

# Network Analysis

Alex Iordan, Ph.D.

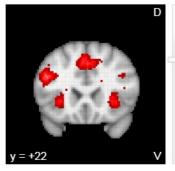
Assistant Professor Department of Psychiatry, University of Michigan <u>adiordan@med.umich.edu</u>

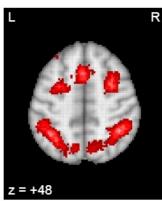
U-M fMRI Course 2023

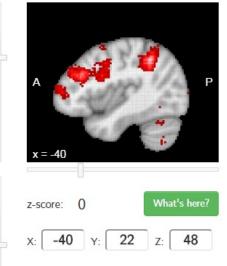
# From brain regions to brain graphs

Neurosynth – "working memory"

Automated meta-analysis of 901 studies



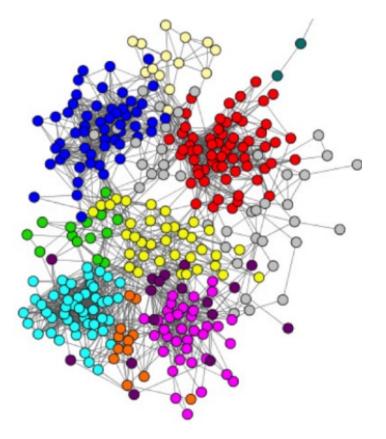




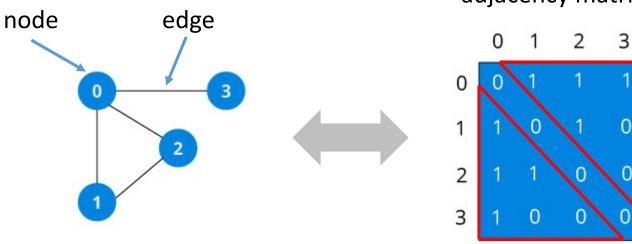
### The Graph-theoretic Approach

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

#### Network organization of brain areas



### What is a graph?



#### adjacency matrix

- 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

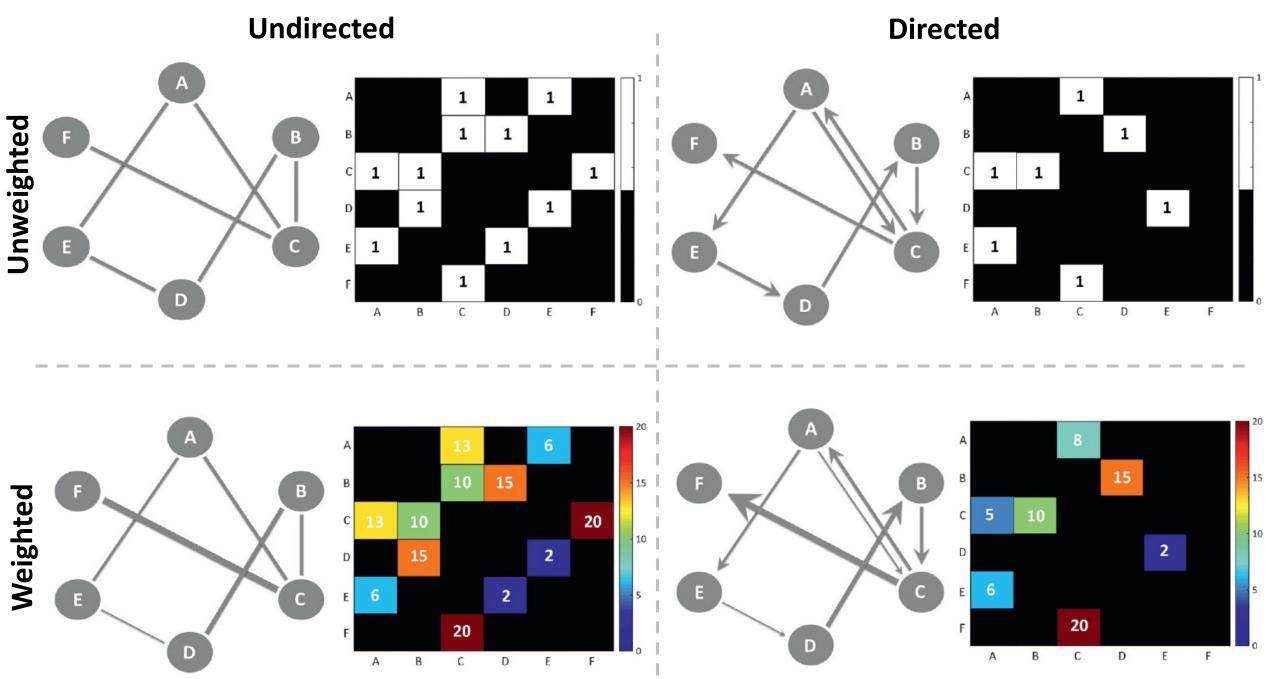
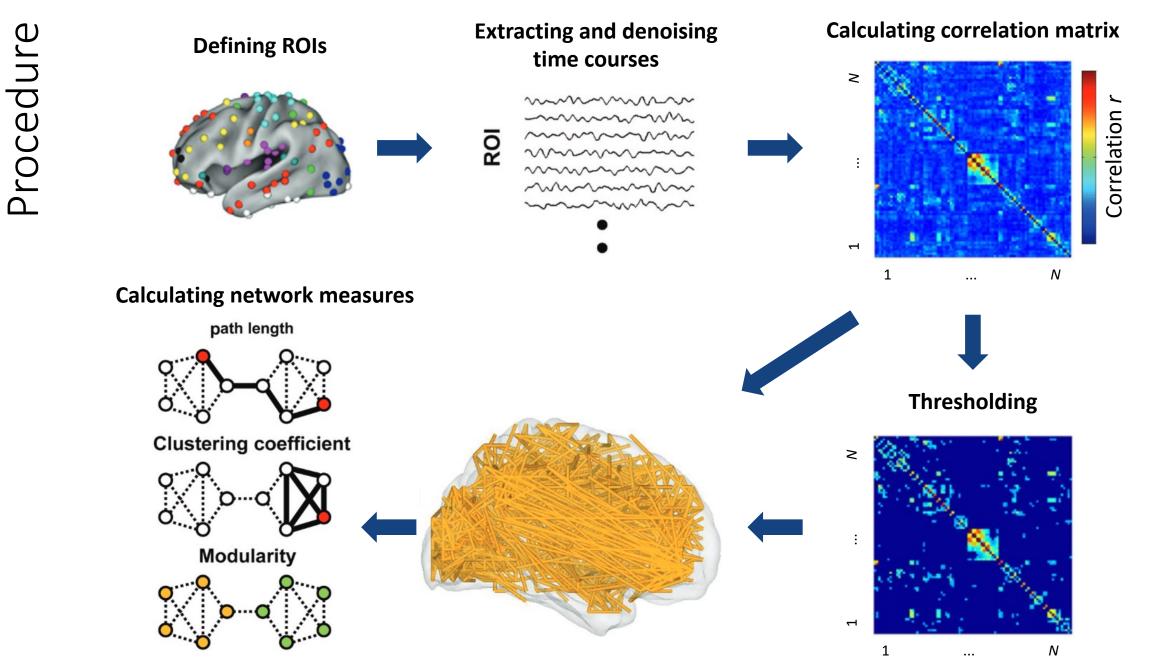


image: Fornito et al., 2016

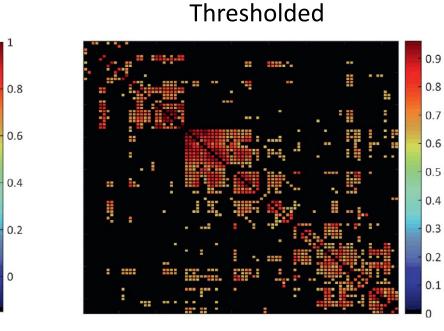


images: Uehara et al., 2013; Taya et al., 2016; Power et al., 2013

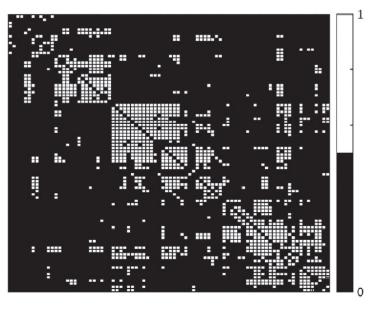
### Thresholding and binarizing an adjacency matrix

E.g., functional connectivity connectivity data

#### Unthresholded



Binarized



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

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

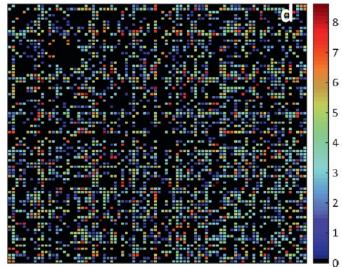
 $A_{ij} = \begin{cases} 1 & \text{if } C_{ij} > \tau, \\ 0 & \text{otherwise} \end{cases}.$ 

image: Fornito et al., 2016

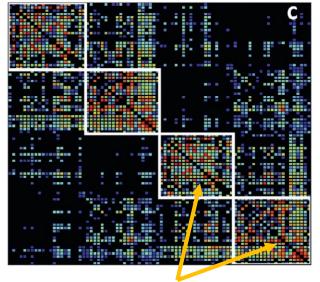
### Visualizing adjacency matrices

E.g., structural connectivity data

#### Random order

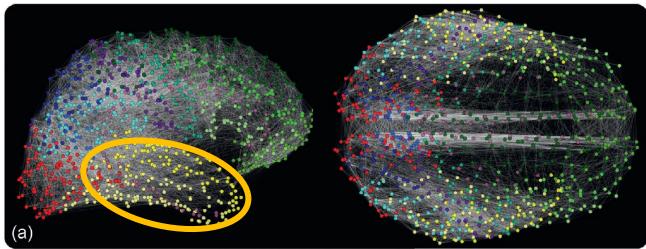


#### Modular structure

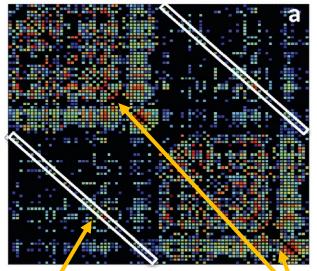


Modules

#### Anatomical projection



#### L vs R hemisphere

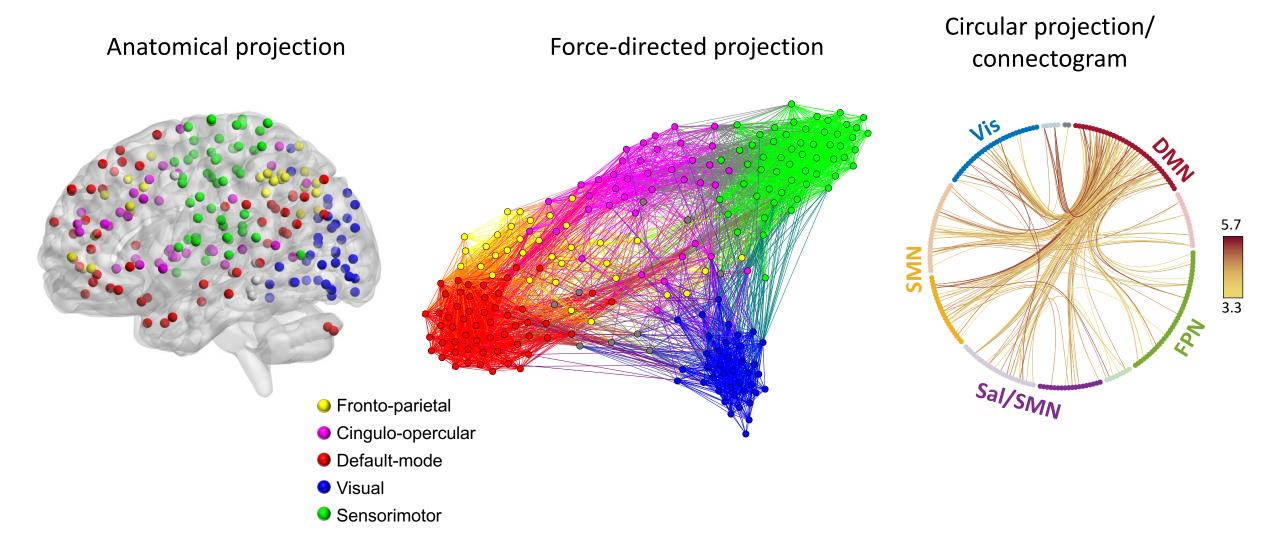


#### Intra-hemispheric connectivity

Connectivity of each region with homologue in the other hemisphere

image: Fornito et al., 2016

### Common types of visualizations



# Modularity – Key topological property

Description (Newman & Girvan, 2004)

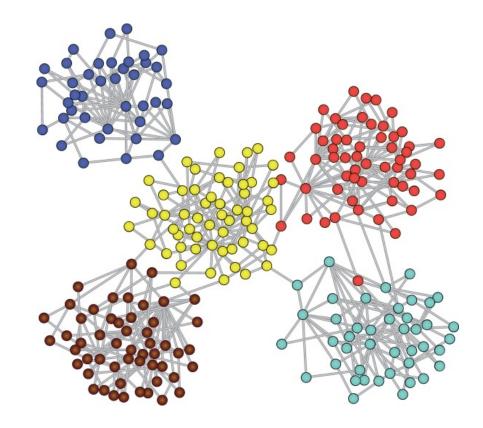
- Nodes cluster into highly cohesive modules.
- Degree of intramodule connectivity is greater than expected by chance (i.e., in a random network).

