CAJAL ADVANCED NEUROSCIENCE TRAINING

BORDEAUX SCHOOL OF NEUROSCIENCE

Baycrest Rotman Research Institute

Part 3: Resting State fMRI

Cajal Course on Aging Cognition

Workshop: Approaches to functional and structural neuroimaging analysis

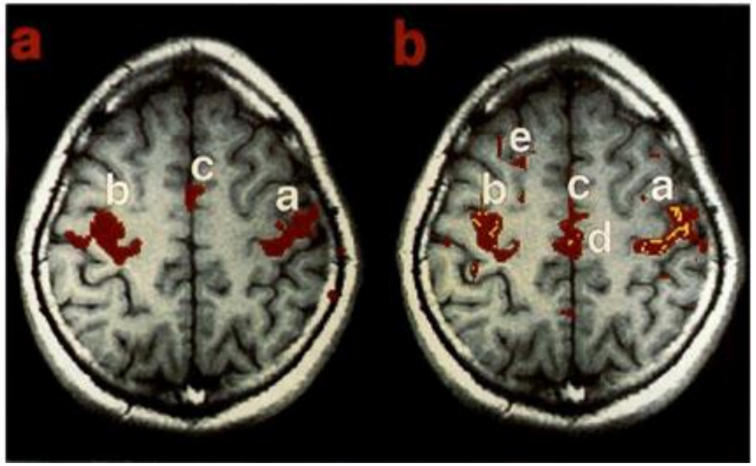
Materials: https://github.com/jennyrieck/workshops/tree/master/2021_Cajal_NeuroImaging

27 Sep 2021

Jenny Rieck

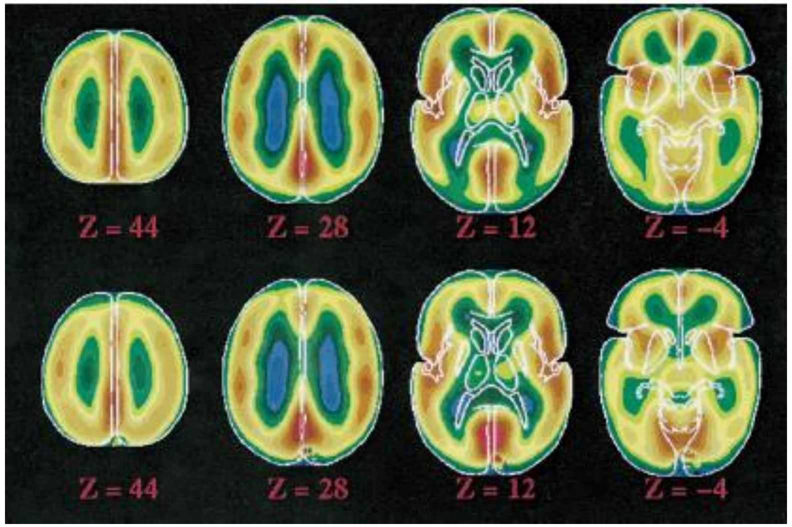
Background of resting state fMRI

fMRI signals fluctuate synchronously during rest in regions that co-activate



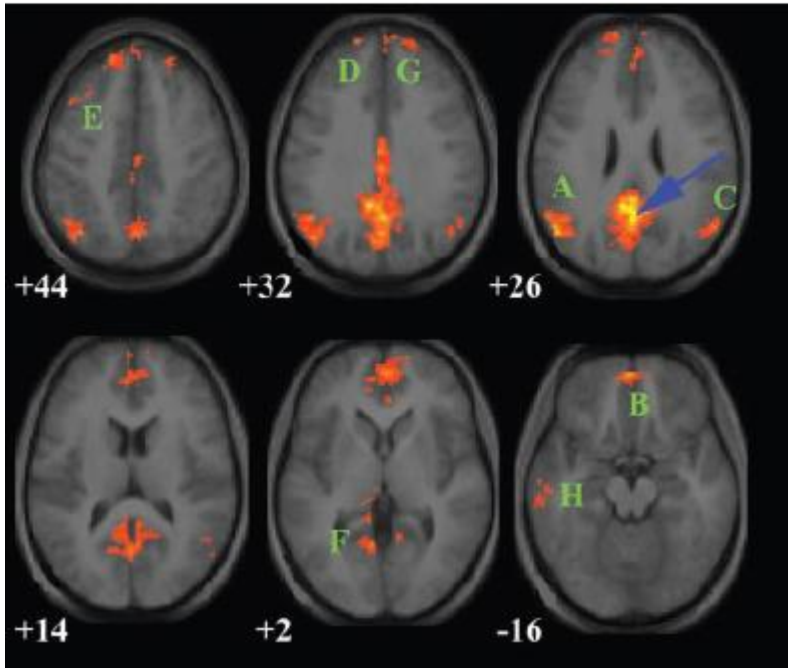
Biswal, 1995, *Mag Res Med*

An organized "default mode" of brain function during rest exists



Raichle, 2001, *PNAS*

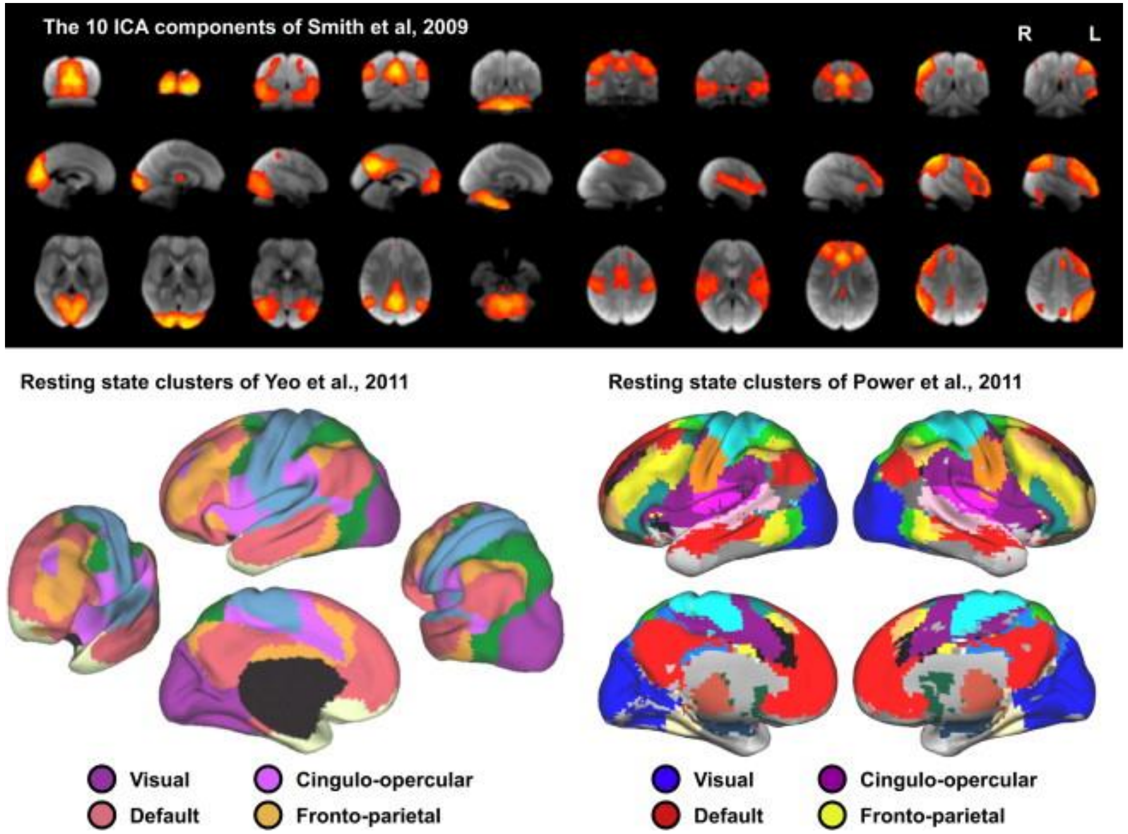
Using posterior cingulate as a seed reveals a connected default network



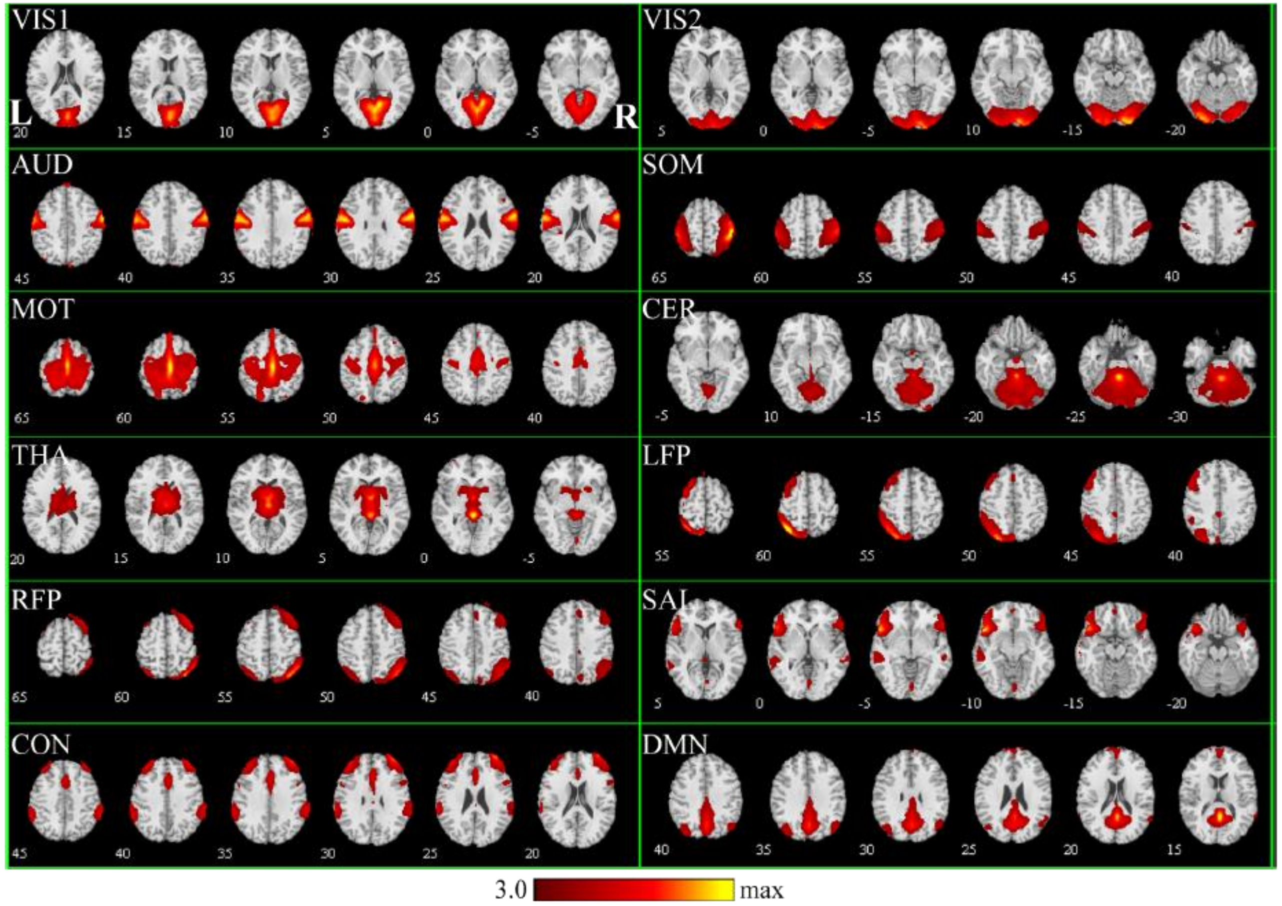
Greicius, 2003, *PNAS*

Spontaneous activity during rest is structured and organized into networks that reflect higher order cognitive processes

