Tools to parcellate the brain and its relation to function: Part II

Resting State Functional Connectivity Subdivision (with Supervised Learning)

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Course Objectives

- The fundamental techniques used to analyze resting state BOLD fMRI data
- How a parcellation scheme can be built using these techniques
- Special challenges that result from the hierarchical organization of resting state networks
- How to use supervised learning to build on the data-driven techniques and address these challenges

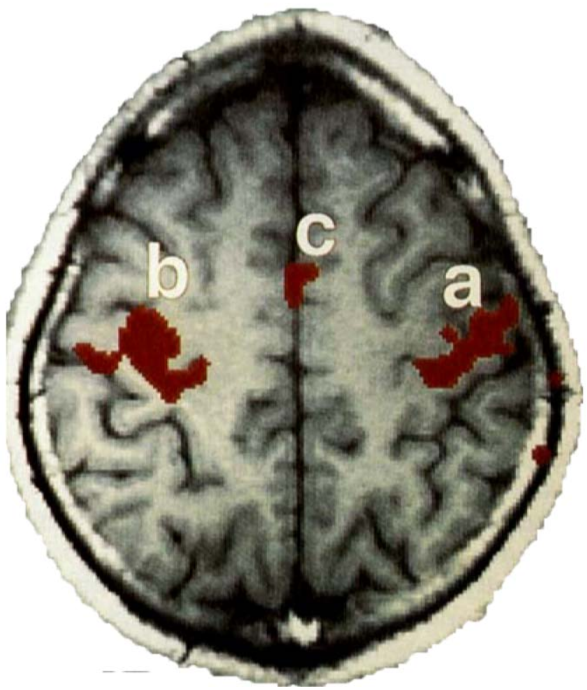
Overview

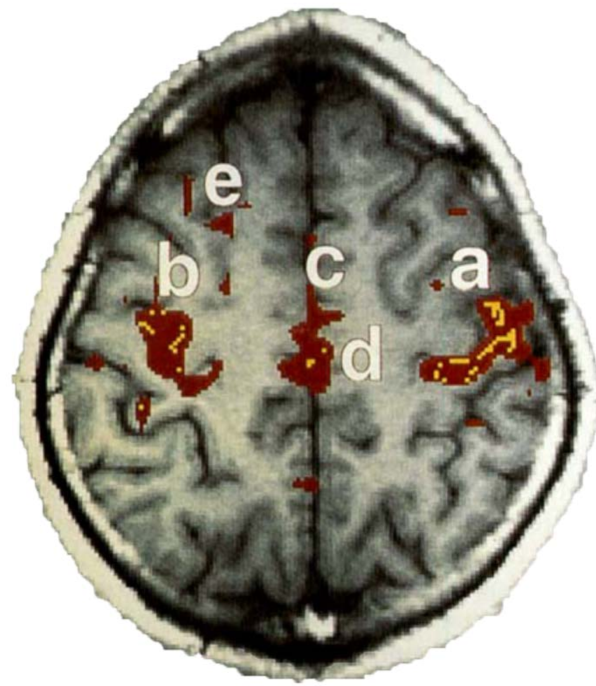
- Introduction:
  - Seed-based correlation mapping
  - Independent component analysis
- Unsupervised RSN definition
  - Hierarchical organization of RSNs
- Supervised RSN definition
  - Setting up the problem
- Evaluating performance
  - Generalizability
  - Inter-subject variability
- Practical tricks for brain imaging
  - Methodological optimization tool

Seed-based Correlation Mapping

- Definition: Spatial map of brain regions correlated with mean time-course of region of interest

Task Response **Regions Correlated with "b"**

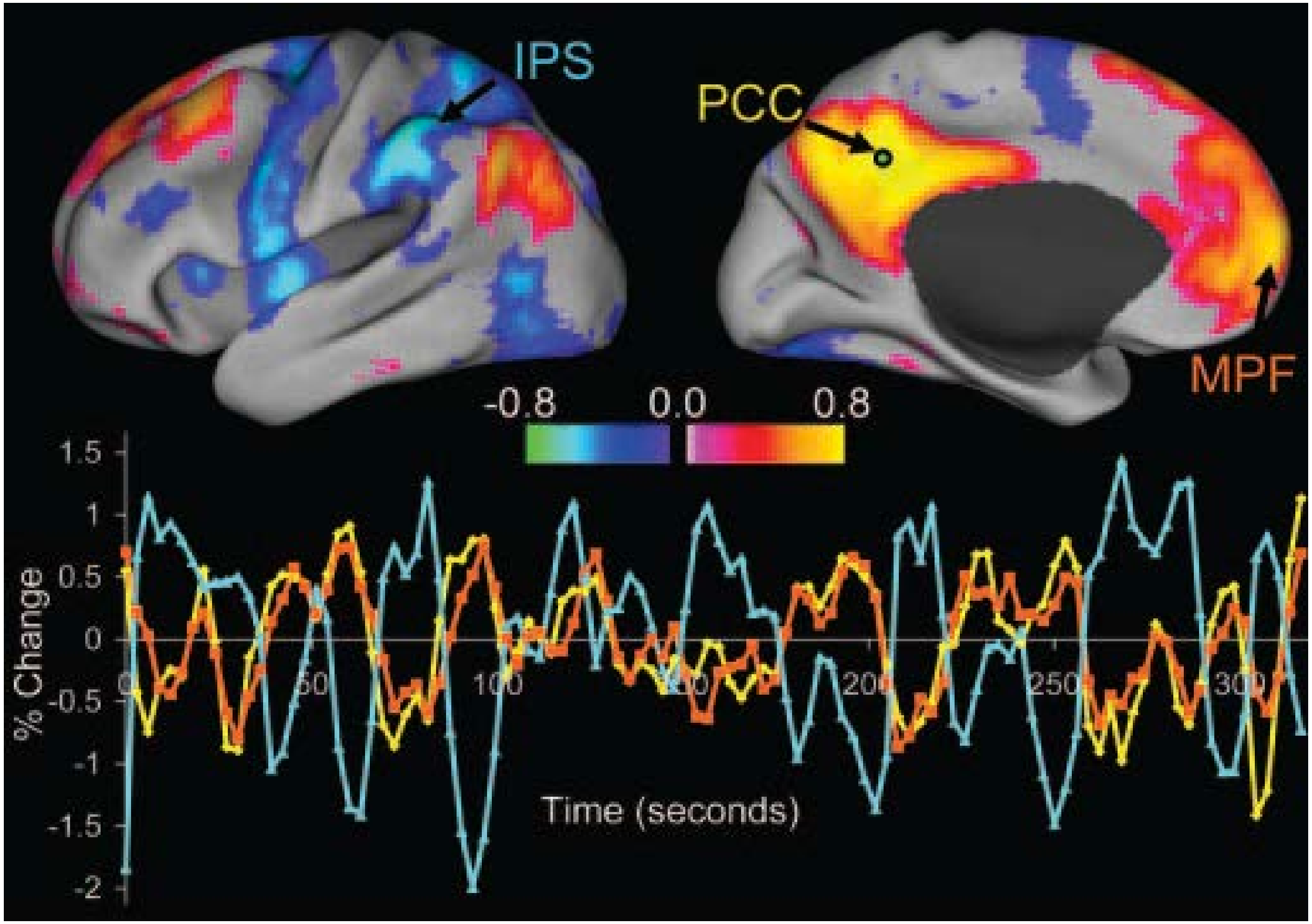




- **Motivation: Regions that correspond to similar brain functions have spontaneously correlated signals**