Quantification – *Modularity Index* 

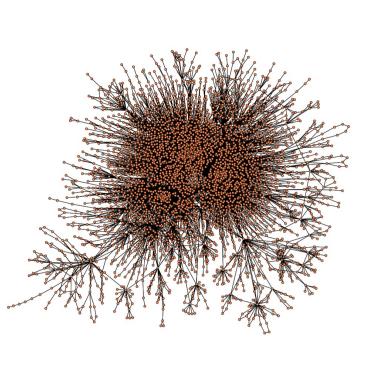
$$Q = \frac{1}{2E} \sum_{ij} \left[ A_{ij} - \gamma e_{ij} \right] \delta(m_i, m_j)$$

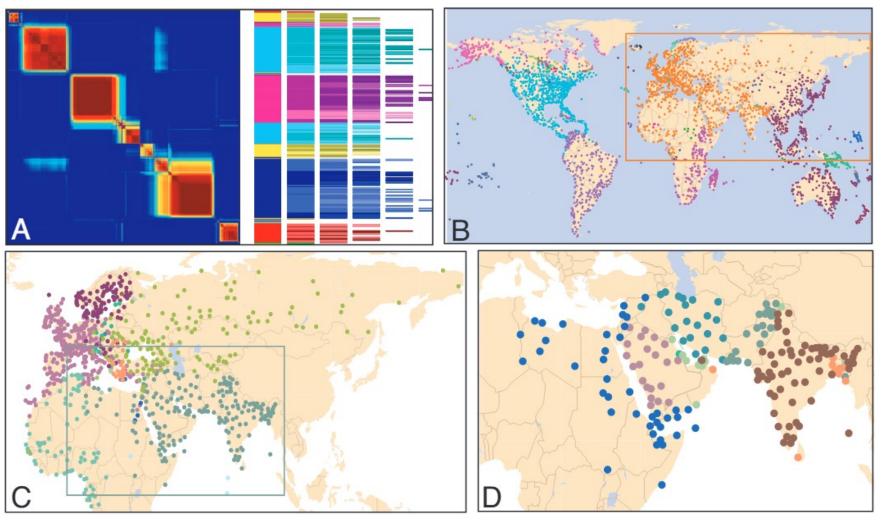
Detection

• community detection algorithms



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





Sales-Pardo et al., 2007

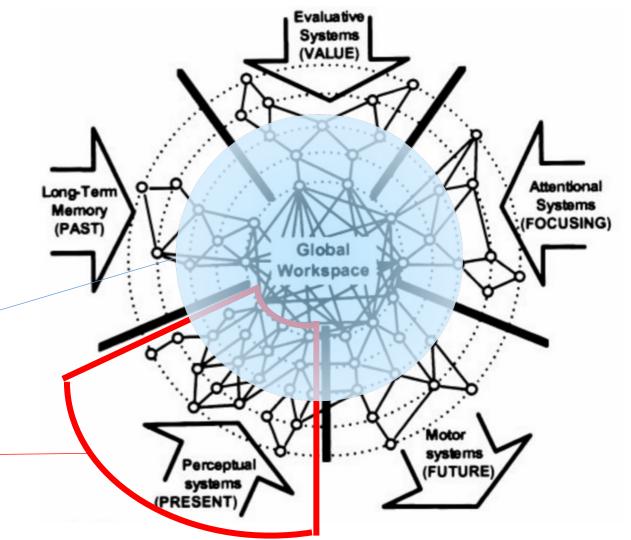
### Cognitive modules and global workspace

Modularity of mind (Fodor, 1983)

Functional segregation & integration

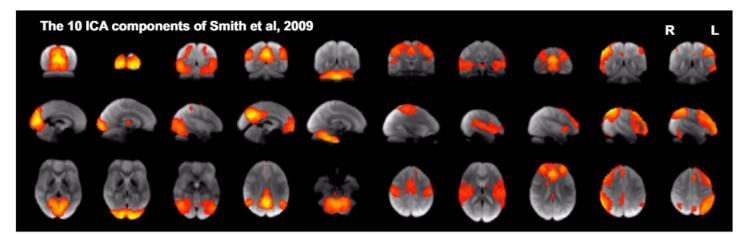
*High-level* cognitive functions (eg. WM) rely more on a *global workspace* than on segregated modular functions.

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



### Large-scale functional organization of the brain

Resting state clusters of Yeo et al., 2011 Resting state clusters of Power et al., 2011 Visual Visual Default Resting state clusters of Power et al., 2011 Resting state clusters of Power et al., 2011 Visual Default Cingulo-opercular Fronto-parietal

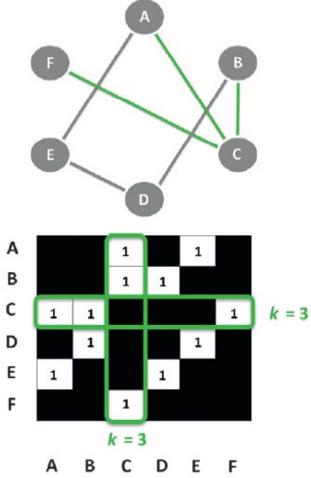


# Node degree & strength

- 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
- 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)

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

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



 $s_i = \sum [w_{ij}]$ 

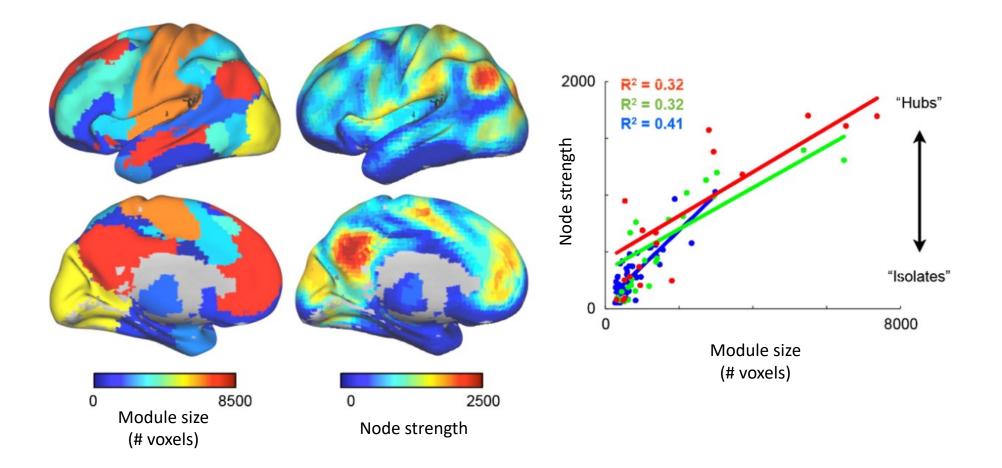
 $\langle k \rangle$ 

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

Fornito et al., 2016

### Node roles: Hubs

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



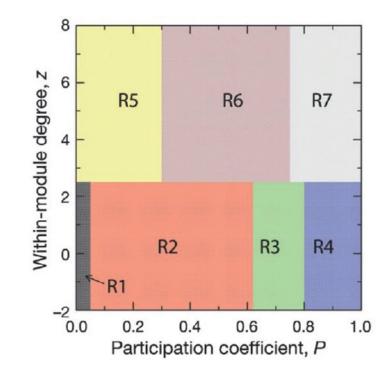
### Node roles

- Within-module degree z-score  $z_i = \frac{k_i(m_i) \bar{k}(m_i)}{\sigma_{k(m_i)}}$ 
  - 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
  - How a node's links are distributed across different modules

$$P_i = 1 - \sum_{m=1}^{M} \left(\frac{k_i(m)}{k_i}\right)^2$$

#### **Topological Roles for Network Nodes**

Guimera & Amaral, 2005

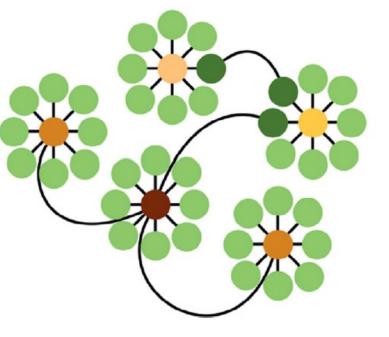


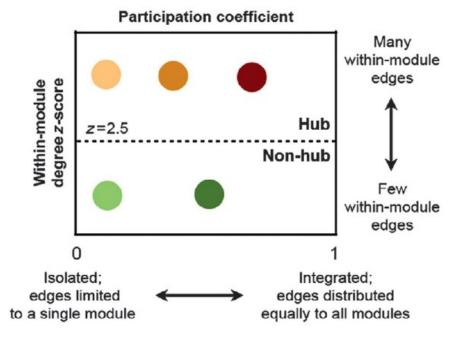
R5, provincial hub R6, connector hub R7, kinless hub