Resting state networks



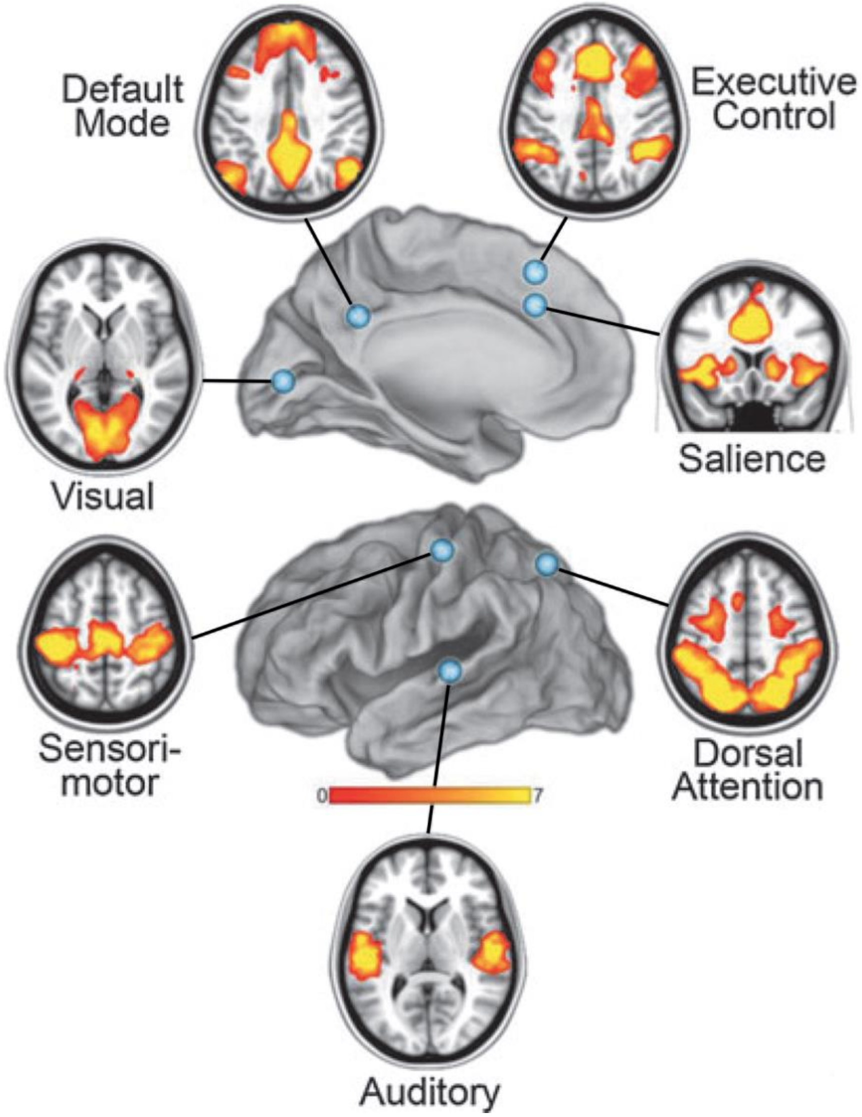
Power, 2014, *Neuron*



Li, 2015, *Brain Topogr*

Canonical and consistent resting state networks are observed across participants and datasets

Most common resting state networks



Raichle, 2011, *Brain Conn*

Network	Regions	Function
DMN	precuneus, PCC, ACC vmPFC, inf parietal	introspection, memory
Control	mesiofrontal, sup parietal, ACC, paracingulate	executive function, working memory
Salience	dACC, insula	bottom-up attention
Dorsal Attention	sup parietal, sup frontal	top-down attention
Auditory	sup temporal	auditory processing
Sensori-motor	pre/postcentral; supp motor,	sensory input; motor function
Visual	occipital, ventral temporal	visual processing

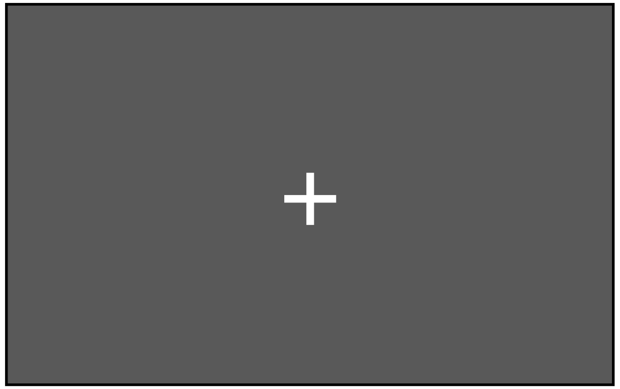
Other networks: limbic, subcortical, cingulo-opercular, medial temporal, ventral attention

Why study the brain at rest?

- Understand communication between brain regions rather than localization of specific cognitive processes
- Understand inherent functional architecture of the brain
- High potential as a clinical cognitive biomarker
- Can be done in many populations (including those with cognitive impairment)
- Easy to implement and setup in clinical settings

Collecting resting state data

- Participants asked to relax and let their mind wander while staying awake (no specific "task")
- Recommendations for quality data:
  - Collect data at beginning of scanning session
  - Eyes open, looking at fixation cross
  - As many volumes as possible (at least ~6minutes, 10-15minutes is best)
  - Short repetition time (ideally 1 second)
  - Multiple resting state session
  - Auxiliary data collection (respiration, heart rate)



Please keep your eyes open and look at the + in the center of the screen.

Resting state preprocessing

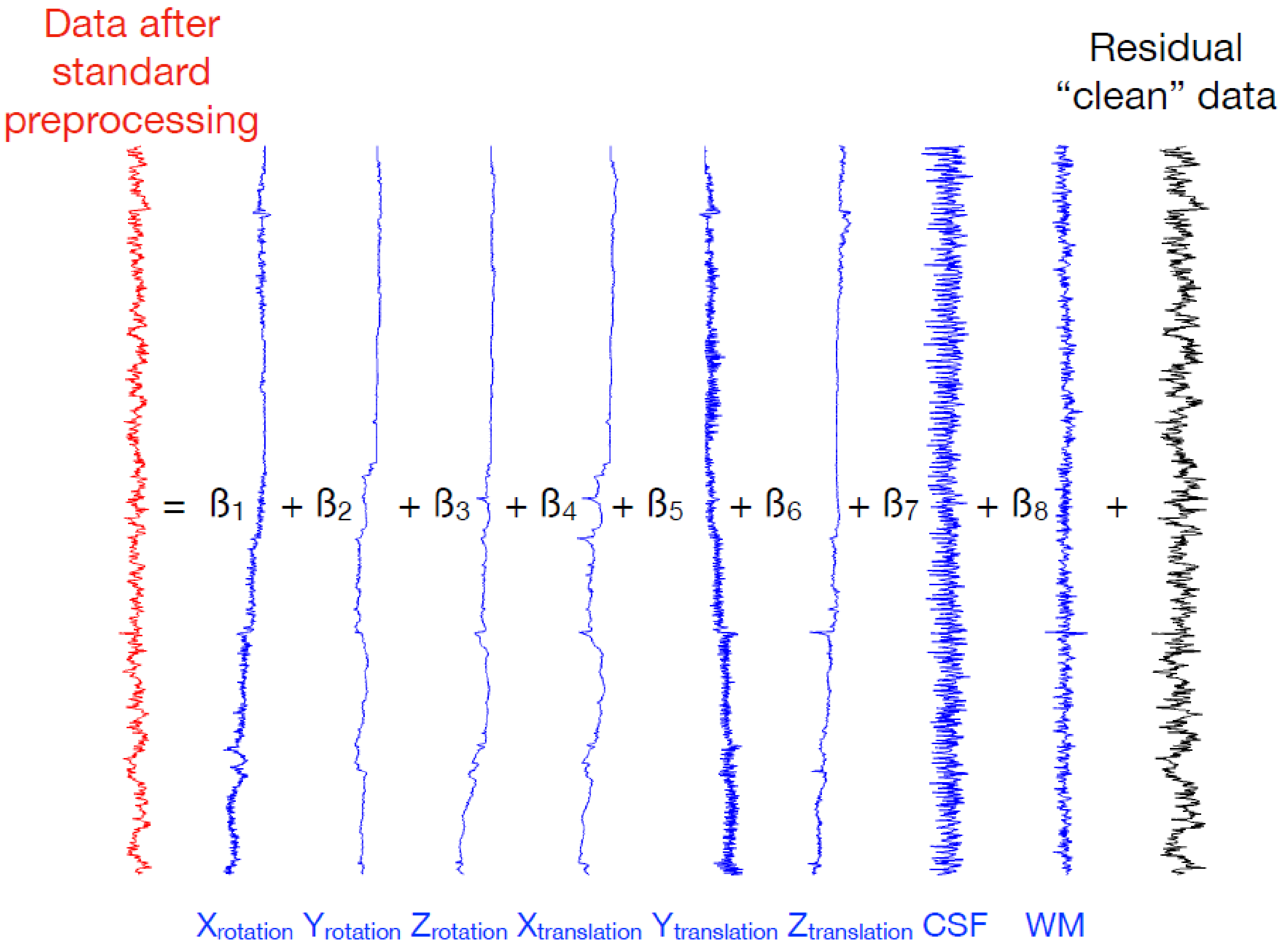
Preprocessing steps

- Conventional preprocessing steps
  - Motion correction
  - Slice timing correction*
  - Temporal filtering (high pass filter)
  - Spatial Smoothing
  - Warp to common space

- Additional noise reduction steps (pick at least one for rest data!)
  - Temporal filtering (low pass)
  - Nuisance regression
  - Volume censoring
  - ICA-based denoising

Noise reduction: Nuisance regression

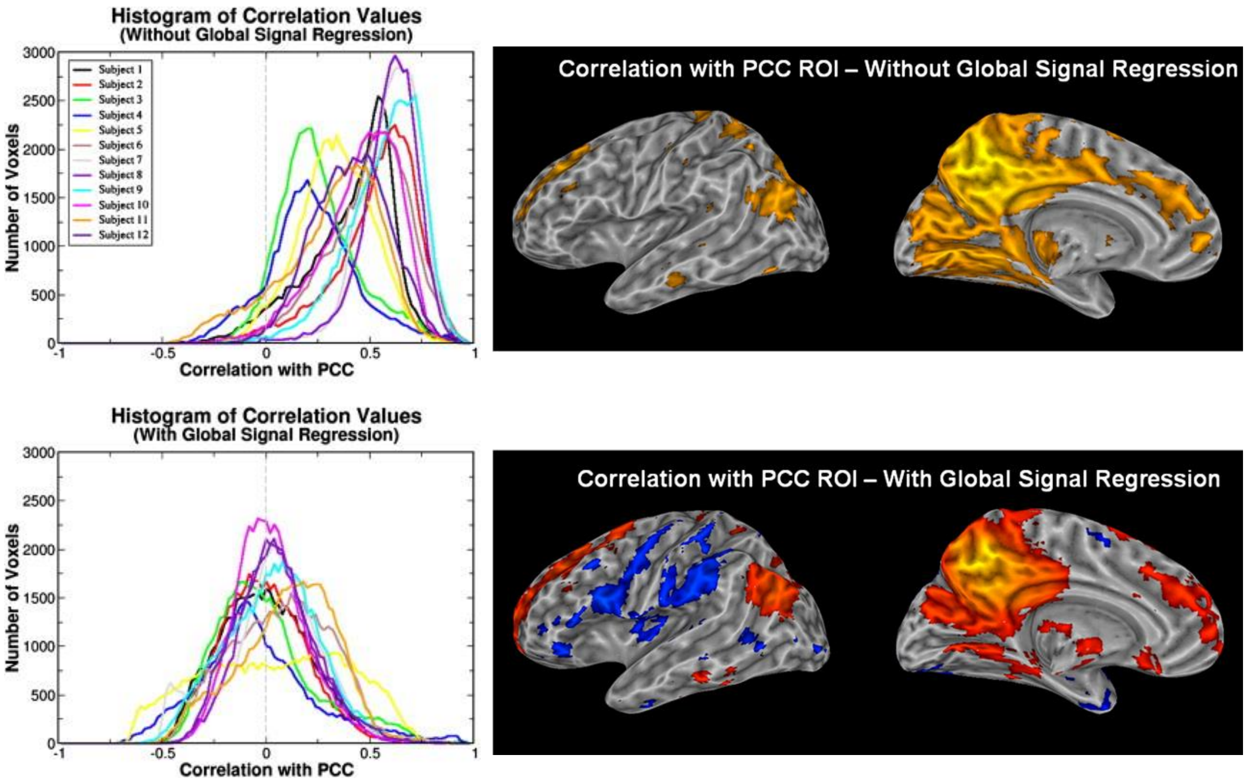
- Use GLM to remove nuisance timeseries:
  - Motion parameters
  - White matter/ CSF signal
  - Physiological measures
- Analyze residualized time series



FSL course, *Networks*

Noise reduction: Global signal regression?