Biswal et al., 1995

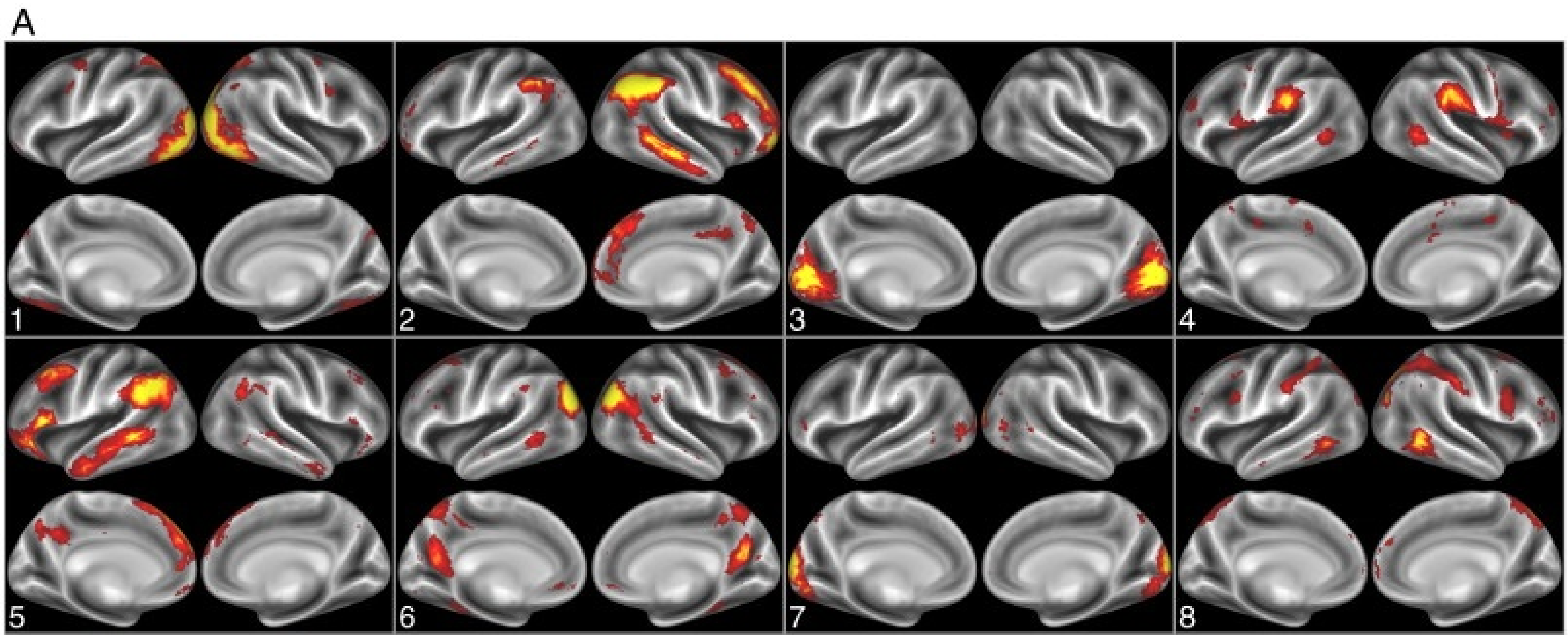
Seed-based Correlation Mapping



Fox et al., PNAS 2005

(Spatial) Independent Component Analysis

1. Resting-state data is composed of **a superposition of fixed spatial maps**, each evolving with some timecourse
2. Components can be spatially overlapping – a given region can belong to multiple networks



Smith et al., NeuroImage (2013)

Seed-based Mapping vs ICA

	Spatial ICA (sICA)	Seed-based correlation mapping
Algorithmic basis	Maximization of component independence	Computation of ROI-voxel correlation (over time)
Major attribute	Data-driven (unsupervised)	Directed at pre-determined regions and functional systems
Noise reduction strategy	Elimination of noise components after sICA	Regression prior to correlation mapping

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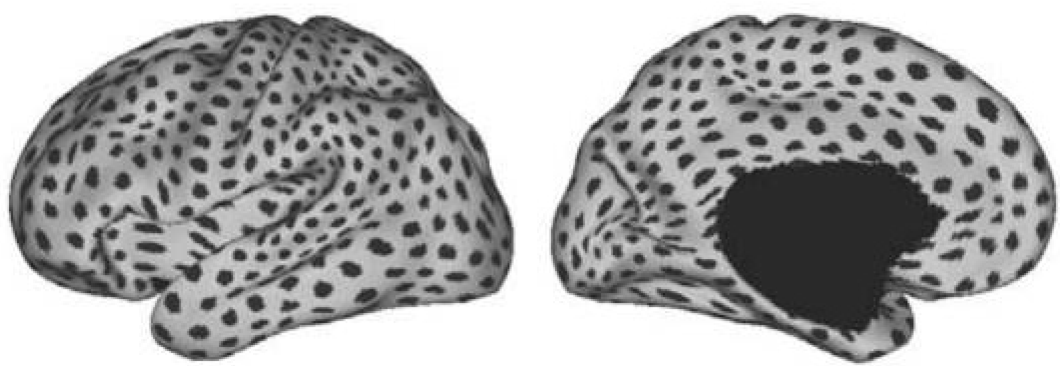
Unsupervised Learning in rs-fMRI

- Organize resting state data into regions with homogeneous signal statistics
  - Similar time-courses
  - Similar topography of correlation maps
- In other words: find structure in data with no prior labels

“Unsupervised” Seed-based Mapping

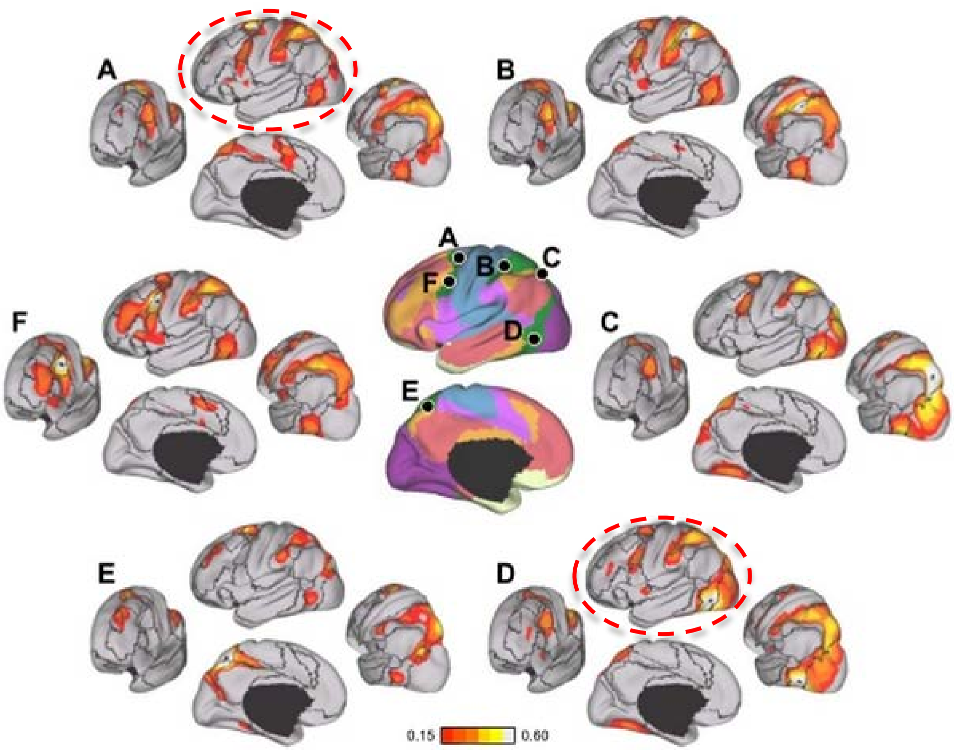
- Seed-based mapping heavily biased by choices of seed region
- Independence from priors can be achieved by systematic seeding of entire brain