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

# Node role distinctions in brain imaging

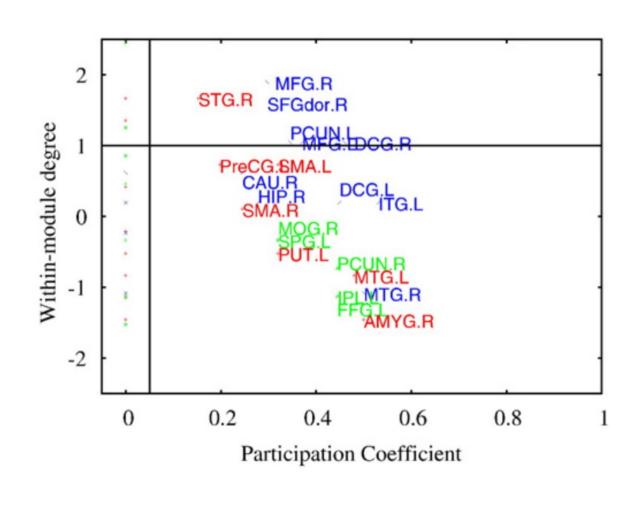
Power et al., 2013

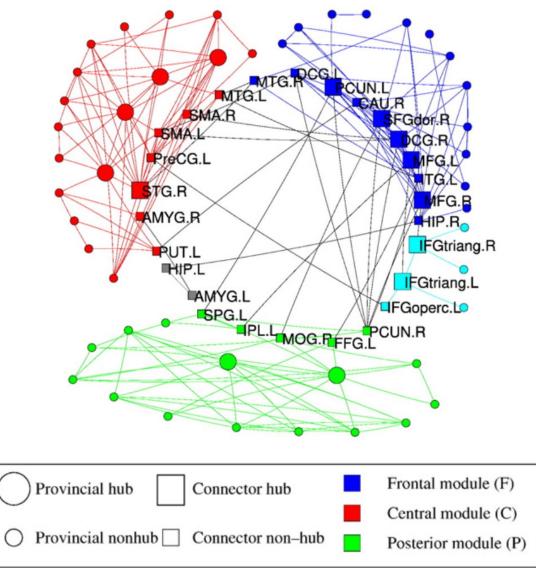




### Brain modules and regional node roles

Resting state data, 90 anatomically defined brain regions



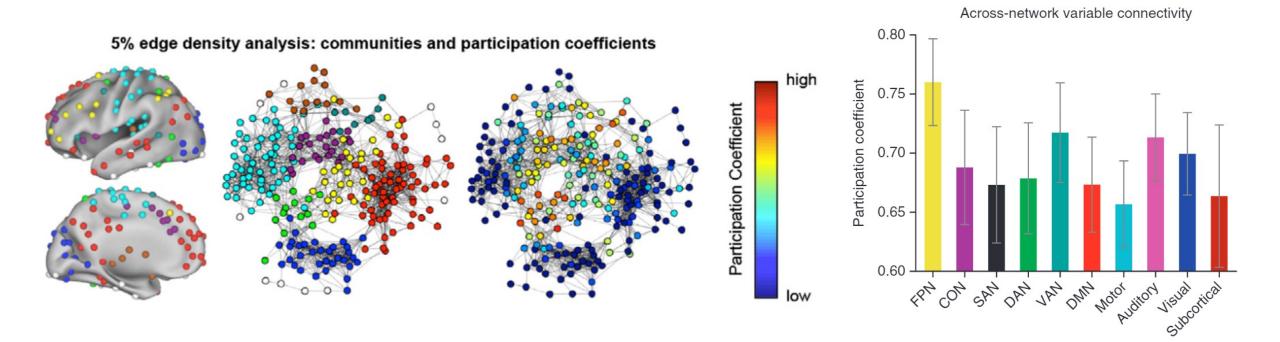


Meunier et al., 2009

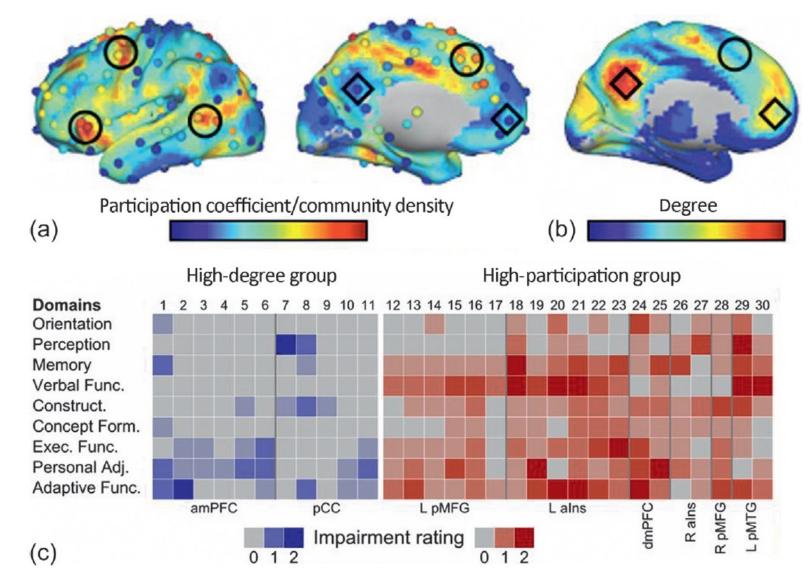
### Variation of participation coefficient across the brain

**During resting-state** 

#### Across tasks

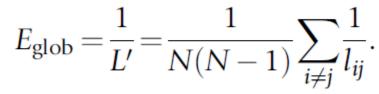


Experimental evidence: Neuropsychological deficits are more consistent and widespread in patients with lesions to areas with high community participation.



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

# Efficiency



- Efficiency of information exchange in a parallel system
- Nodal efficiency

Global efficiency

$$E_{\text{nodal}}(j) = \frac{1}{N-1} \sum_{i} \frac{1}{l_{ij}}.$$

• Measures node integration within network

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

- Local efficiency
  - Measures integration between the immediate neighbors of a given node

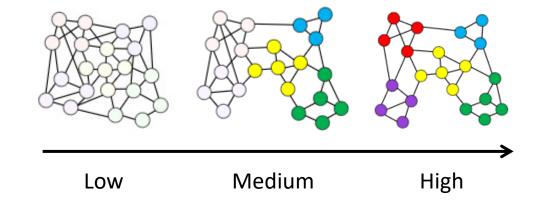
 Modularity -> network distinctiveness, functional segregation

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

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

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

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



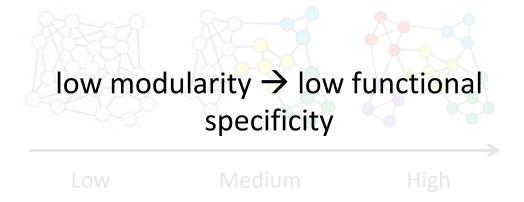
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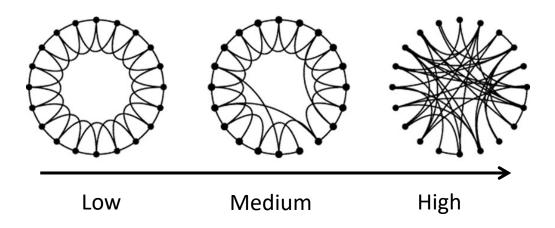
 Modularity -> network distinctiveness vs. dedifferentiation

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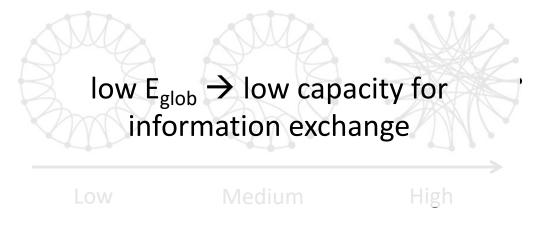
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 Modularity -> network distinctiveness vs. dedifferentiation

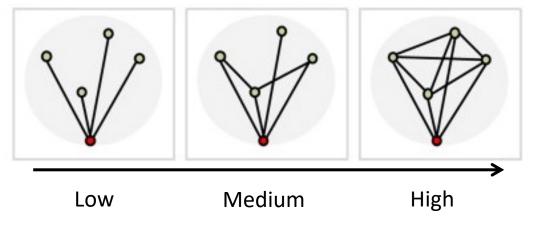
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 Local efficiency -> regional integration, fault tolerance

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



Onoda & Yamaguchi, 2015

 Modularity -> network distinctiveness vs. dedifferentiation

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

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

$$low E_{loc} \rightarrow low cost-efficiency$$

$$low Medium High$$

Onoda & Yamaguchi, 2015

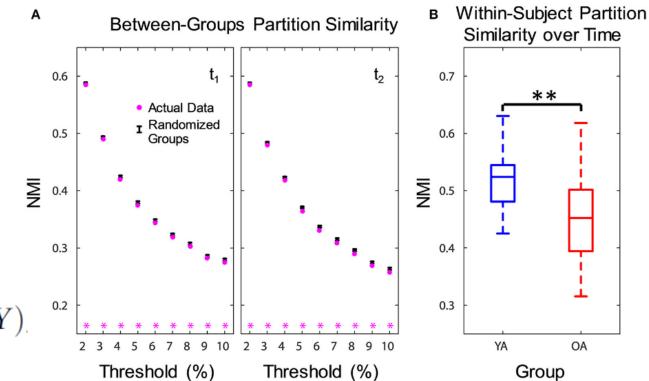
# Comparing partitions

- 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

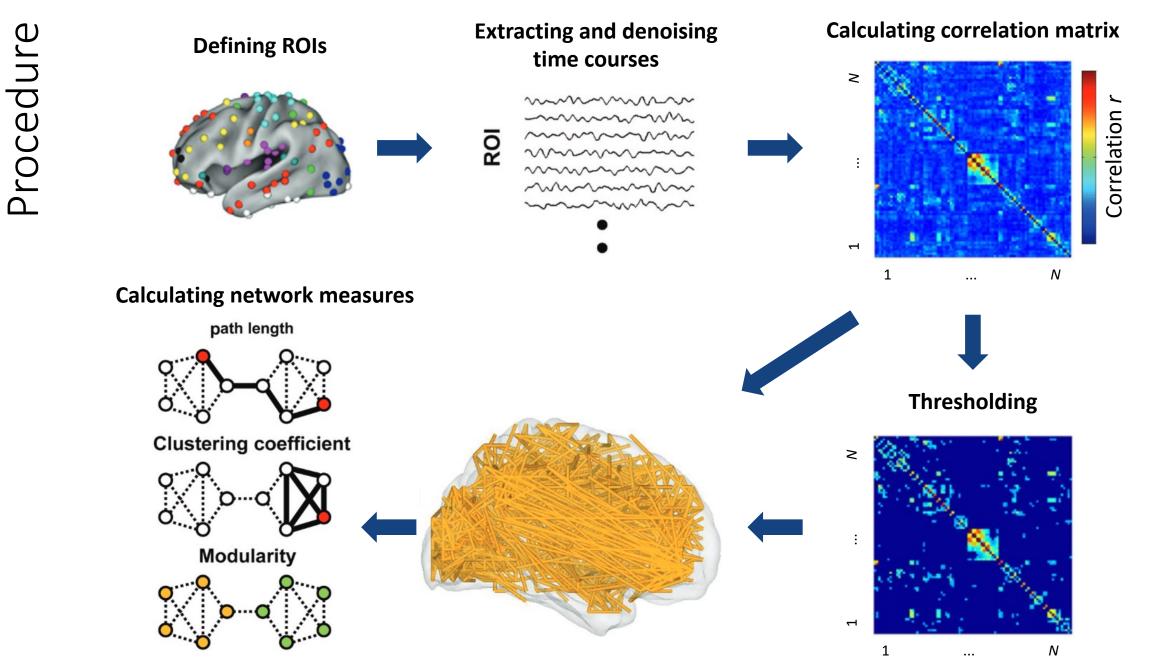
$$MI'(X, Y) = \frac{2MI(X, Y)}{H(X) + H(Y)}.$$

 Variation of information (metric of partition distance)

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



# Methodological issues



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

### Tools



### Artifact Detection Tools (ART)

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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).

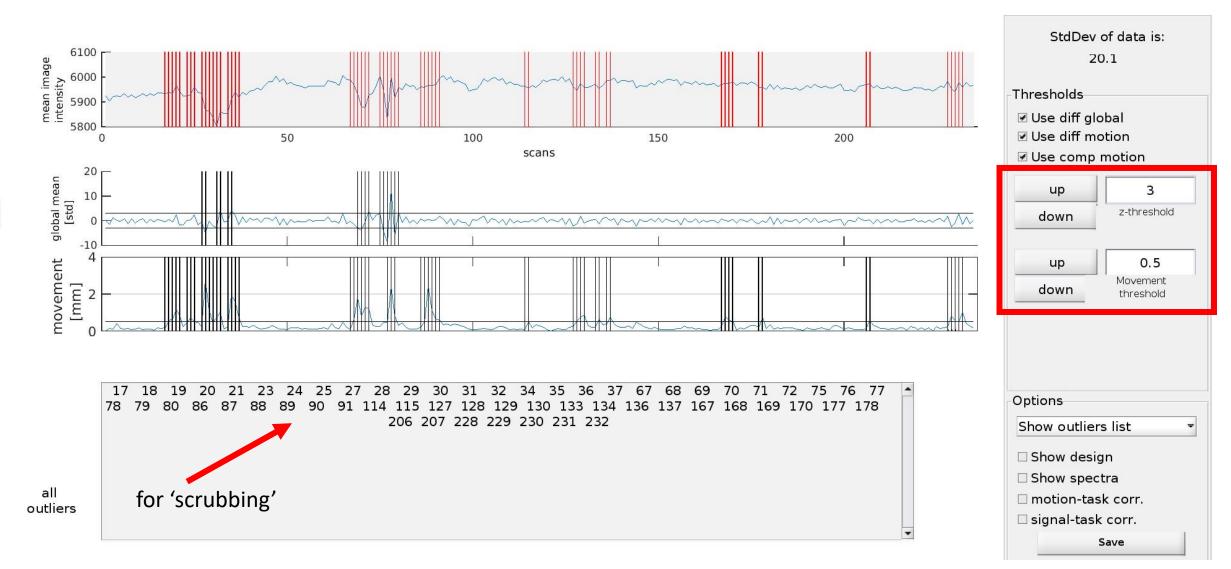
CONN includes a rich set of connectivity analyses (seed-based correlations, ROI-to-ROI graph analyses, group ICA, masked ICA, generalized PPI, ALFF, ICC, GCOR, LCOR, etc.) in a simple-to-use and powerful software package

### **Brain Connectivity Toolbox**



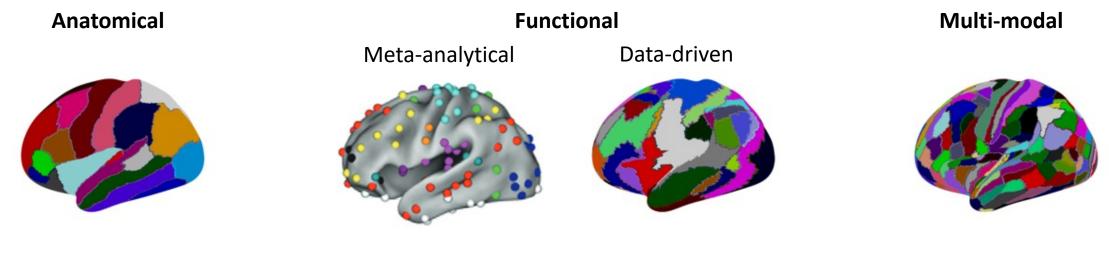
The Brain Connectivity Toolbox (brain-connectivity-toolbox.net) is a MATLAB toolbox for complex-network (graph) analysis of structural and functional brain-connectivity data sets. Several people have contributed to the toolbox and users are welcome to contribute new functions with due acknowledgement.