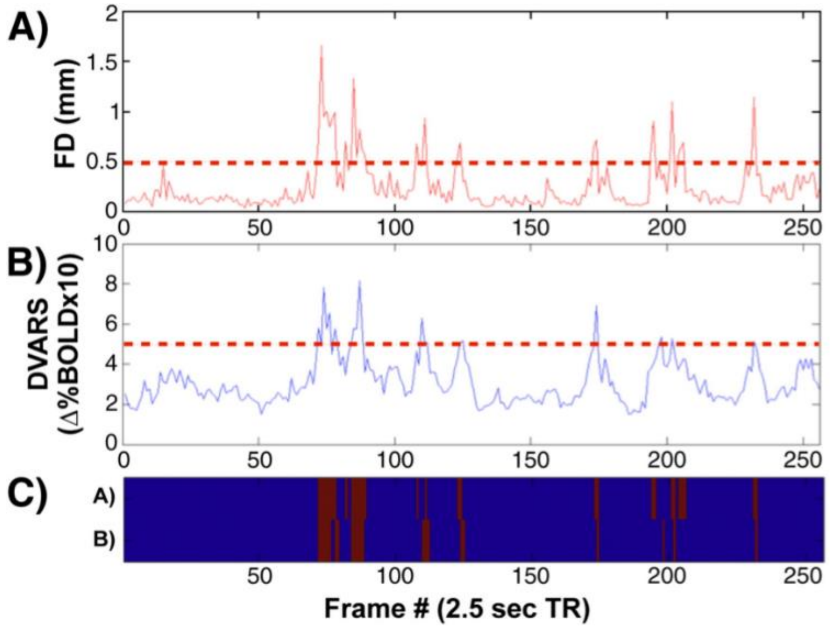
- Regress out average signal from entire brain which is dominated by physiological artifacts
- Controversial because may induce “negative” correlations
- If used, see if results replicate without GSR



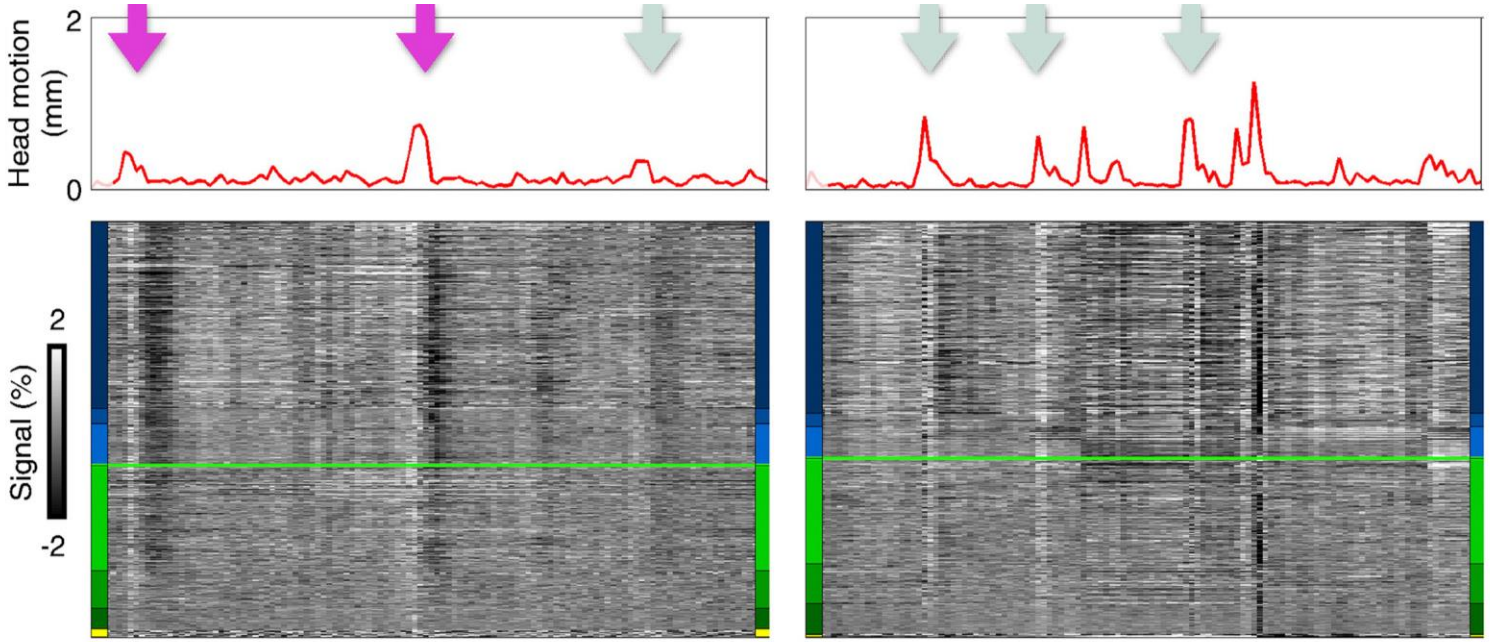
Murphy, 2009, *NeuroImage*

Noise reduction: Volume censoring

- AKA “scrubbing”
- Flag volumes that “spike” the time series due to motion



Power, 2012, *NeuroImage*



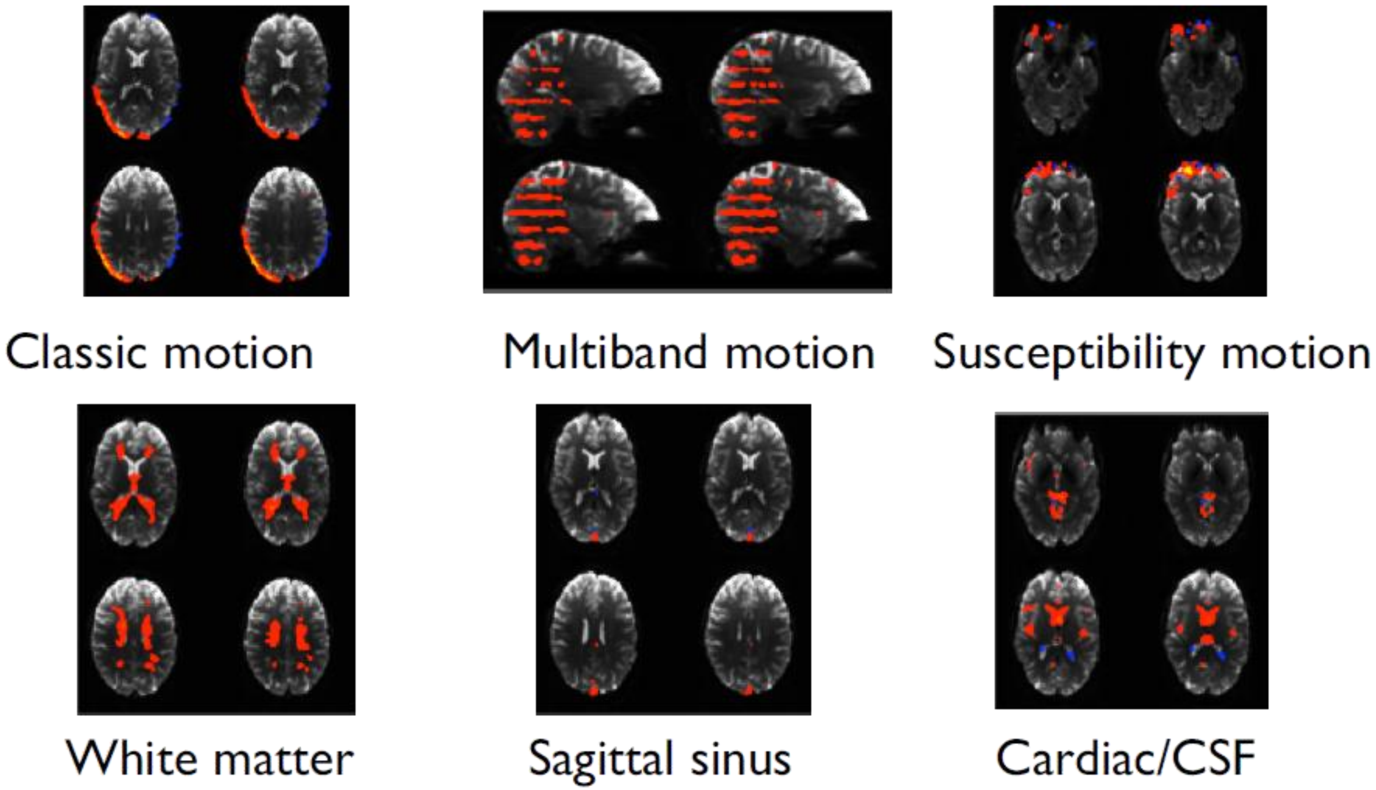
Power, 2017, *NeuroImage*

- Use flagged volumes as regressor or remove completely

Noise reduction: ICA-based denoising

- Data-driven approach to decompose data into “noise” and “true signal”
- Takes into account both spatial and temporal information
- Manual, semi-automated (FIX), or completely automated (AROMA) approaches to classify components

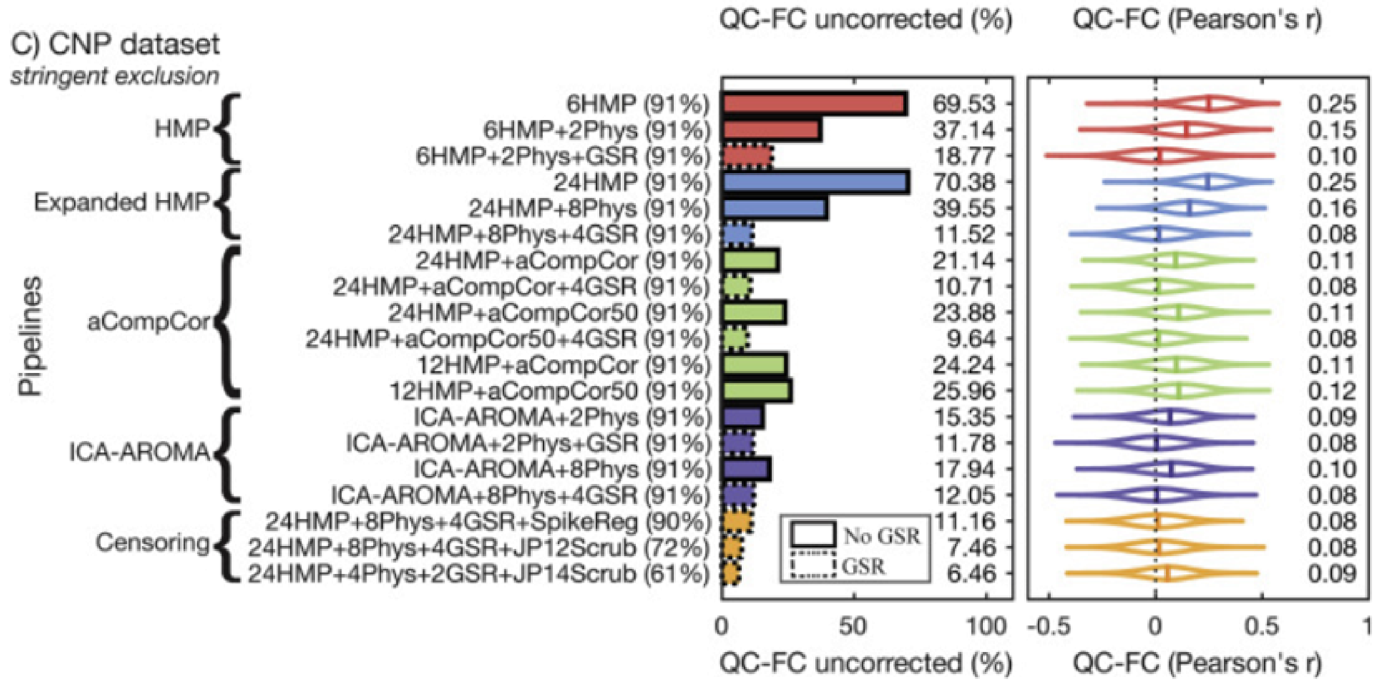
Example noise components



FSL course, *fMRI Advanced Preprocessing*

General recommendations

- Some form of ICA-based denoising (e.g., AROMA)
- Exclude participants with excessive motion
  - Lenient: >.55mm mean frame displacement
  - Stringent: >.25mm mean frame displacement AND >20% volumes flagged as high motion

