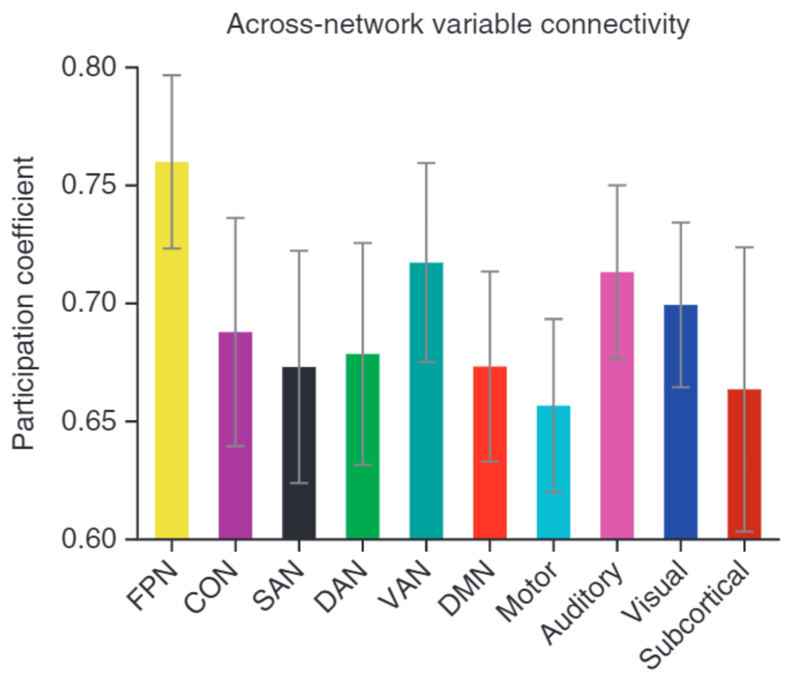
Variation of participation coefficient across the brain

During resting-state



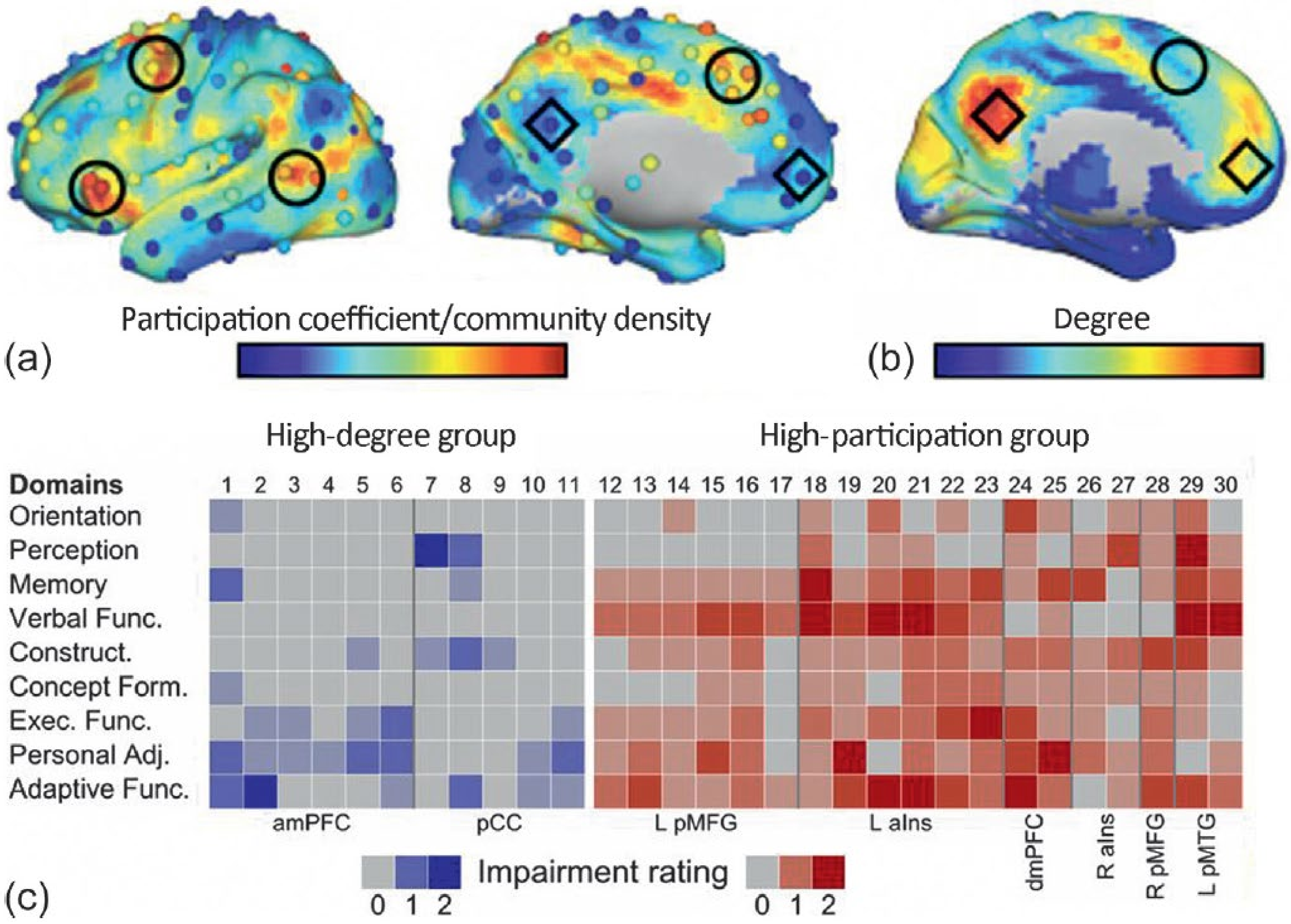
Power et al., 2013

Across tasks



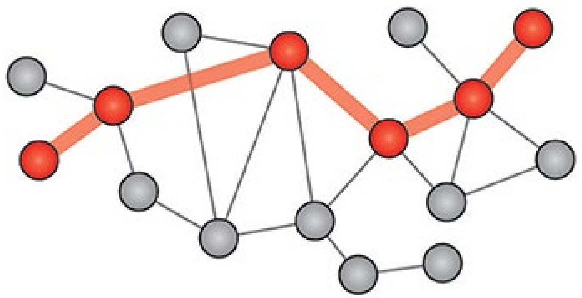
Cole et al., 2013

Experimental evidence: Neuropsychological deficits are more consistent and widespread in patients with lesions to areas with high community participation.



Warren et al., 2014; image: Fornito et al., 2016

Efficiency



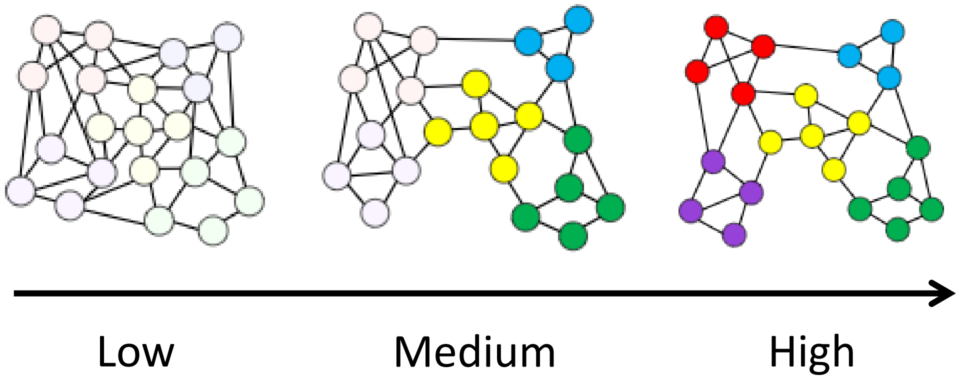
- Global efficiency $$E_{\text{glob}} = \frac{1}{L'} = \frac{1}{N(N-1)} \sum_{i \neq j} \frac{1}{l_{ij}}.$$
  - Efficiency of information exchange in a parallel system
- Nodal efficiency $$E_{\text{nodal}}(j) = \frac{1}{N-1} \sum_{i} \frac{1}{l_{ij}}.$$
  - Measures node integration within network
- Local efficiency $$E_{\text{loc}}(i) = \frac{1}{N_{G_i}(N_{G_i}-1)} \sum_{j,\, h \in G_i} \frac{1}{l_{jh}},$$
  - Measures integration between the immediate neighbors of a given node

image: Farahani et al., 2019

Network measures interpretation

- ***Modularity*** -> network distinctiveness,
  functional segregation

$$Q = \frac{1}{2E}\sum_{ij}[A_{ij} - \gamma e_{ij}]\delta(m_i, m_j)$$



- ***Global efficiency*** -> graph-wide integration,
  rapid information exchange

$$E_{glob} = \frac{1}{N(N-1)}\sum_{i \neq j}\frac{1}{L_{ij}}$$

- ***Local efficiency*** -> regional integration,
  fault tolerance

$$E_{loc}(i) = \frac{1}{N_{G_i}(N_{G_i}-1)}\sum_{j,h \in G_i}\frac{1}{L_{jh}}$$

Wig, 2017

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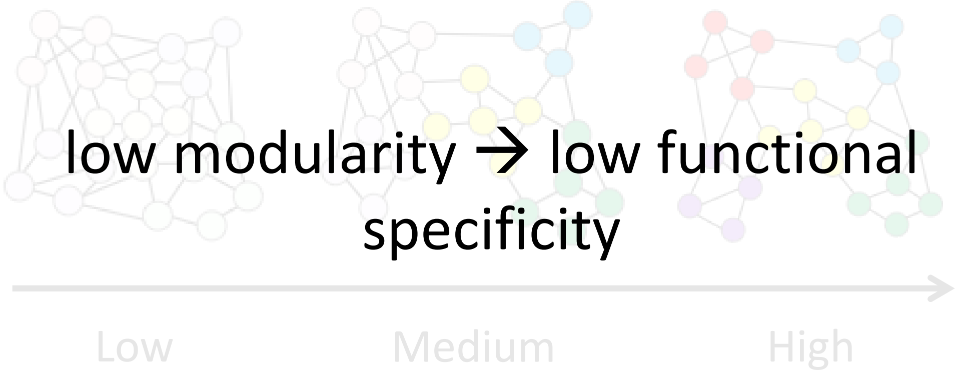

low modularity → low functional specificity

Wig, 2017

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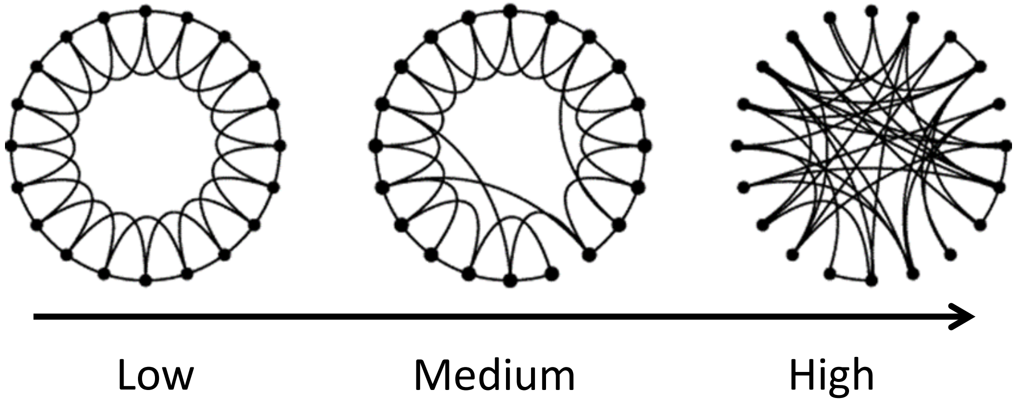

Watts & Strogatz, 1998

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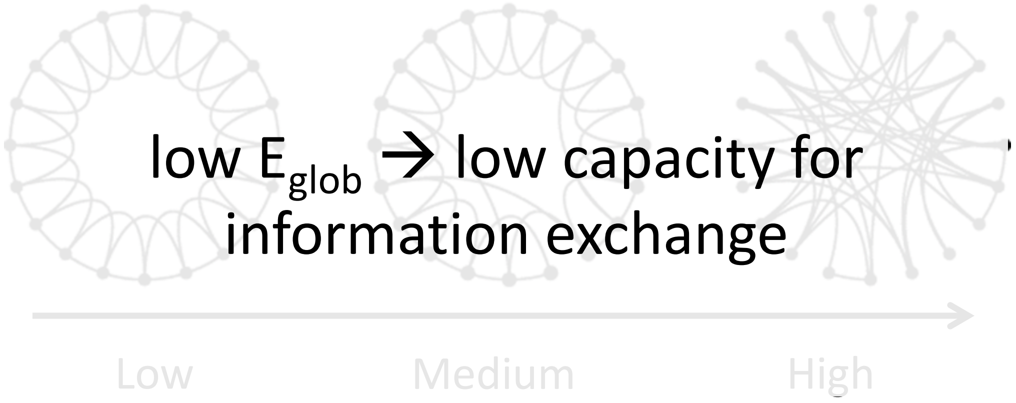

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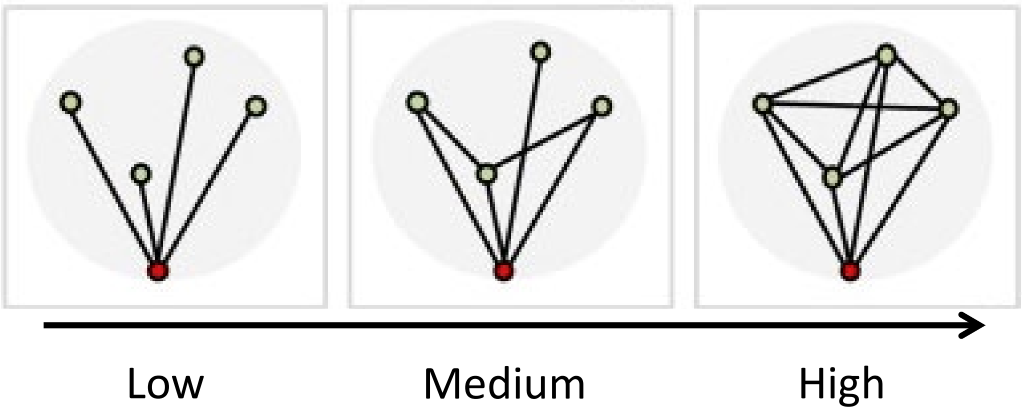

Onoda & Yamaguchi, 2015

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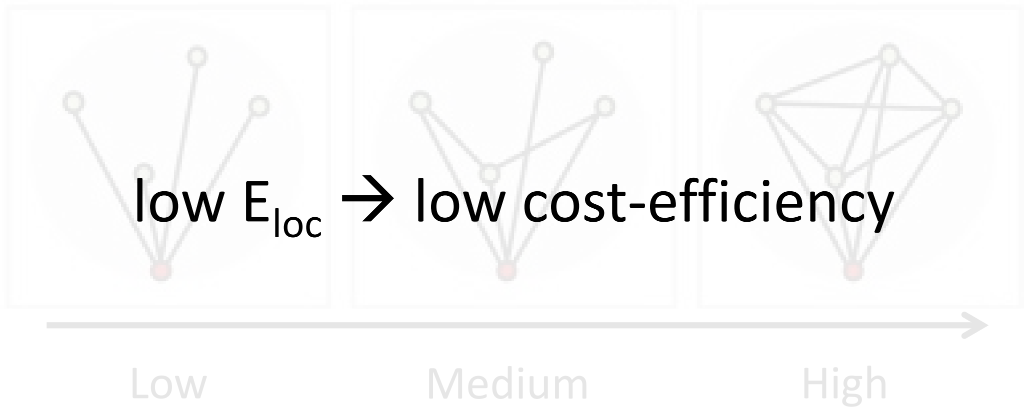


low E_{loc} → low cost-efficiency

Onoda & Yamaguchi, 2015

Comparing partitions

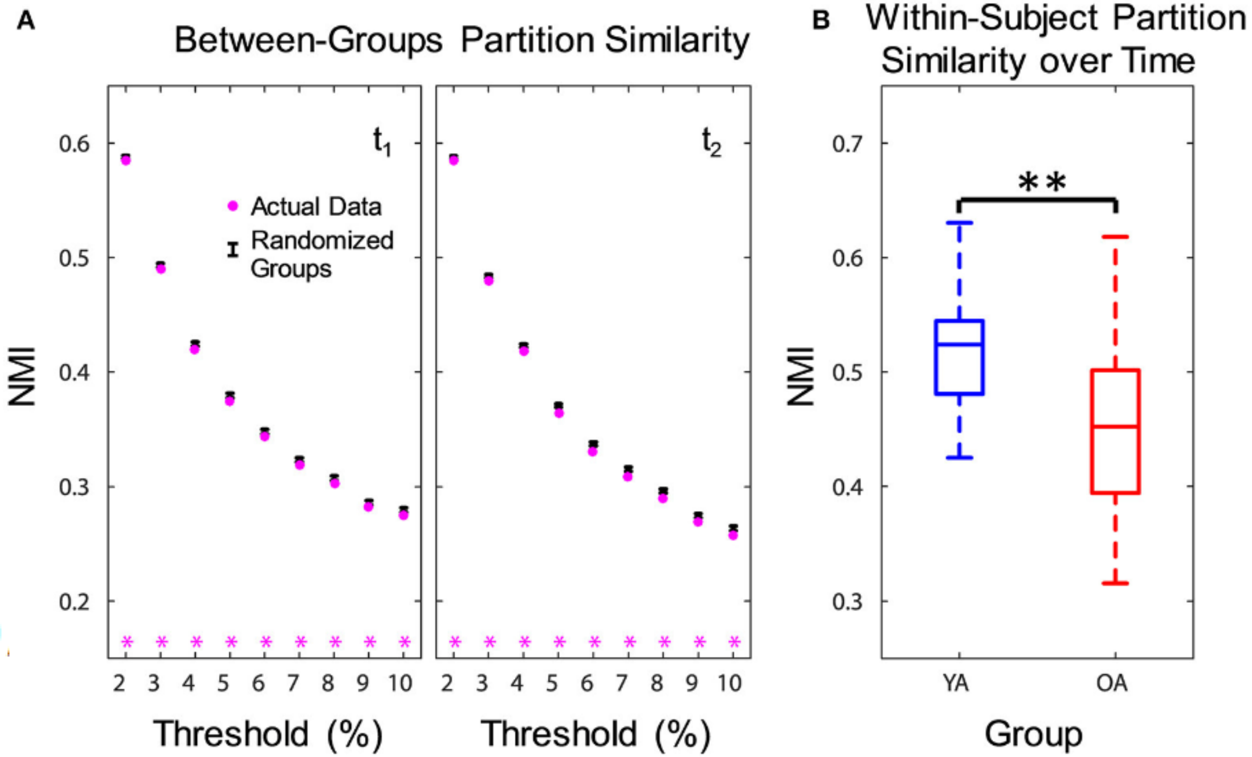
- **Mutual information**: degree to which knowing the community assignment of a node in partition Y reduces uncertainty about that node's community assignment in partition X

  - Normalized mutual information

$$MI'(X,Y) = \frac{2\mathrm{MI}(X,Y)}{H(X)+H(Y)}.$$

  - Variation of information (metric of partition distance)

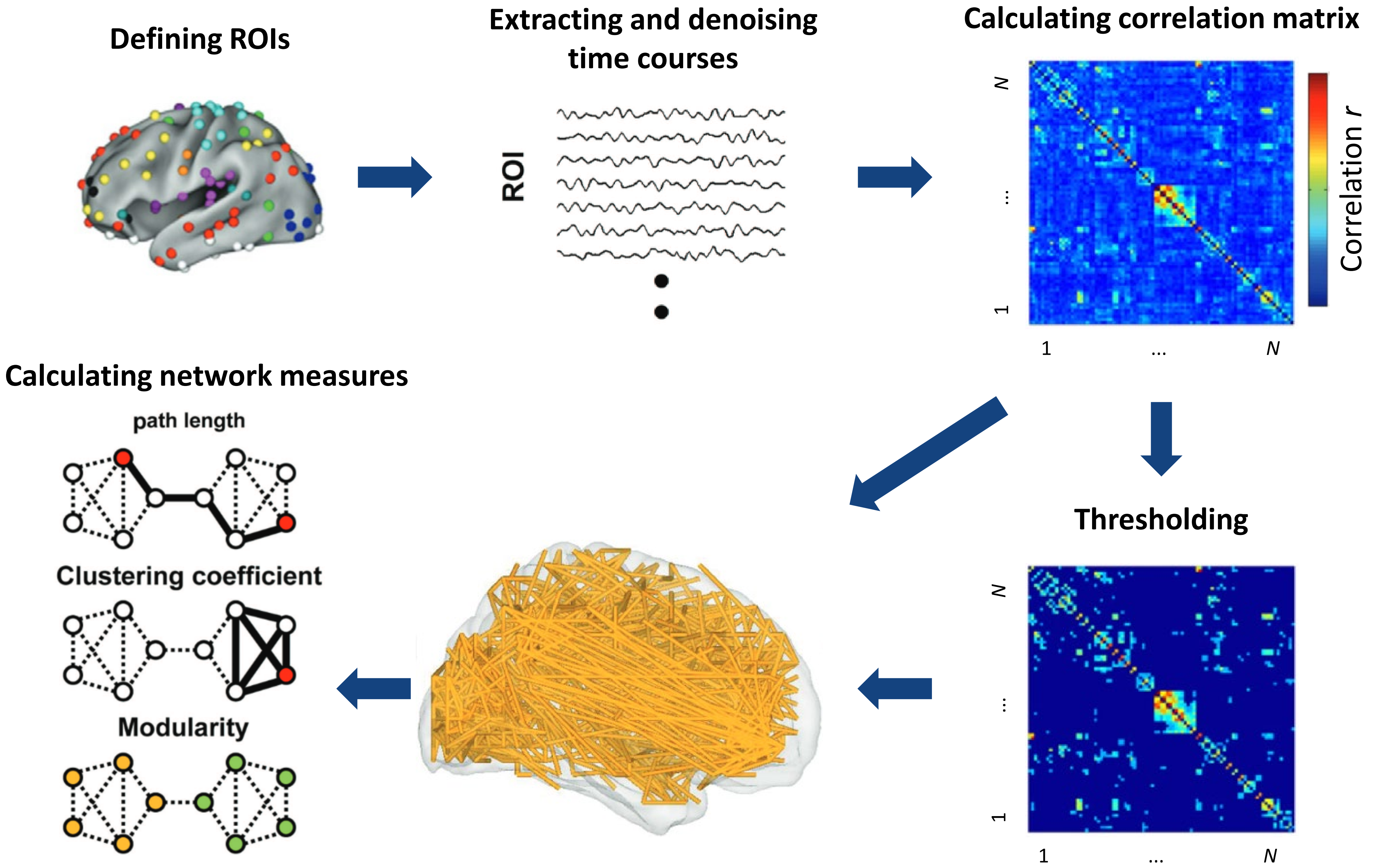
$$VI(X,Y) = H(X) + H(Y) - 2MI(X,Y)$$



Iordan et al., 2018

Methodological issues

Procedure

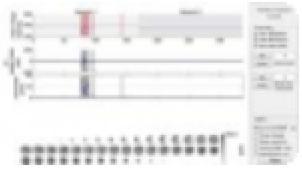


images: Uehara et al., 2013; Taya et al., 2016; Power et al., 2013

Tools

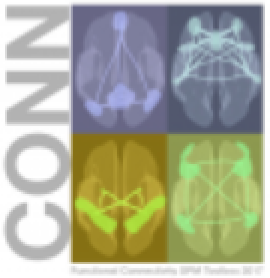
NITRC
The source for neuroinformatics tools & resources
Neuroimaging data repository
Cloud computing environment

Artifact Detection Tools (ART)



Toolbox for post-processing fMRI data. Includes software for comprehensive analysis of sources of artifacts in timeseries data including spiking and motion. Most compatible with SPM processing, but adaptable for FSL as well.