### Identifying outlier volumes (ART)



+

# Choosing ROI atlas

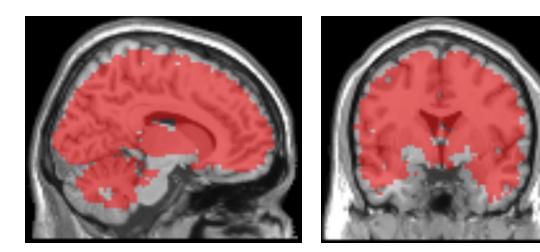


Tzurio-Mazoyer et al., 2002 Desikan et al., 2006 Dosenbach et al., 2010 Power et al., 2011 Yeo et al., 2011 Craddock et al., 2012

Glasser et al., 2016

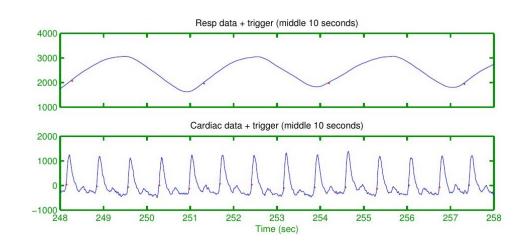
# Signal vs. Noise

### Signal Intensity Mask

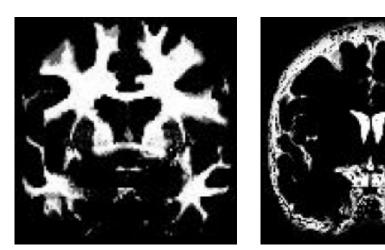


Excluding ROIs that lack good coverage.

### Physiological noise



### WM and CSF Masks



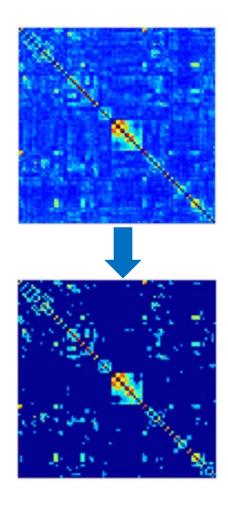
### Removing physiological and other sources of noise

- 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



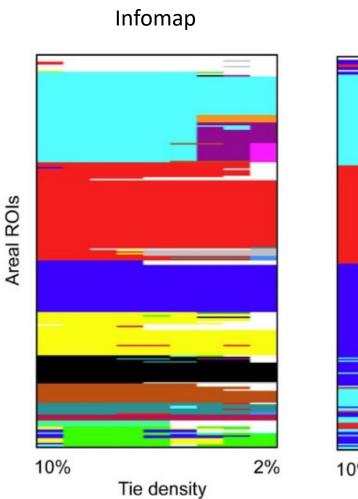
# Issues re: Thresholding

- 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!

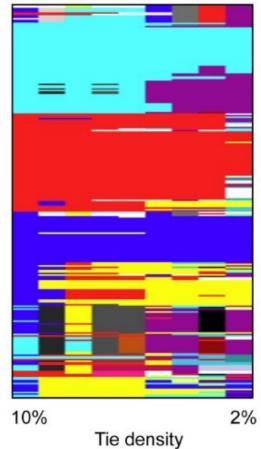


# Community detection

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



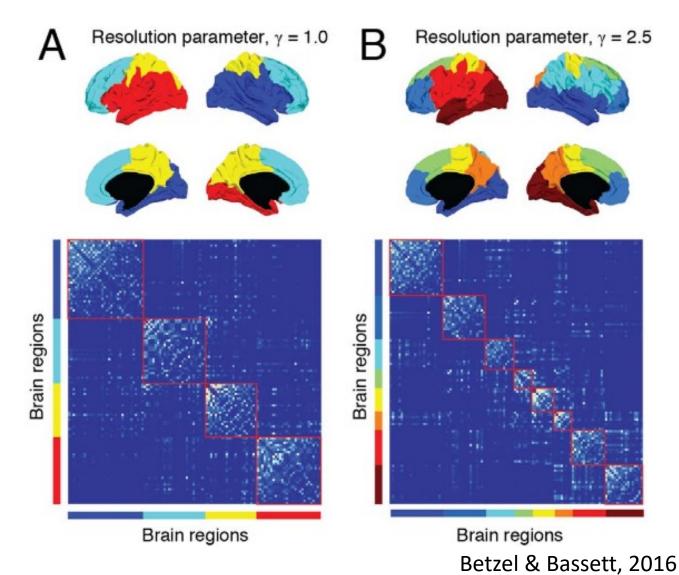
Louvain



Power et al., 2011

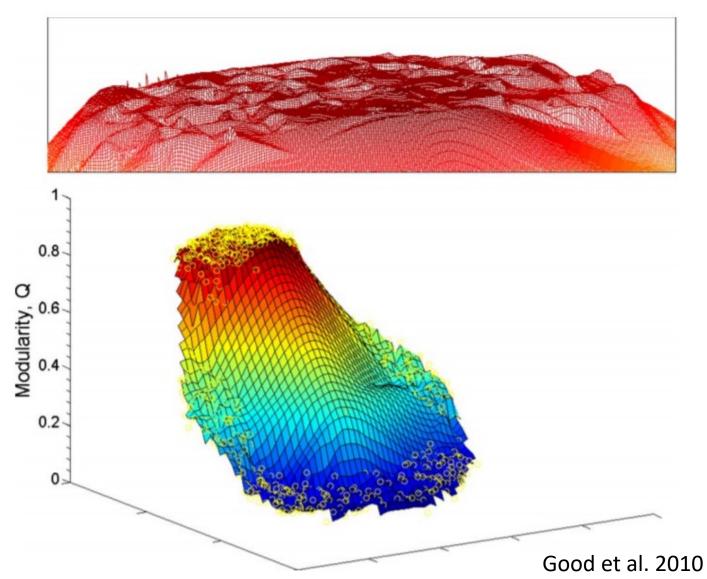
# Community detection

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



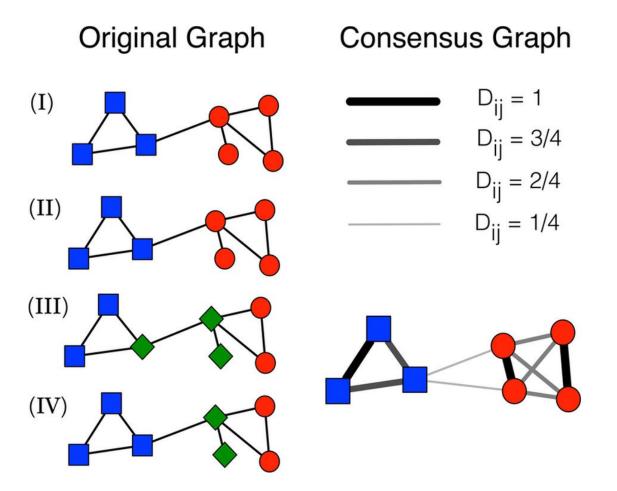
# Community detection

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



# Community detection

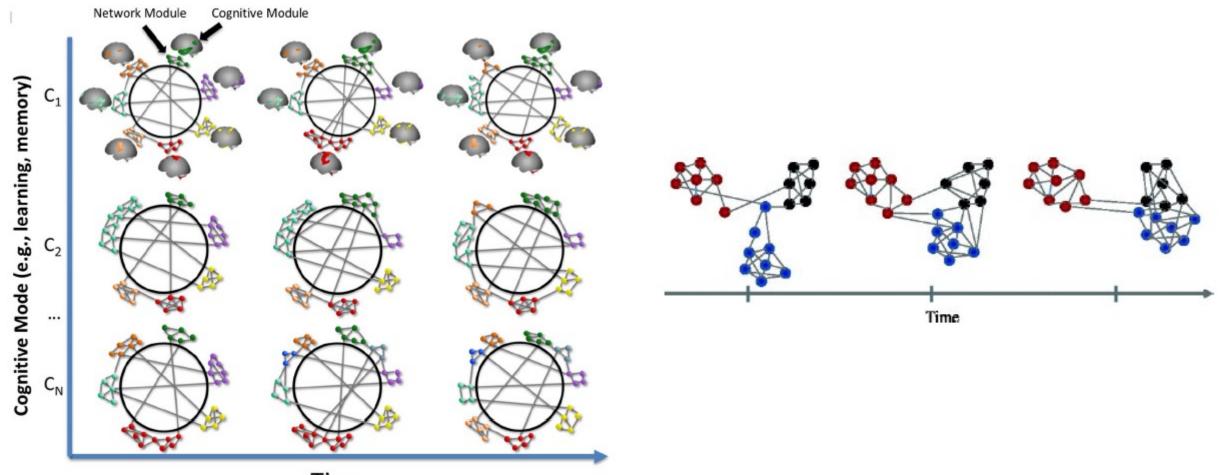
- Algorithms
- Resolution
- Degeneracy
- Consensus clustering
  - Building a representative partition



#### Dynamic Networks

#### Cognitive Processes are Dynamic

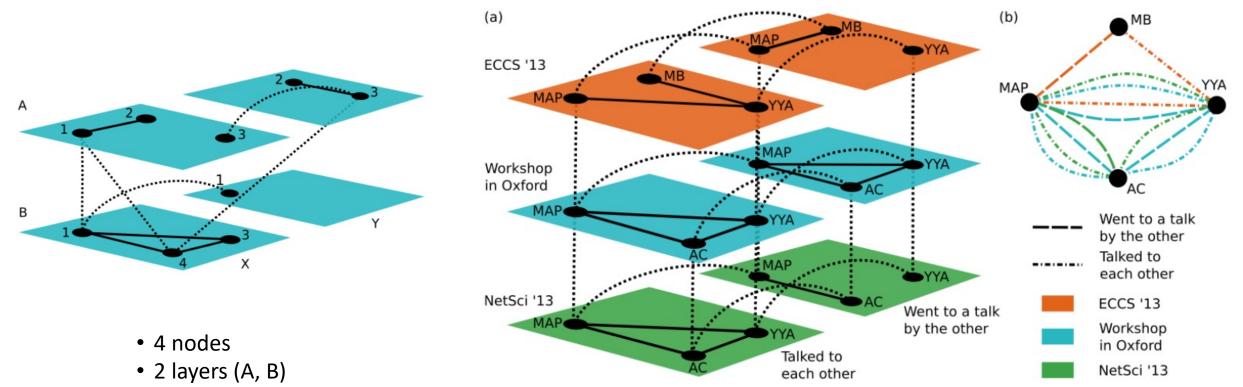
Network Structure Changes over Time



Bassett et al. (2013)

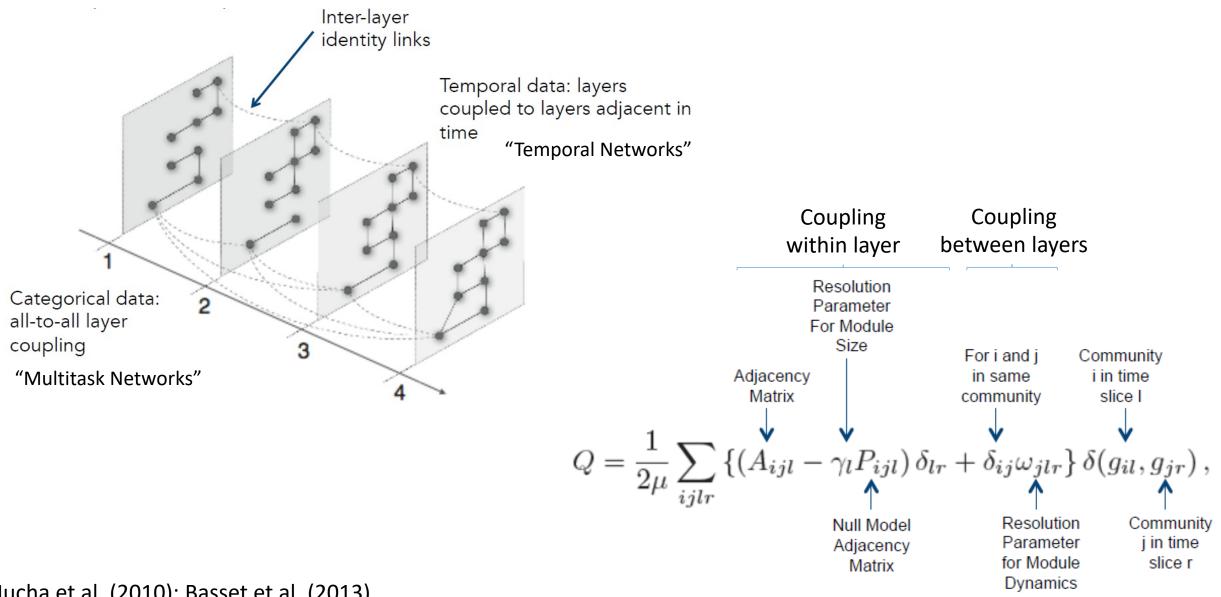
Medaglia et al. (2015)