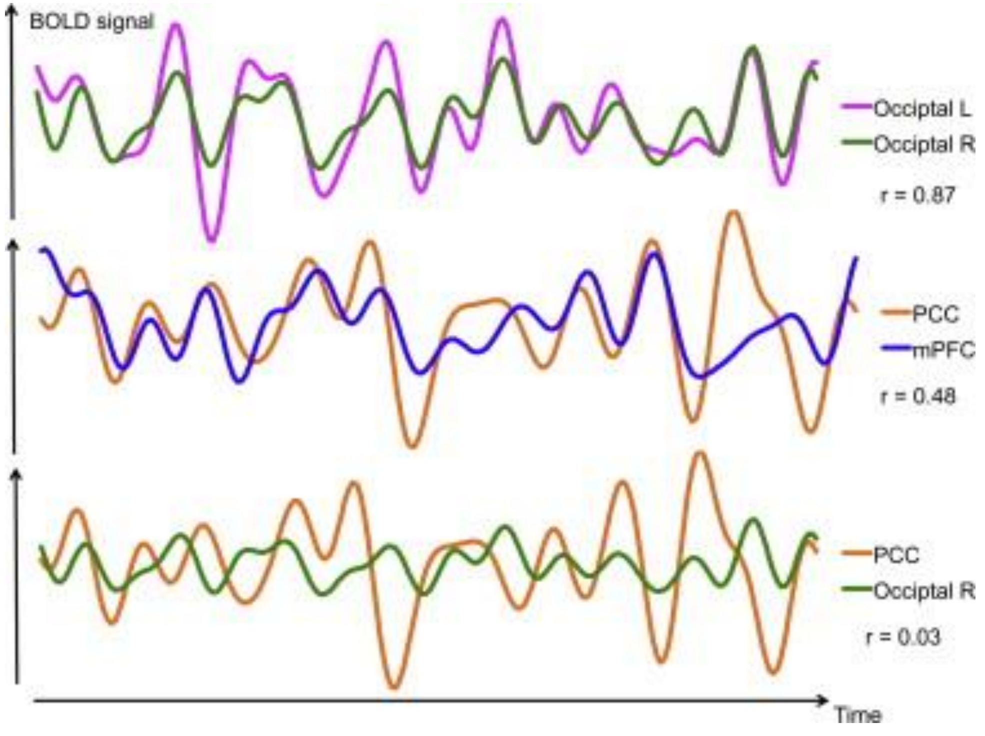


Parkes, 2017, *NeuroImage*
See also Ciric, 2018, *NeuroImage*

Resting state analysis

What is functional connectivity?

- Assumption:
  - if two brain regions show similarities in BOLD timeseries they are functionally connected
- Based on a statistical dependency between timeseries
- Many methods available to quantify “connectivity”

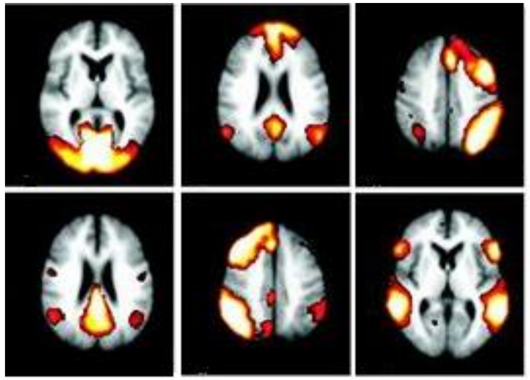


Ferreira & Busatto, 2013, *Neurosci Biobeh Rev*

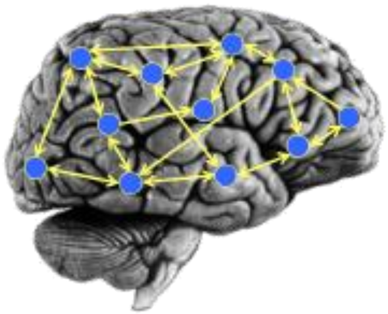
Analyzing functional connectivity

- Seed-based correlations
  - *A priori* selection of region of interest

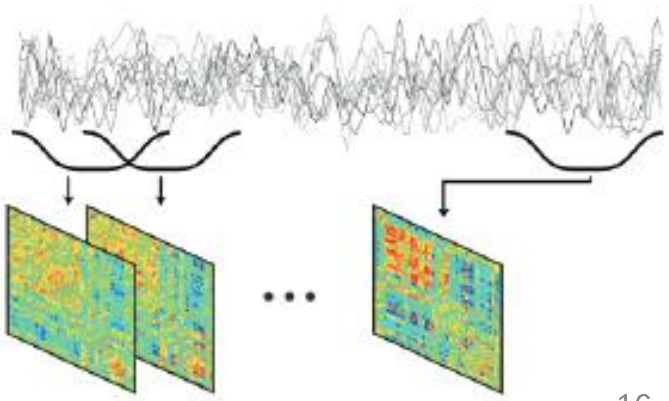
- Independent component analysis
  - Data-driven approach



- Network-level parcellation
  - Network- and graph-based analyses

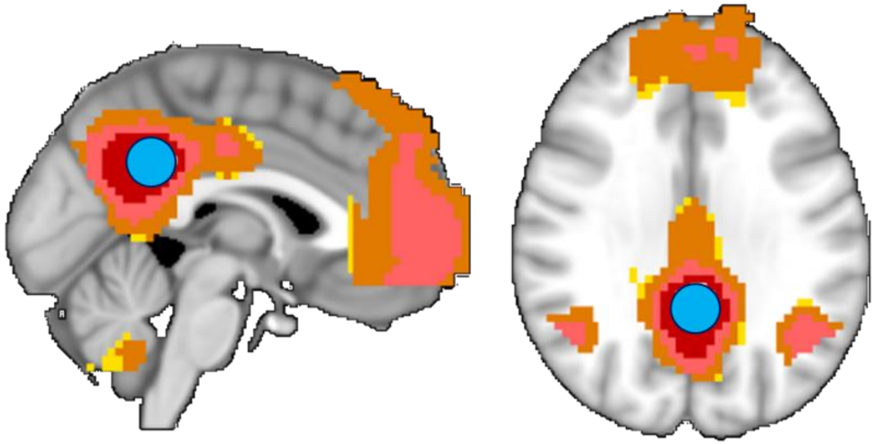


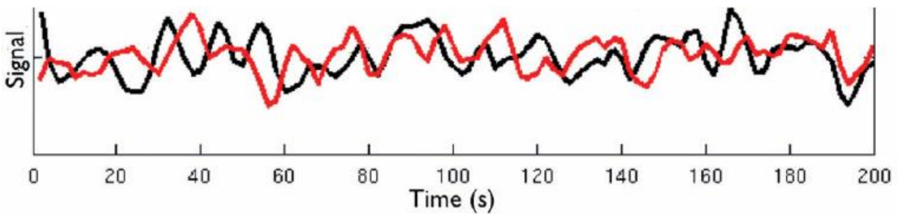
- Dynamic functional connectivity
  - Changes in brain states over time



Seed-based correlations

Posterior cingulate seed to identify default mode network





- Examine connectivity of a specific region
- Extract time series from seed region and correlate with other regions or voxels
- How to select a seed:
  - Based on anatomy
  - Literature or meta-analyses (neurosynth.org)
  - Functional localizer

Pros:

- Hypothesis driven
- Easy to interpret

Cons:

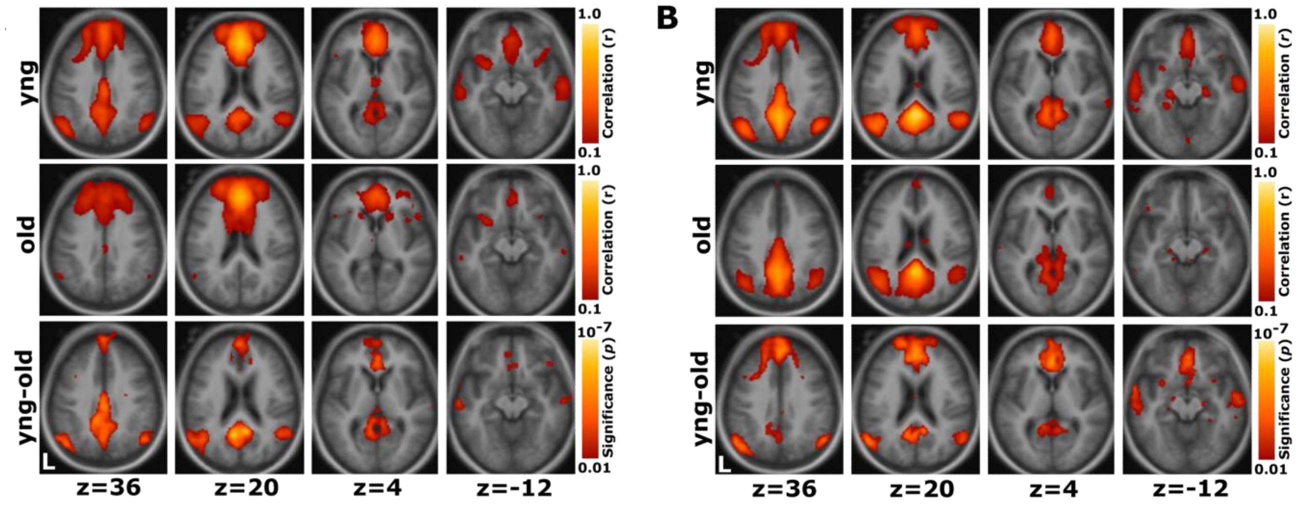
- Seed selection (size, location) can affect results

Seed-based analyses in aging

Older adults show decreased connectivity within default mode network

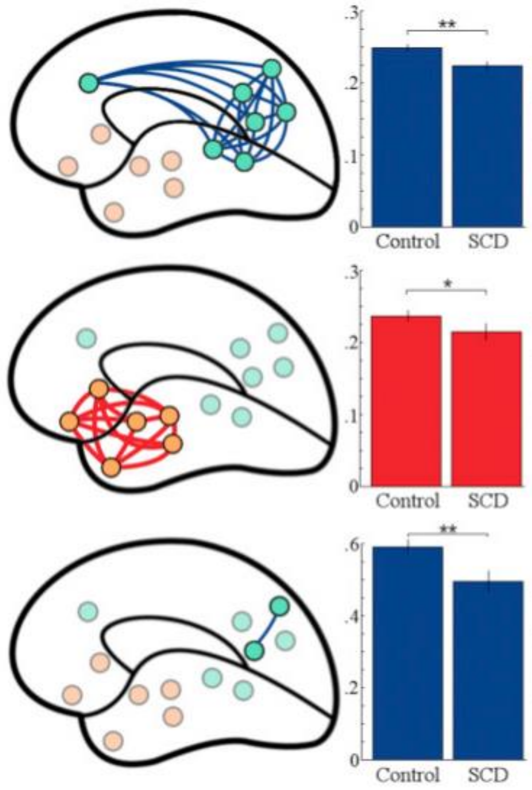
medial prefrontal seed

posterior cingulate seed



Andrews-Hanna, 2007, *Neuron*

Lower memory system connectivity in adults with subjective cognitive decline



Posterior Memory System Functional Connectivity

	b	β	T	sr^2	p		R^2	$F(4, 78)$
Model					<.001	**	.38	12.18
SCD	-.035	-.22	-2.37	.045	.020	**		
Age	-.002	-.20	-2.23	.039	.029	*		
Sex	.006	.04	.39	.001	.697			
Site	-.097	-.60	-5.98	.283	<.001	**		