CONN : functional connectivity toolbox



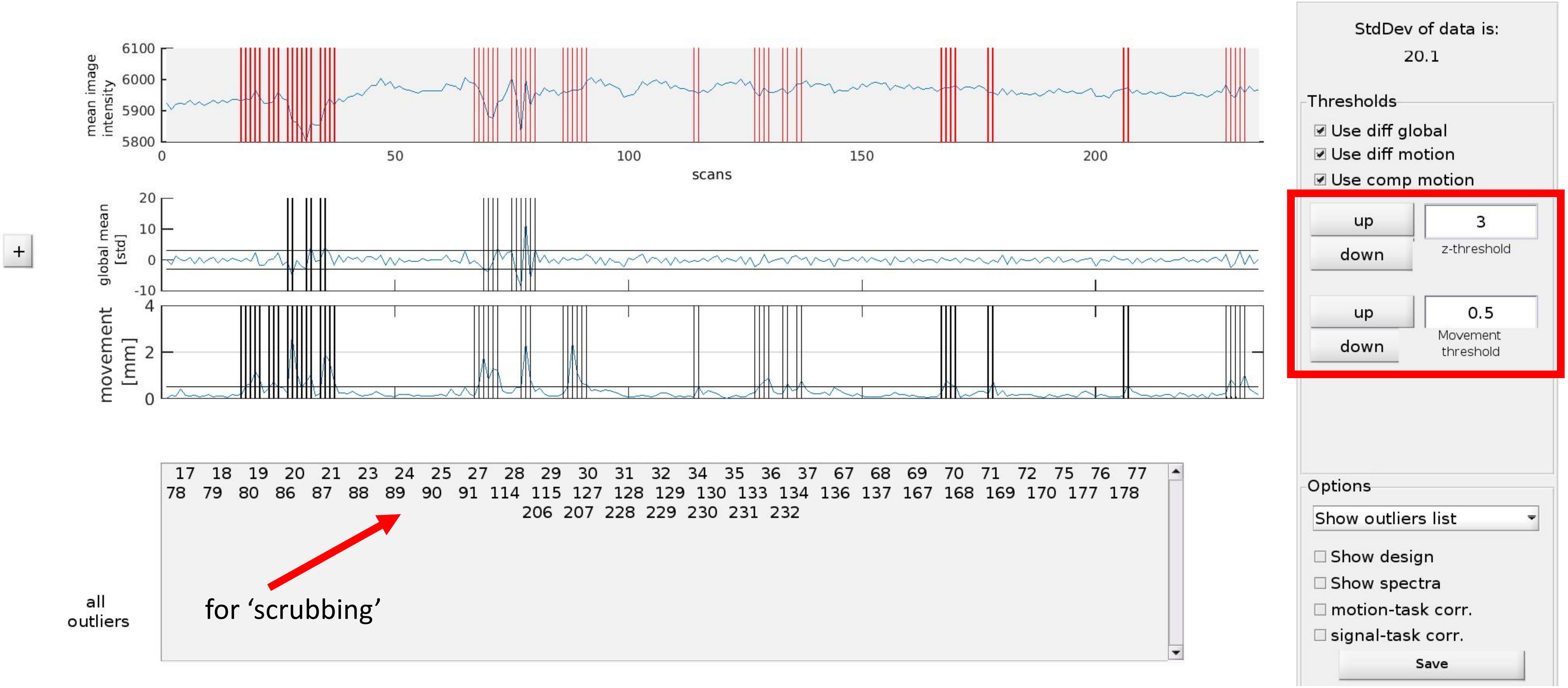
CONN is a Matlab-based cross-platform software for the computation, display, and analysis of functional connectivity in fMRI (fcMRI).

CONN includes a rich set of connectivity analyses (seed-based correlations, ROI-to-ROI graph analyses, group ICA, masked ICA, generalized PPI, ALFF, ICC, GCOR, LCOR, etc.) in a simple-to-use and powerful software package

Brain Connectivity Toolbox

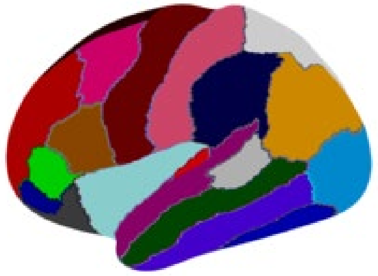
The Brain Connectivity Toolbox (brain-connectivity-toolbox.net) is a MATLAB toolbox for complex-network (graph) analysis of structural and functional brain-connectivity data sets. Several people have contributed to the toolbox and users are welcome to contribute new functions with due acknowledgement.

Identifying outlier volumes (ART)



Choosing ROI atlas

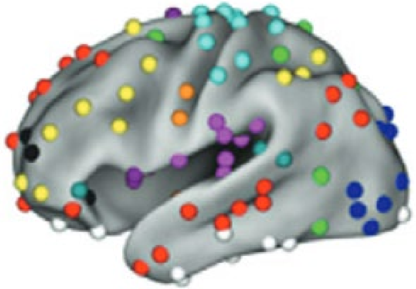
Anatomical



Tzurio-Mazoyer et al., 2002
Desikan et al., 2006

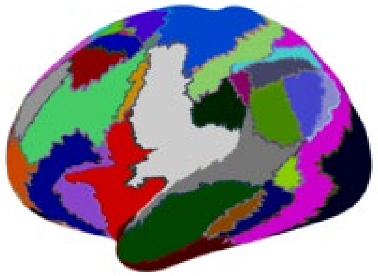
Functional

Meta-analytical



Dosenbach et al., 2010
Power et al., 2011

Data-driven



Yeo et al., 2011
Craddock et al., 2012

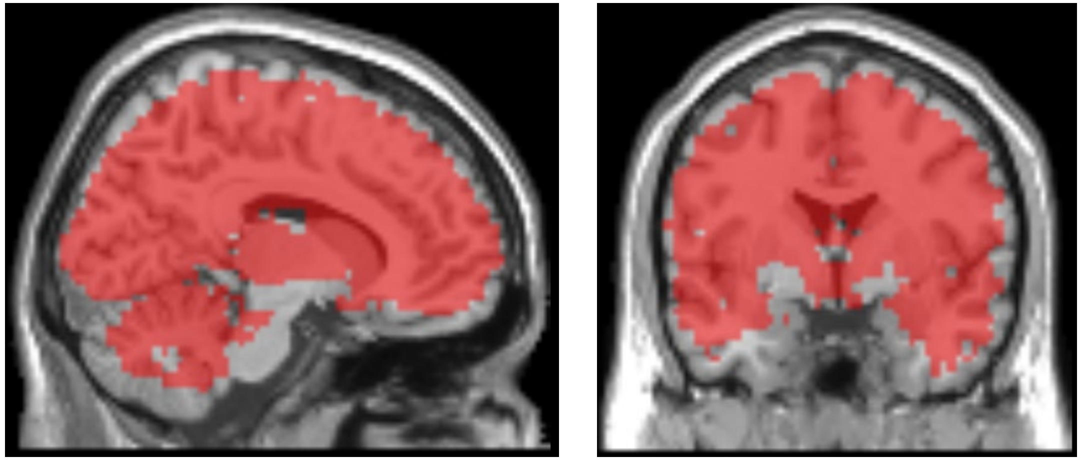
Multi-modal

Glasser et al., 2016

images: biomedia.doc.ic.ac.uk; Power et al., (2013)

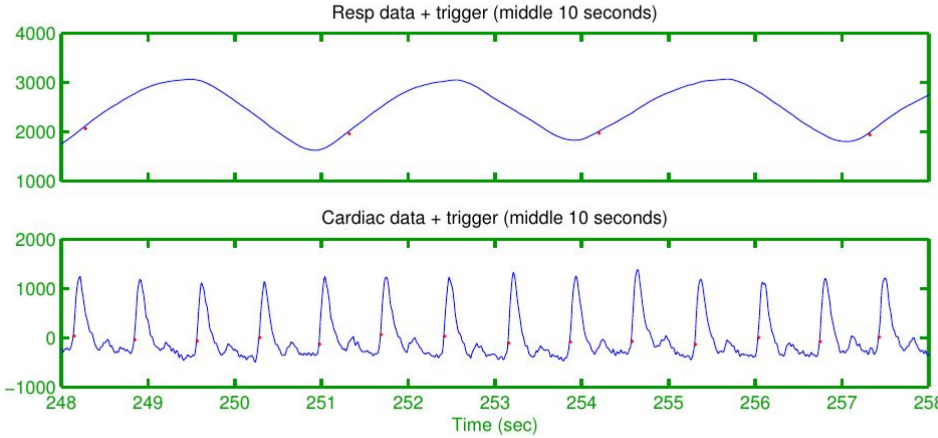
Signal vs. Noise

Signal Intensity Mask

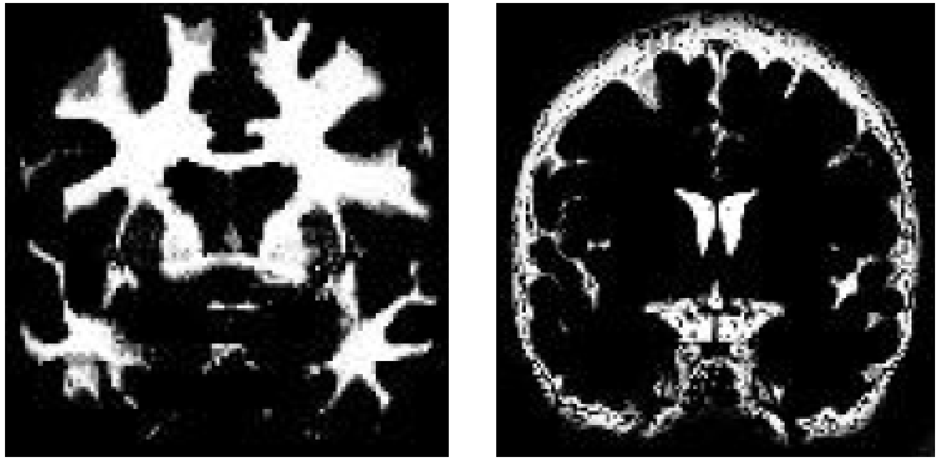


Excluding ROIs that lack good coverage.

Physiological noise



WM and CSF Masks

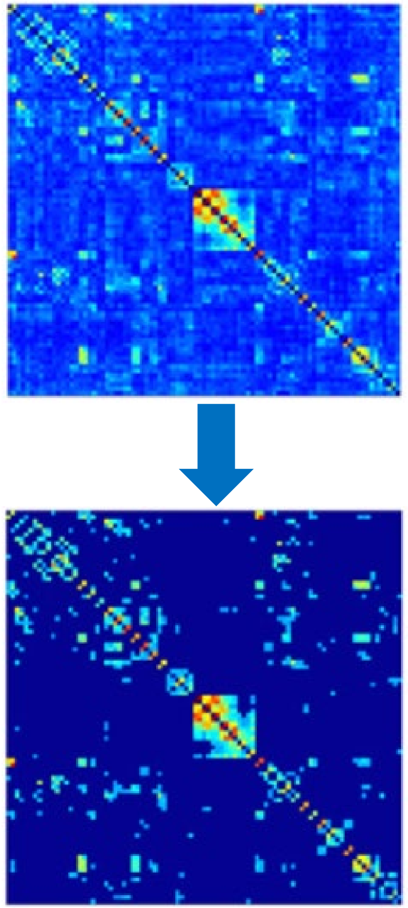


Removing physiological and other sources of noise

- aCompCor (Behzadi et al., 2007) temporal covariates:
  - signal extracted from noise ROIs (white matter, CSF) (PCA)
  - motion parameters (+ derivatives)
  - regressors for outlier volumes (‘scrubbing’)
- band-pass filtering – e.g. [.01 .1]
- detrending
- despiking

Issues re: Thresholding

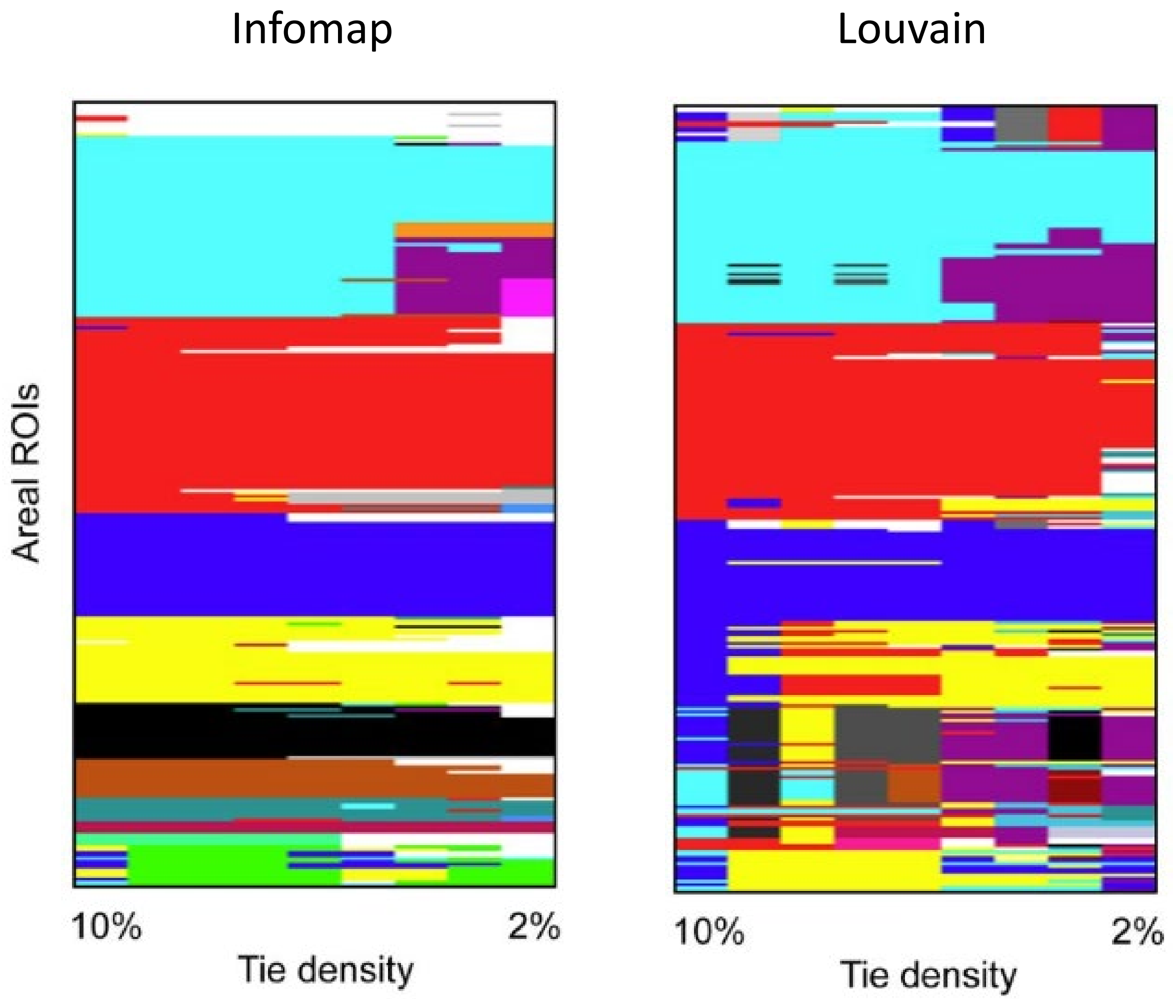
- Is it necessary to threshold or binarize?
- Comparing partitions between 2 groups:
  - Weight-based/absolute thresholding
    - Measures may be influenced by trivial differences in the number of edges.
  - Density/'cost'-based thresholding
    - Adequate if groups are matched in edge weight-distribution.
    - Otherwise, may be influenced by spurious edges.
- Use stringent thresholds
  - False positives are more detrimental than false negatives!



Zalesky, OHBM, 2017; Zalesky et al., 2016; image: Taya et al., 2016

Community detection

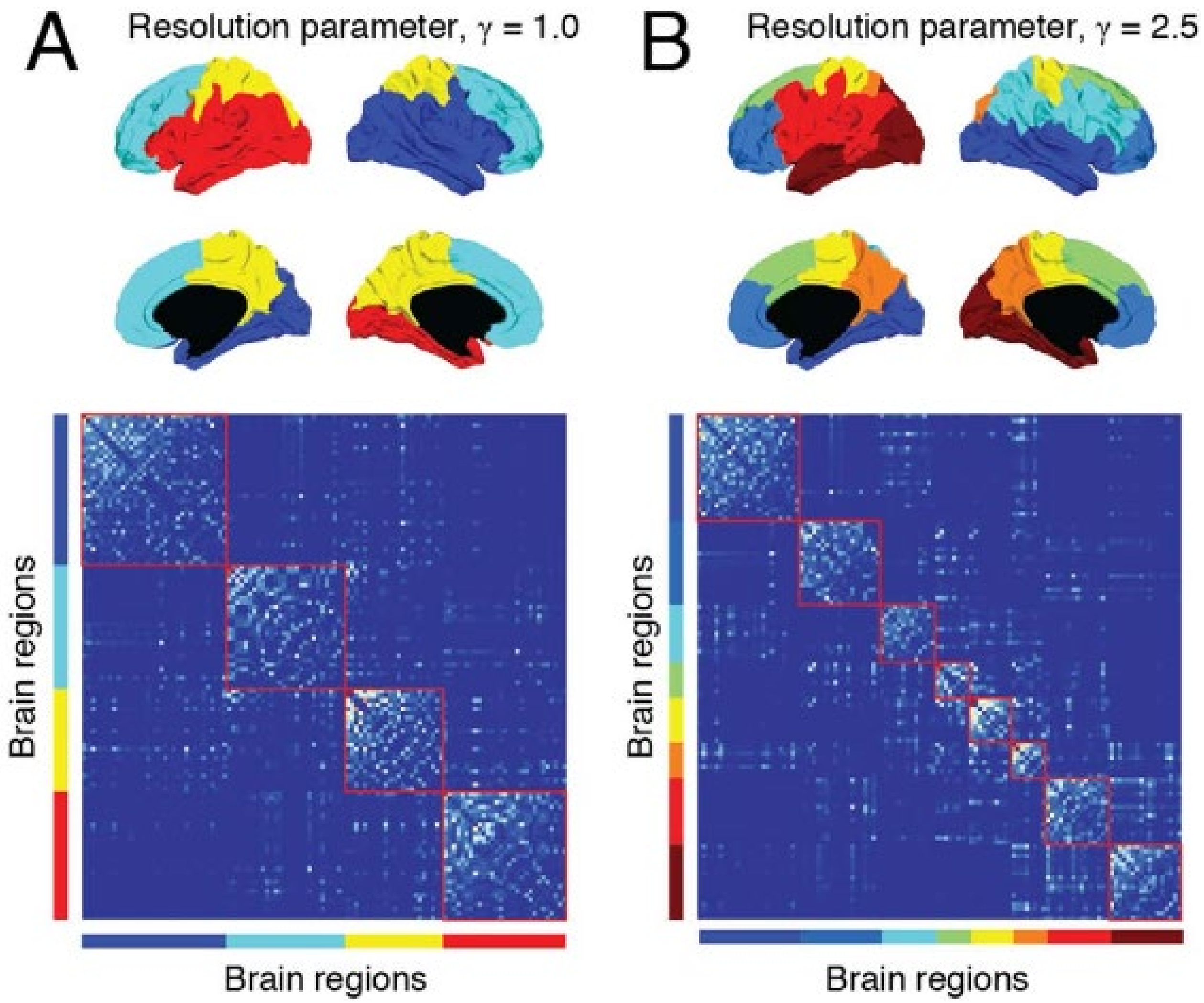
- Algorithms
  - 'Louvain' (Blondel et al., 2008)
  - 'Infomap' (Rosvall & Bergstrom, 2008)
  - …
- Resolution
- Degeneracy
- Consensus clustering