#### Multilayer Networks



• 2 aspects (X, Y)

#### Multilayer Modularity



Mucha et al. (2010); Basset et al. (2013)

# Application

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#### RESEARCH ARTICLE

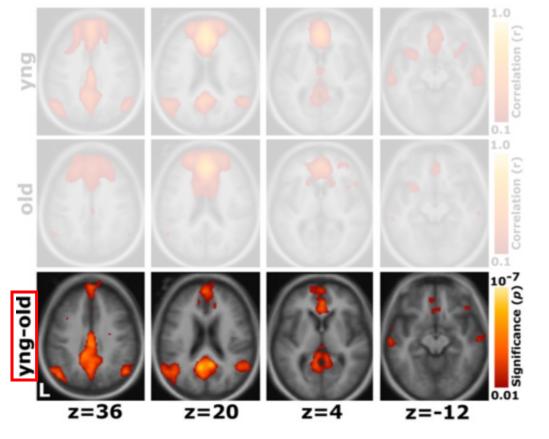
#### WILEY

# Age differences in functional network reconfiguration with working memory training

Alexandru D. Iordan<sup>1</sup> | Kyle D. Moored<sup>2</sup> | Benjamin Katz<sup>3</sup> | Katherine A. Cooke<sup>1</sup> | Martin Buschkuehl<sup>4</sup> | Susanne M. Jaeggi<sup>5</sup> | Thad A. Polk<sup>1</sup> | Scott J. Peltier<sup>6,7</sup> | John Jonides<sup>1</sup> | Patricia A. Reuter-Lorenz<sup>1</sup>

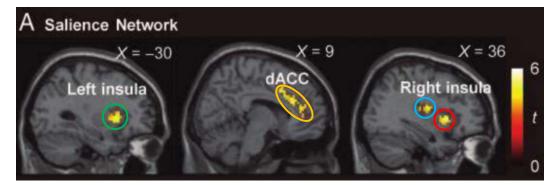
# Aging influences the functional organization of the brain

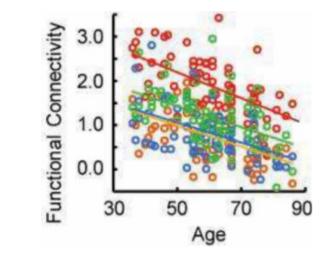
Default-mode Network



Andrews-Hanna et al., 2007

Salience/Cingulo-Opercular Network

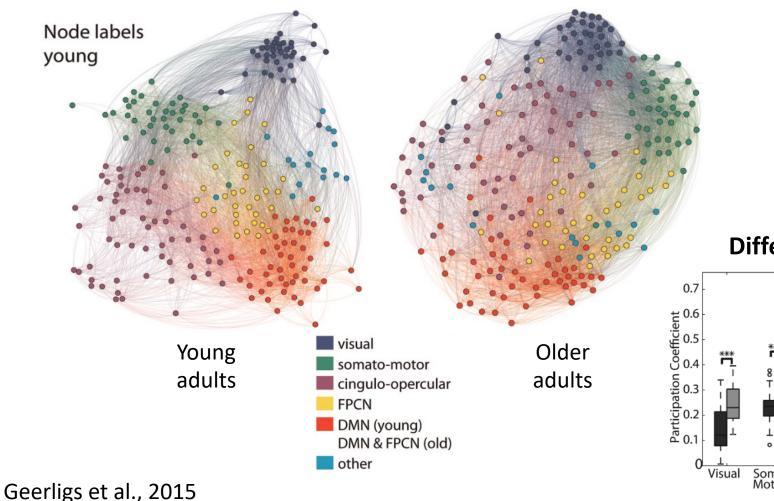




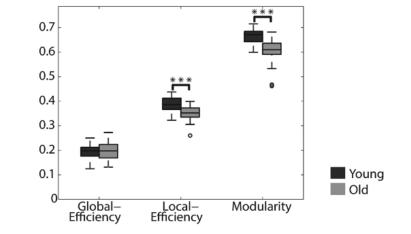
Onoda et al., 2012

# Evidence for network differences between young and older adults

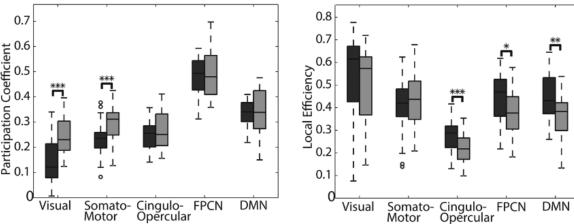
#### **Differences in community structure**



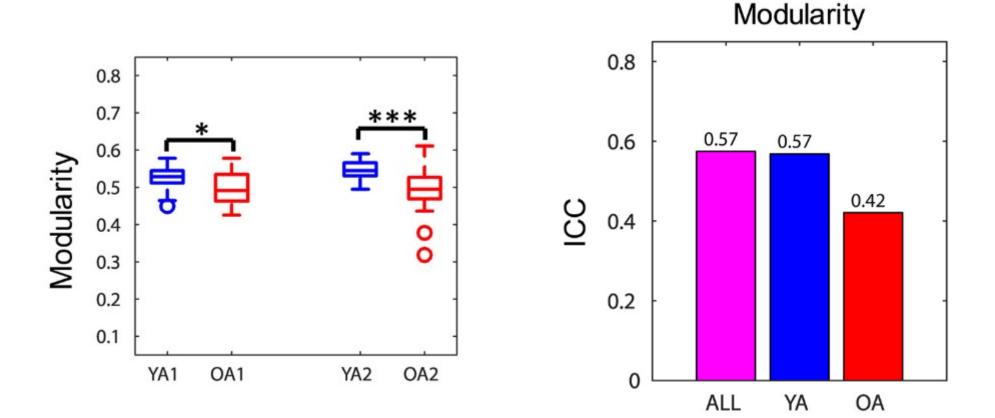
#### **Differences in brain-wide network measures**



#### Differences in individual network measures



### Modularity decreases with aging



Similar results:

Betzel et al., 2014; Cao et al., 2014; Chan et al., 2014; Gallen et al., 2016;

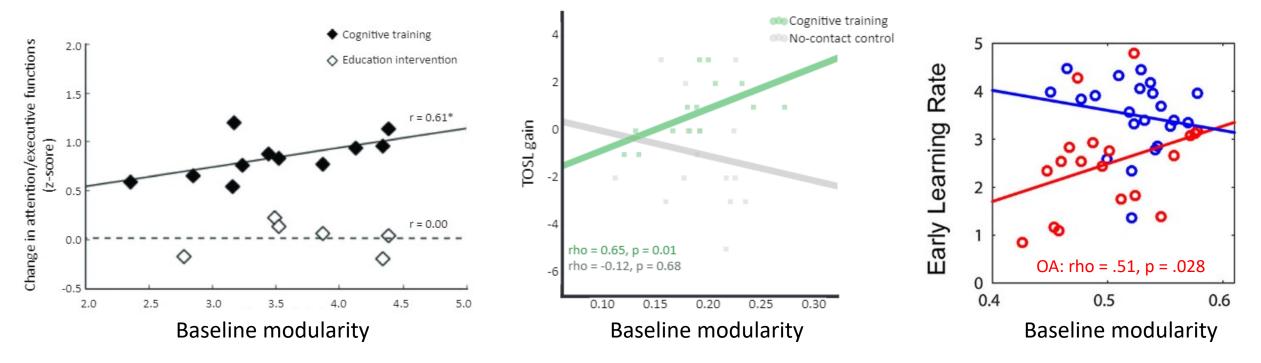
Geerligs et al., 2015; Onoda & Yamaguchi, 2013; Song et al., 2014

lordan et al., 2018

#### Modularity Predicts Training-related Cognitive Gains

Patients with acquired brain injury





Gallen et al., 2016

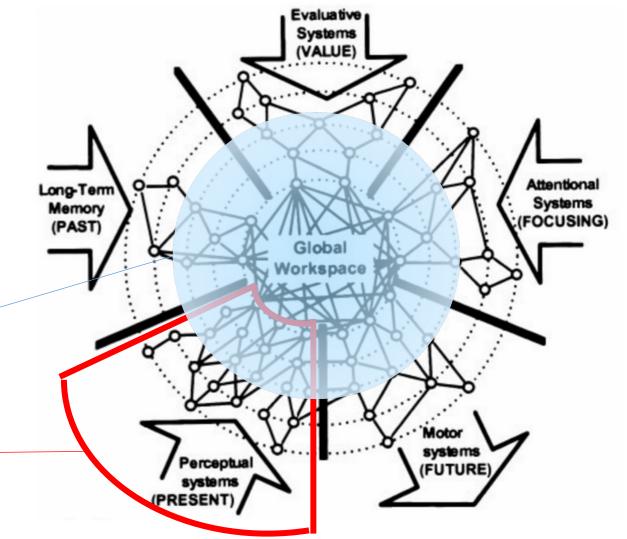
### Cognitive modules and global workspace

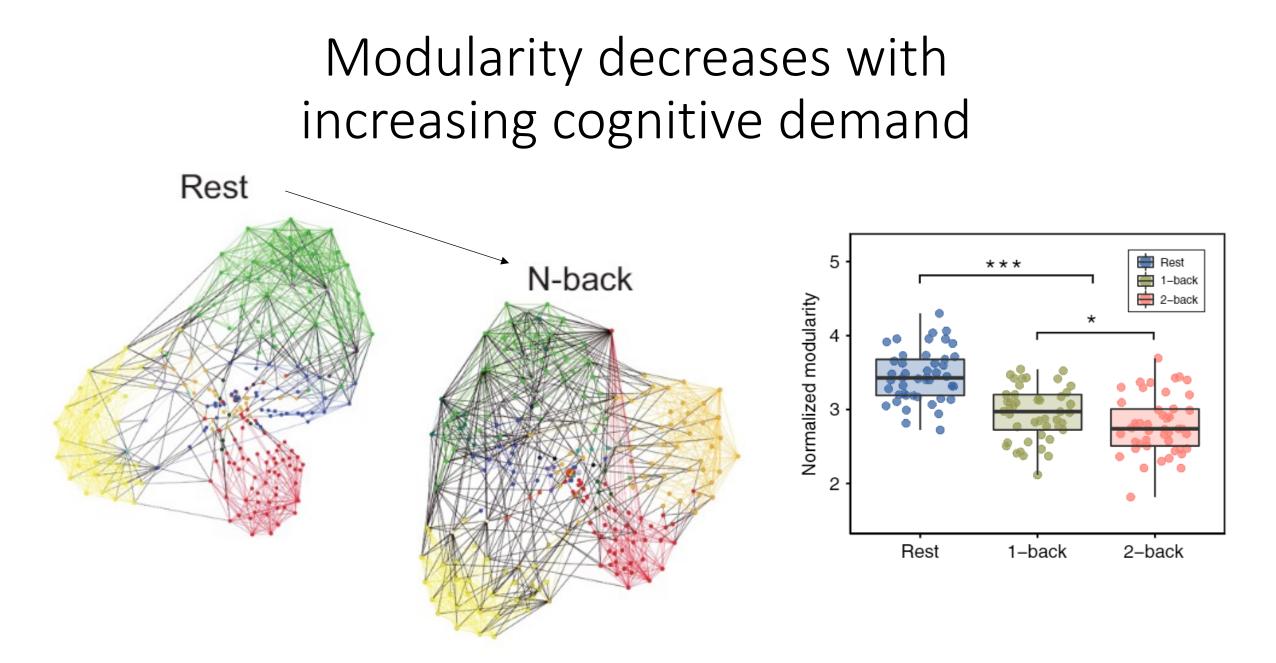
• Modularity of mind (Fodor, 1983)

• Functional segregation & integration

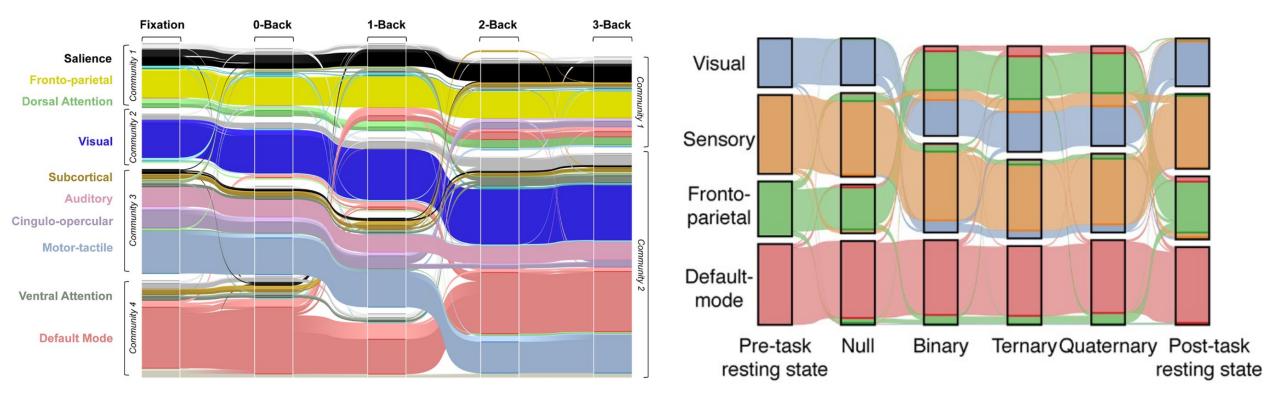
*High-level* cognitive functions (eg. WM) rely more on a *global workspace* than on segregated modular functions.