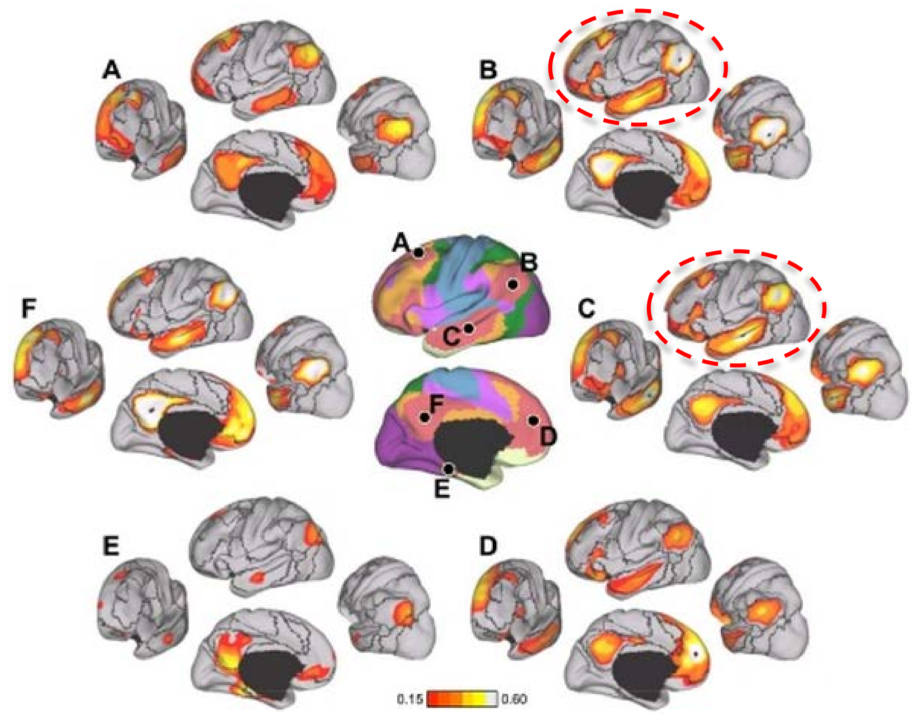
Yeo et al., J Neurophysiol (2011)

Similar correlation map topography for widely separated seed regions

Dorsal Attention Network Seeds



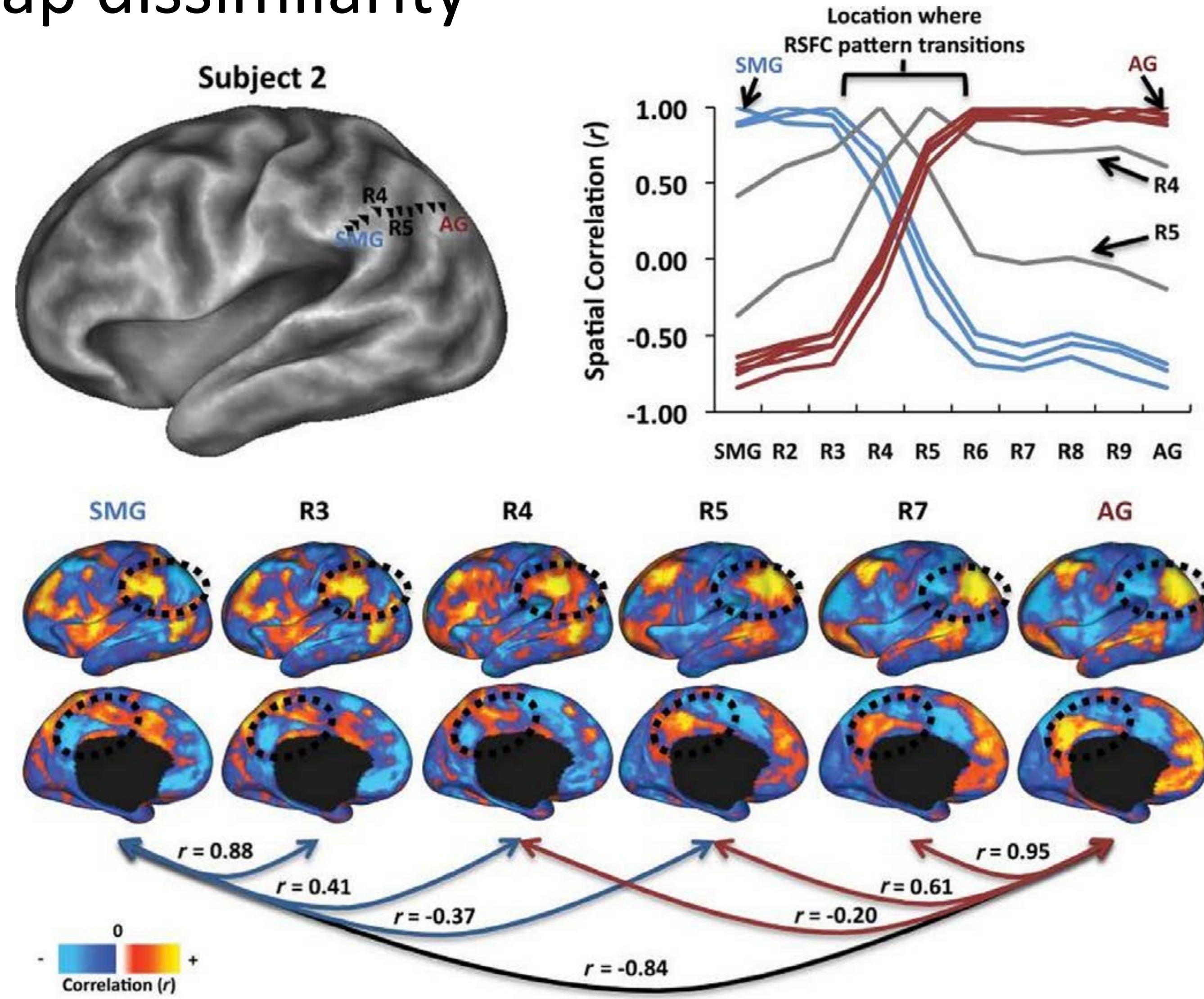
Default Mode Network Seeds



Yeo et al., J Neurophysiol (2011)