Power et al., 2011

Community detection

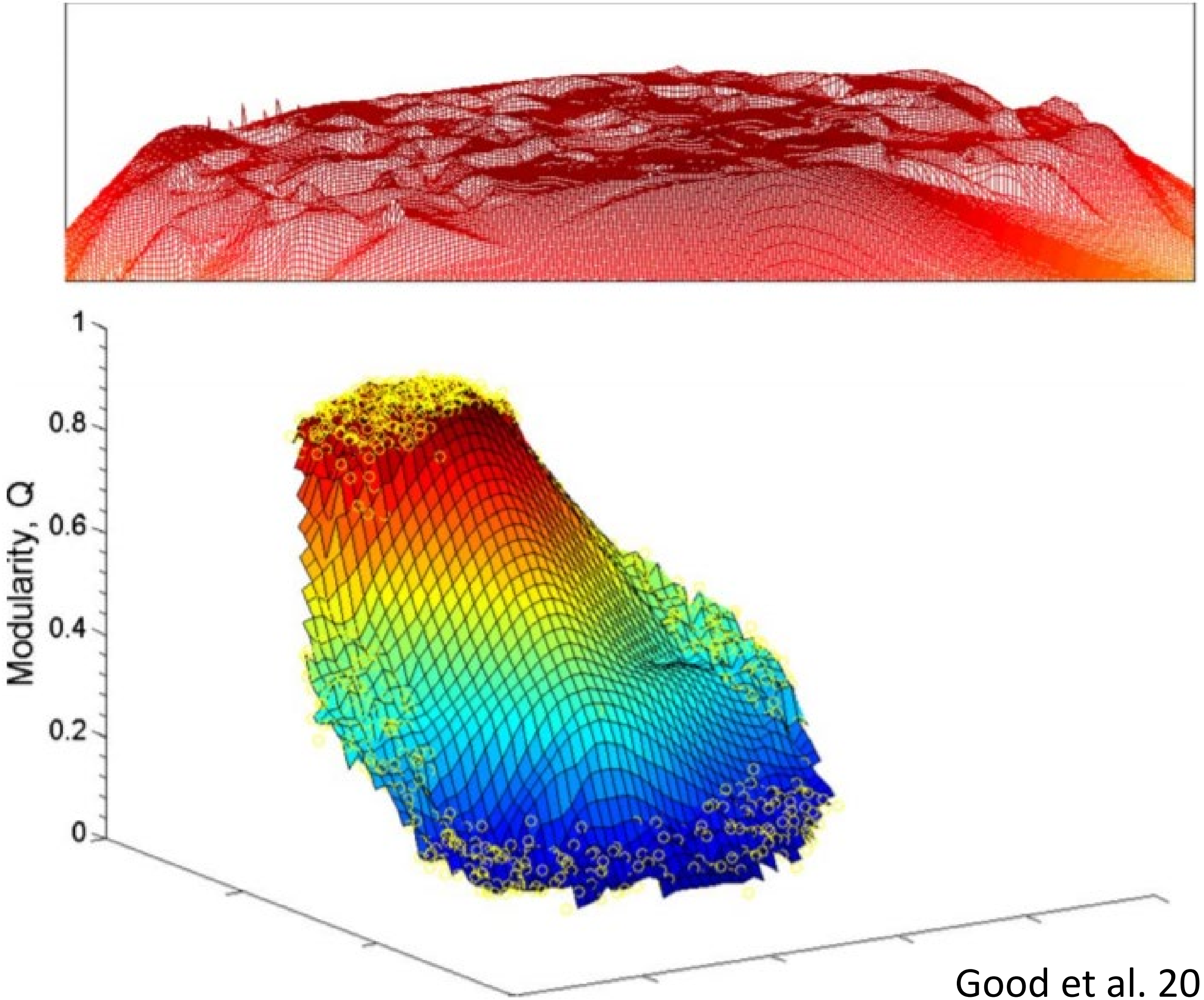
- Algorithms
- Resolution
  - Multi-scale community detection
- Degeneracy
- Consensus clustering



Betzel & Bassett, 2016

Community detection

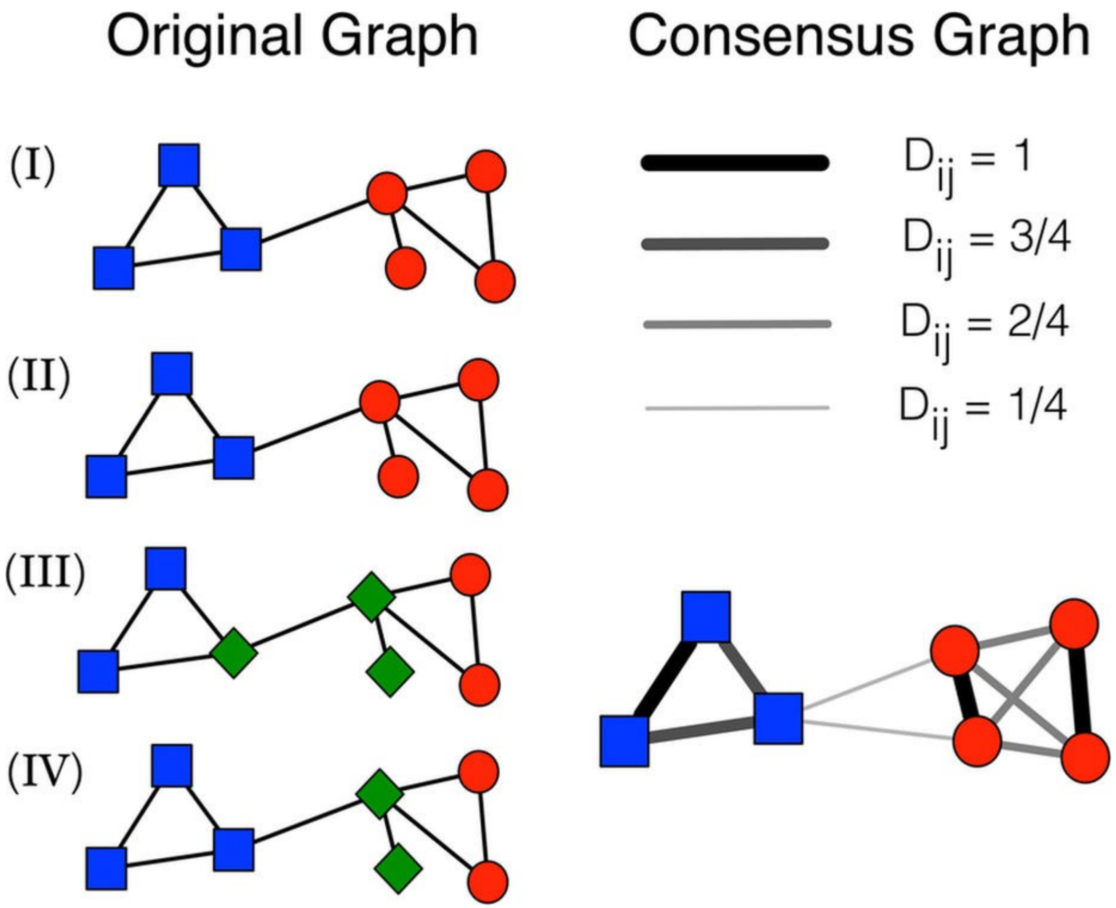
- Algorithms
- Resolution
- Degeneracy
  - There is no clear maximum modularity
- Consensus clustering



Good et al. 2010

Community detection

- Algorithms
- Resolution
- Degeneracy
- Consensus clustering
  - Building a representative partition



Lancichinetti & Fortunato, 2012

Application

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RESEARCH ARTICLE

WILEY

Age differences in functional network reconfiguration with working memory training

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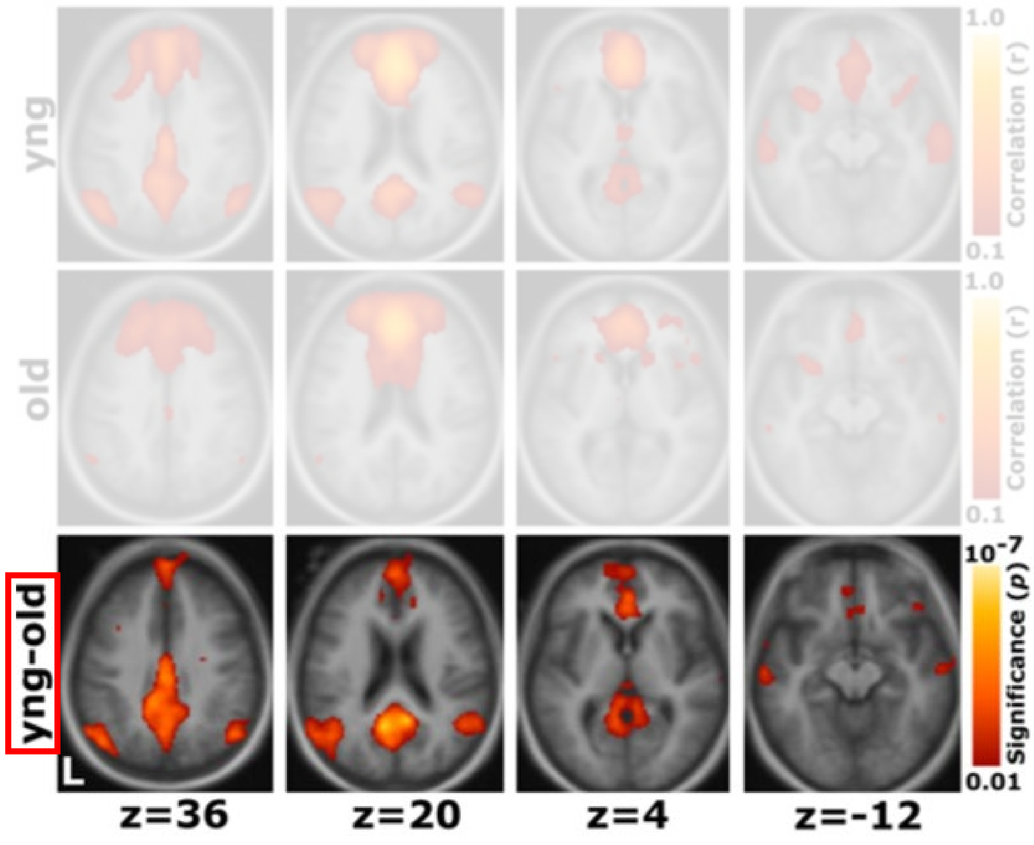
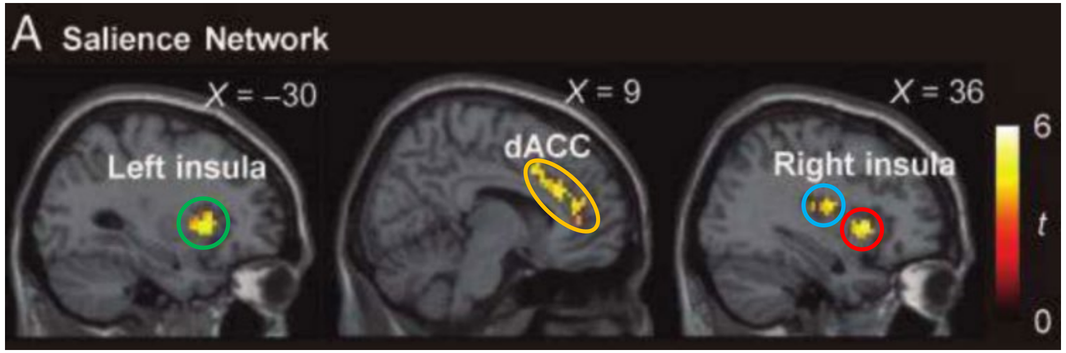
Aging influences the functional organization of the brain

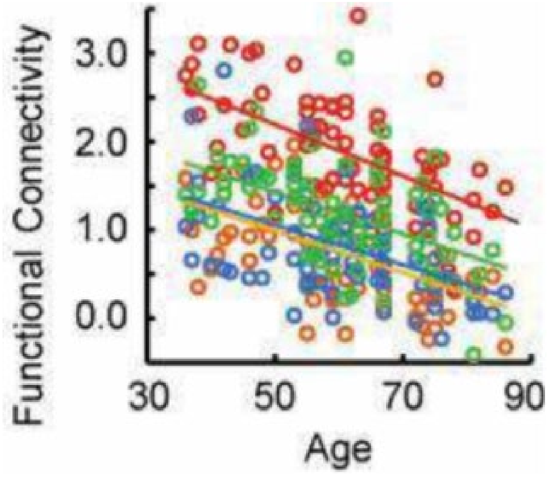
Default-mode Network



Andrews-Hanna et al., 2007

Salience/Cingulo-Opercular Network

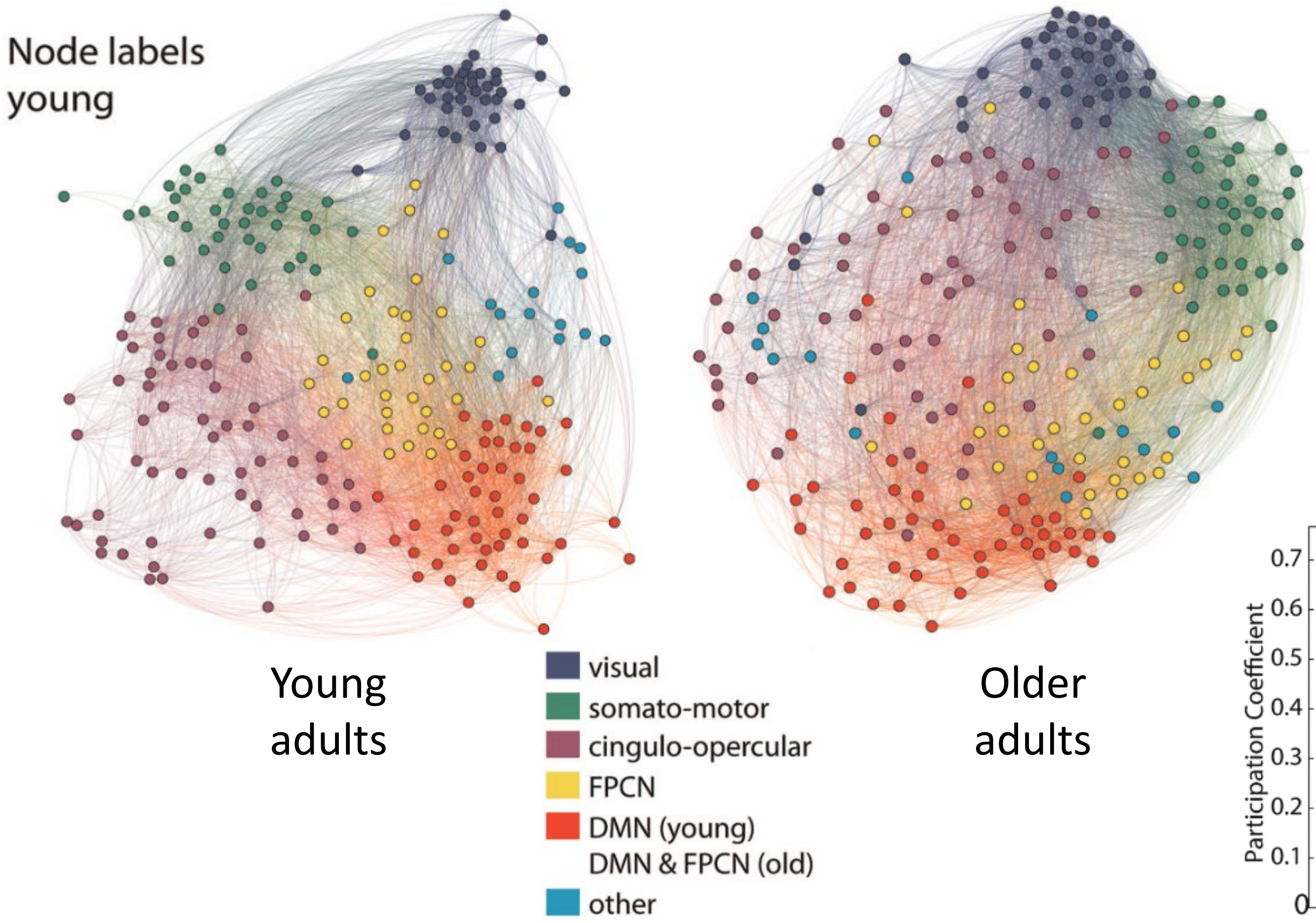




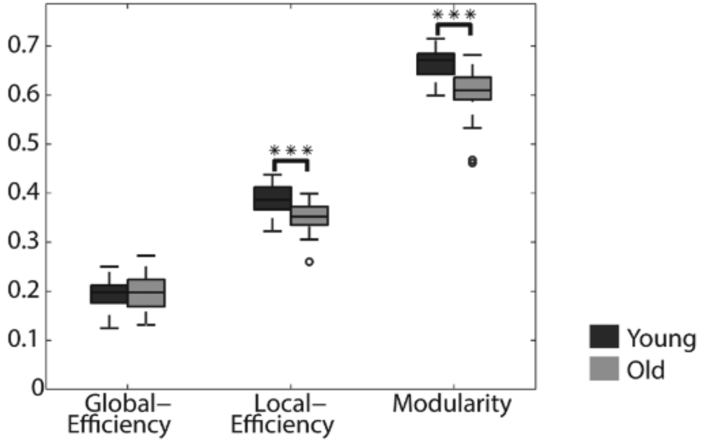
Onoda et al., 2012

Evidence for network differences between young and older adults

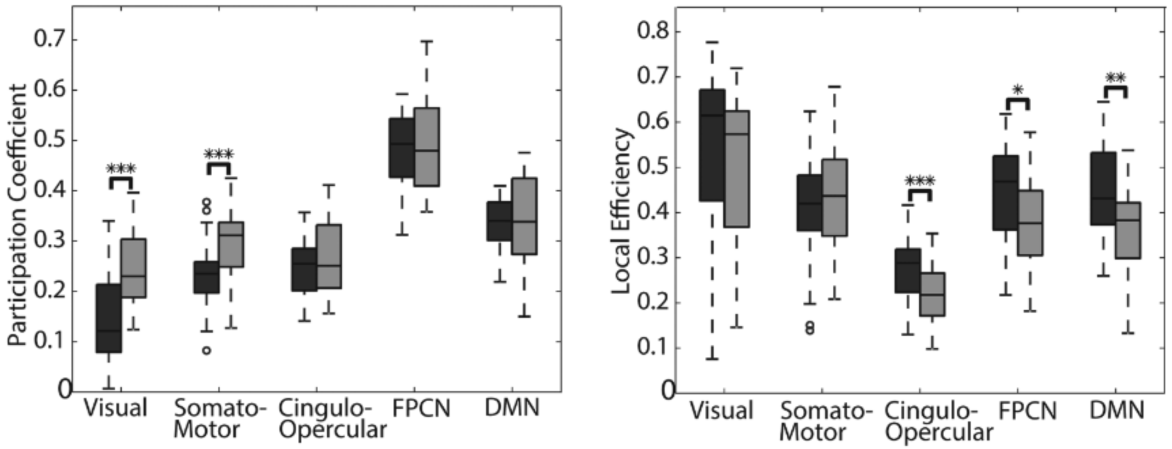
Differences in community structure



Differences in brain-wide network measures

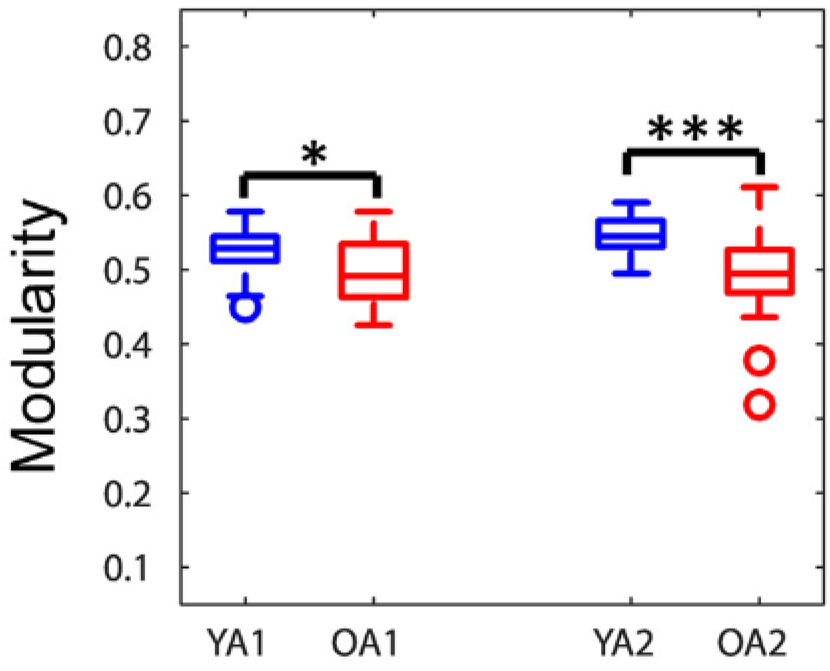


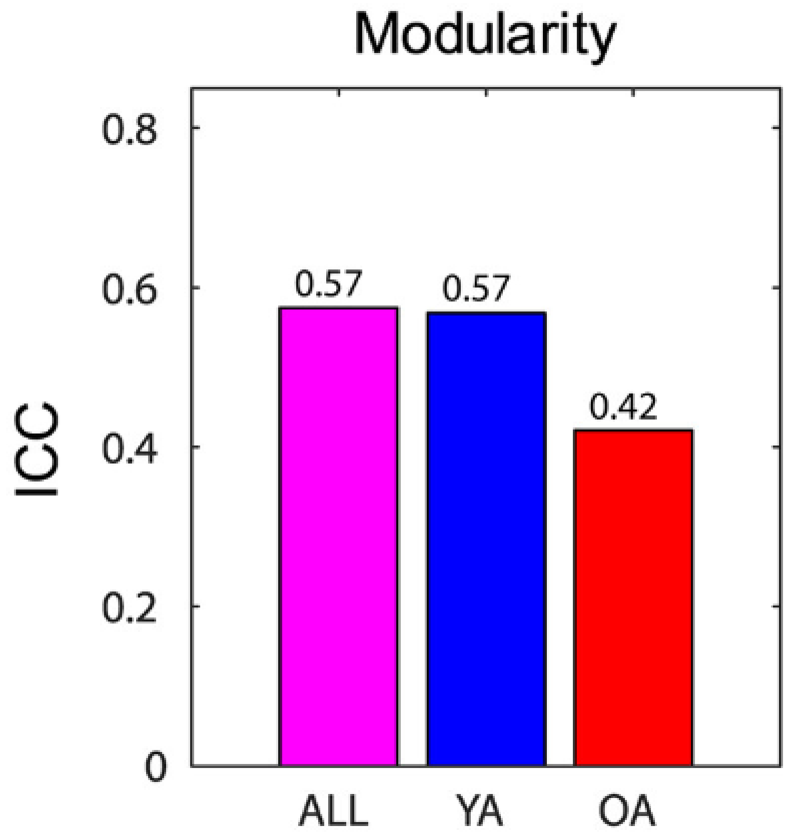
Differences in individual network measures