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

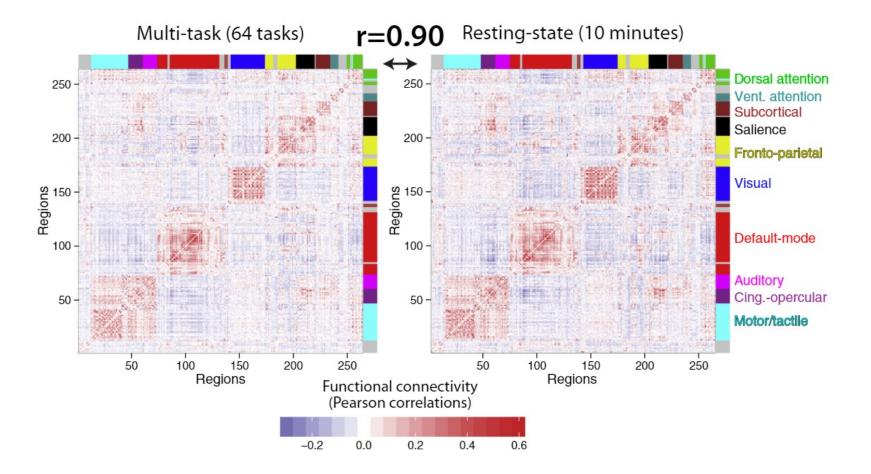




# Community structure is influenced by (large shifts in) cognitive demand

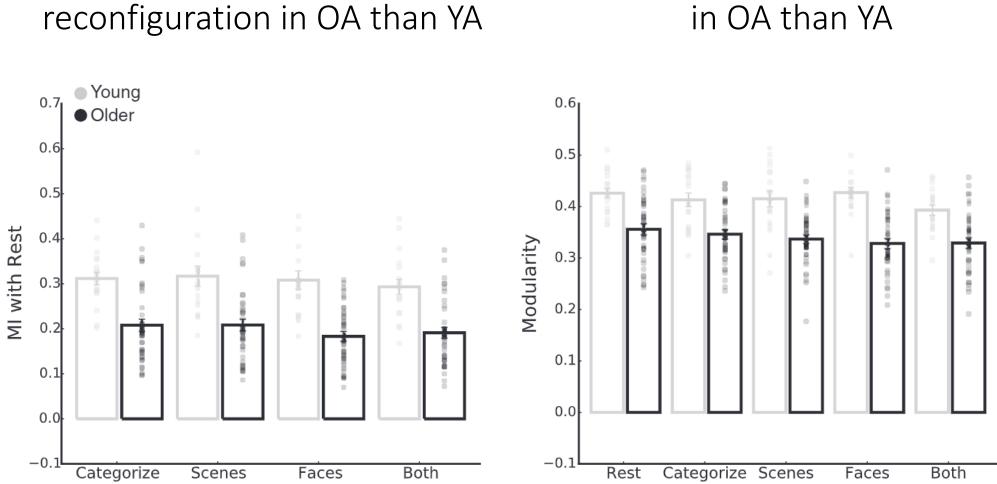


### Task-related reconfigurations are "relatively small"



### Questions

- How does aging affect brain network reconfigurations elicited by demanding cognitive tasks?
- Can these be influenced by cognitive training?

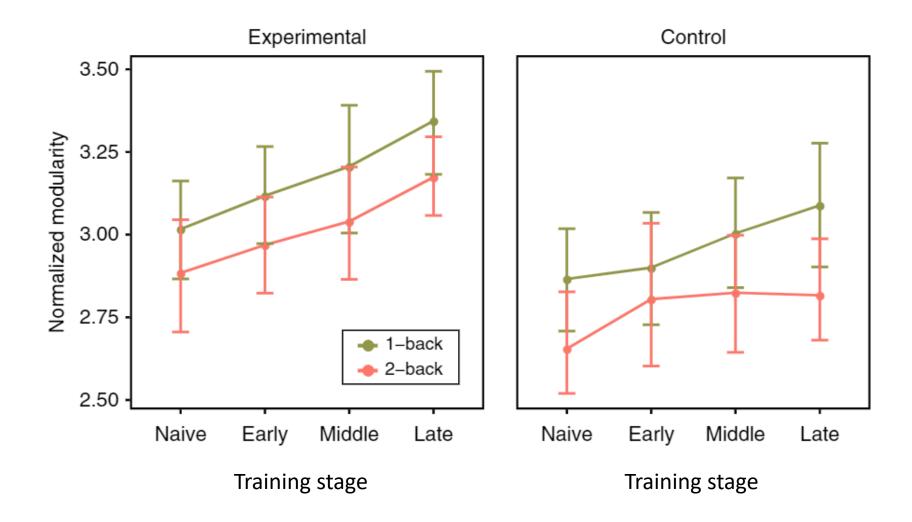


Greater rest-to-task

#### Lower overall modularity in OA than YA

Gallen et al., 2016

# Modularity increases with training in YA



Finc et al., 2020

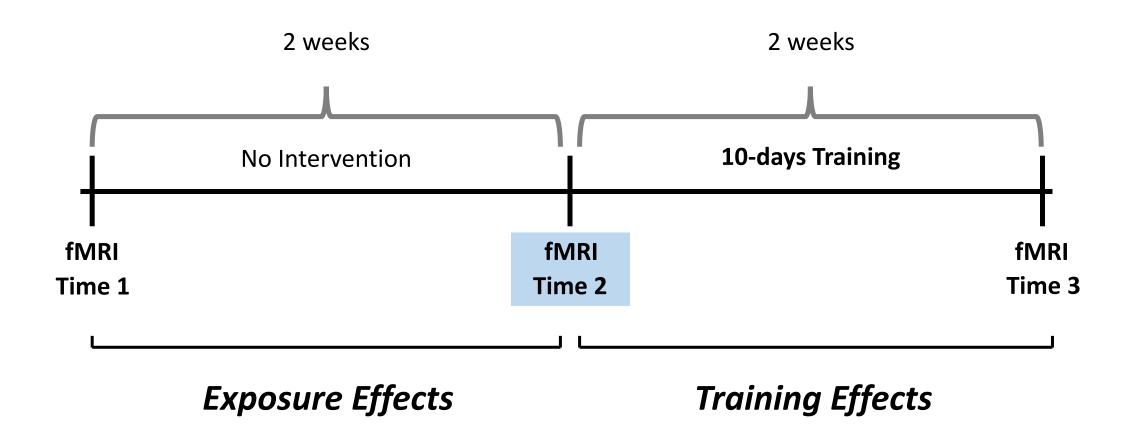
How does aging affect brain network reconfigurations elicited by demanding cognitive tasks?

- 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?

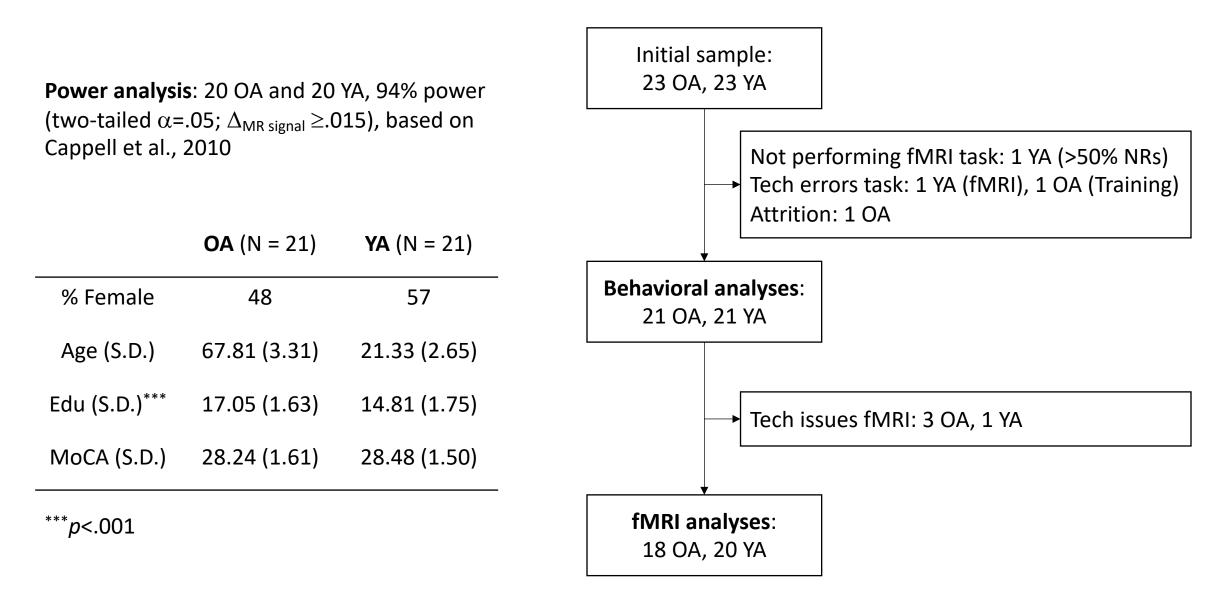
- We expect:
  - network reorganization elicited by training not task-exposure
  - task-related FC more sensitive to training than resting-state
- Open question:
  - Greater modularity enhancement with training in YA vs. OA?
- Brain networks level:
  - Training reconfigures primarily associative brain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

#### <u>Present study</u>: Design



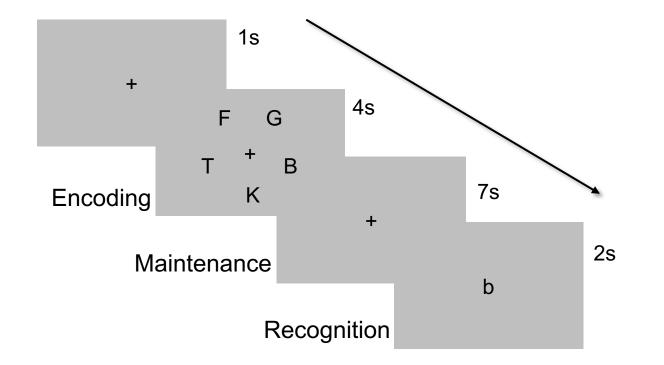
Neuropsychological testing was performed at each time point (Not discussed here).