Anterior Memory System Functional Connectivity

	b	β	T	sr^2	p		R^2	$F(4, 78)$
Model					<.001	**	.33	9.52
SCD	-.032	-.21	-2.23	.043	.029	*		
Age	-.002	-.23	-2.52	.054	.014	**		
Sex	.006	.04	.36	.001	.721			
Site	-.080	-.53	-5.07	.221	<.001	**		

Retrosplenial Cortex - Precuneus Functional Connectivity

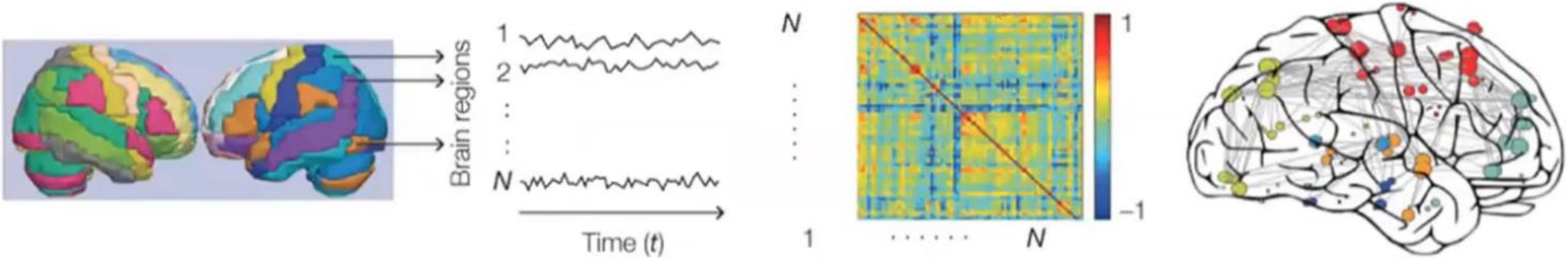
	b	β	T	sr^2	p		R^2	$F(4, 78)$
Model					.003	*	.18	4.29
SCD	-.126	-.35	-3.33	.116	.001	**		
Age	-.002	-.11	-1.06	.012	.290			
Sex	.024	.07	.58	.003	.570			
Site	-.108	-.30	-2.60	.071	.010	*		

Viviano, 2019, *NeuroImage*

Network-level parcellation

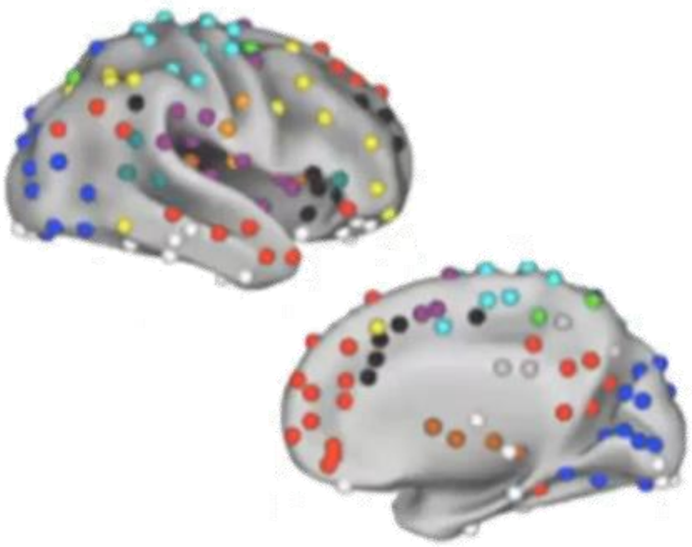
- Used to examine large-scale network organization
- Extract timeseries from a pre-defined atlas or set of regions (nodes)
- Compute correlation between all pairwise nodes/regions
- Use graph-based metrics to quantify connectivity associations

Brain Nodes | Extract timeseries | Association matrix | Connectivity map

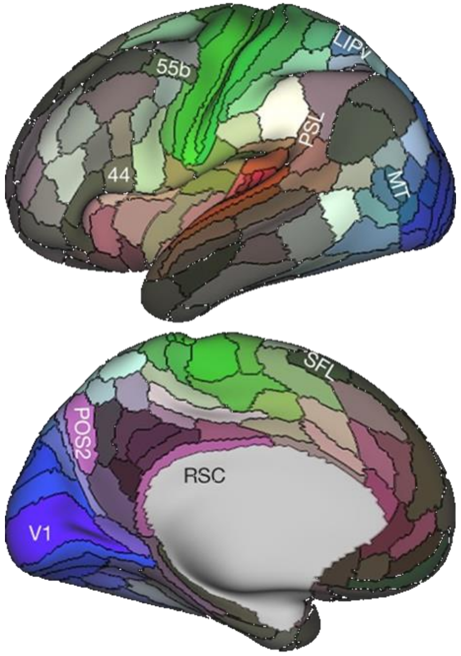


Network-level parcellation

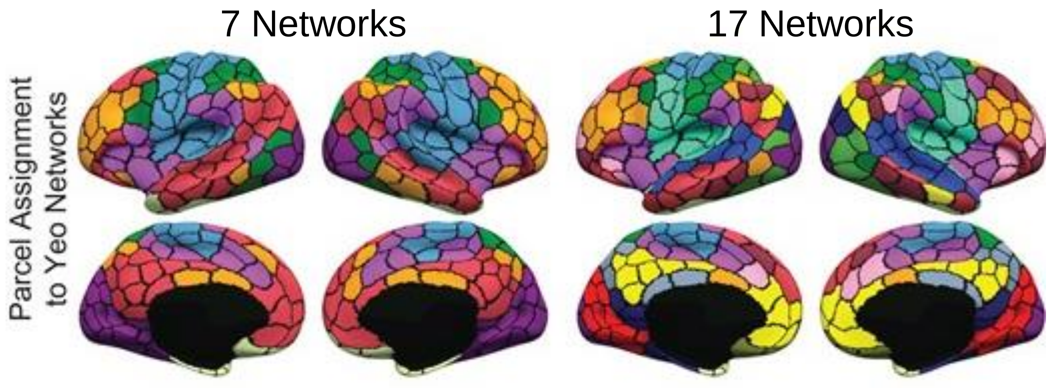
- How to choose a parcellation:
  - Use existing parcellation scheme
  - Create a data specific parcellation
- Pros:
  - Straightforward to implement
  - Many graph theory based metrics can be computed
- Cons:
  - Parcellation method may bias results
  - Many graph theory based metrics can be computed



Power, 2011, *Neuron*



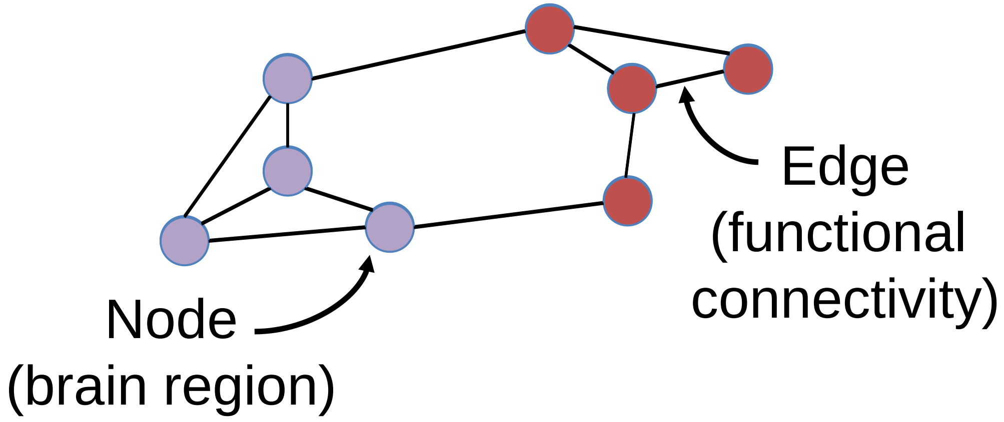
Glasser, 2016, *Nature*



Schaefer, 2018, *Cereb Cortex*

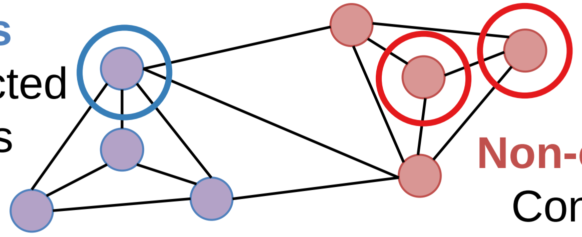
Networks can be analyzed with graph theory

Sample network



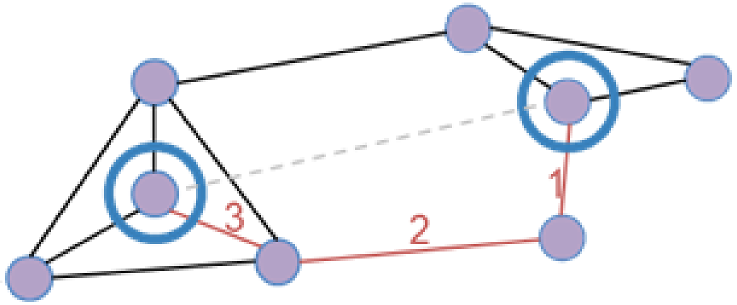
Participation coefficient is a ratio of connections to other communities relative to total connections

Connector nodes
Preferentially connected with other systems

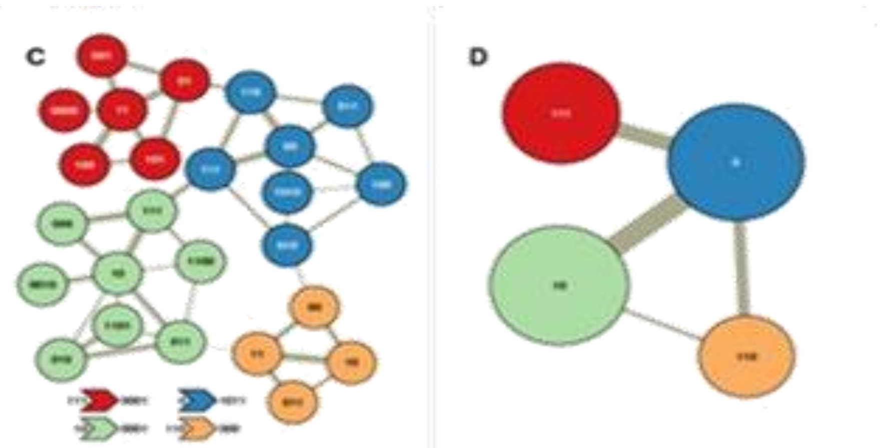


Non-connector nodes
Connections largely within their own system

Graph theory allows for consideration of indirect connections via **node degree**