Geerligs et al., 2015

Modularity decreases with aging





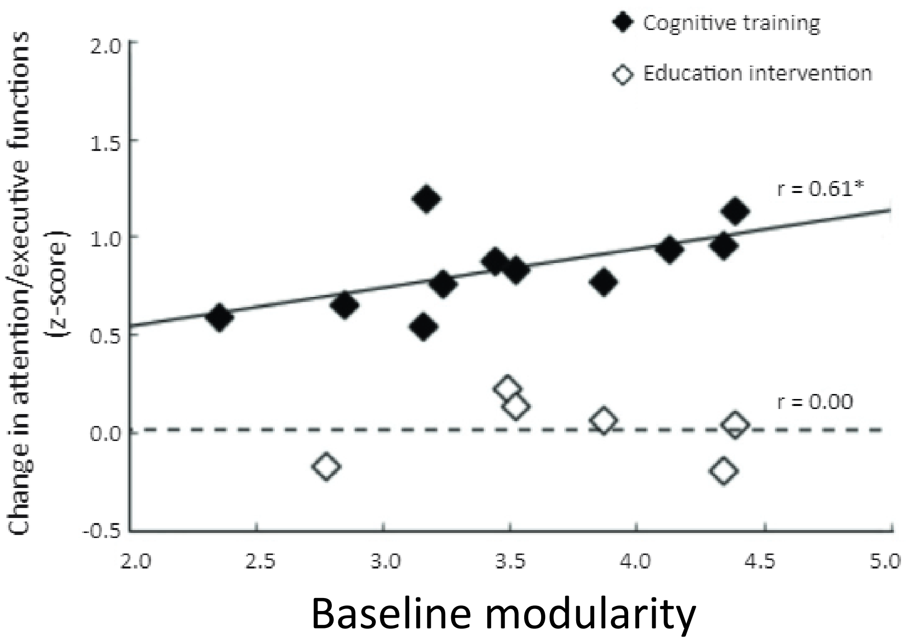
Similar results:
Betzel et al., 2014; Cao et al., 2014; Chan et al., 2014; Gallen et al., 2016;
Geerligs et al., 2015; Onoda & Yamaguchi, 2013; Song et al., 2014

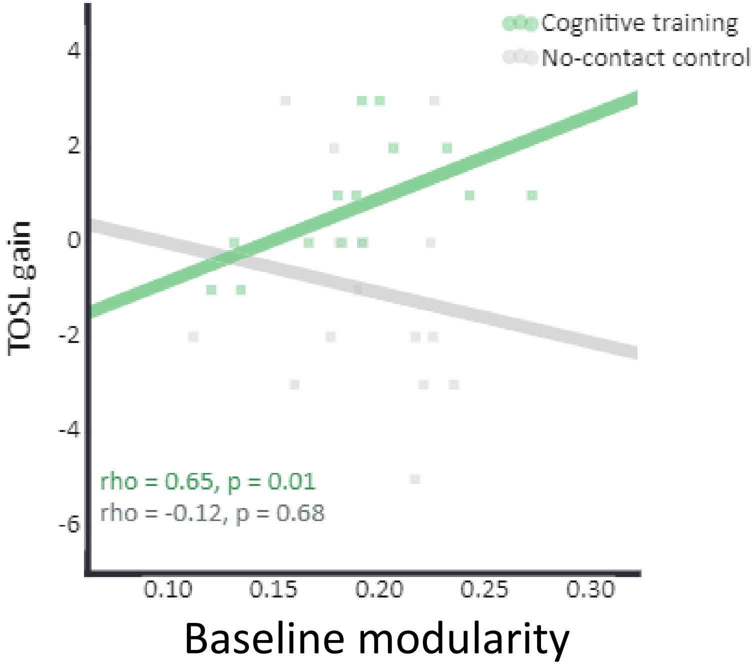
Iordan et al., 2018

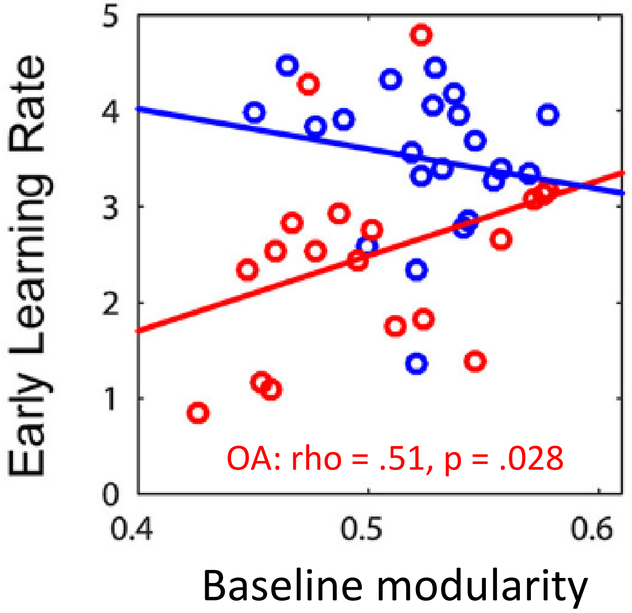
Modularity Predicts Training-related Cognitive Gains

Patients with
acquired brain injury

Healthy older adults







Arneman et al., 2015

Gallen et al., 2016

Iordan et al., 2018

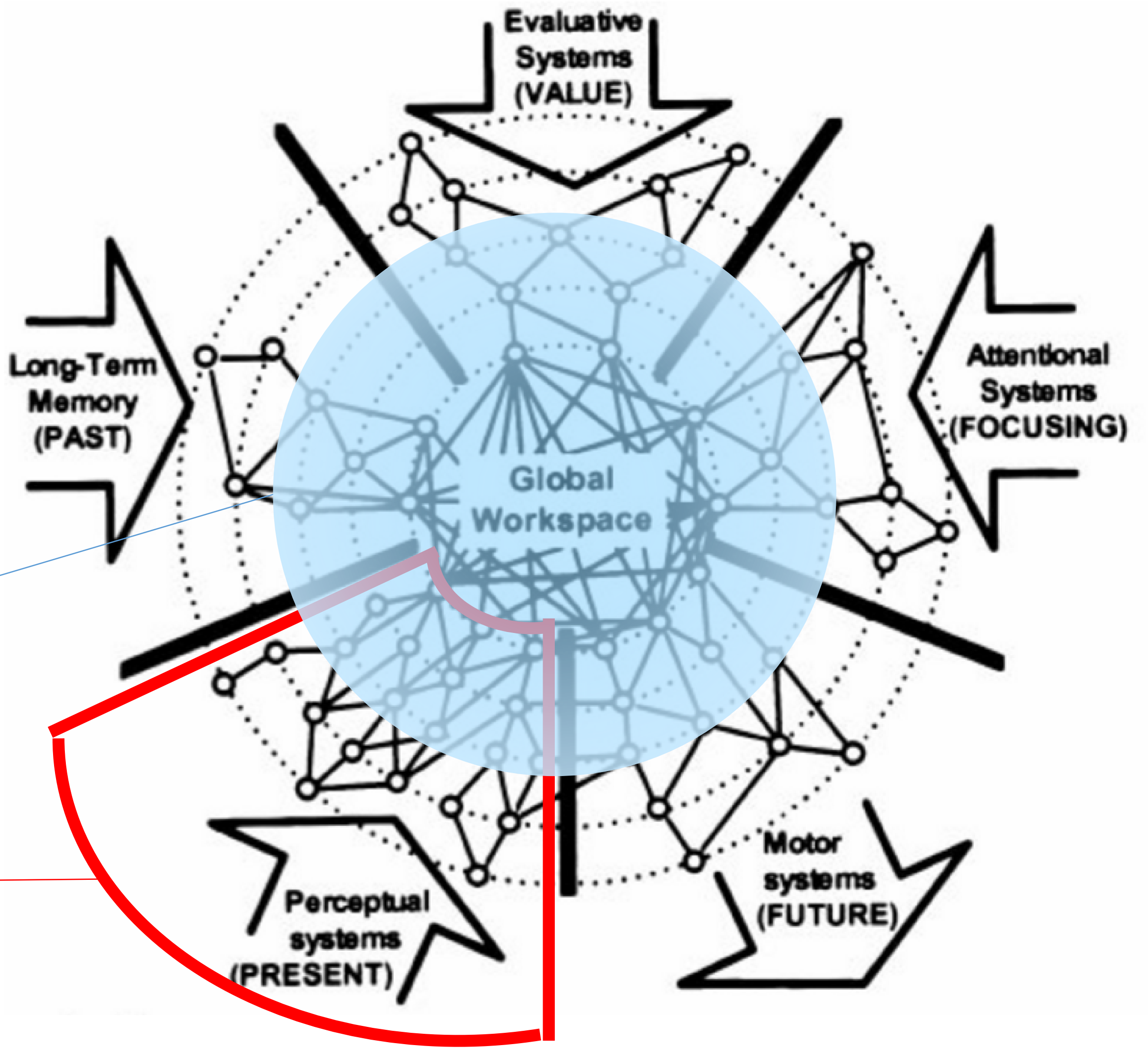
Cognitive modules and global workspace

- *Modularity of mind* (Fodor, 1983)

- Functional segregation & integration

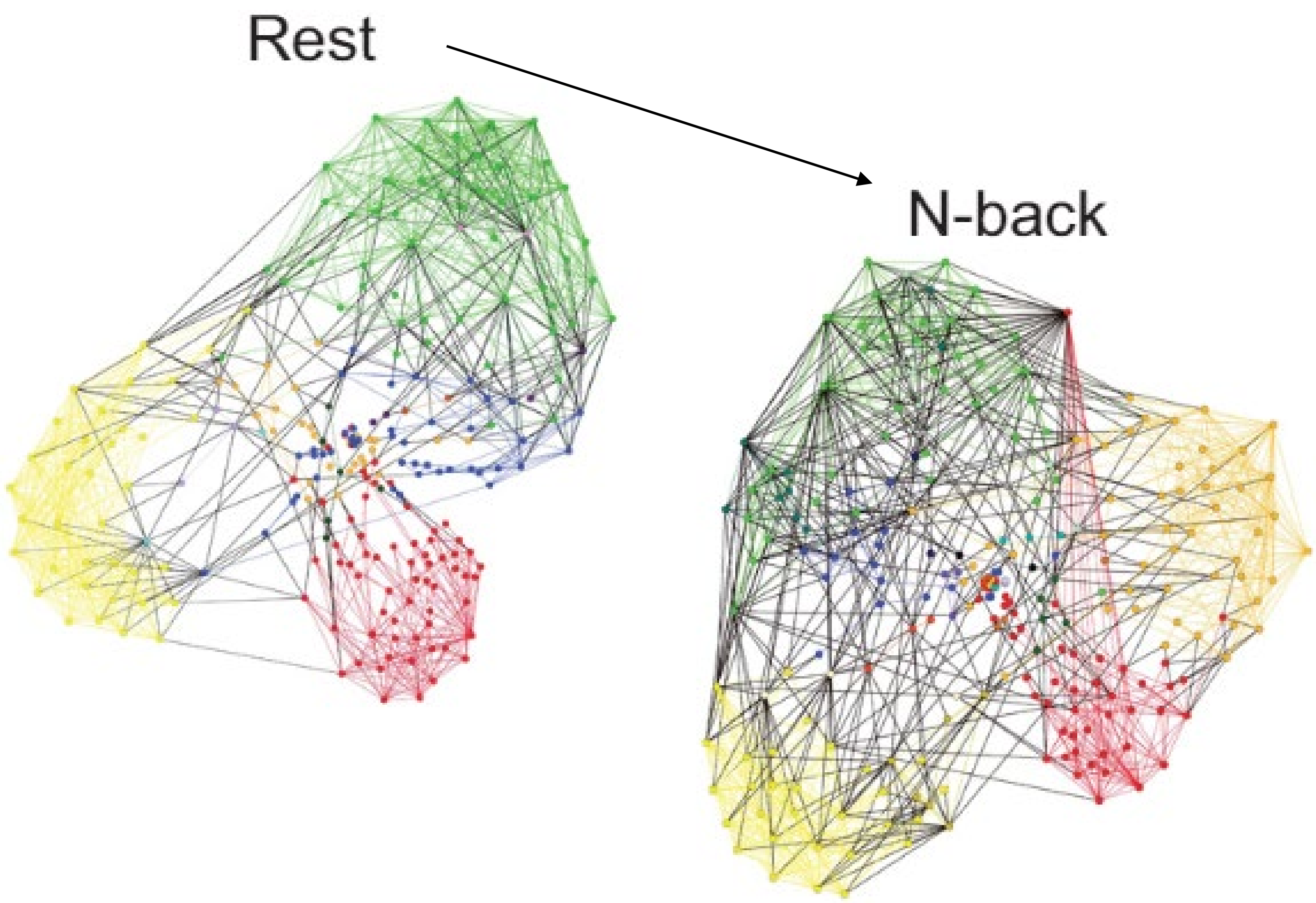
High-level cognitive functions (eg. WM) - rely more on a ***global workspace*** than on segregated modular functions.

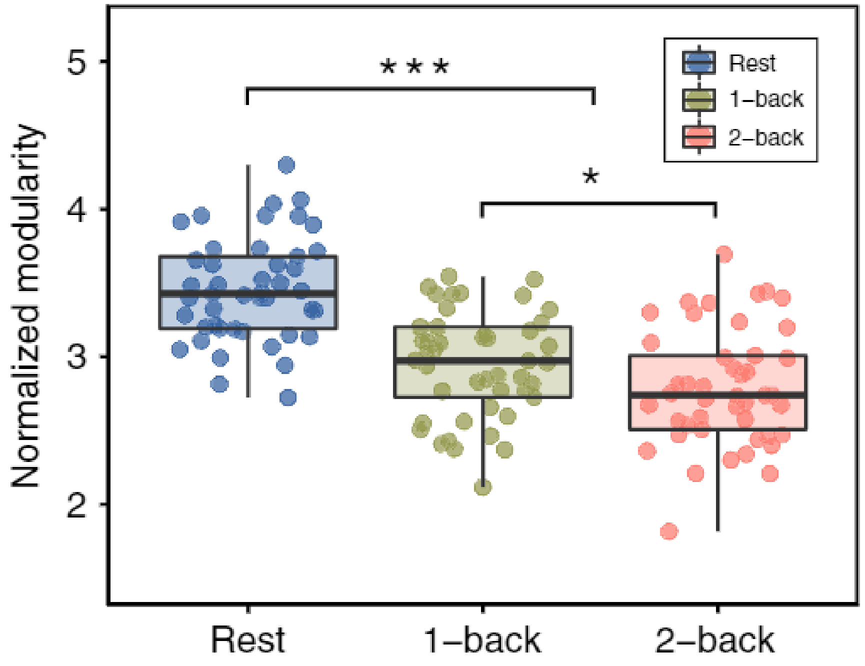
Modules - spatially localized and include specialized brain areas (visual, auditory, motor ...)