### Participants



#### MoCA, Montreal Cognitive Assessment

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



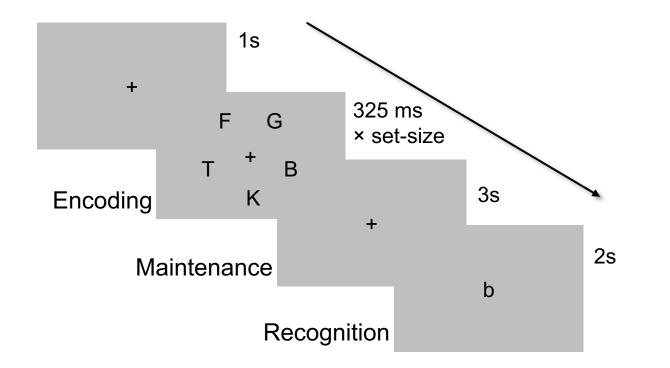
#### fMRI (Criterion) Task:

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

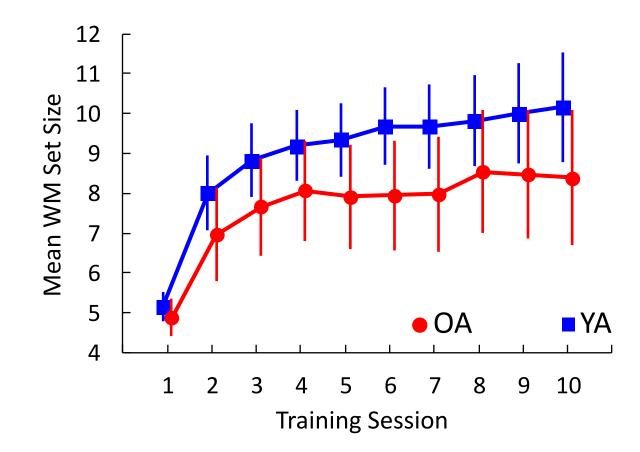
Set-size was randomized (6 blocks of 24 trials)

#### 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)

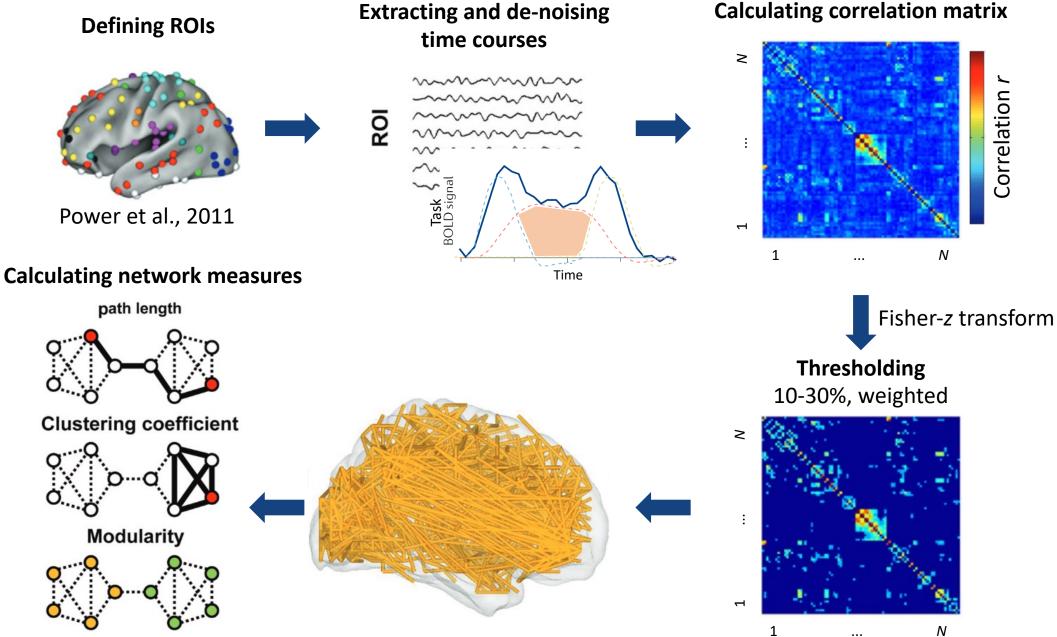
### Adaptive Training Task Results



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

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

connectivity" Procedure "Background

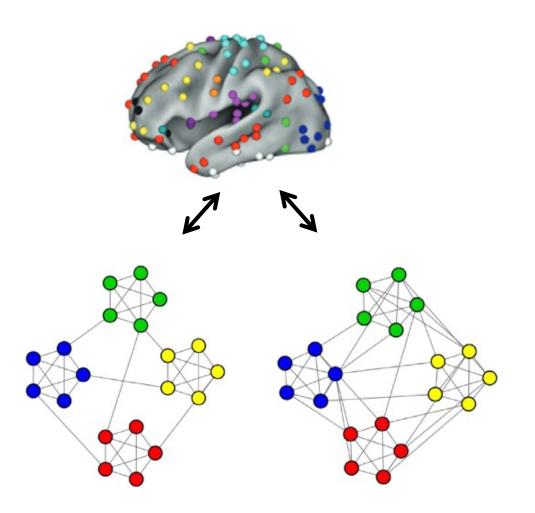


images: Uehara et al., 2013; Taya et al., 2016; Power et al., 2013; Sreenivasan & D'Esposito, 2019

•••

# 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

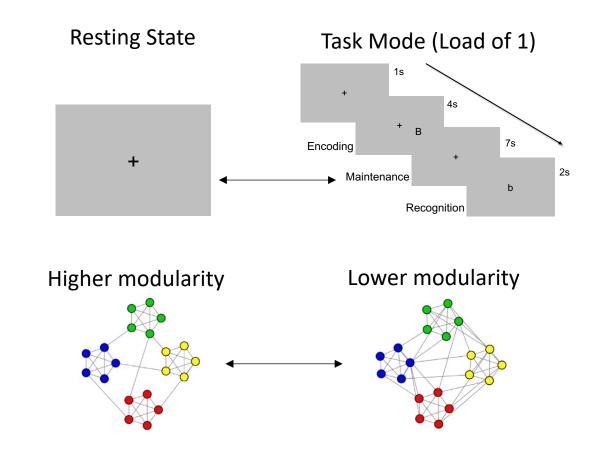


## 1. Whole-Brain Results

#### **Modularity: Whole-brain segregation/integration**

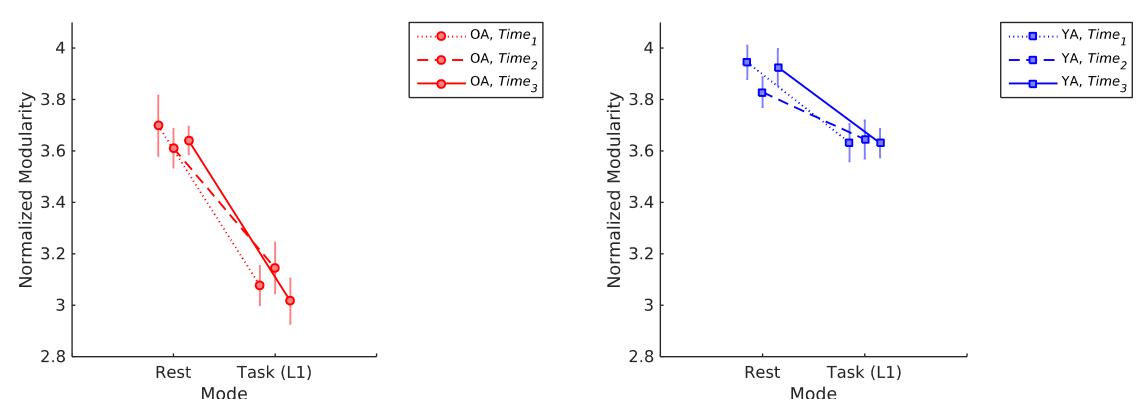
#### Rest-to-task shift

- 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



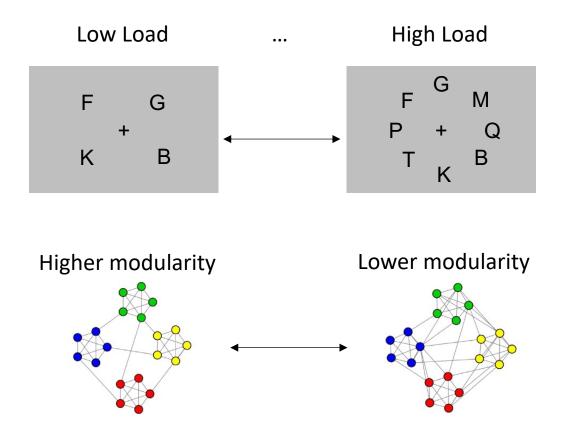
- Lower overall modularity in OA vs. YA. Group:  $F_{1,36}$ =31.99, p<0.001,  $\eta_p^2$ =0.47
- Lower modularity during task than rest. Mode:  $F_{1,36}$ =141.51, p<0.001,  $\eta_p^2$ =0.8
- Greater modularity decrement with rest-to-task shift in OA. Group×Mode:  $F_{1,36}$ =19.14, p<0.001,  $\eta_p^2$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

## 1. Whole-Brain Results

#### **Modularity: Whole-brain segregation/integration**

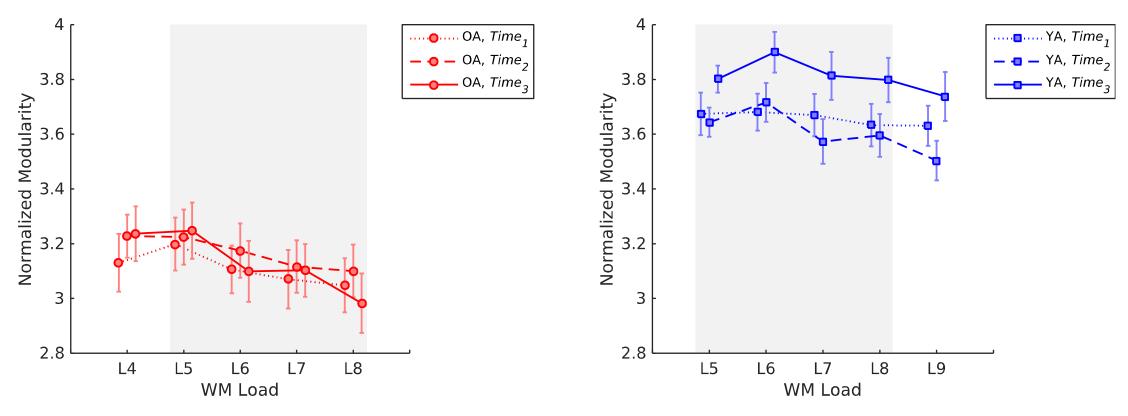
#### Increasing task demand

- 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

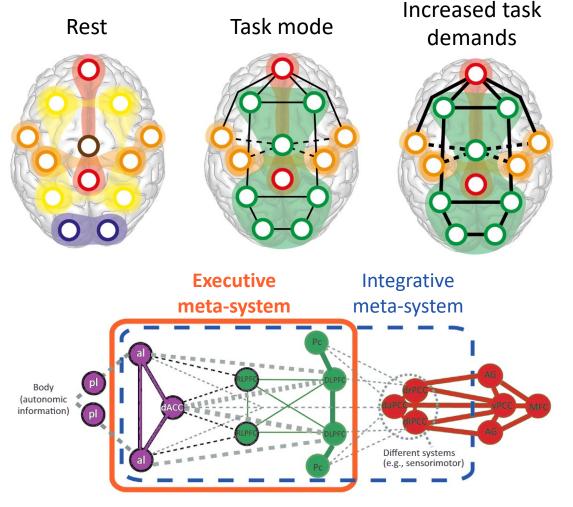


- Lower overall modularity in OA vs. YA. Group:  $F_{1,36}$ =37.38, p<0.001,  $\eta_p^2$ =0.51
- Lower modularity with increasing load. Load:  $F_{3,108}=5.89$ , p=0.001,  $\eta_p^2=0.14$ , linear trend p<0.001;
- Steeper modularity decrement in OA vs YA. Group×Load:  $F_{3,108}=3.21$ , p=0.026,  $\eta_p^2=0.08$
- Group×Time interaction.  $F_{2,72}$ =4.64, p=0.013,  $\eta_p^2$ =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,  $\eta_p^2=0.58$

## 1. Whole-Brain Results

#### **Community structure: Network/module composition**

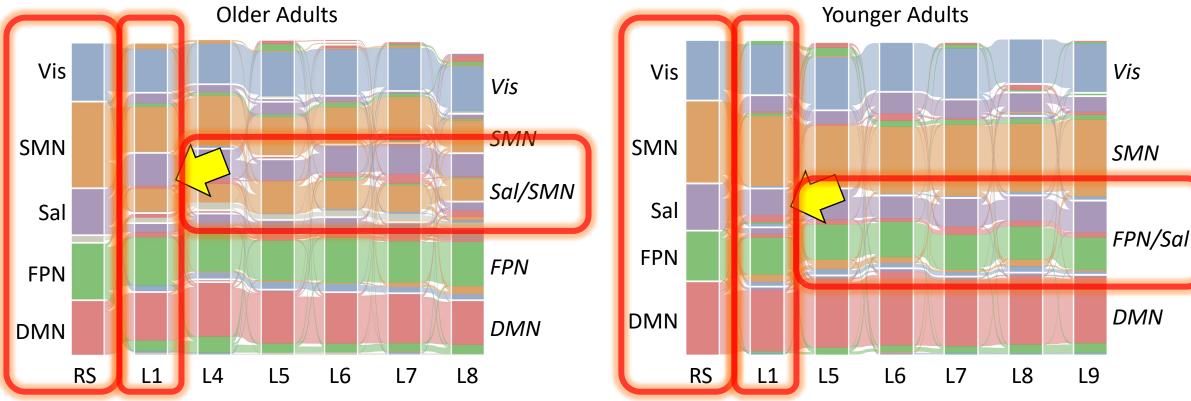
- Demand and training effects
  - Change from rest to task
  - Greater reorganization in OA than YA?
  - Less change with increasing demand
    - Integrative -> Executive meta-system
  - Effect of training?