Community detection can identify network clusters

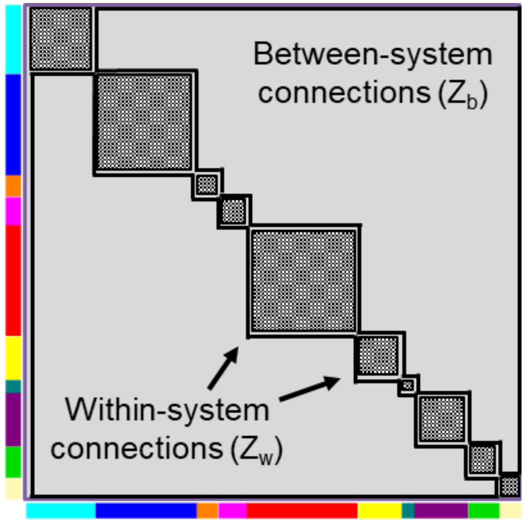


Visualizations courtesy of Micaela Chan

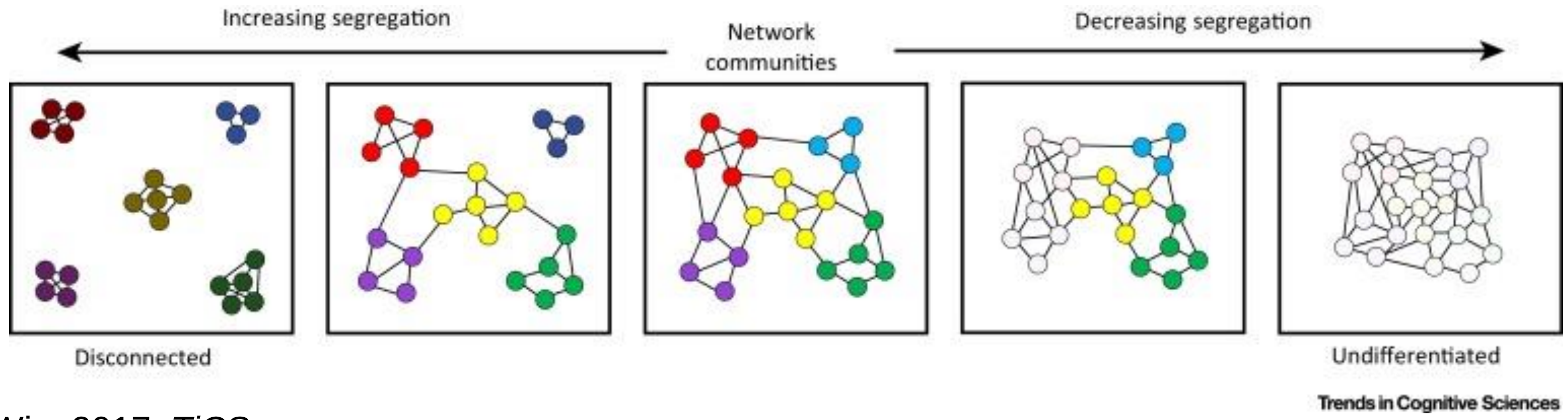
Rosvall & Bergstrom, 2008, *PNAS*

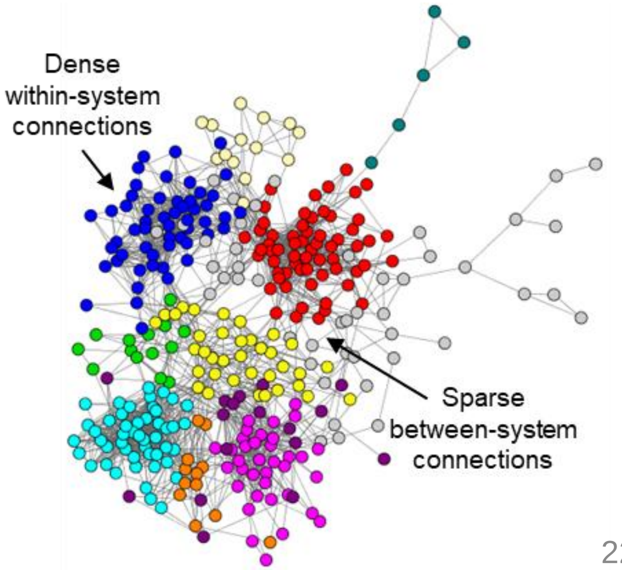
Networks can be analyzed with graph theory

- Segregation describes the degree to which nodes within a network are connected to each other vs. nodes in other networks



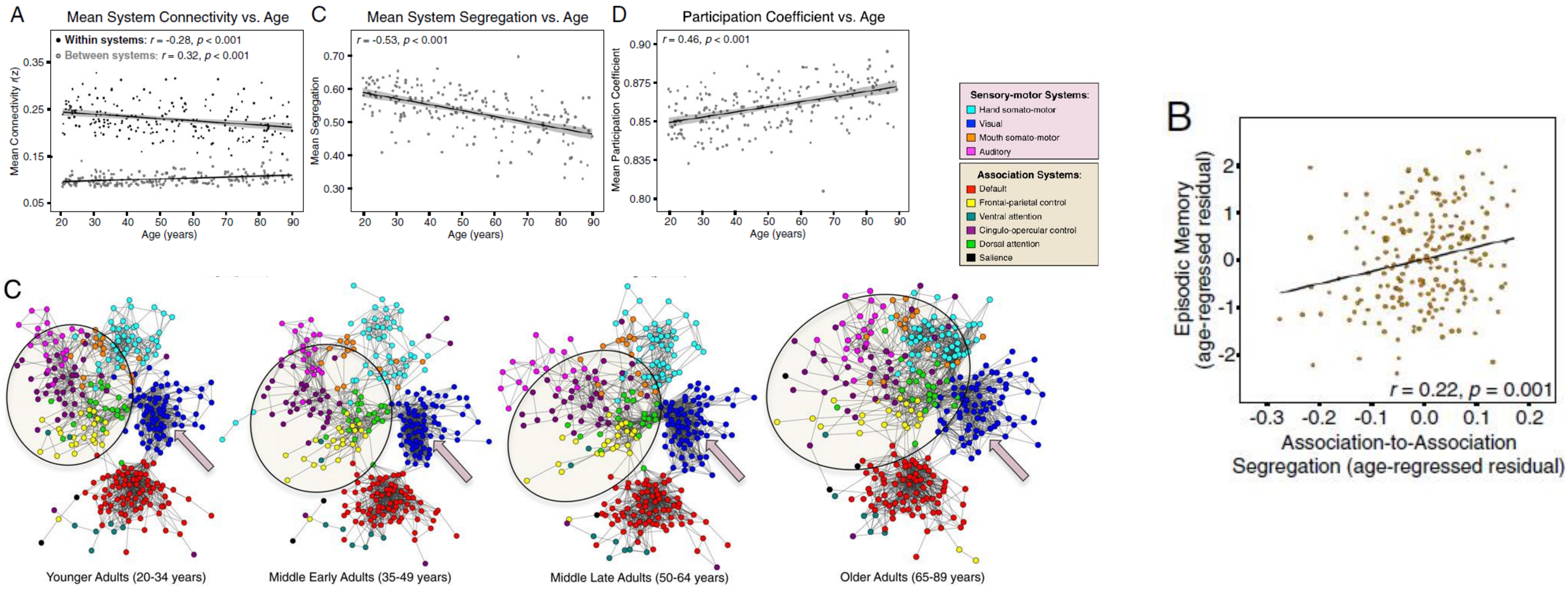
$$\text{System Segregation} = \frac{\bar{Z}_w - \bar{Z}_b}{\bar{Z}_w}$$





Wig, 2017, *TiCS*

Networks are less segregated in old age

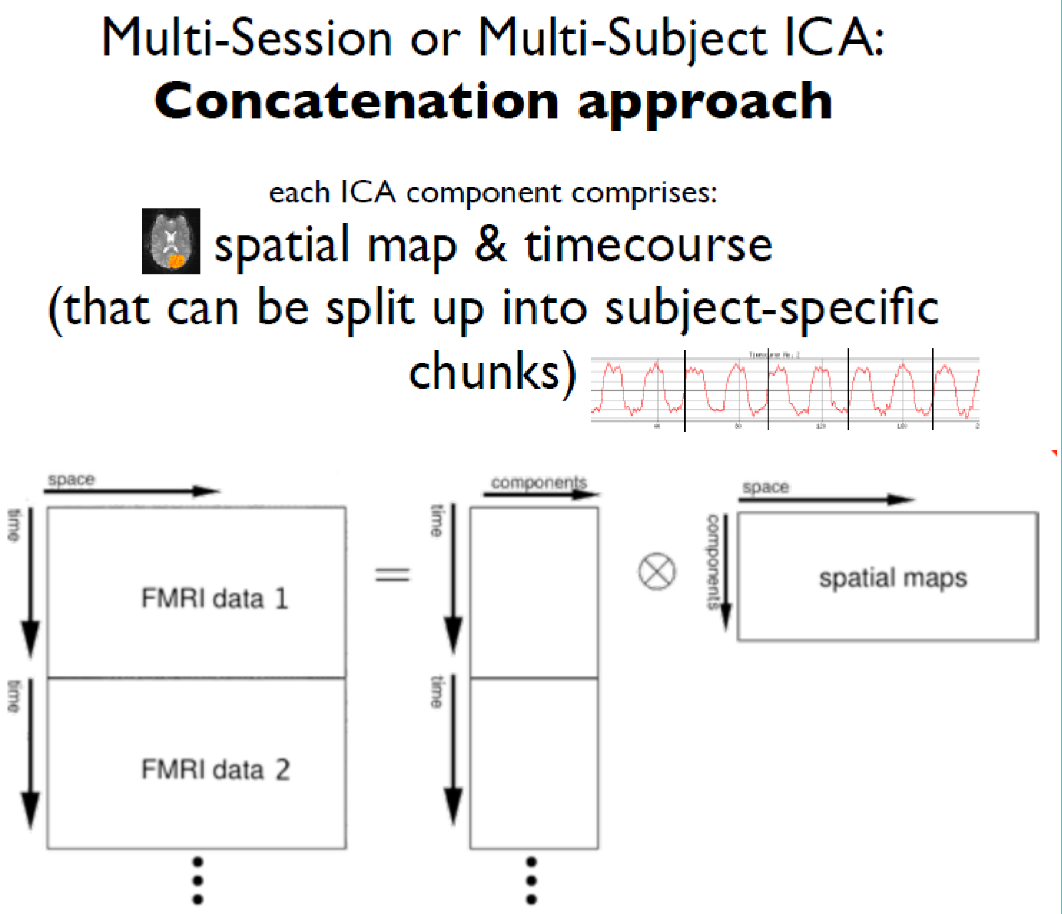


Decreased network segregation in older adults may reflect neural dedifferentiation and predicts worse memory performance

Chan, 2014, *PNAS*

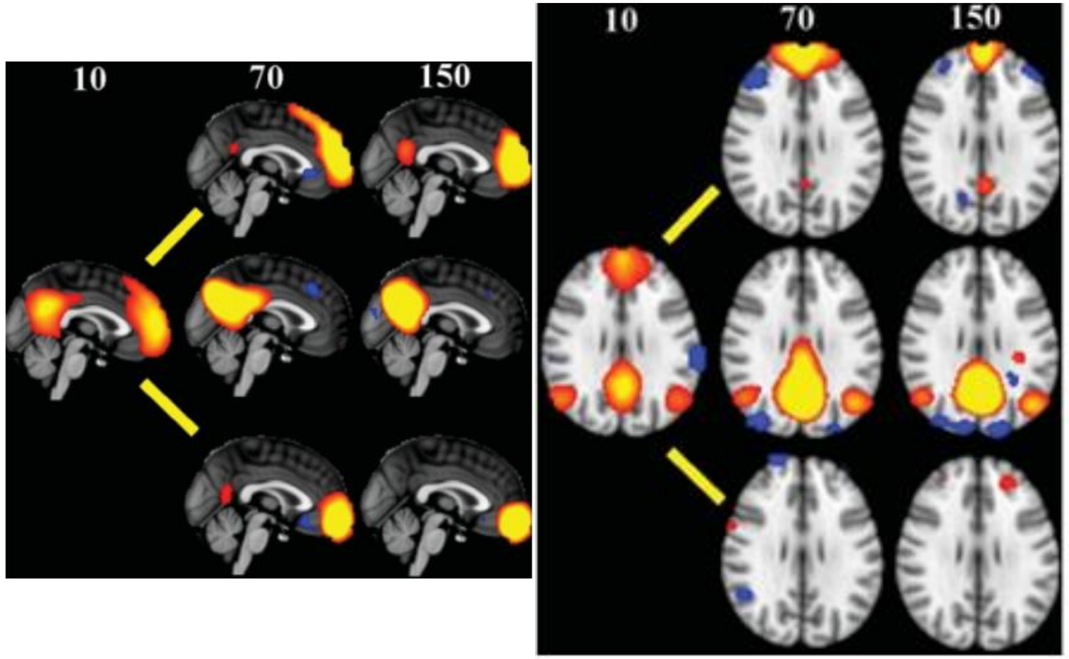
Independent component analysis (ICA)