Dehaene et al., 1998

Modularity decreases with increasing cognitive demand

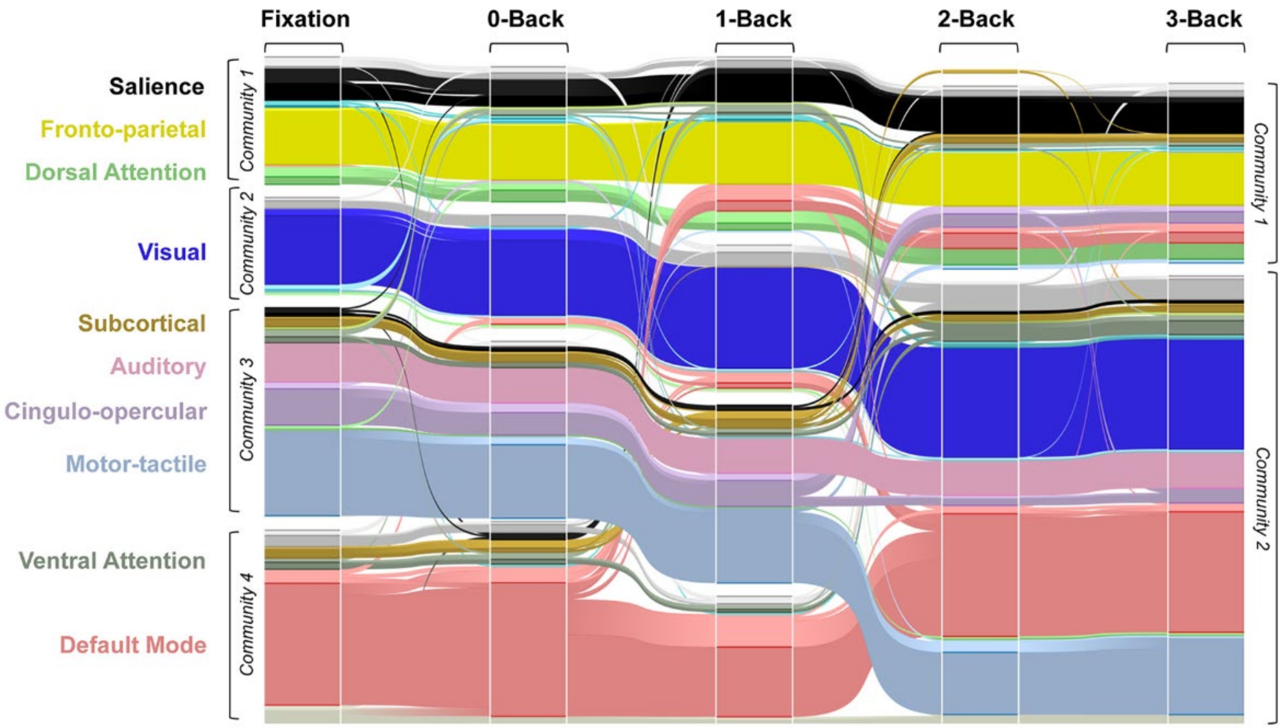




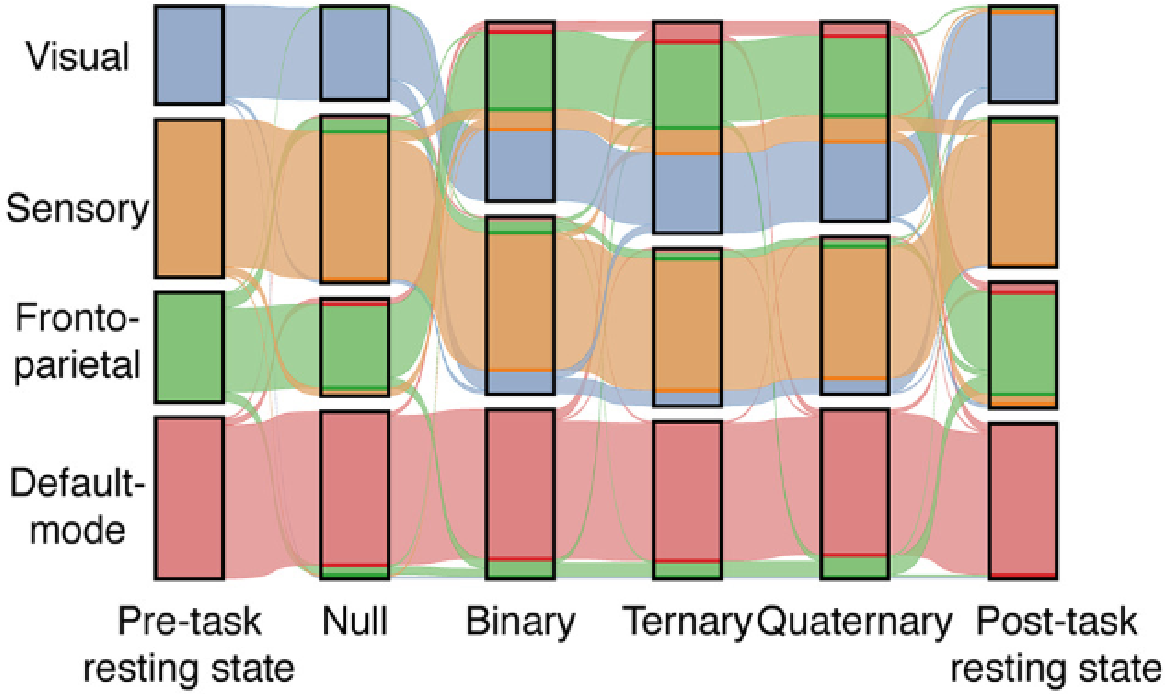
Cohen & D'Esposito, 2016

Finc et al., 2020

Community structure is influenced by (large shifts in) cognitive demand

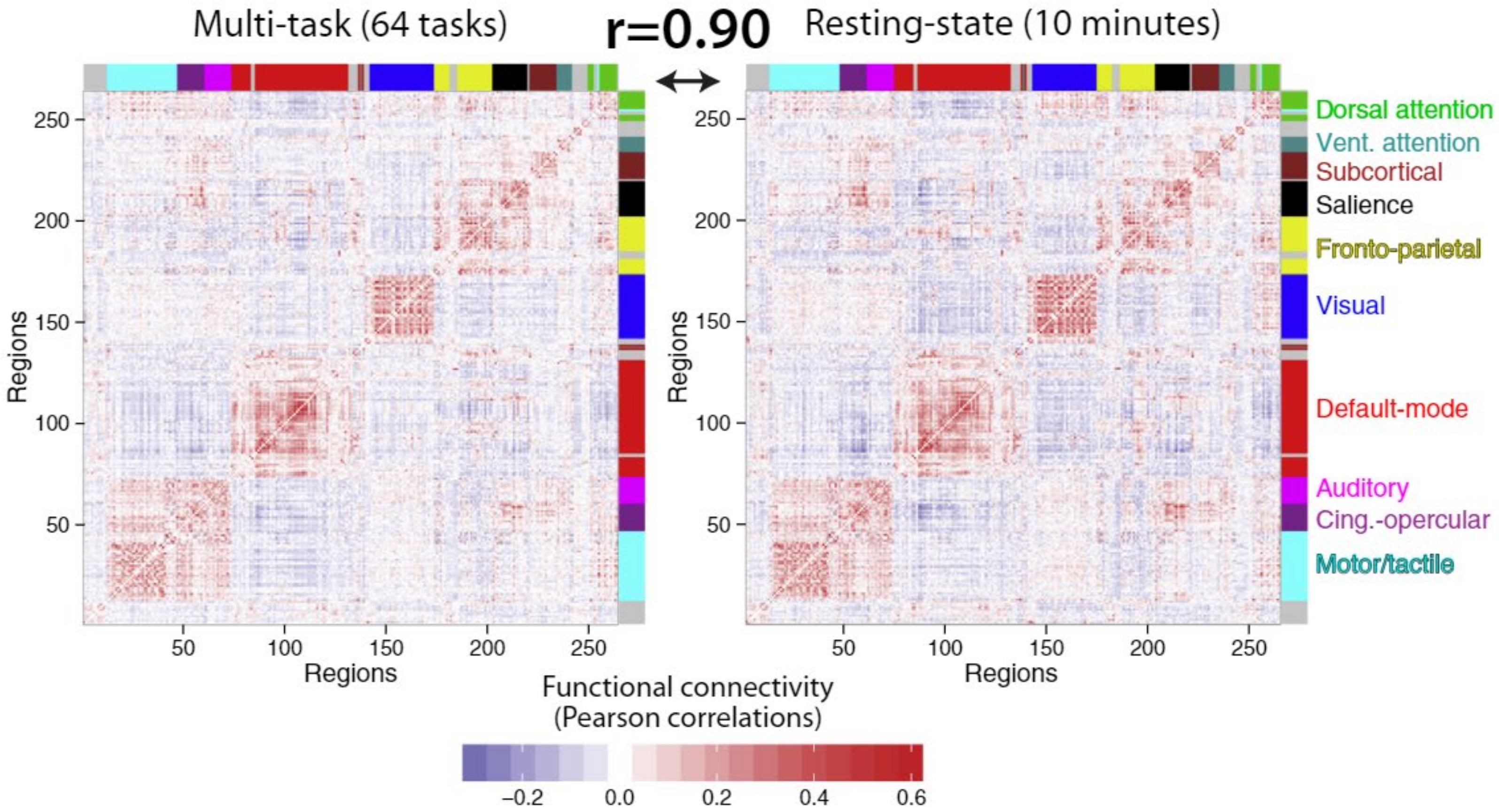


Vatansever et al., 2015



Hearne et al., 2016

Task-related reconfigurations are “relatively small”



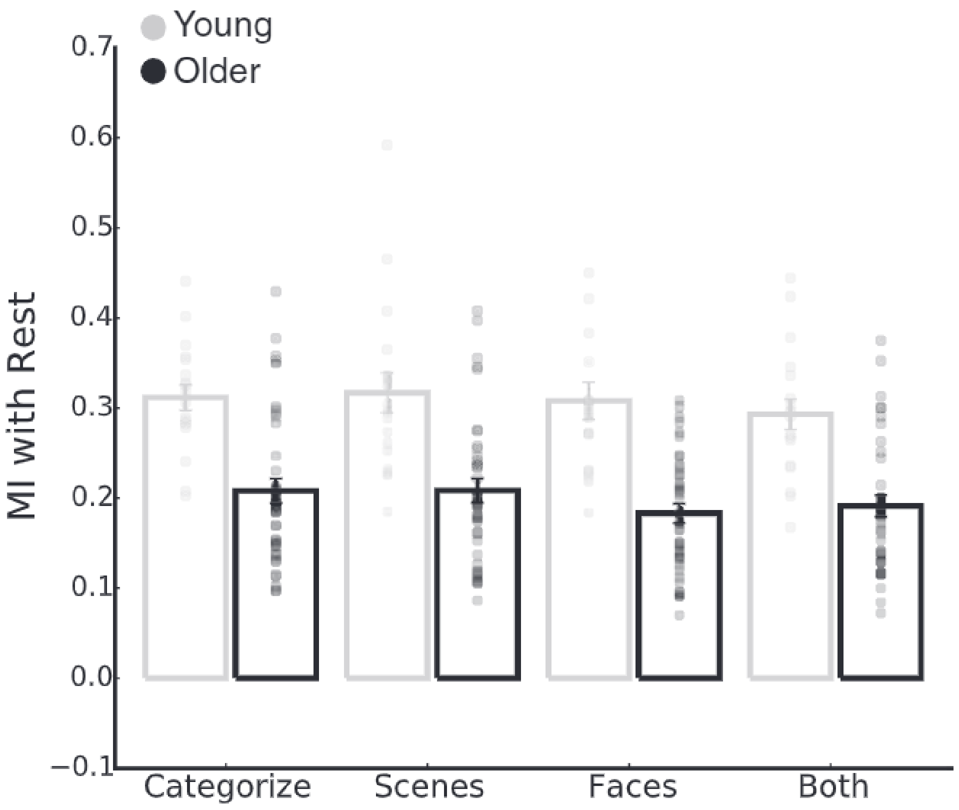
Cole et al., 2014

Questions

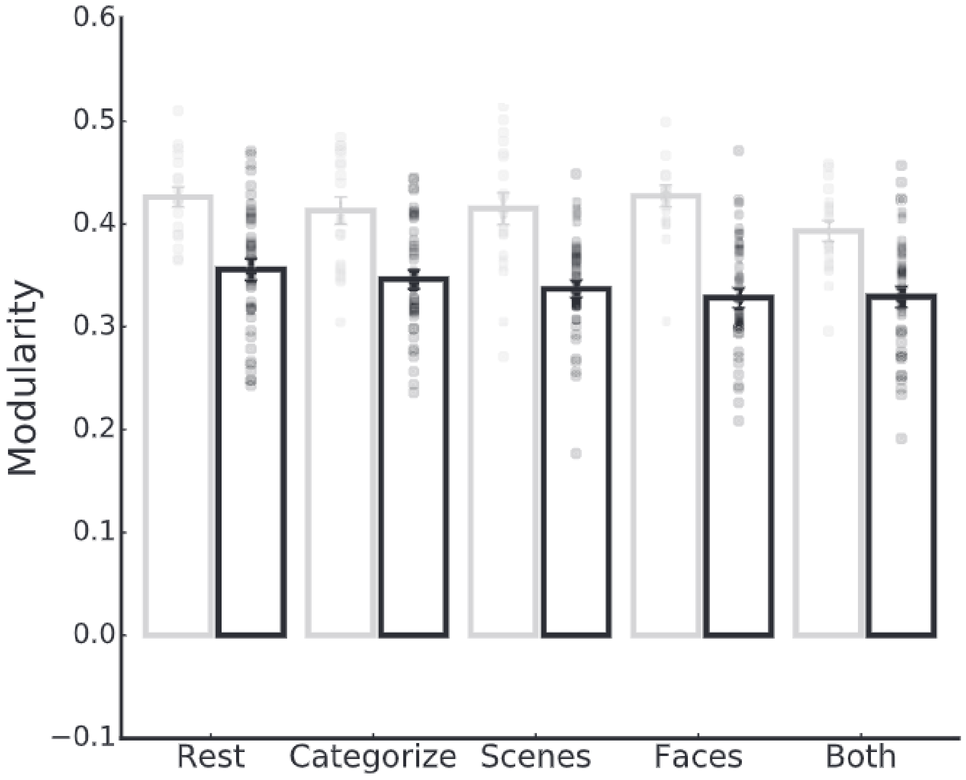
- How does aging affect brain network reconfigurations elicited by demanding cognitive tasks?

- Can these be influenced by cognitive training?

Greater rest-to-task reconfiguration in OA than YA

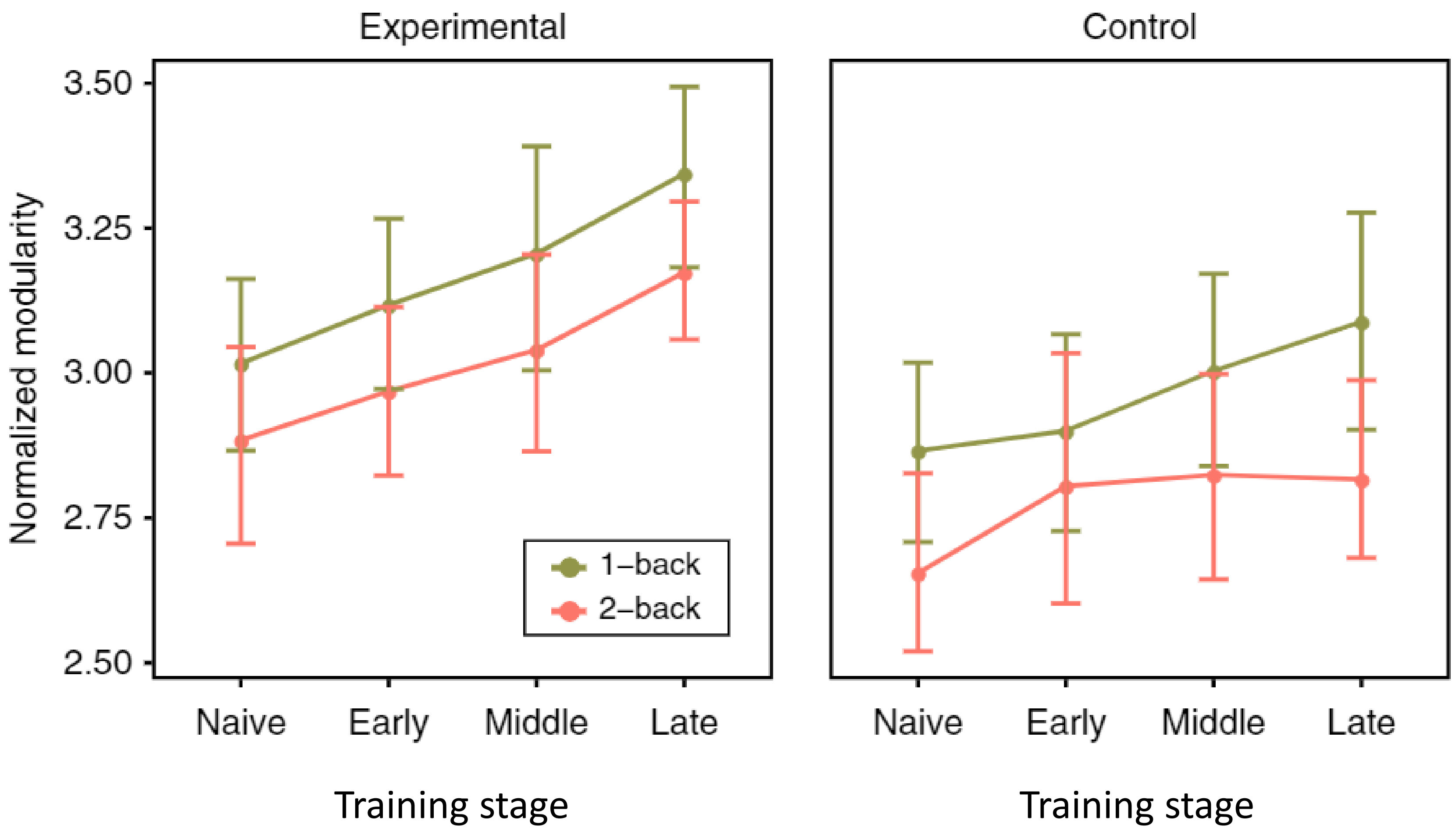


Lower overall modularity in OA than YA



Gallen et al., 2016

Modularity increases with training in YA



Finc et al., 2020

How does aging affect brain network reconfigurations elicited by demanding cognitive tasks?

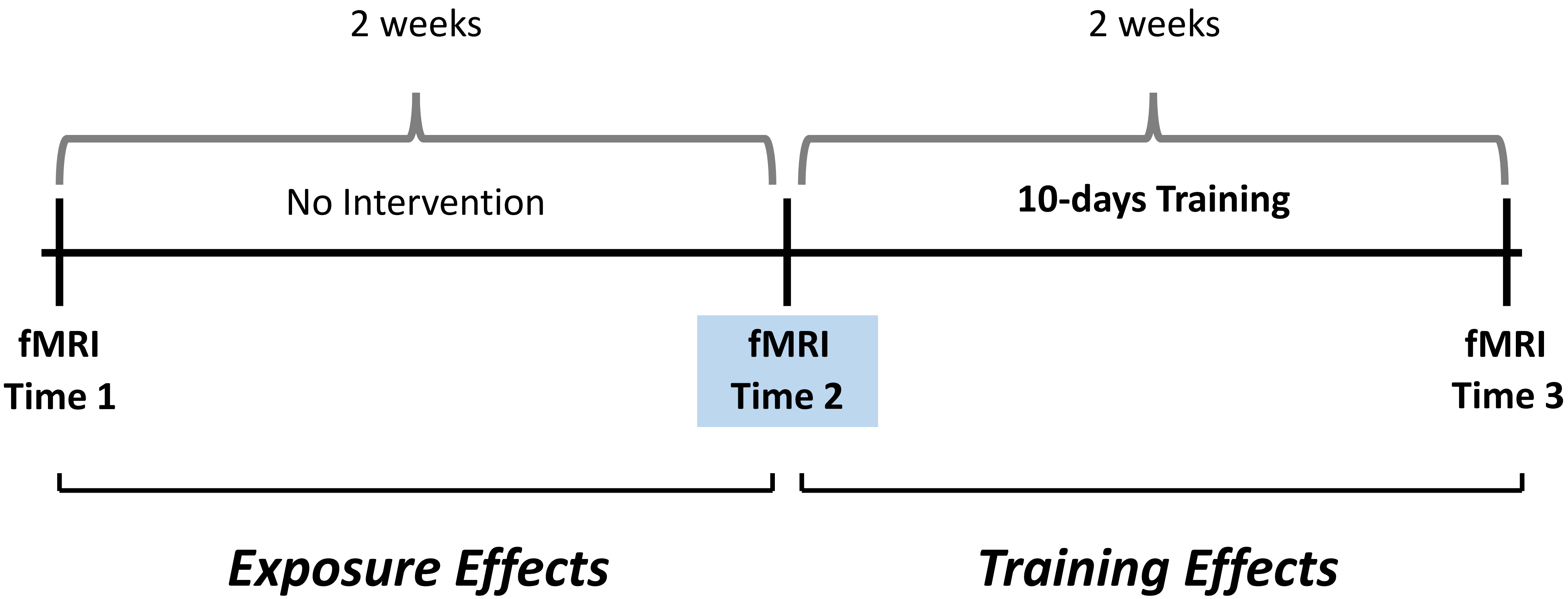
- We expect:
  - Overall lower modularity in older compared to younger adults
  - Lower modularity during task performance compared to resting-state
  - Progressively lower modularity with increasing WM load

- Open questions OA vs. YA
  - Greater decrease in modularity when shifting from resting-state to task mode?
  - Steeper decrease in modularity with increasing task load?

What is the influence of cognitive training?

- We expect:
  - network reorganization elicited by *training* not *task-exposure*
  - task-related FC more sensitive to training than resting-state
- Open question:
  - Greater modularity enhancement with training in YA vs. OA?
- Brain networks level:
  - Training reconfigures primarily associative brain networks (FPN and DMN)

Present study: Design



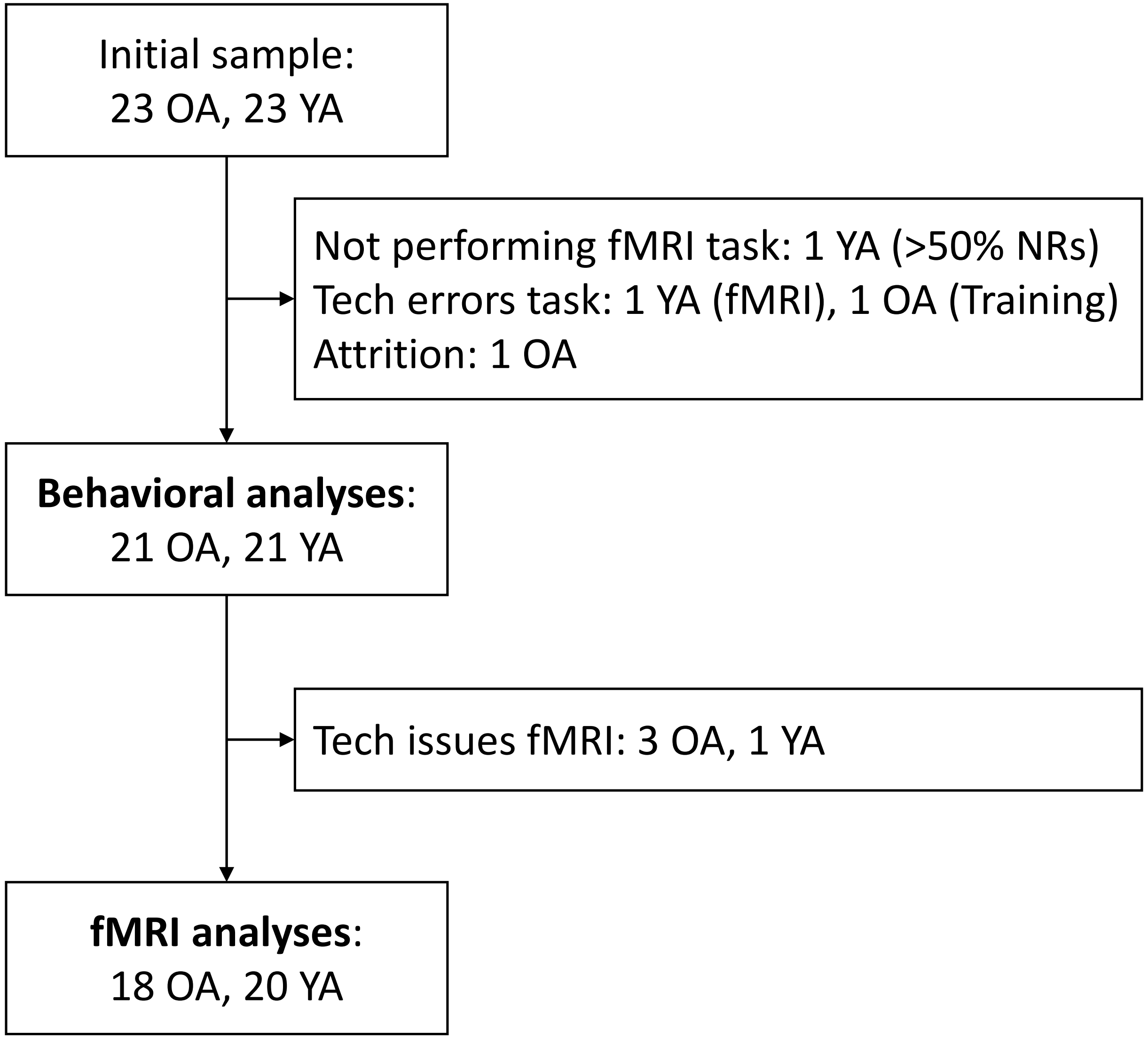
Neuropsychological testing was performed at each time point (Not discussed here).