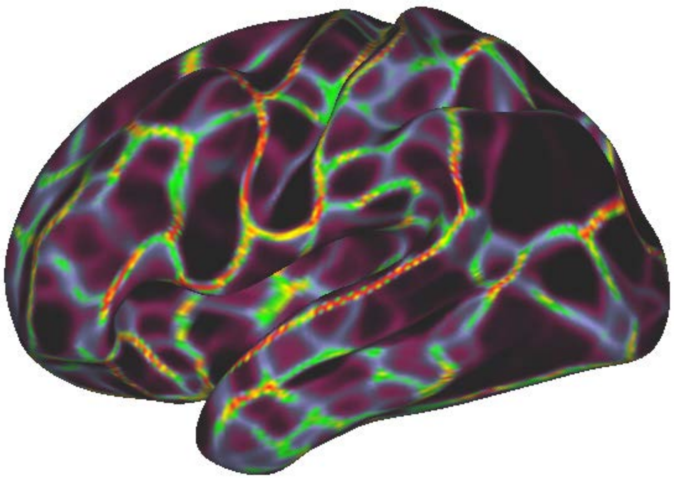
Correlation Gradient-based Parcellation

- Compute boundaries of maximum correlation map dissimilarity

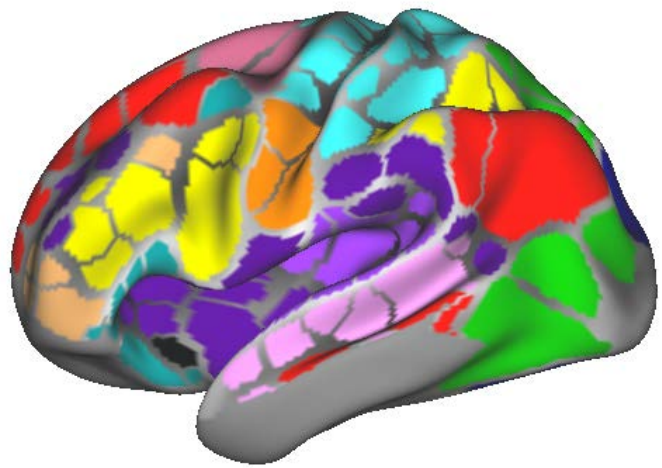


Wig et al., 2014

Gradient-based Parcels Assigned to RSNs



Functional Connectivity Gradients



Assignment of Parcels to Networks

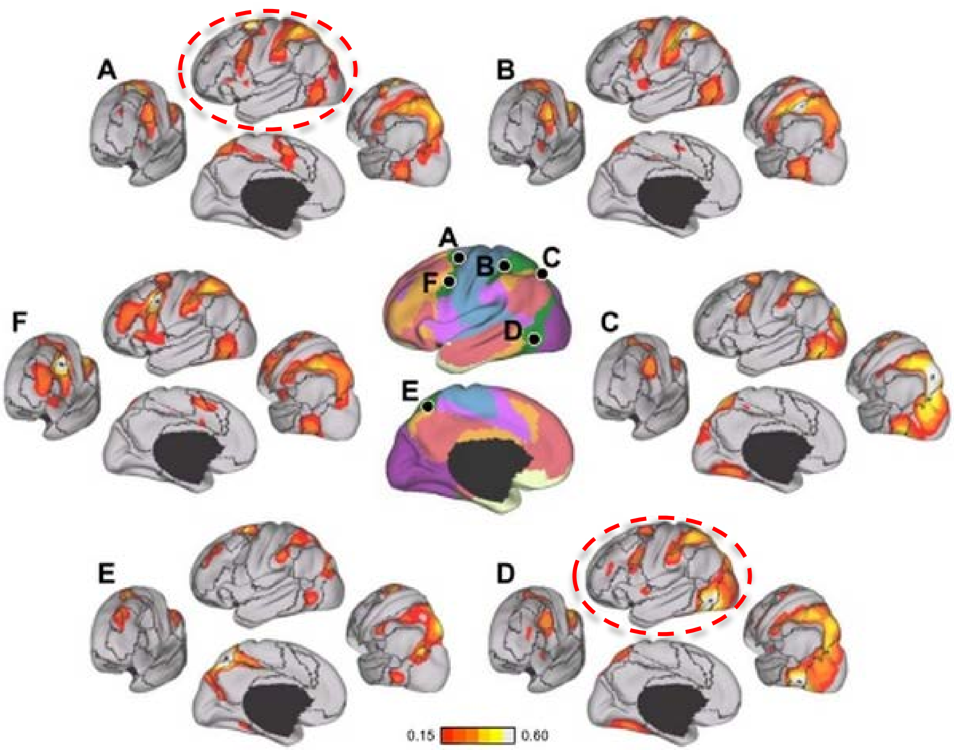
- Default
- Visual
- FrontoParietal
- Dorsal Attn
- Ventral Attn
- Salience
- Cingulo-Opercular
- SM-Hand
- SM-Mouth
- Auditory
- Cingulo-Parietal
- Retrospenial-Temporal

- Edge-detection and thresholding required
- Implicitly finds internally homogeneous regions
- Clusters are inherently divided parcels
- Emphasizes areal level of organization

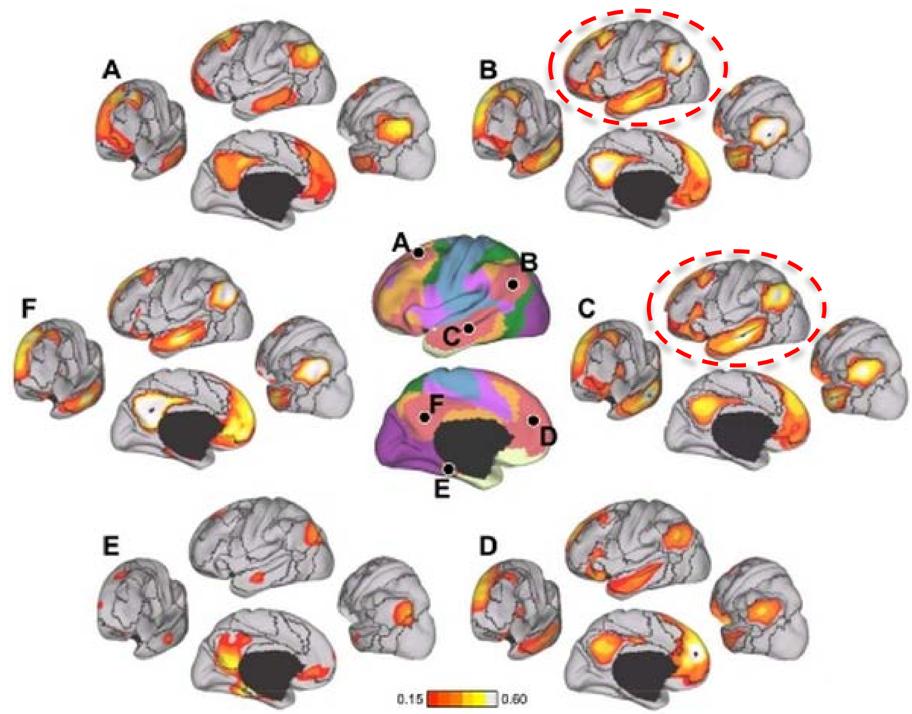
Available at: http://www.nil.wustl.edu/labs/petersen/Resources.html