- Multivariate, data-driven approach to find resting state networks (model free)
- Pros:
  - Dataset is decomposed into multiple different networks simultaneously
  - No *a priori* region of interest selection
- Cons:
  - Not guaranteed to get network you want
  - Must specify the number of networks in advance (model order selection)



Independent component analysis

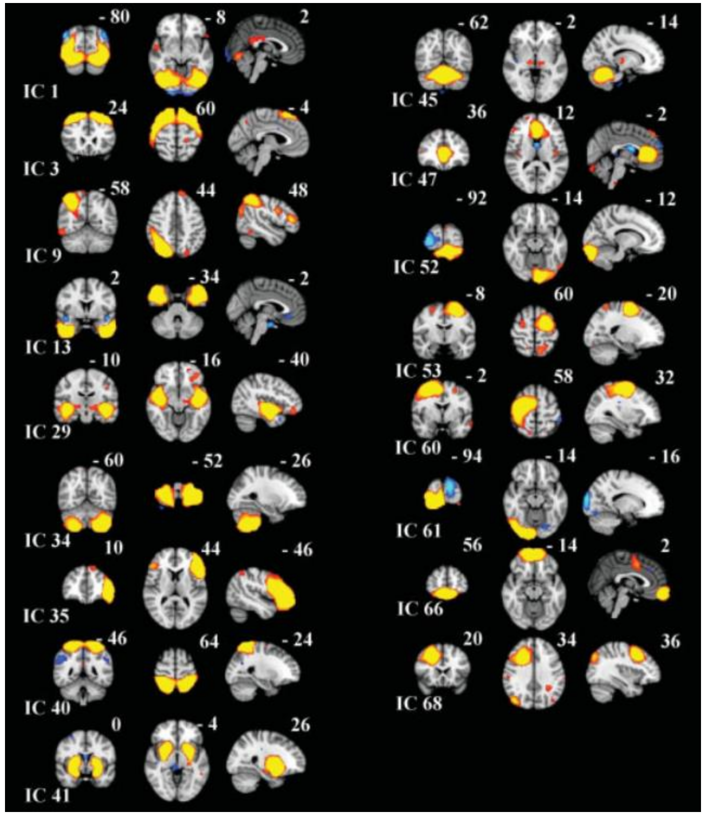
Higher model orders can split networks across components



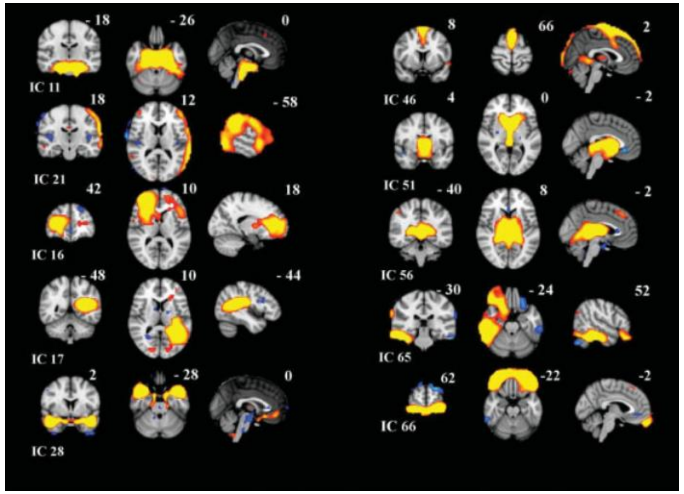
Default mode network splits across 3 separate networks at model order 70 and 150

Components need to be inspected to ensure they represent "true" networks

True rs ICs



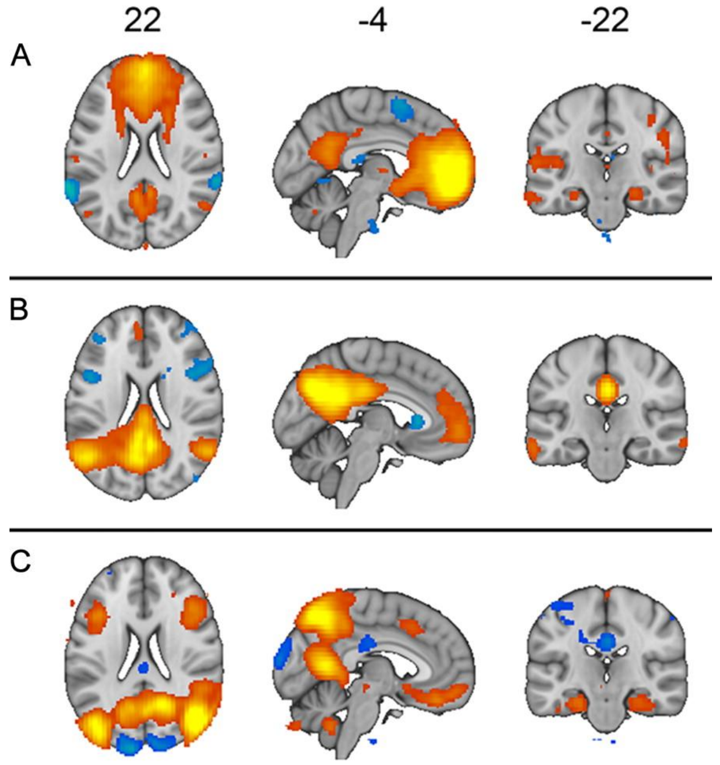
Artefactual, non-rs ICs



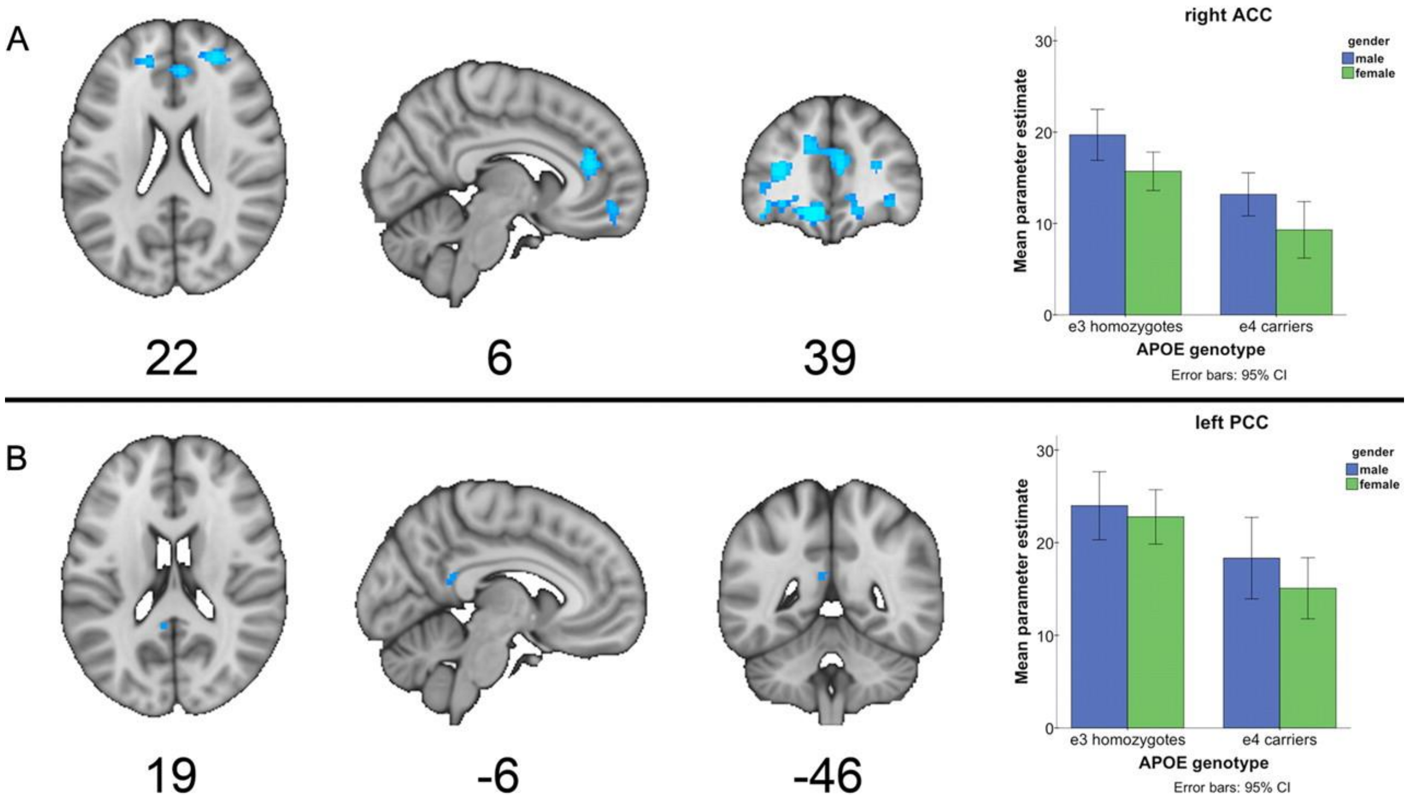
Kiviniemi, 2009, *Hum Brain Mapp*

Independent component analysis

ICA to define default mode sub-networks



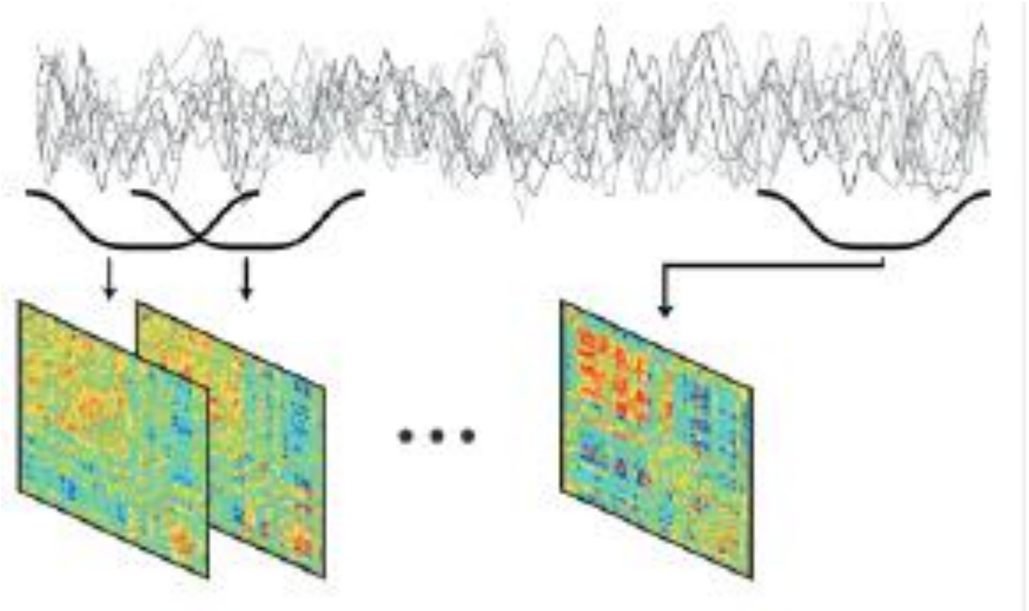
APOE e4 carriers show decreased connectivity within default mode network