Participants

Power analysis: 20 OA and 20 YA, 94% power (two-tailed α=.05; $\Delta_{\text{MR signal}} \geq .015$), based on Cappell et al., 2010

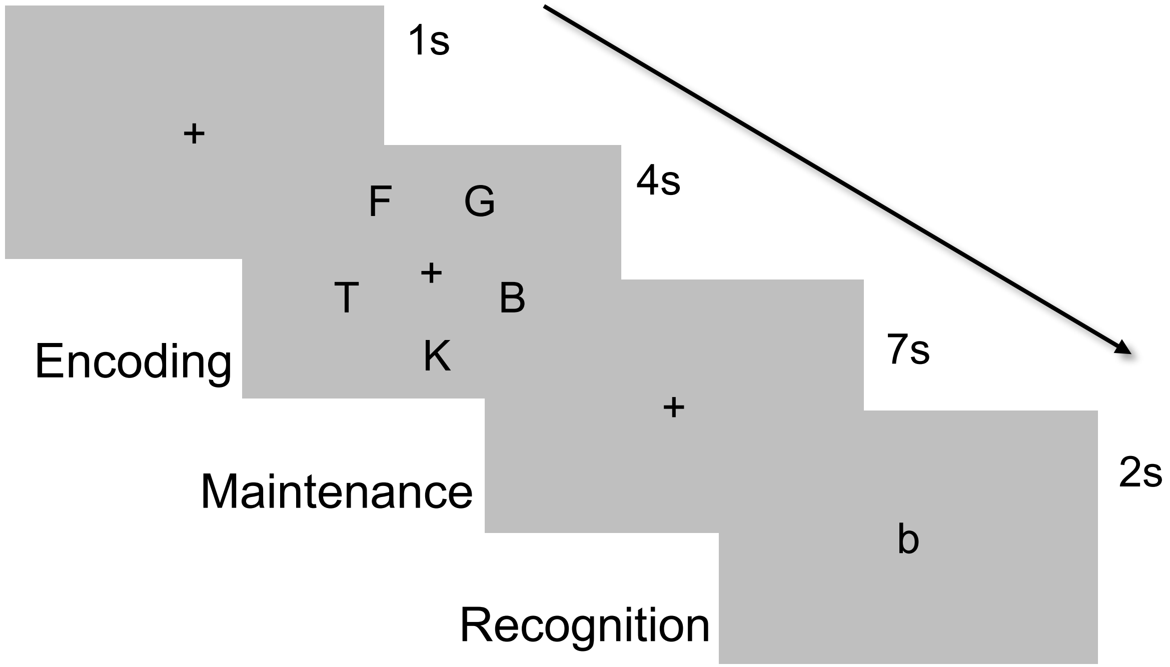
	OA (N = 21)	**YA** (N = 21)
% Female	48	57
Age (S.D.)	67.81 (3.31)	21.33 (2.65)
Edu (S.D.)***	17.05 (1.63)	14.81 (1.75)
MoCA (S.D.)	28.24 (1.61)	28.48 (1.50)

$^{***}p<.001$



MoCA, Montreal Cognitive Assessment

fMRI & Training Tasks:
Verbal WM (Sternberg) tasks with varying Load



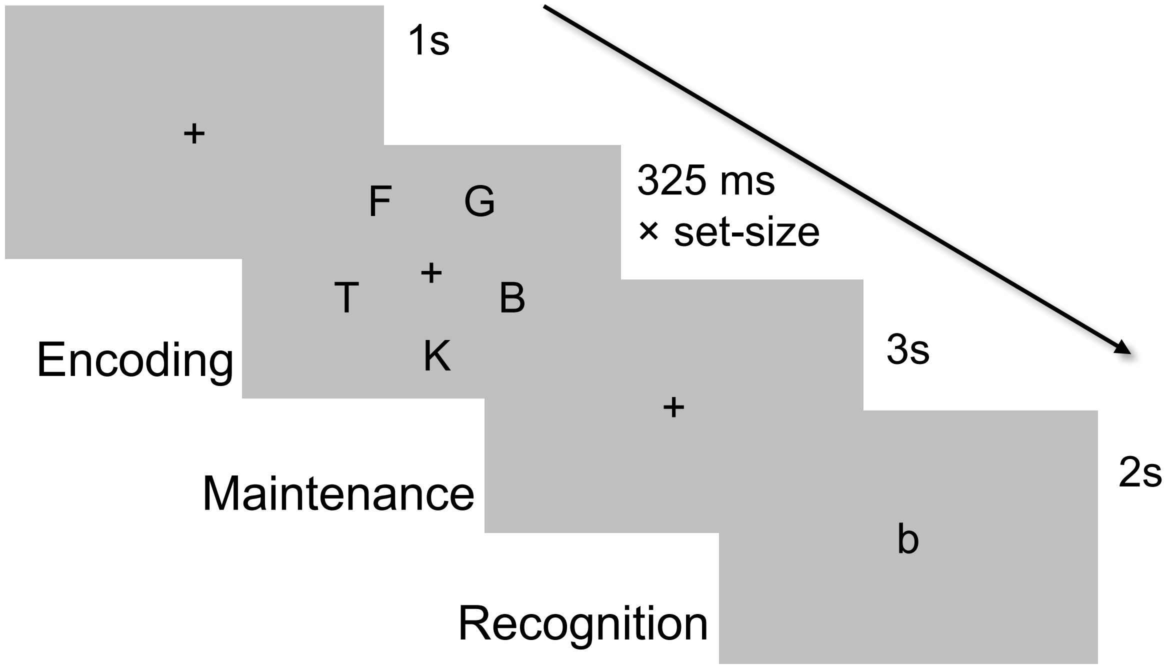
fMRI (Criterion) Task:

OA: loads 1 (task mode), 4-8

YA: loads 1 (task mode), 5-9

- Set-size was randomized (6 blocks of 24 trials)

fMRI & Training Tasks:
Verbal WM (Sternberg) tasks with varying Load



fMRI (Criterion) Task:

OA: loads 1 (Baseline), 4-8

YA: loads 1 (Baseline), 5-9

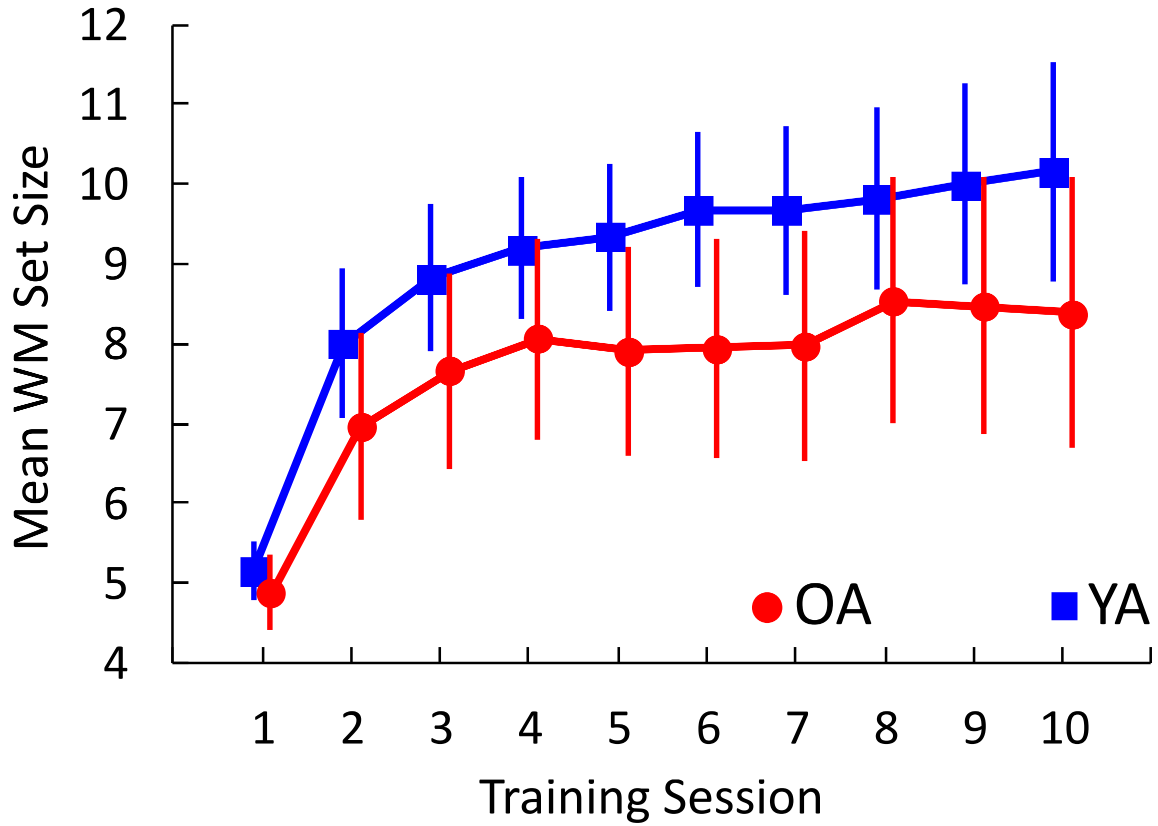
- Set-size was randomized (6 blocks of 24 trials)

Adaptive Training Task:

Initial set size = 3 letters

- Set-size was blocked: increased if accuracy >86%, decreased if <72% (6 blocks of 14 trials/sess)

Adaptive Training Task Results

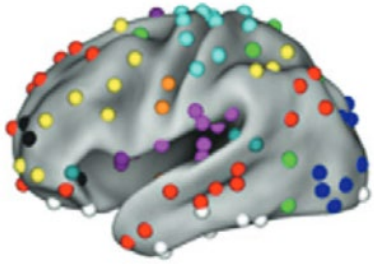


Both groups improved in WM performance across the course of training, $F_{9,378}$=103.9, p<.001, η_p^2=.712

YA improved more than OA, $F_{1,378}$=15.7, p<.001, η_p^2=.40

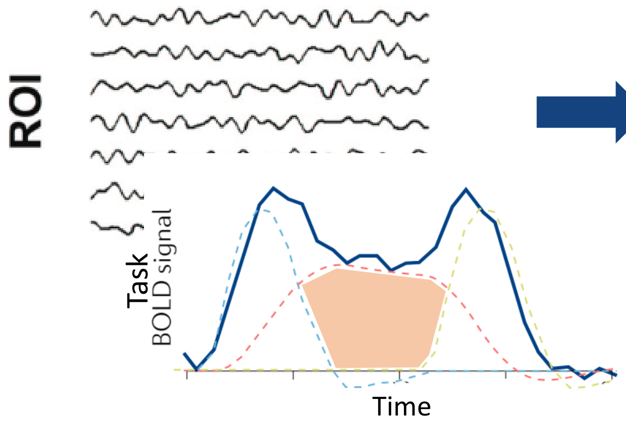
Procedure
"Background connectivity"

Defining ROIs

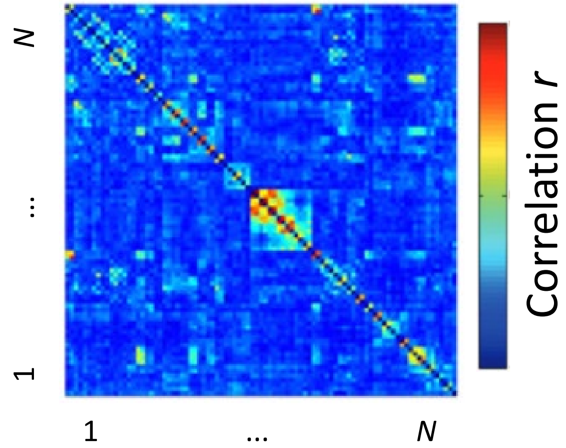


Power et al., 2011

Extracting and de-noising time courses

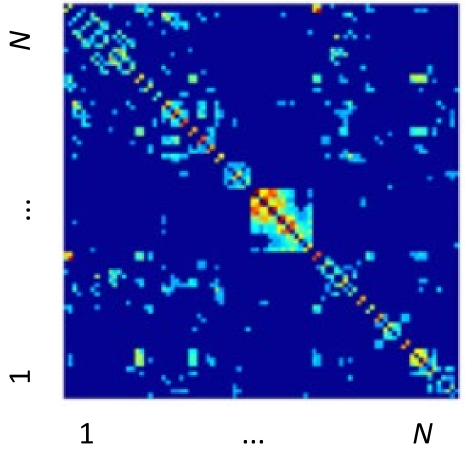


Calculating correlation matrix

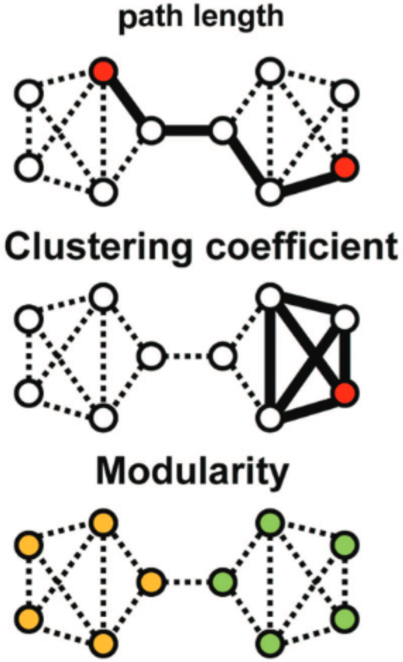


Fisher-*z* transform

Thresholding
10-30%, weighted



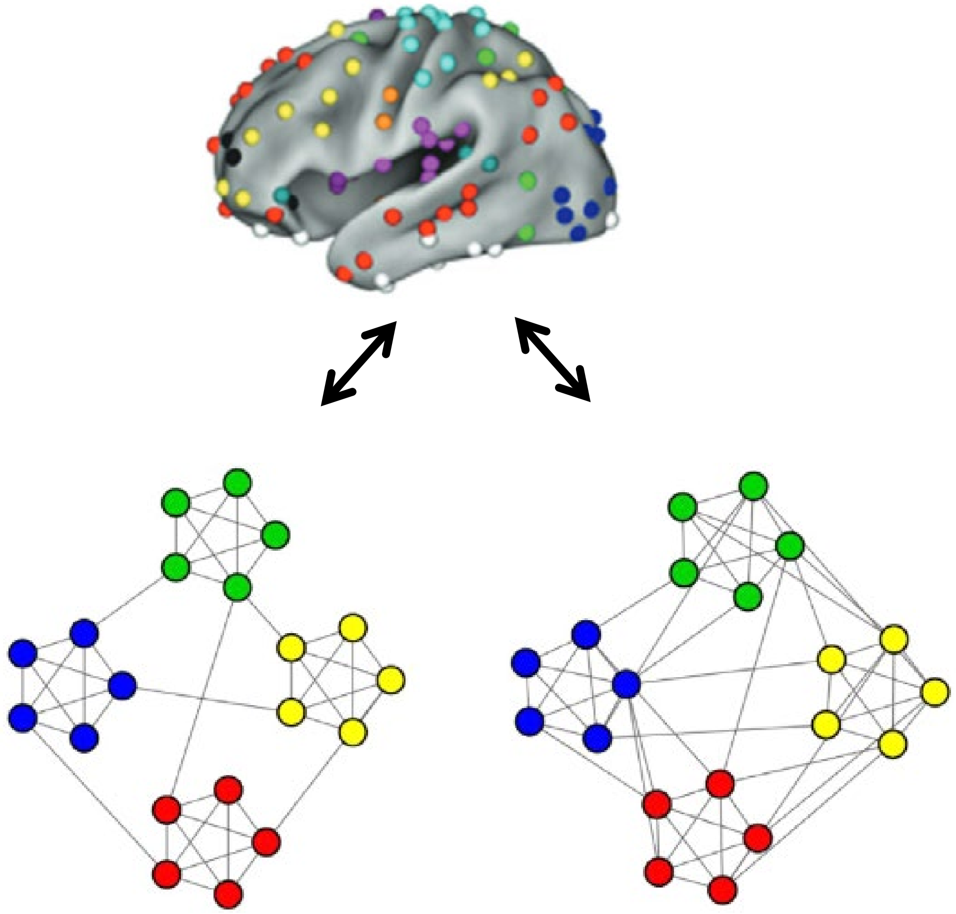
Calculating network measures



images: Uehara et al., 2013; Taya et al., 2016; Power et al., 2013; Sreenivasan & D'Esposito, 2019

3 levels of analysis

- Whole brain
  - Segregation/integration
- Individual networks
  - Within-network communication
  - Between-network communication
- Network components (sub-network)
  - Pairwise relations between brain regions

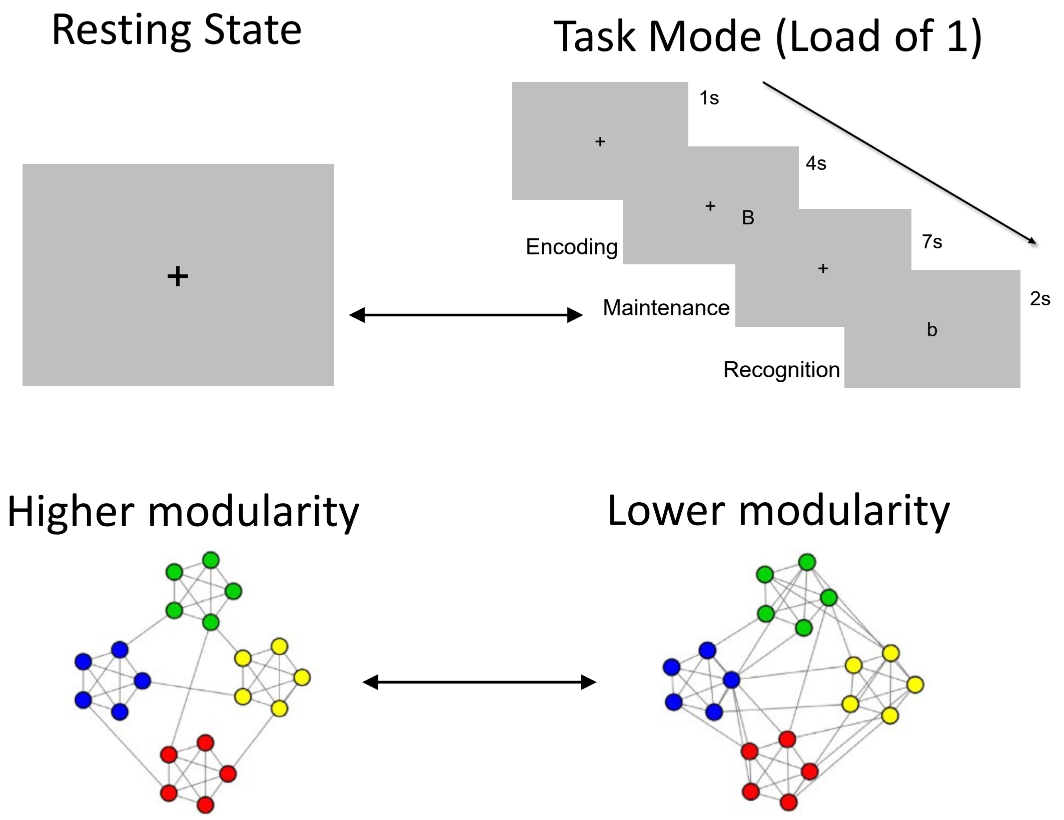


Images: Power et al., 2013; Wig, 2017

1. Whole-Brain Results

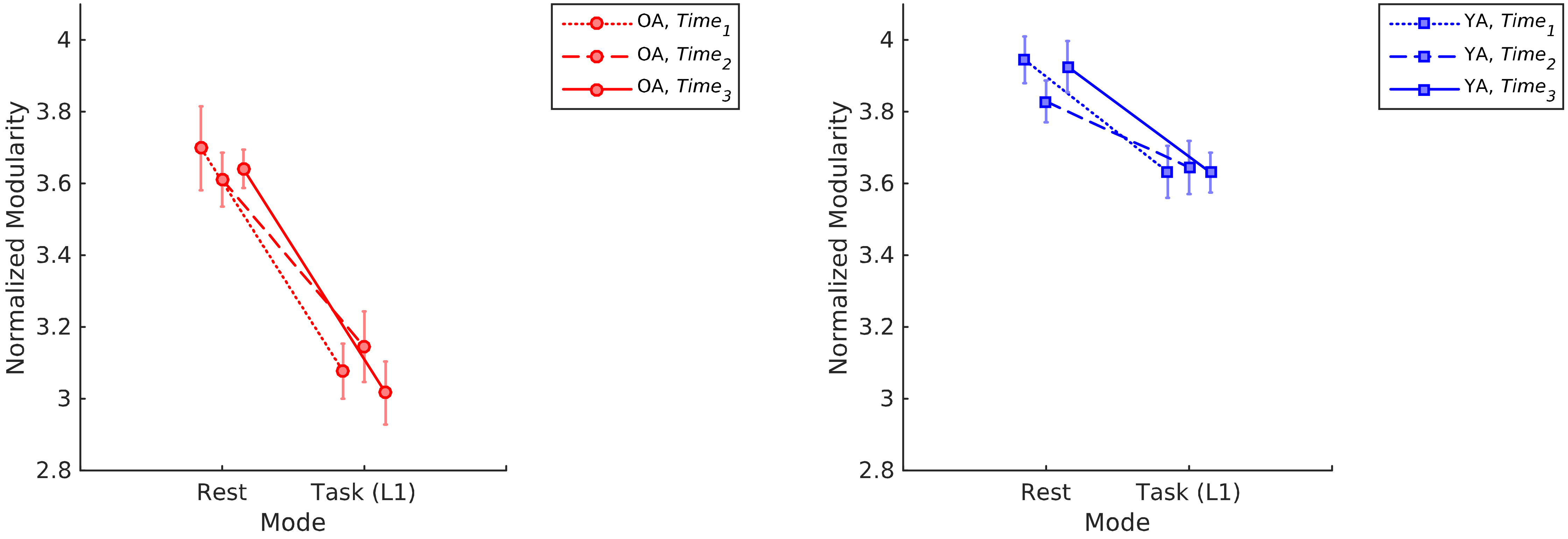
Modularity: Whole-brain segregation/integration