Similar correlation map topography for widely separated seed regions

Dorsal Attention Network Seeds



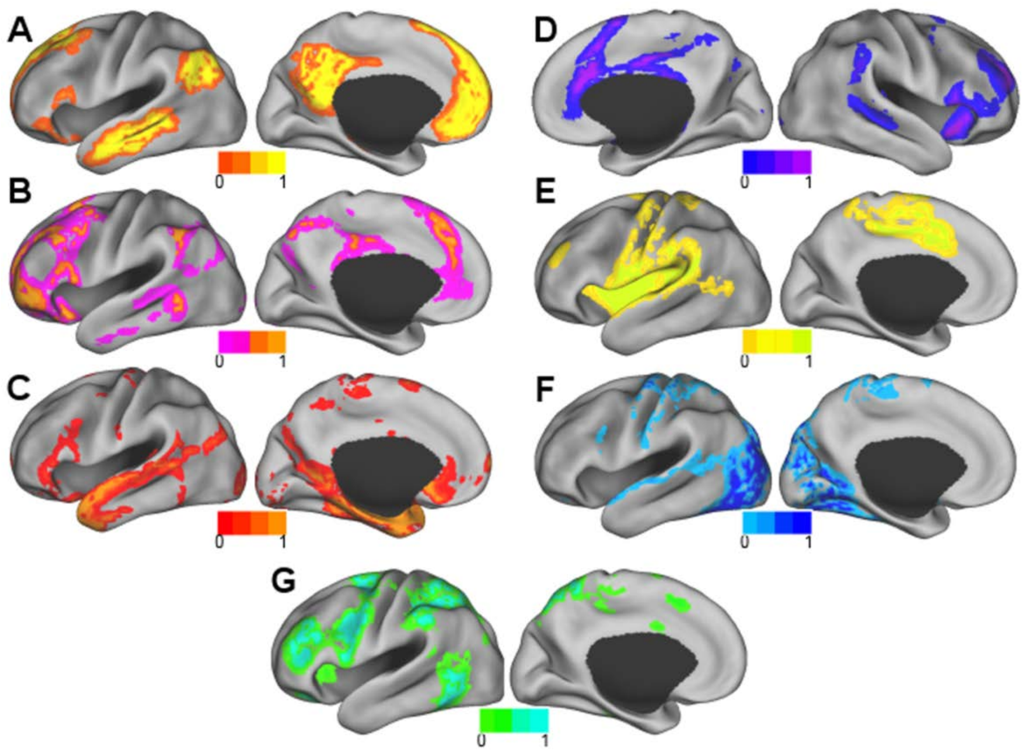
Default Mode Network Seeds

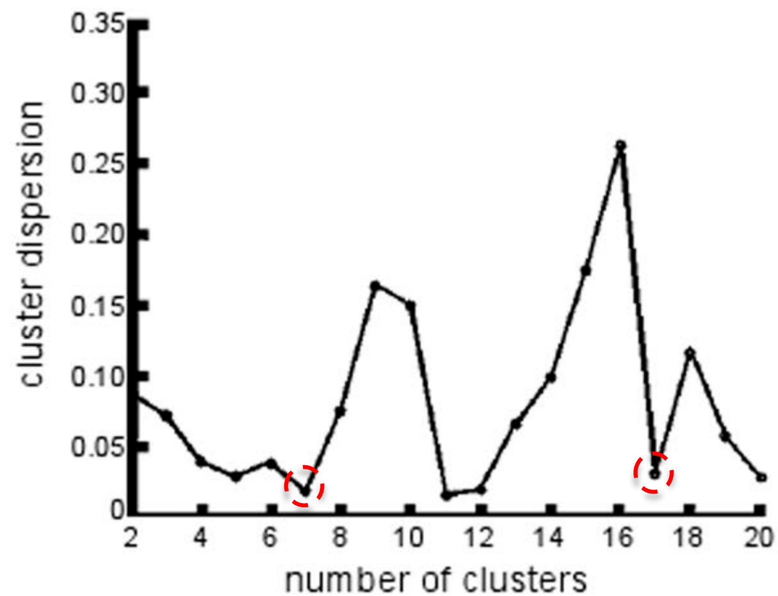


Yeo et al., J Neurophysiol (2011)

Clustering Approaches

- Fuzzy C-means:
  - Each voxel yields one correlation map
  - Clusters are formed from groups of maps with high spatial similarity



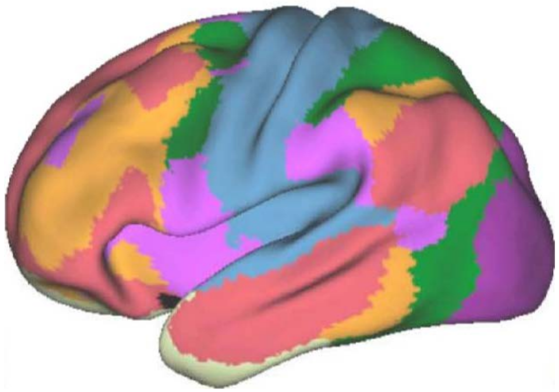


•Multiple “good” answers

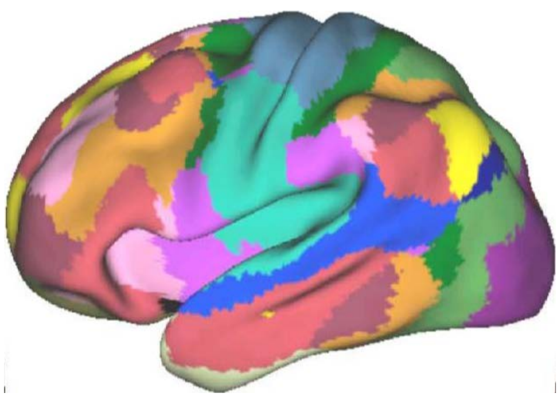
Lee et al., PLoS One (2012)