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

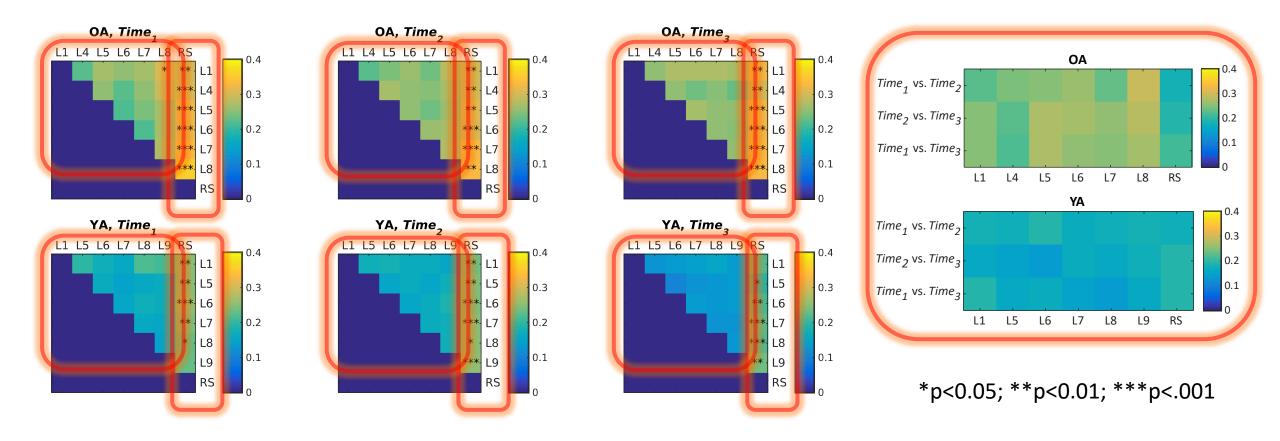
### 1. Whole-Brain Results: Community Structure

Node-module assignments across rest and task loads at Time1



- 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,  $\eta_0^2$ =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**

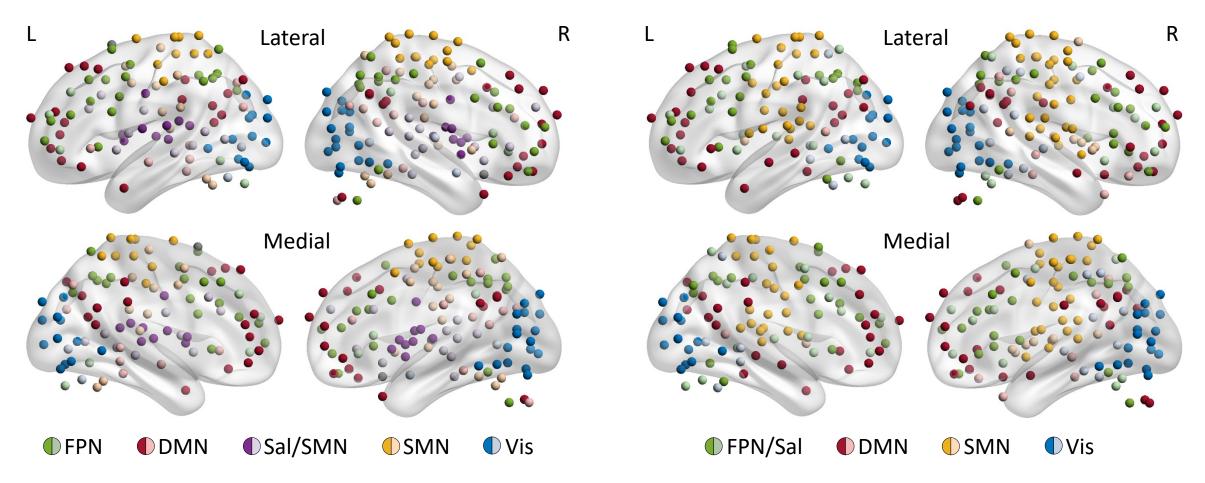


- Community structure is different for rest compared to WM loads
- No (consistent) differences in community structure between loads
- No differences in community structure across time

#### Node-module assignments across loads at Time1

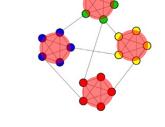
**Older Adults** 

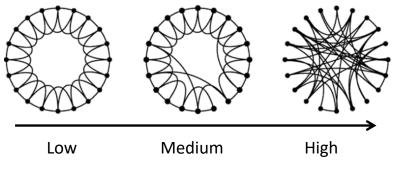
Younger Adults



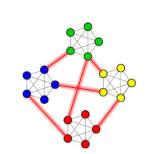
#### **Primary targets: FPN and DMN**

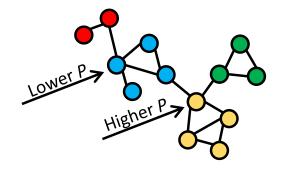
- Within-network communication: Global Efficiency
  - Parallel information transfer, integrated processing





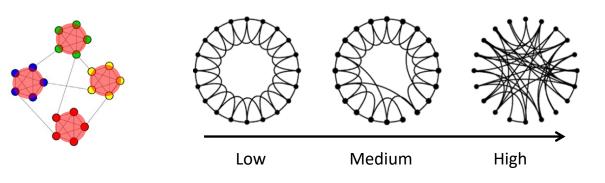
- Between-network communication: Participation Coefficient
  - Distribution of node connections across modules



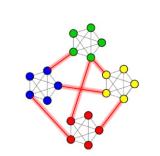


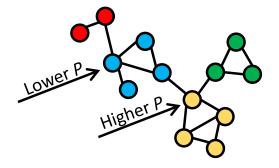
#### **Outcomes:**

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

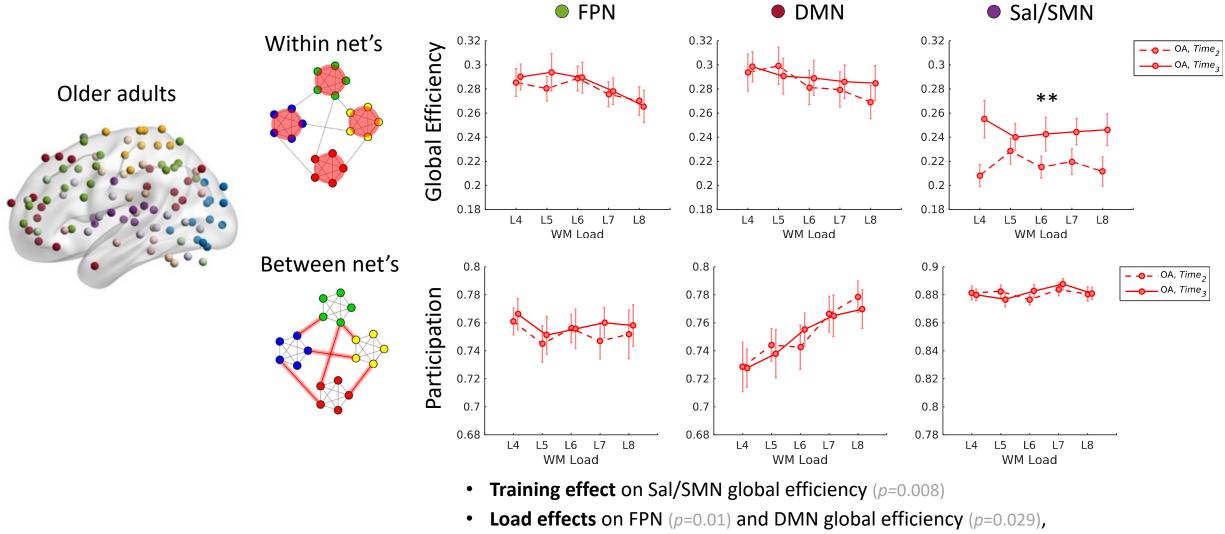


- Between-network communication: Participation Coefficient
  - Training: Greater decrease = more automatic processing (less integration required)
     Load: Less increase = better coping with demand (less integration required)



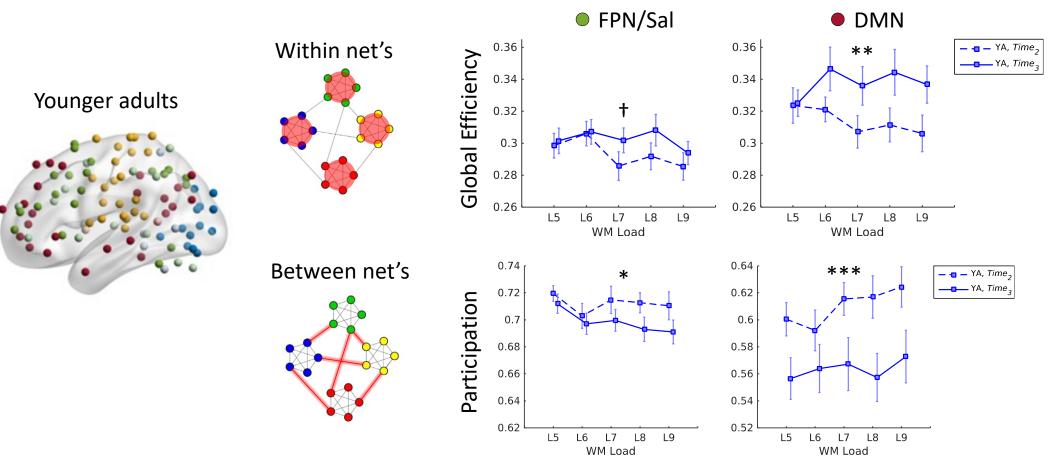


#### **OA:** Increased global efficiency within Sal/SMN with training



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



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

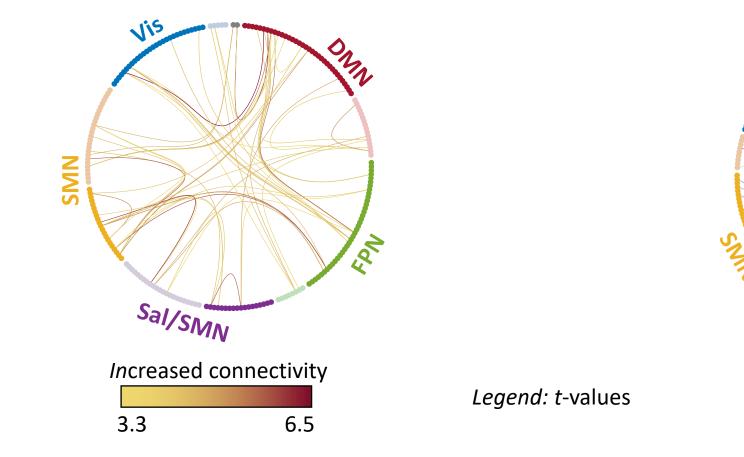
Decreased connectivity

6.0

OMA

Jis

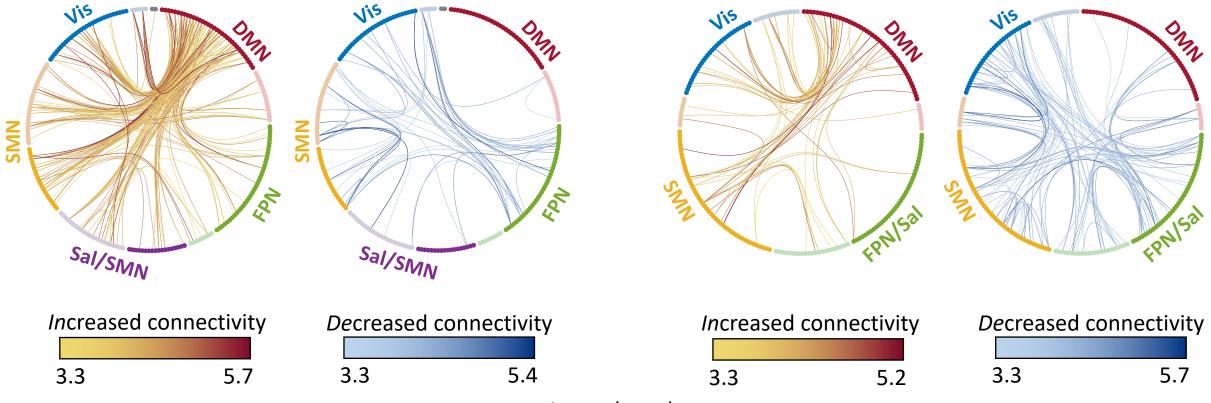
3.3



### 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.

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