- **Rest-to-task shift**
  - Lower modularity in OA than YA
  - Lower modularity during task than during rest
  - Greater modularity decrement with rest-to-task shift in OA than YA?
  - Minimal effect of training



1. Whole-Brain Results: Modularity

Lower modularity and greater decrement with rest-to-task shift in OA

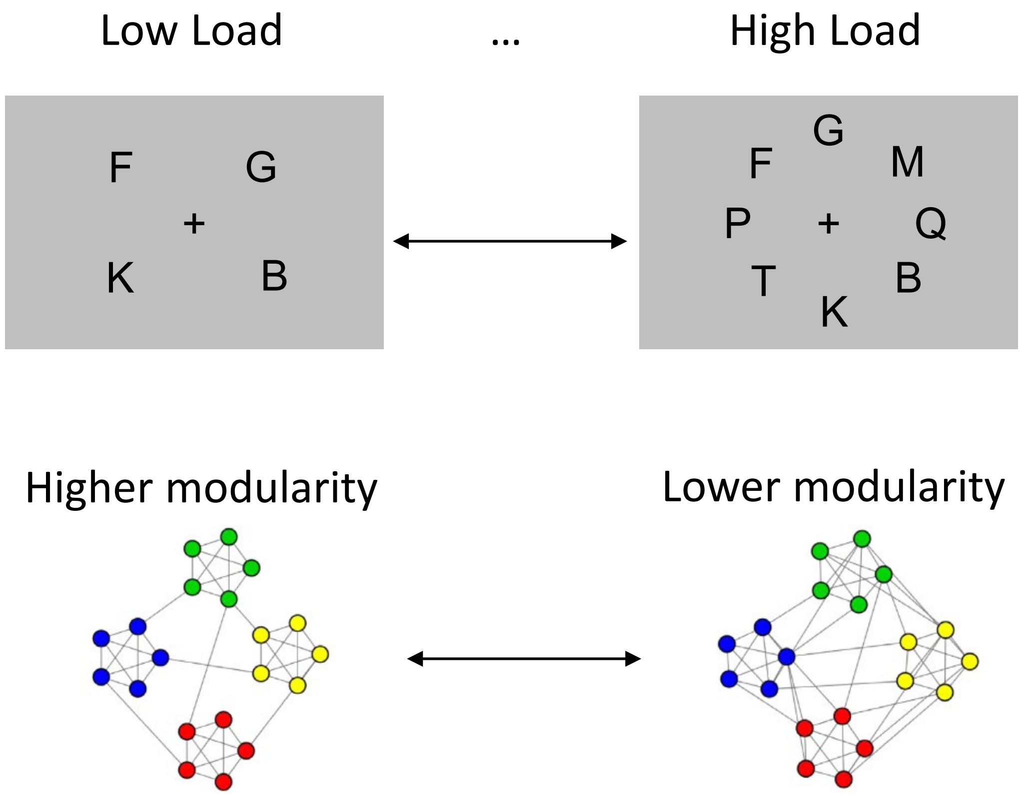


- Lower overall modularity in OA vs. YA. Group: $F_{1,36}=31.99$, $p<0.001$, $\eta_p^2=0.47$
- Lower modularity during task than rest. Mode: $F_{1,36}=141.51$, $p<0.001$, $\eta_p^2=0.8$
- Greater modularity decrement with rest-to-task shift in OA. Group×Mode: $F_{1,36}=19.14$, $p<0.001$, $\eta_p^2=0.35$

1. Whole-Brain Results

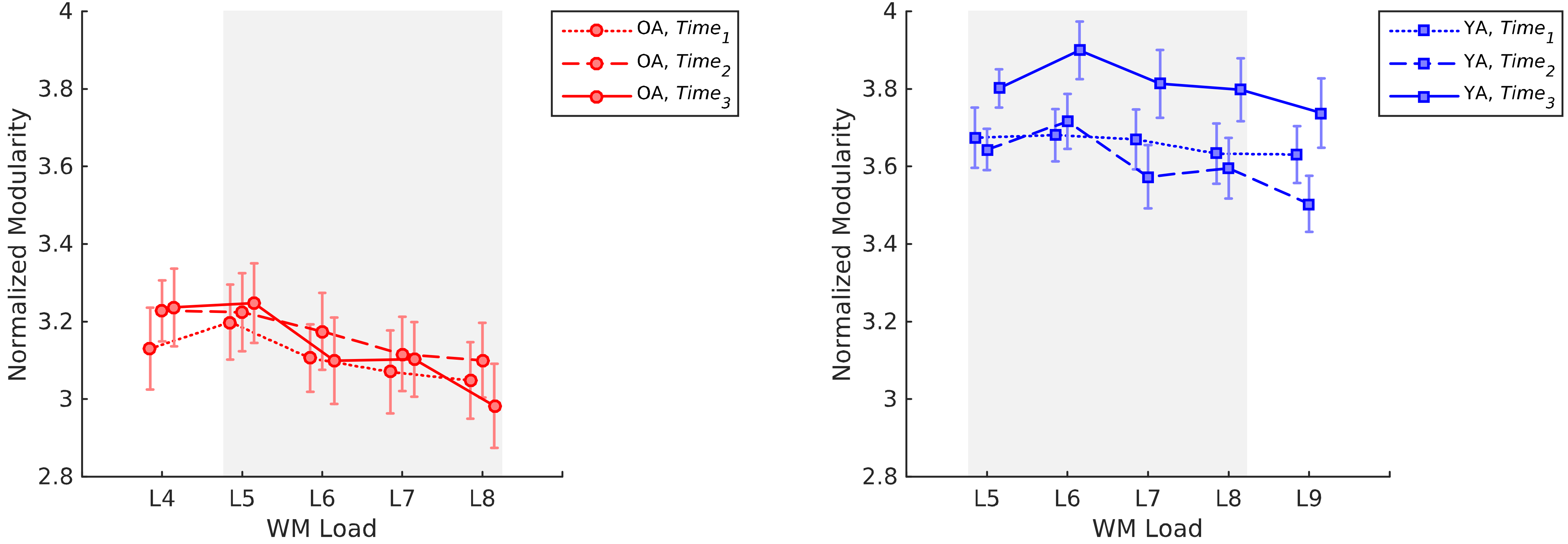
Modularity: Whole-brain segregation/integration

- **Increasing task demand**
  - Lower modularity in OA than YA
  - Lower modularity with increasing load
  - Steeper modularity decrement in OA than YA?
  - Changes with *training*, not simple *task-exposure*
  - Greater modularity with training in YA than OA?



1. Whole-Brain Results: Modularity

Increased task-related modularity with training in YA

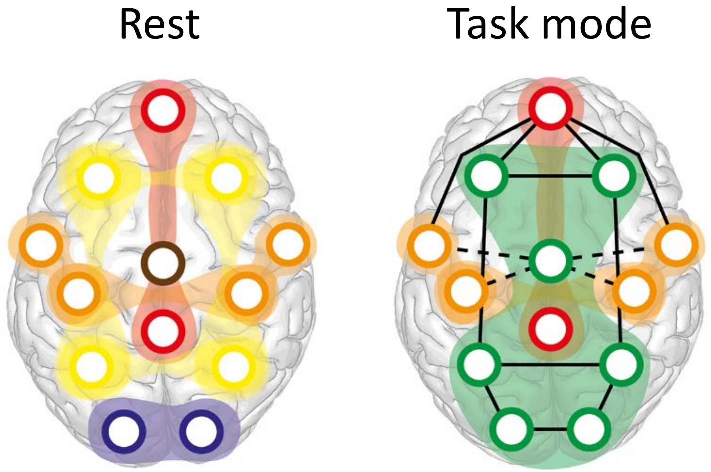


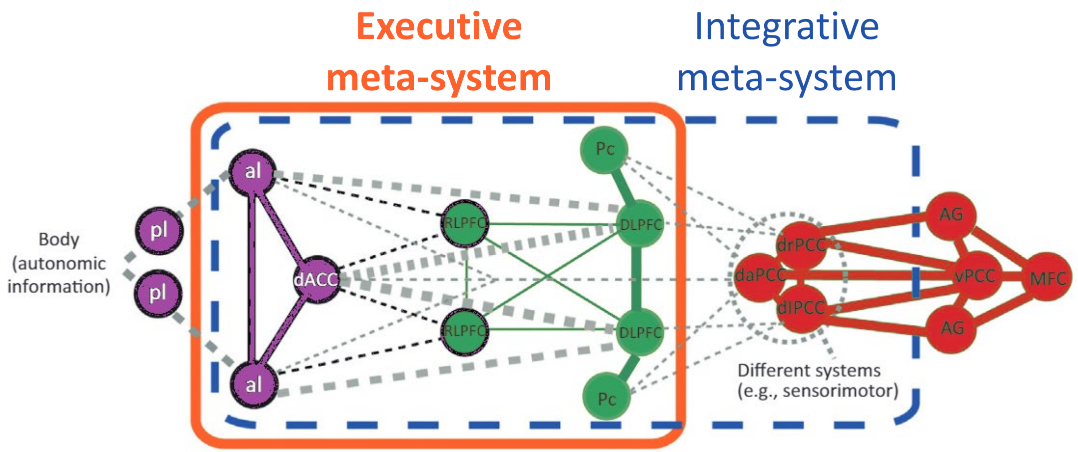
- Lower overall modularity in OA vs. YA. Group: $F_{1,36}$=37.38, p<0.001, η_p^2=0.51
- Lower modularity with increasing load. Load: $F_{3,108}$=5.89, p=0.001, η_p^2=0.14, linear trend p<0.001;
- Steeper modularity decrement in OA vs YA. Group×Load: $F_{3,108}$=3.21, p=0.026, η_p^2=0.08
- Group×Time interaction. $F_{2,72}$=4.64, p=0.013, η_p^2=0.11
    - OA: No *task exposure* or training effects
    - YA: No *task exposure* but significant *training* effect, Time: $F_{1,19}$=25.88, p<0.001, η_p^2=0.58

1. Whole-Brain Results

Community structure: Network/module composition

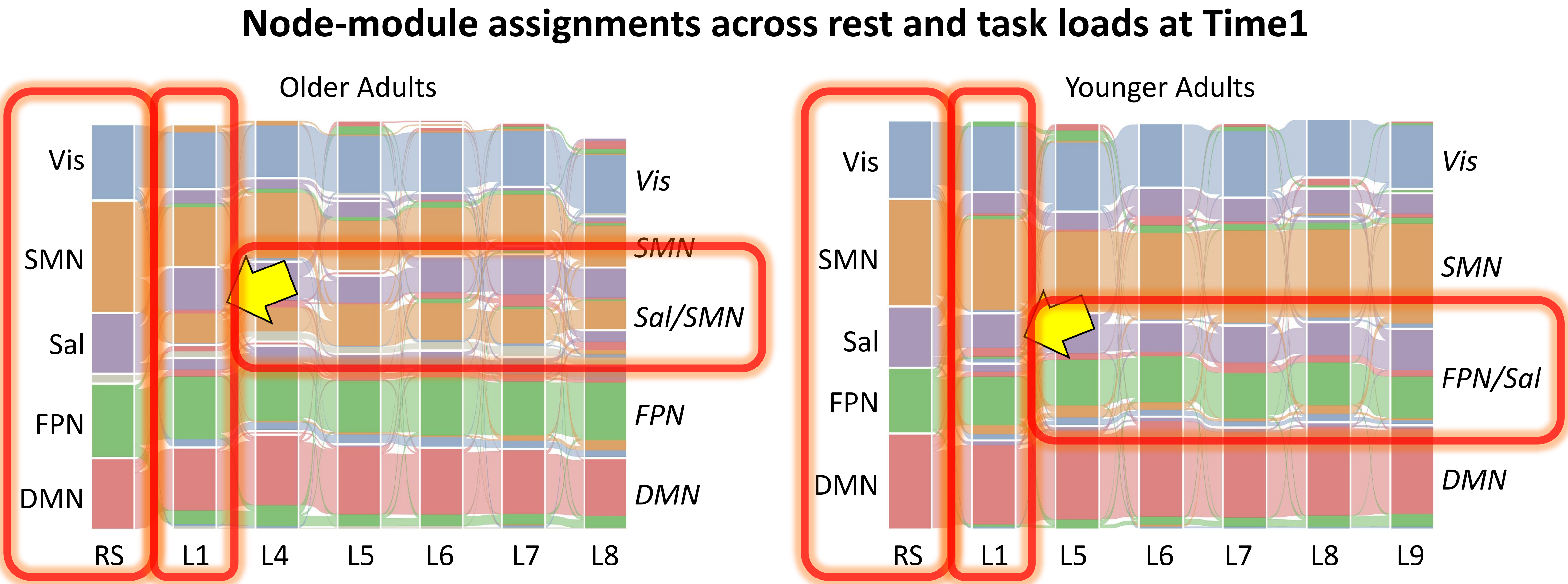
- **Demand and training effects**
  - Change from rest to task
  - Greater reorganization in OA than YA?
  - Less change with increasing demand
    - Integrative -> Executive meta-system
  - Effect of training?





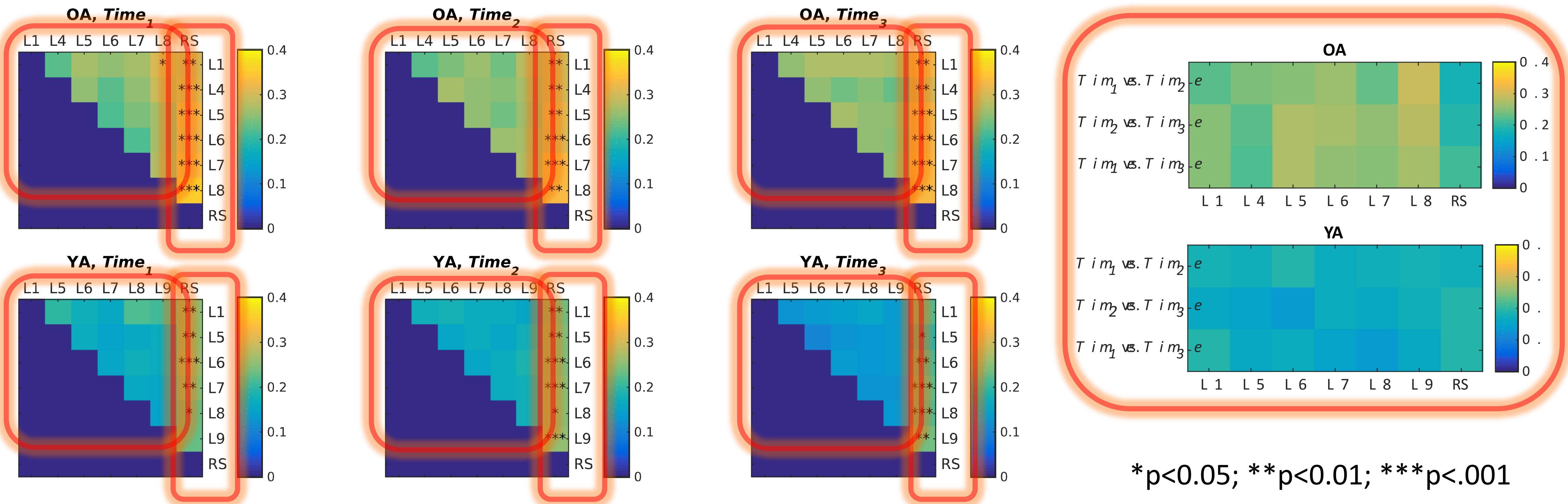
Images: Hearne et al., 2017; Cocchi et al., 2013

1. Whole-Brain Results: Community Structure



- OA and YA show 5 main modules at rest
- Switching from rest (RS) to task (L1) leads to different configurations
  - OA: emergence of *salience/sensorimotor module* (Sal/SMN)
  - YA: relatively less reorganization; Group×Time ANOVA on VIn, Group: $F_{1,36}$=75.89, p<0.001, η_p^2=0.68
- Increasing WM load
  - OA: Task community structure largely preserved
  - YA: emergence of *fronto-parietal/salience module* (FPN/Sal)

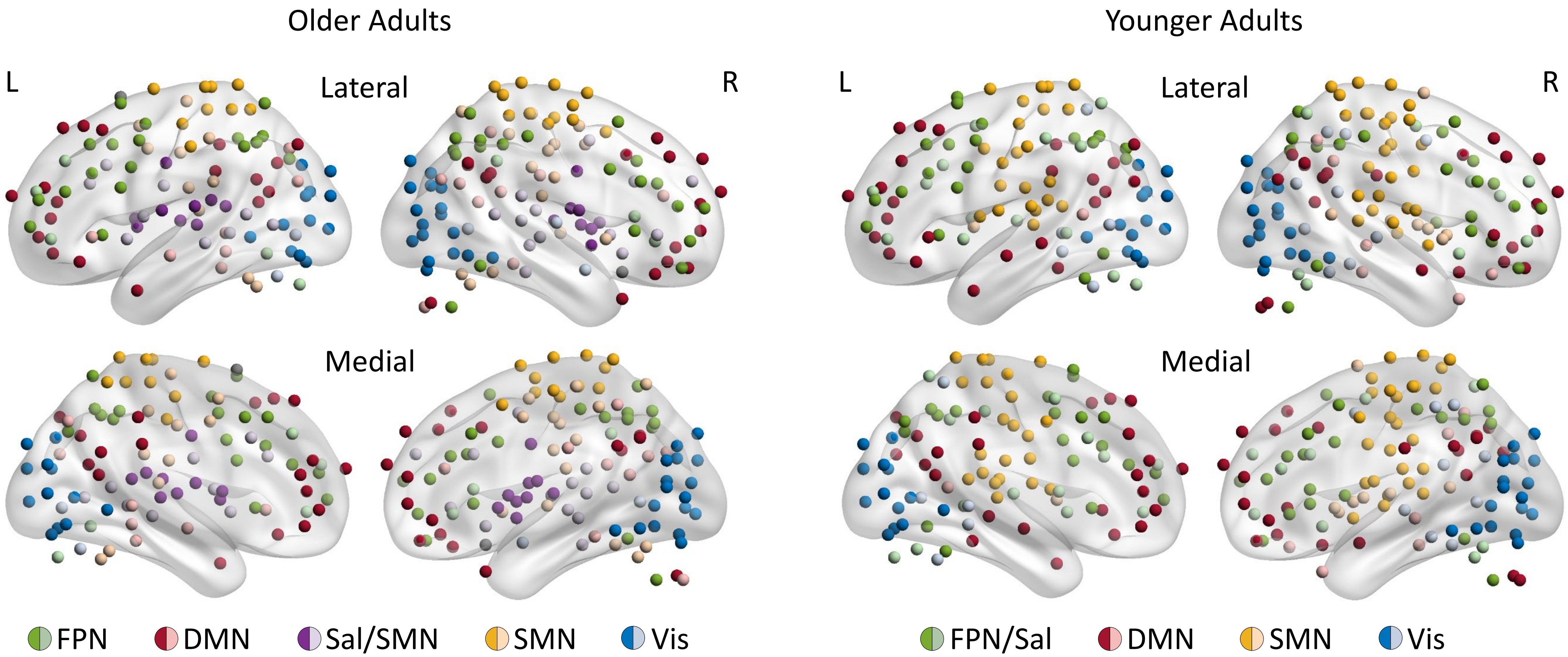
Rest-to-task differences in community structure



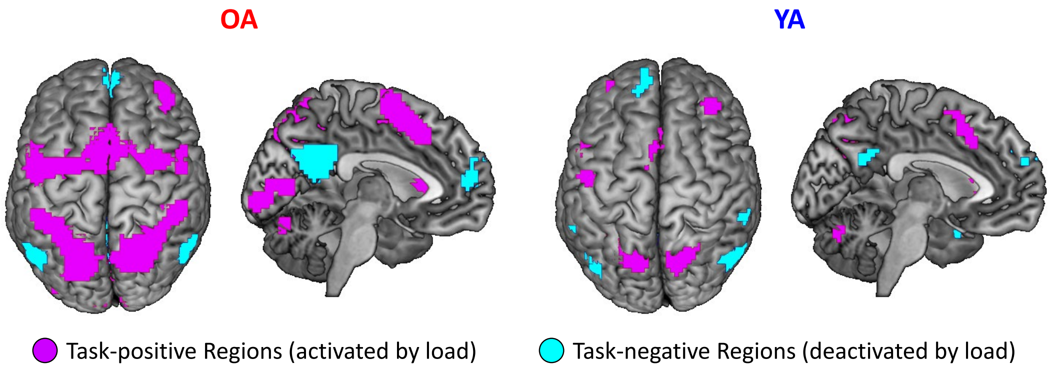
- Community structure is different for rest compared to WM loads
- No (consistent) differences in community structure between loads
- No differences in community structure across time