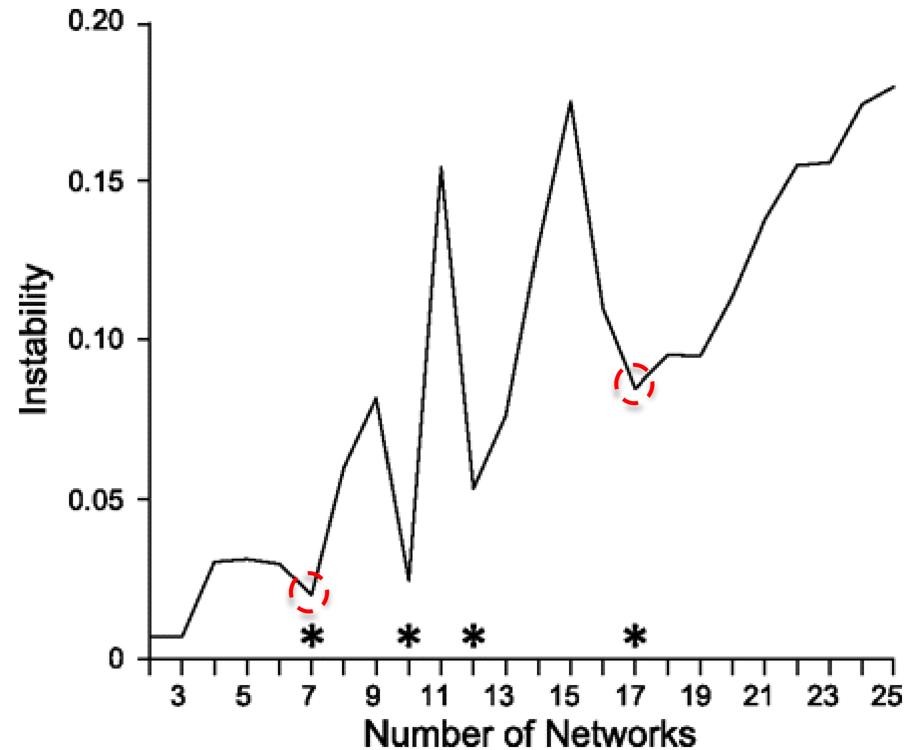
Clustering Approaches

7 Clusters



17 Clusters





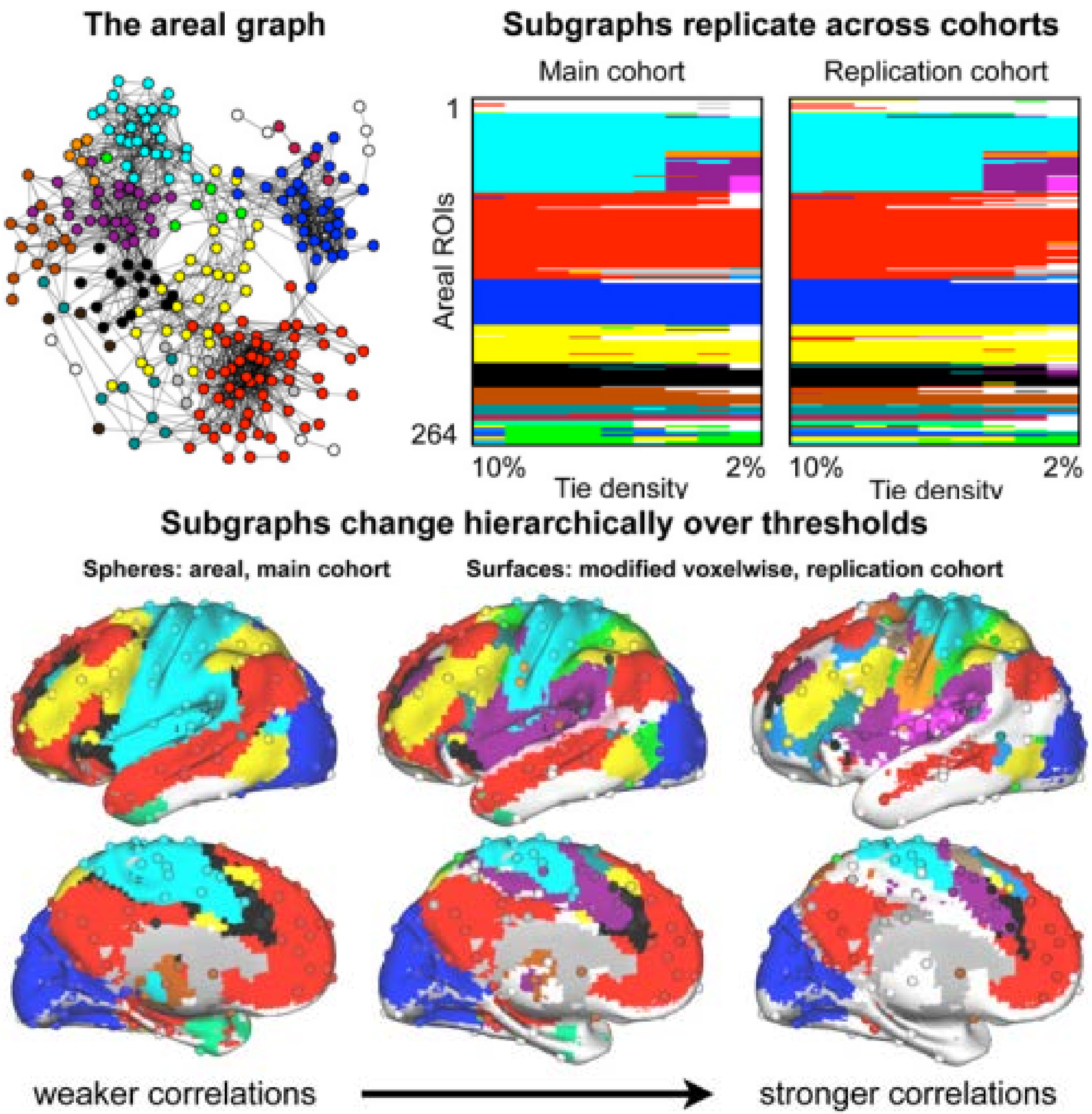
Sub-regions are nested

Multiple local minima in cluster instability

<u>Reproducible, hierarchical organization</u>

Yeo et al., J Neurophysiol (2011)

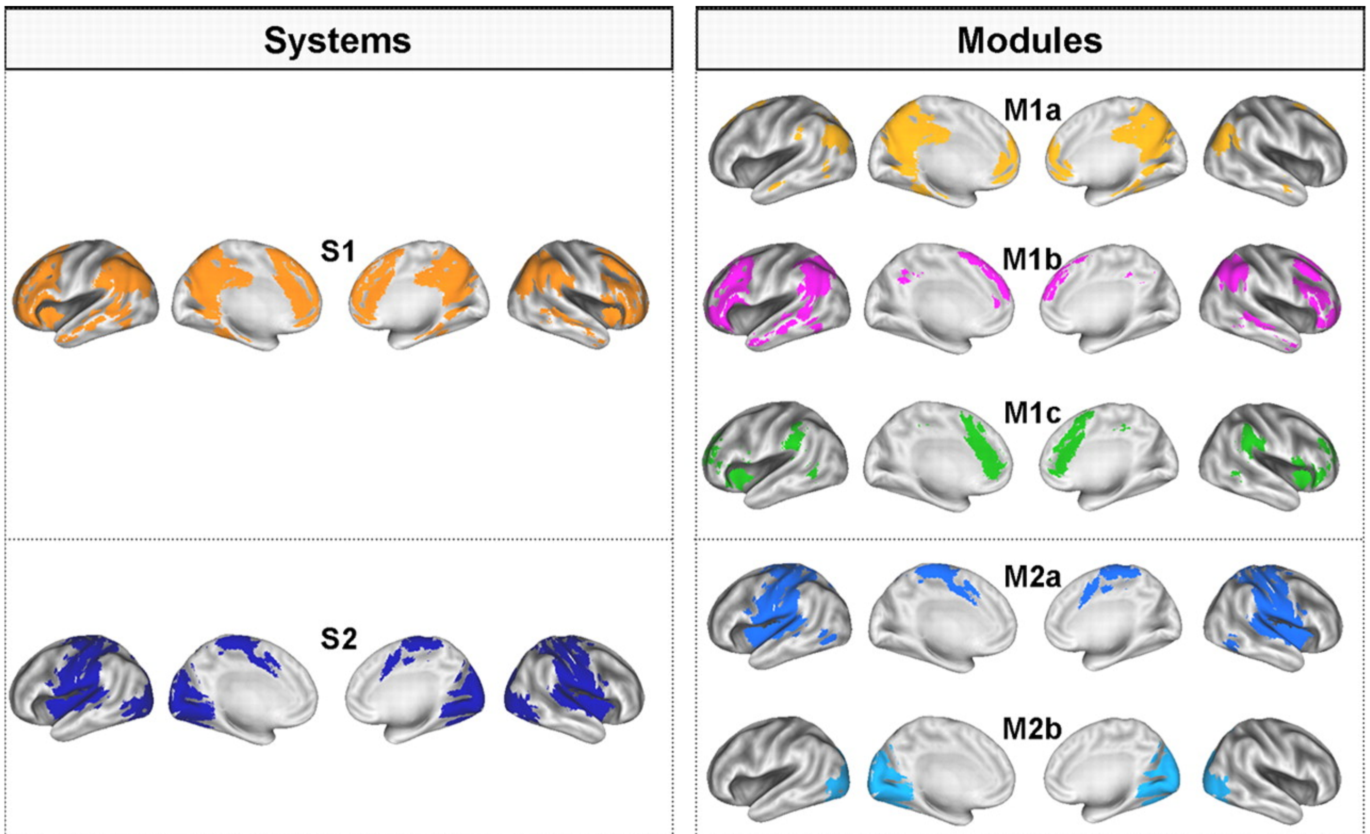
Graph Theoretic Approaches



Power et al., Neuron (2011)

RSNs are Hierarchically Organized

- Agglomerative ICA results:
  - RSNs(23) ∈ Modules (5) ∈ Systems(2)



Doucet et al., J Neurophysiol (2011)

Choosing a Dimensionality

- Multiple "correct" answers in hierarchically organized data.
- What level of granularity is appropriate for the research objective?
  - Trade-off of sensitivity to focal effects vs. statistical significance (multiple comparisons).
- Decision implemented differently across approaches:

Method	Dimensionality increases with:
Correlation gradients	Lower gradient threshold
Clustering	Larger number of clusters
Graph modularity	Lower tie density (High corr. threshold)
ICA	Larger number of ICs