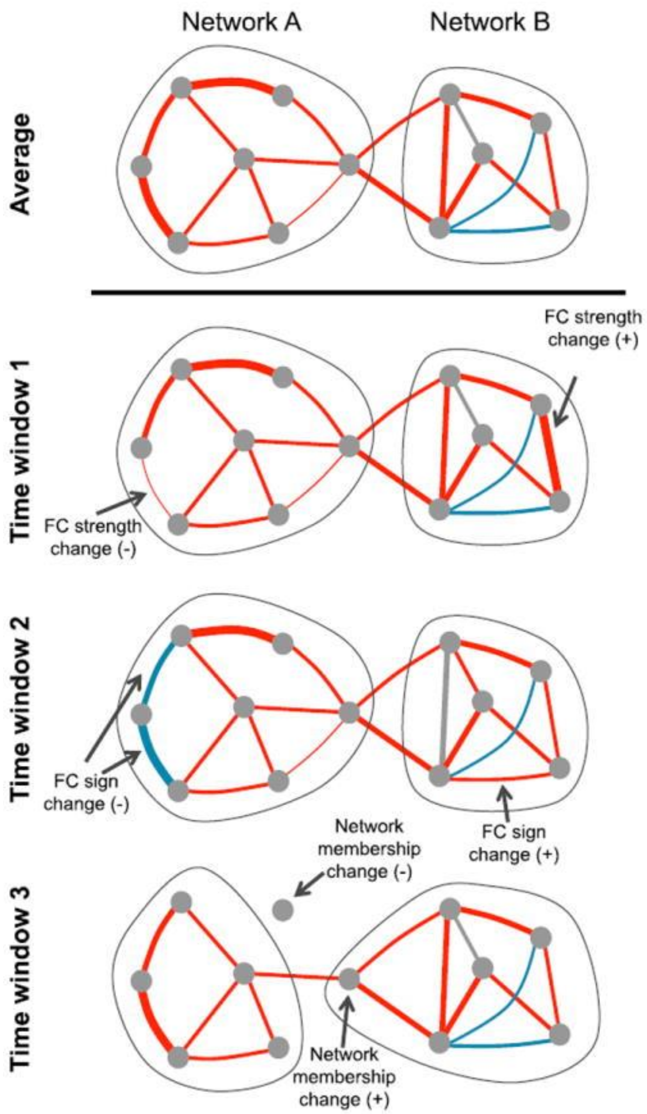


Damoiseaux, 2012, *J Neurosci*

Dynamic functional connectivity

- Examine temporal changes in connectivity
- Sliding window approach splits resting state into smaller time windows (~30-60 sec)
  - Find "brain states" that characterize different connectivity patterns

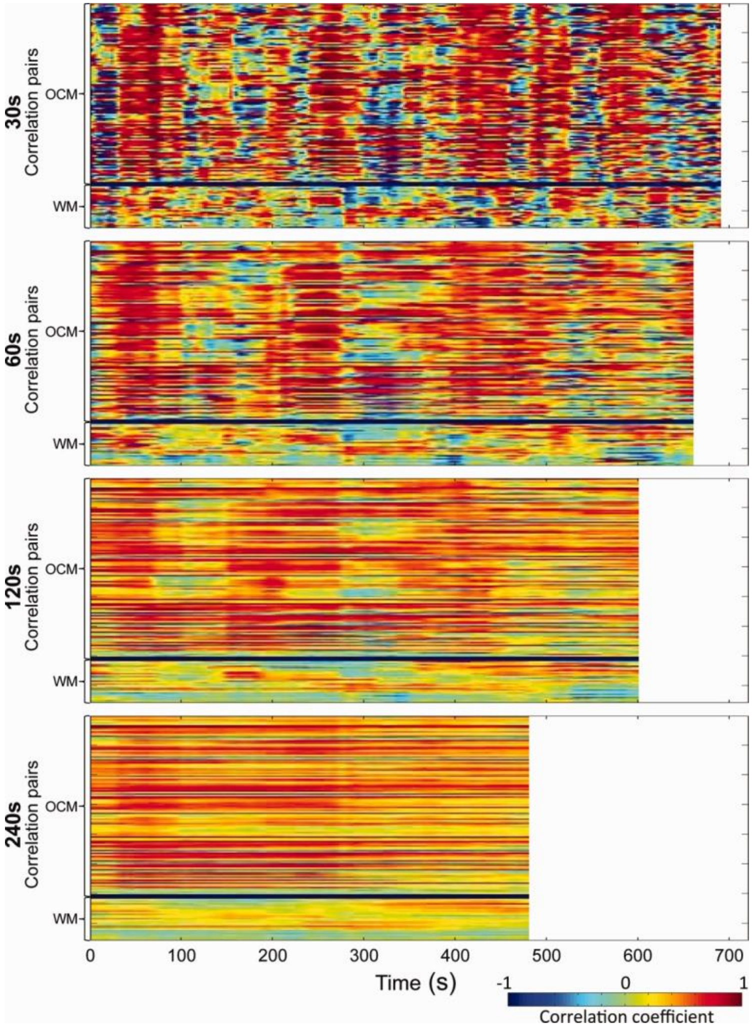




Hutchison, 2013, *NeuroImage*

Dynamic functional connectivity

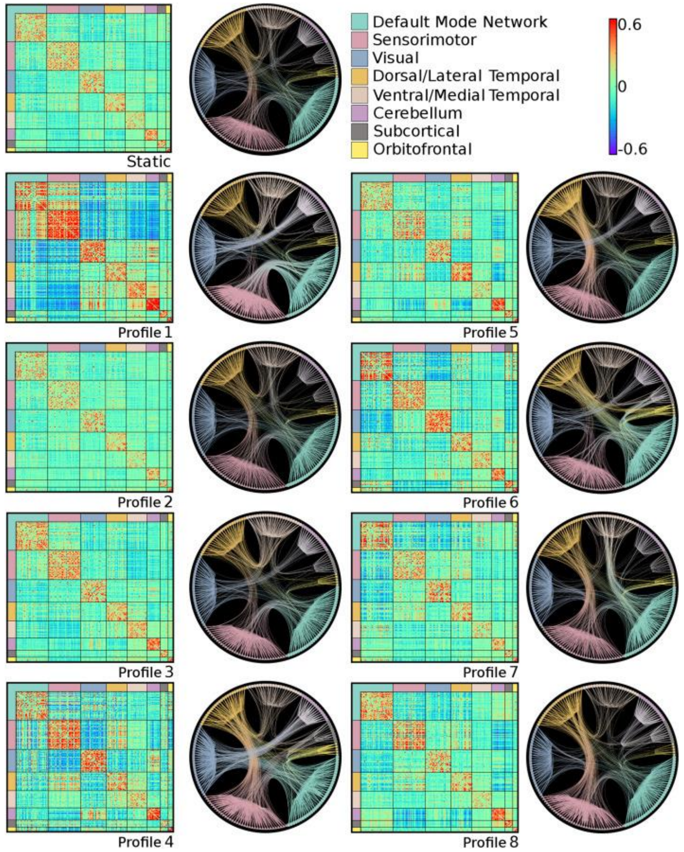
- Pros:
  - Provides insight into temporal dynamics of brain networks
- Cons:
  - Requires longer resting state scans (>10 minutes)
  - Window length selection can affect results
  - Smaller temporal windows have higher susceptibility to noise



Hutchison, 2013, *Hum Brain Mapp*

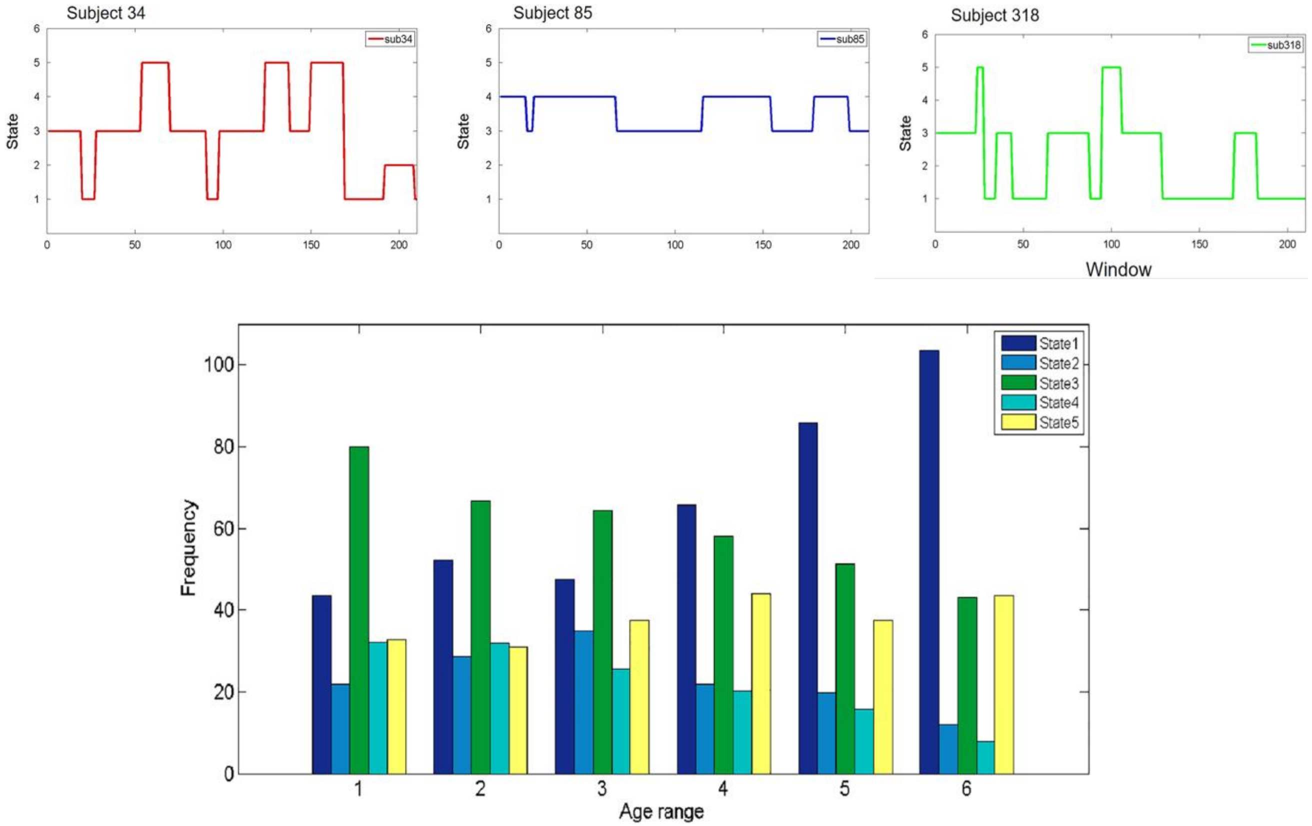
Dynamic functional connectivity in aging

Older adults deviate from "average" profile and exhibit profiles with low DMN-vMTL connectivity



Viviano, 2017, *Neurobio Aging*

Older adults spend longer in the same state and transition states less



Xia, 2018, *Hum Brain Mapp*

Which approach is best?

- Depends on your research question!
- Considerations:
  - Localized vs. network-level measures?
  - Hypothesis driven vs. exploratory?
  - Spatial maps vs. summary metrics?
- Note. All of these functional connectivity can also be applied to task-based fMRI

Open datasets with resting state fMRI

- Harvard Aging Brain study (HABS): https://habs.mgh.harvard.edu/
- Alzheimer's Disease Neuroimaging Initiative (ADNI): http://adni.loni.usc.edu/
- Human Connectome Project (HCP) – Aging: https://www.humanconnectome.org/study/hcp-lifespan-aging
- Open Access Series of Imaging Studies (OASIS)-3: https://www.oasis-brains.org
- Nathan Kline/Rockland: http://fcon_1000.projects.nitrc.org/indi/enhanced/
- Cambridge-Center for Aging and Neuroscience (Cam-CAN): https://camcan-archive.mrc-cbu.cam.ac.uk/
- UK Biobank: https://www.ukbiobank.ac.uk/
- www.openneuro.org

Resources

- FSL courses: https://open.win.ox.ac.uk/pages/fslcourse/website/
- CONN functional connectivity toolbox: https://web.conn-toolbox.org/
- Andy's CONN tutorial: https://andysbrainbook.readthedocs.io/en/latest/FunctionalConnectivity/CONN_Overview.html
- Neurosynth for meta-analysis: https://neurosynth.org/