2. Individual Networks Results

Node-module assignments across loads at Time1

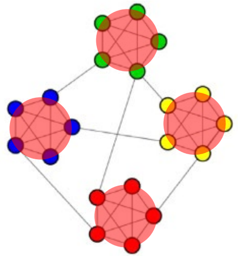


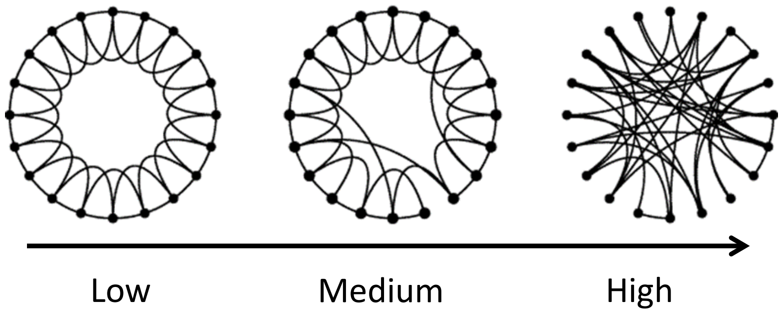
2. Individual Networks Results



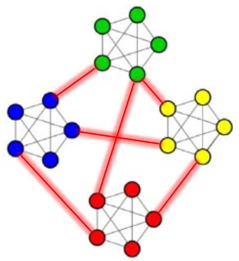
Primary targets: FPN and DMN

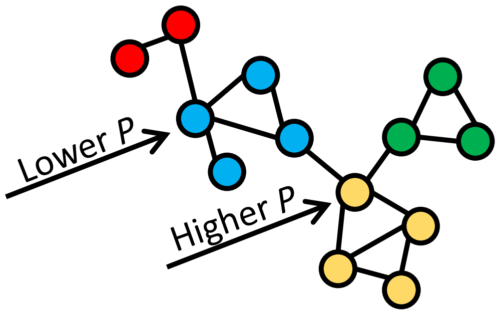
- **Within-network communication: Global Efficiency**
  - Parallel information transfer, integrated processing



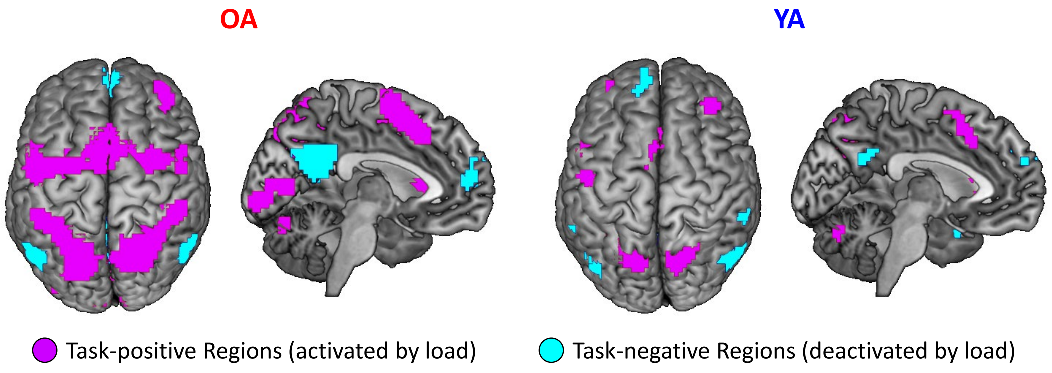


- **Between-network communication: Participation Coefficient**
  - Distribution of node connections across modules



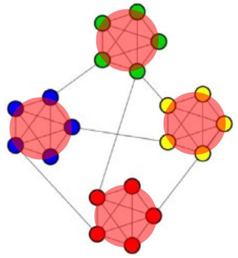


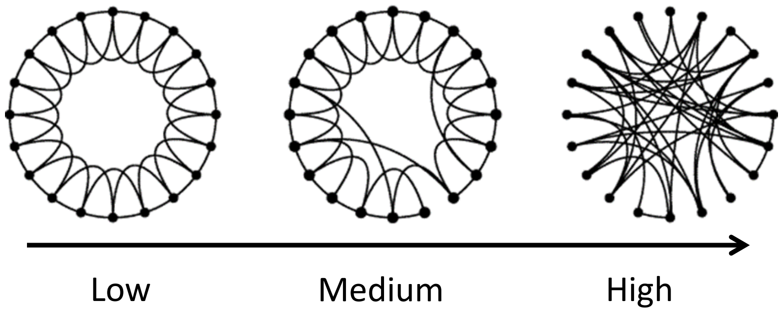
2. Individual Networks Results



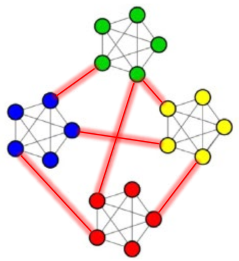
Outcomes:

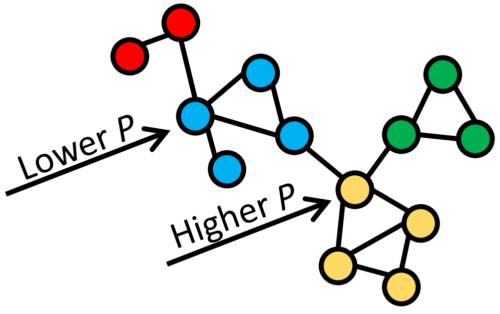
- **Within-network communication:**
  Global Efficiency
  - ↗ Training: Greater increase = more efficient processing
  - ↘ Load: Less decrease = better coping with demand





- **Between-network communication:**
  Participation Coefficient
  - ↘ Training: Greater decrease = more automatic processing (less integration required)
  - ↗ Load: Less increase = better coping with demand (less integration required)

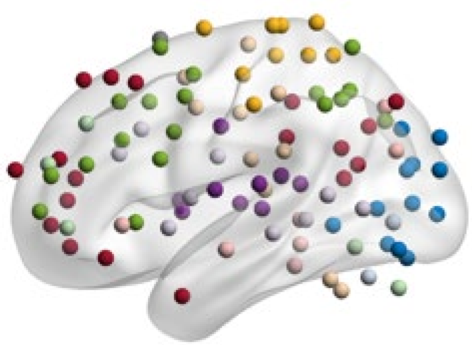




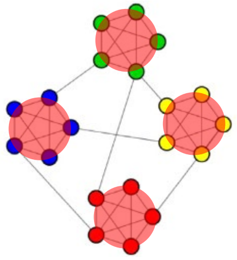
2. Individual Networks Results

OA: Increased global efficiency within Sal/SMN with training

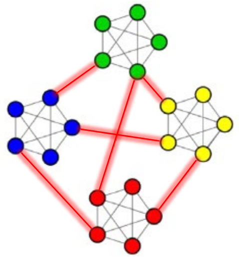
Older adults

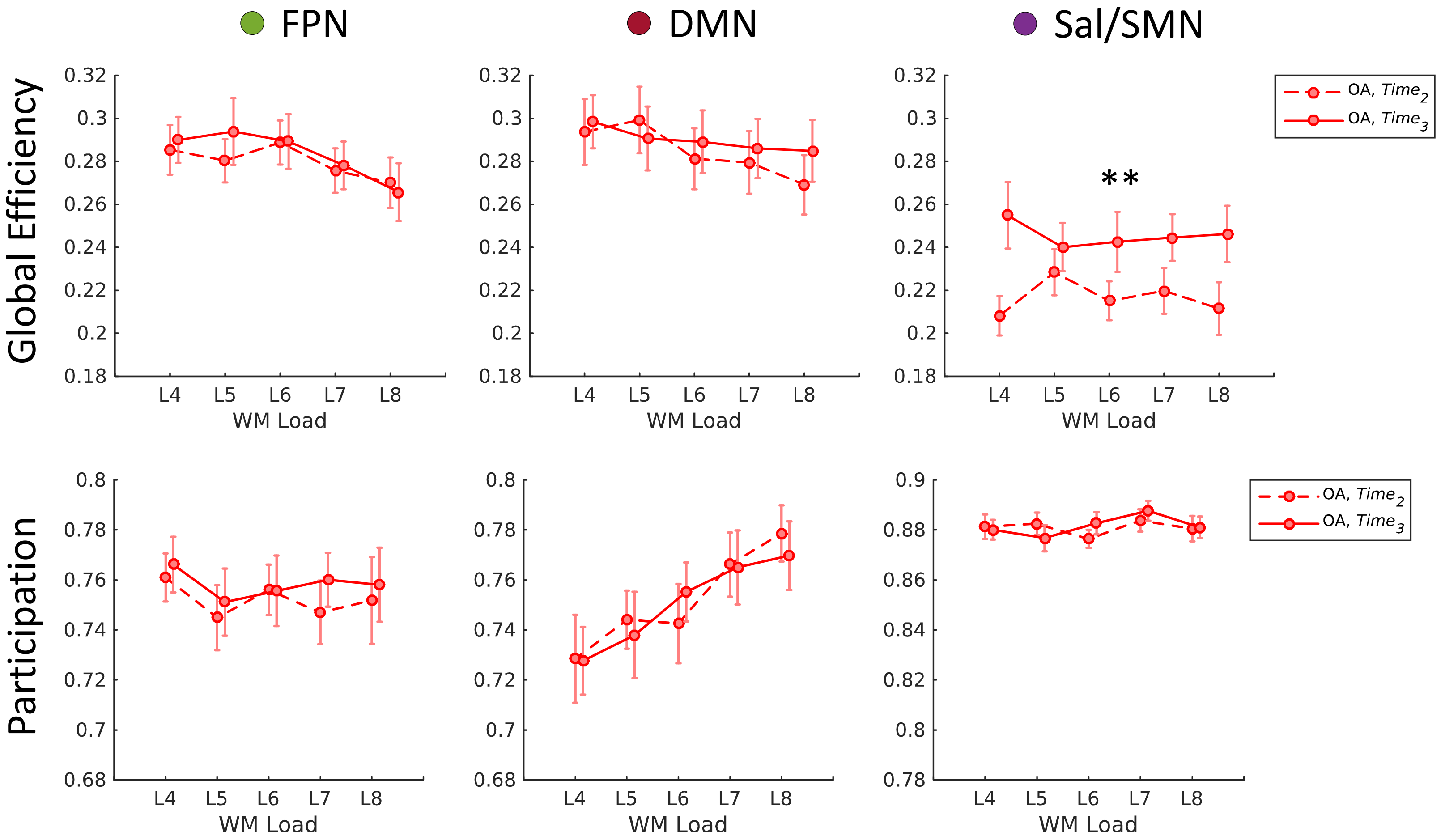


Within net's



Between net's



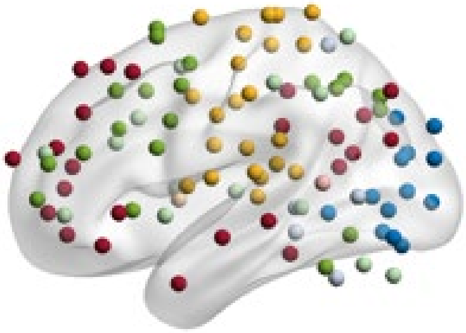


- **Training effect** on Sal/SMN global efficiency (p=0.008)
- **Load effects** on FPN (p=0.01) and DMN global efficiency (p=0.029), and DMN participation (p<0.001).

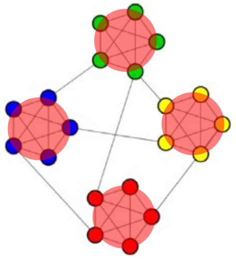
2. Individual Networks Results

YA: Increased global efficiency within and lower participation of FPN/Sal and DMN with training

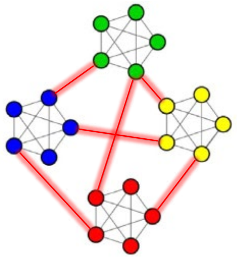
Younger adults

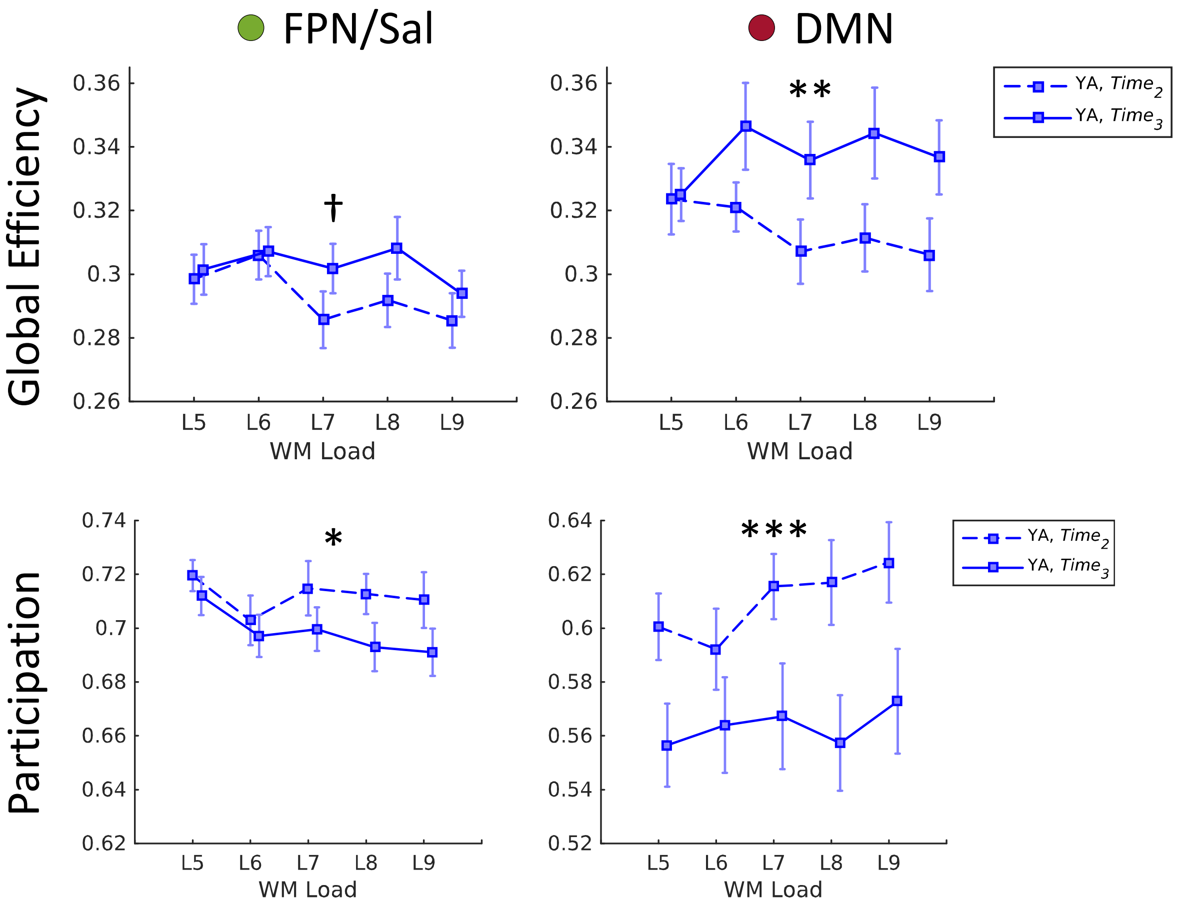


Within net's



Between net's

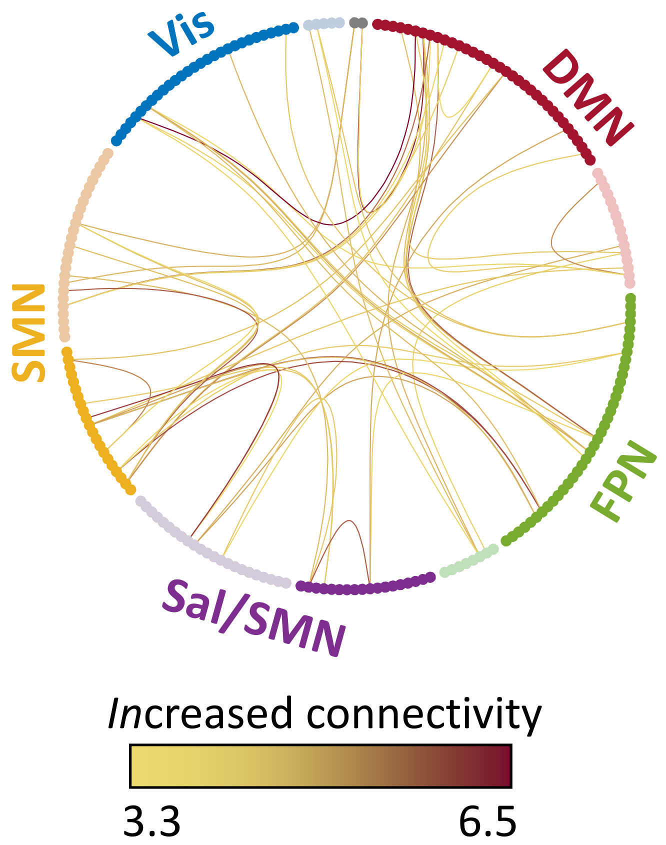




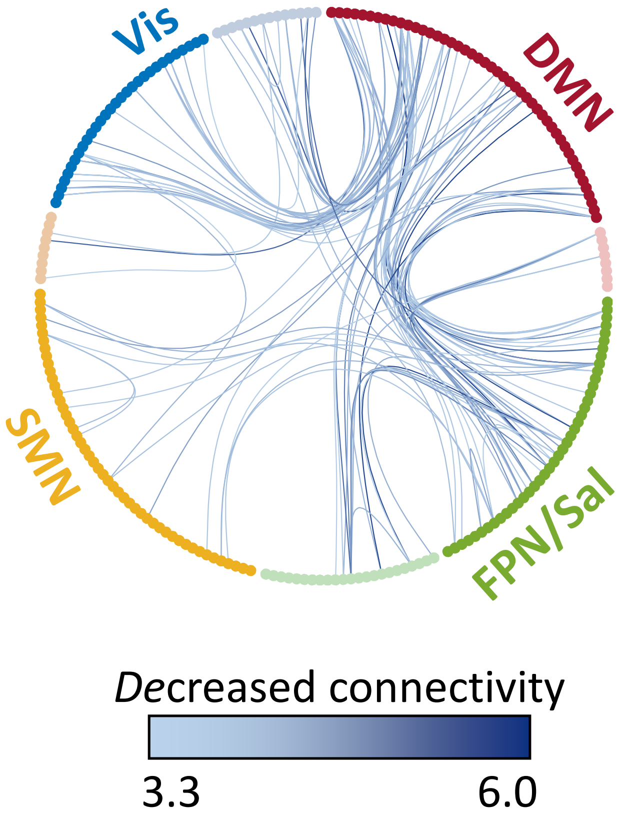
- **Training effects** on:
    - Global efficiency of FPN/Sal (p=0.076) and DMN (p=0.003).
    - Participation of FPN/Sal (p=0.012) and DMN (p<0.001).

3. Pairwise Connectivity Results: Training Effects

OA: Diffusely increased between-network connectivity with training



YA: Increased DMN segregation from FPN/Sal and Vis with training

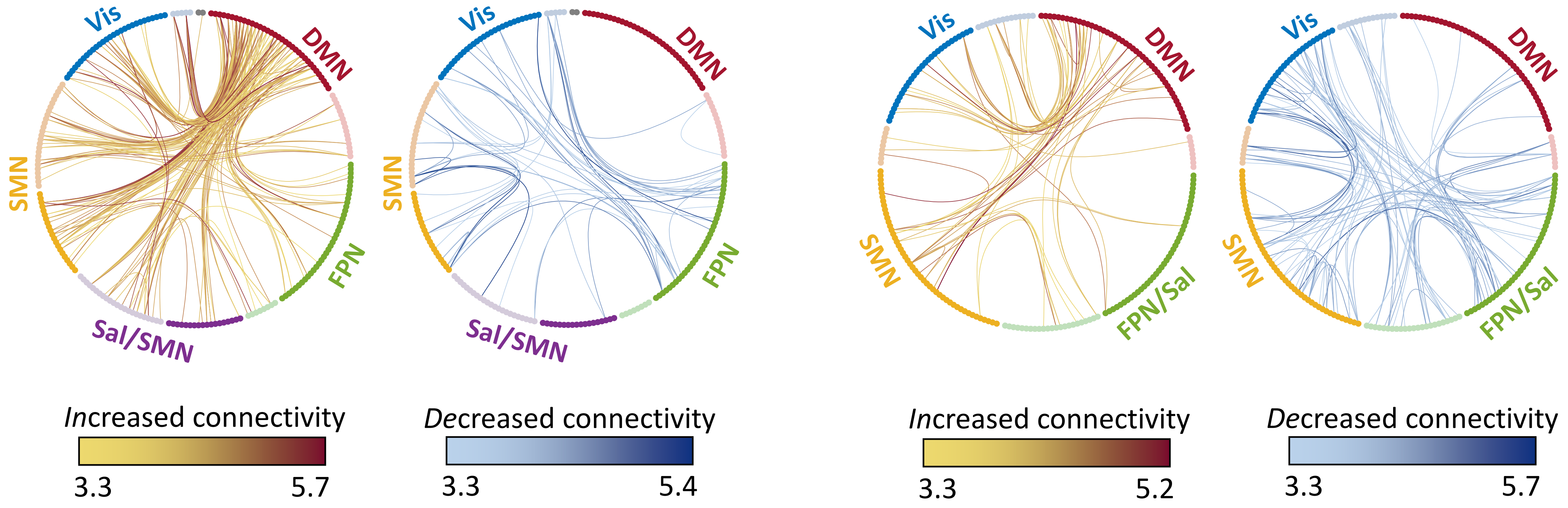


Legend: t-values

3. Pairwise Connectivity Results: Load Effects

OA: Increased integration of DMN with other networks

YA: Increased segregation of FPN/Sal from sensory networks



Legend: t-values

Conclusions

- Despite behavioral gains in both age groups, younger and older brains responded differently to WM training.
- Younger adults increase network segregation with training, suggesting more automated processing with enhanced expertise.
- Older adults maintain, and potentially amplify, a more integrated global workspace, which may enhance capacity for network engagement.
- In sum, WM training promotes different trajectories in functional network reconfiguration for younger and older adults.

https://sites.google.com/site/bctnet/Home

Brain Connectivity Toolbox

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Getting started

The Brain Connectivity Toolbox (brain-connectivity-toolbox.net) is a MATLAB toolbox for complex-network analysis of structural and functional brain-connectivity data sets.

Reference and citation

Complex network measures of brain connectivity: Uses and interpretations.
Rubinov M, Sporns O (2010) NeuroImage 52:1059-69.