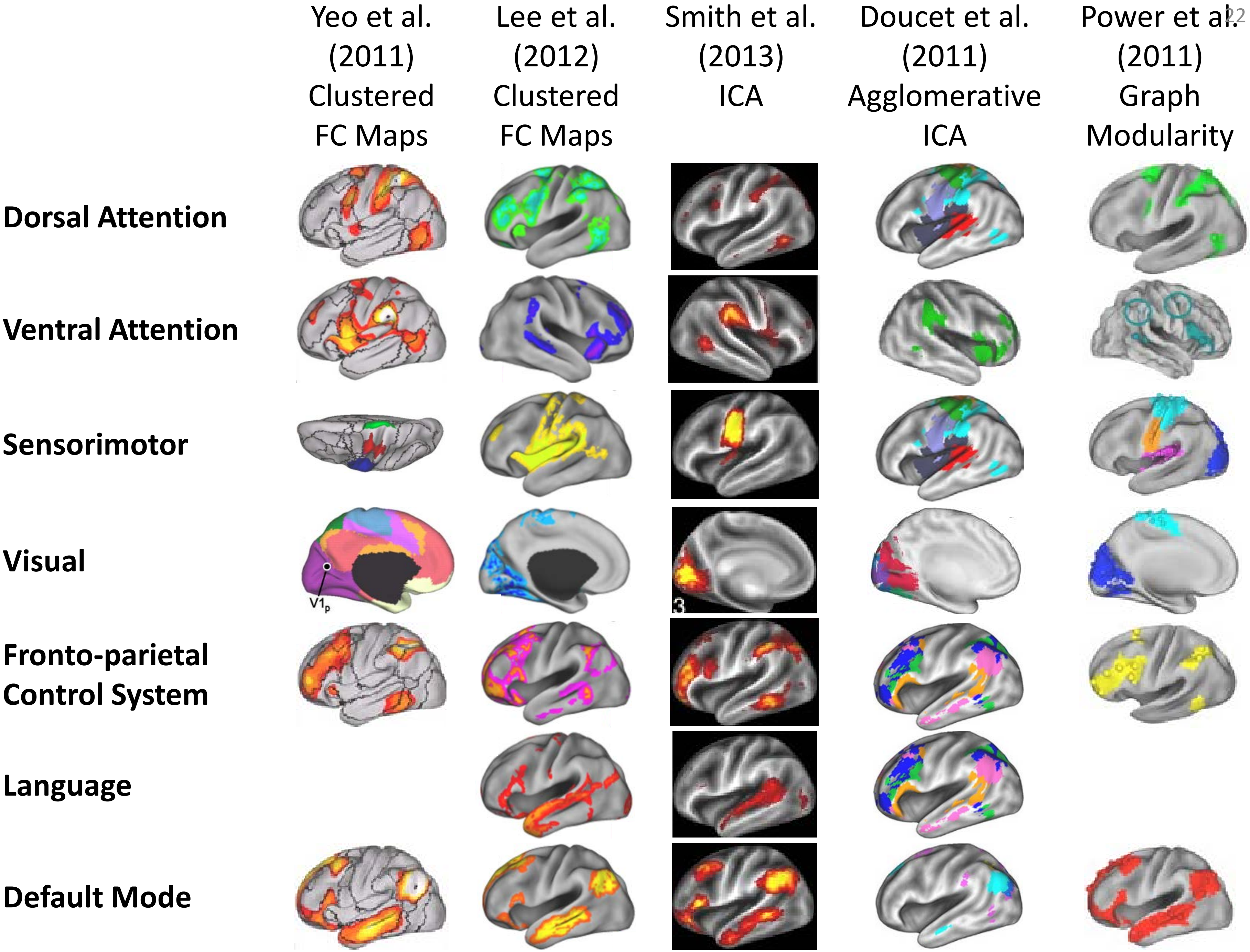
Limitations of Unsupervised Approaches

- Different unsupervised methods may recover the same RSN at different hierarchical levels
  - Superclass: Desired RSN may be agglomerated with other components
  - Subclass: Only fragments of desired RSN may be returned

  → Unstable results across datasets

Limitations of Unsupervised Approaches

- A one-to-one correspondence is not guaranteed in results across datasets or individuals.
- Two choices:
  - Solve “assignment problem:”
    - May have no solution
  - Use a single, group-defined parcellation:
    - Ignores individual differences in RSN topography


Yeo et al. (2011) Clustered FC Maps
Lee et al. (2012) Clustered FC Maps
Smith et al. (2013) ICA
Doucet et al. (2011) Agglomerative ICA
Power et al. (2011) Graph Modularity
Dorsal Attention
Ventral Attention
Sensorimotor
Visual
V1p
Fronto-parietal Control System
Language
Default Mode

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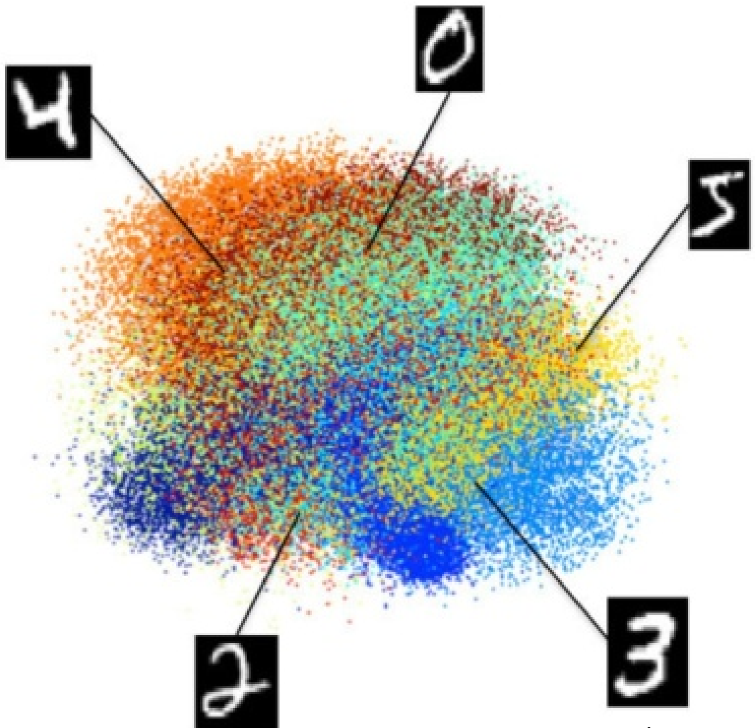
Supervised vs. Unsupervised Approaches

Example application:
Automated postal mail sorting

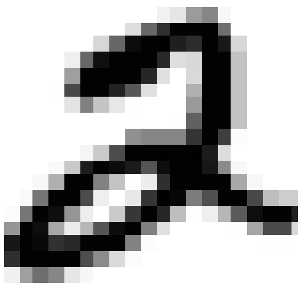
Unsupervised Learning:
(e.g. cluster analysis, ICA)



Bresson et al., 2012

Discovery:
These are the characters of the decimal system

Supervised Learning
- discriminant analysis (LDA/QDA)
- neural networks
- support vector machines

 =“2”

Classification:
This image represents the number “2”

Supervised vs. Unsupervised Methods

- Benefits of unsupervised learning
  - Discovers new structure in data
  - Unbiased
- Benefits of supervised learning
  - Avoids assignment problem: (meaning of “default mode network” is consistent across groups, subjects, runs, etc.)
  - Explicitly targets variance in the data that is related to the components of interest (RSNs)

Supervised vs. Unsupervised Methods

- Complimentary, not competing approaches
  - Unsupervised methods discover meaningful components in the data
  - Supervised methods can optimally extract these known components from new datasets
    - Guaranteed one-to-one correspondence in recovered components across datasets

Dual Regression

- Most common approach to extend group results to individual subjects.
  - Group ICA used to define spatial RSN components
  - Find associated timecourses for these components in an individual
  - Correlate timecourses with each voxel to recover components in the individual
- Allows for variability of RSN topography across individuals.

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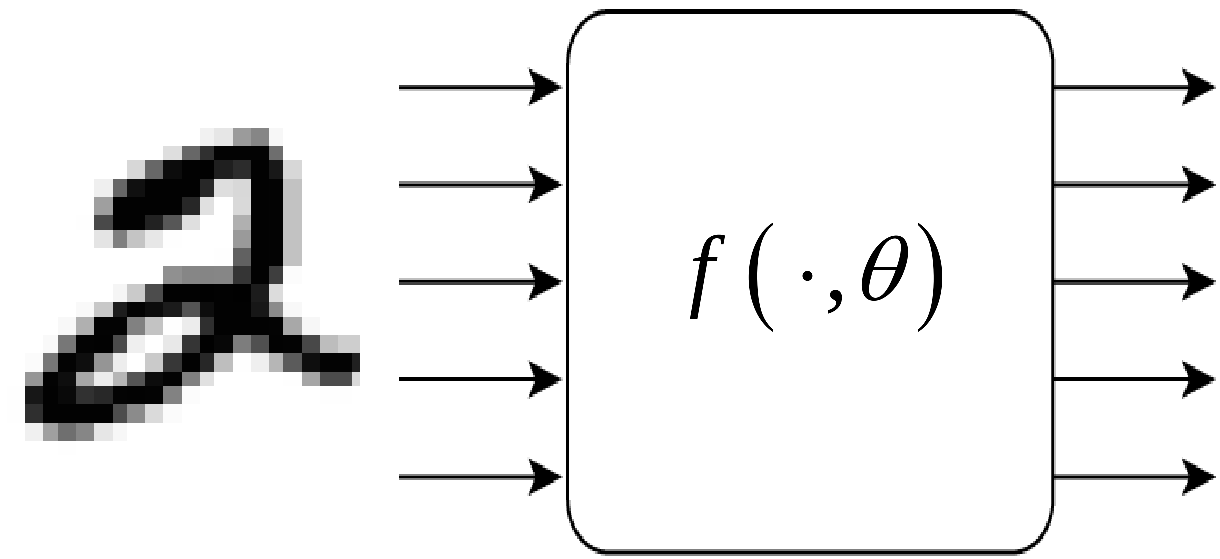
Setting up the problem

Input Space (X):
Array of pixels

Output Space (Y):



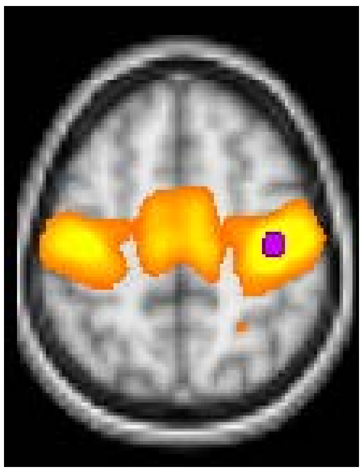
Class	Desired Value
"1"	0
"2"	1
"3"	0
"4"	0
…	0

$$Y \approx f(X,\theta)$$

Θ - learned model parameters

Setting up the problem

Input Space (X):
Array of voxels



$$f\left(\cdot,\theta\right)$$

Output Space (Y):

Class	Desired Value
“DAN”	0
“VAN”	0
“SMN”	1
“VIS”	0
…	0

$$Y \approx f\left(X,\theta\right)$$

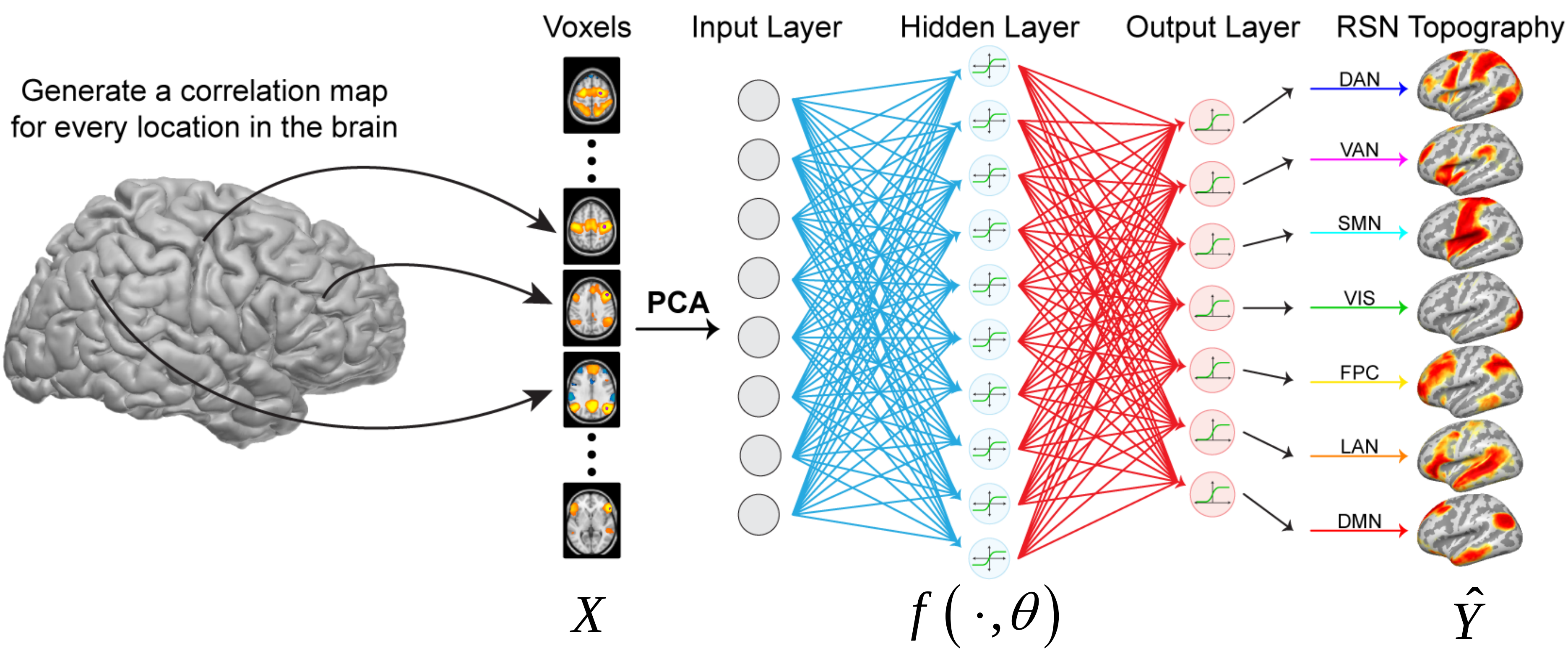
- Training Data:
  - Set of seed-based correlation maps
    - Must include variability across regions and subjects
  - Each seed assigned to one RSN

Supervised Learning

- Theory:
  - Learn an underlying function that maps correlation map topography to RSN identity
- Application:
  - Create correlation map for every region in the brain
  - Apply learned function to these maps
  - Result: map of RSN identity throughout the brain

RSN Classification Technique

- Compute a correlation map for each point in the brain
- Estimate membership in each RSN class based on learned function



Hacker et al., NeuroImage (2013)

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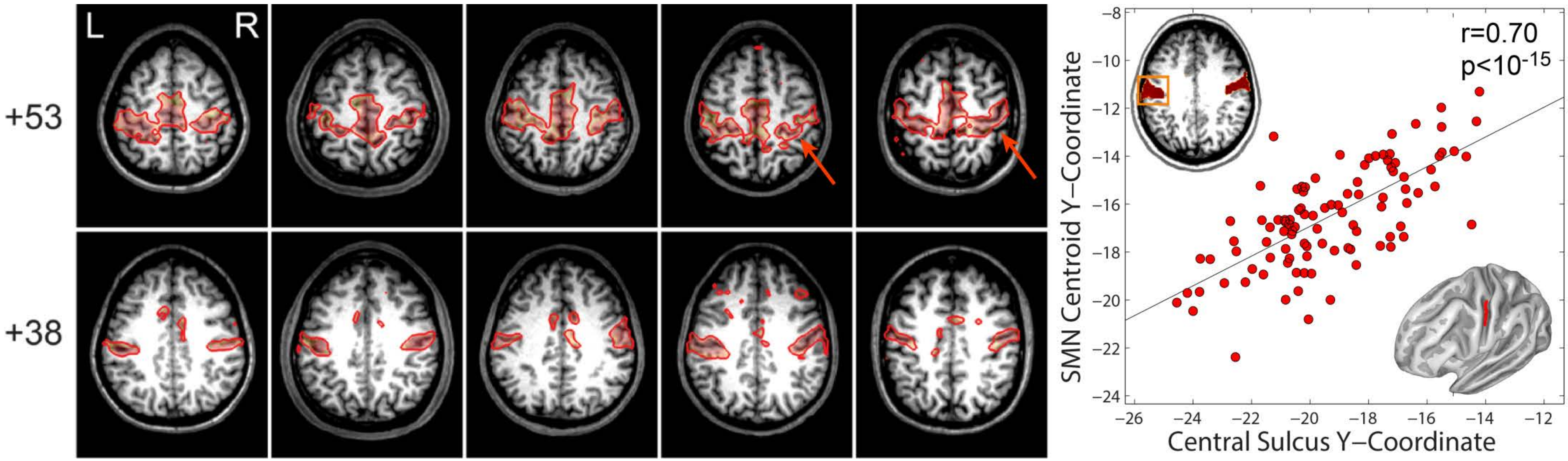
Generalizability to New Subjects

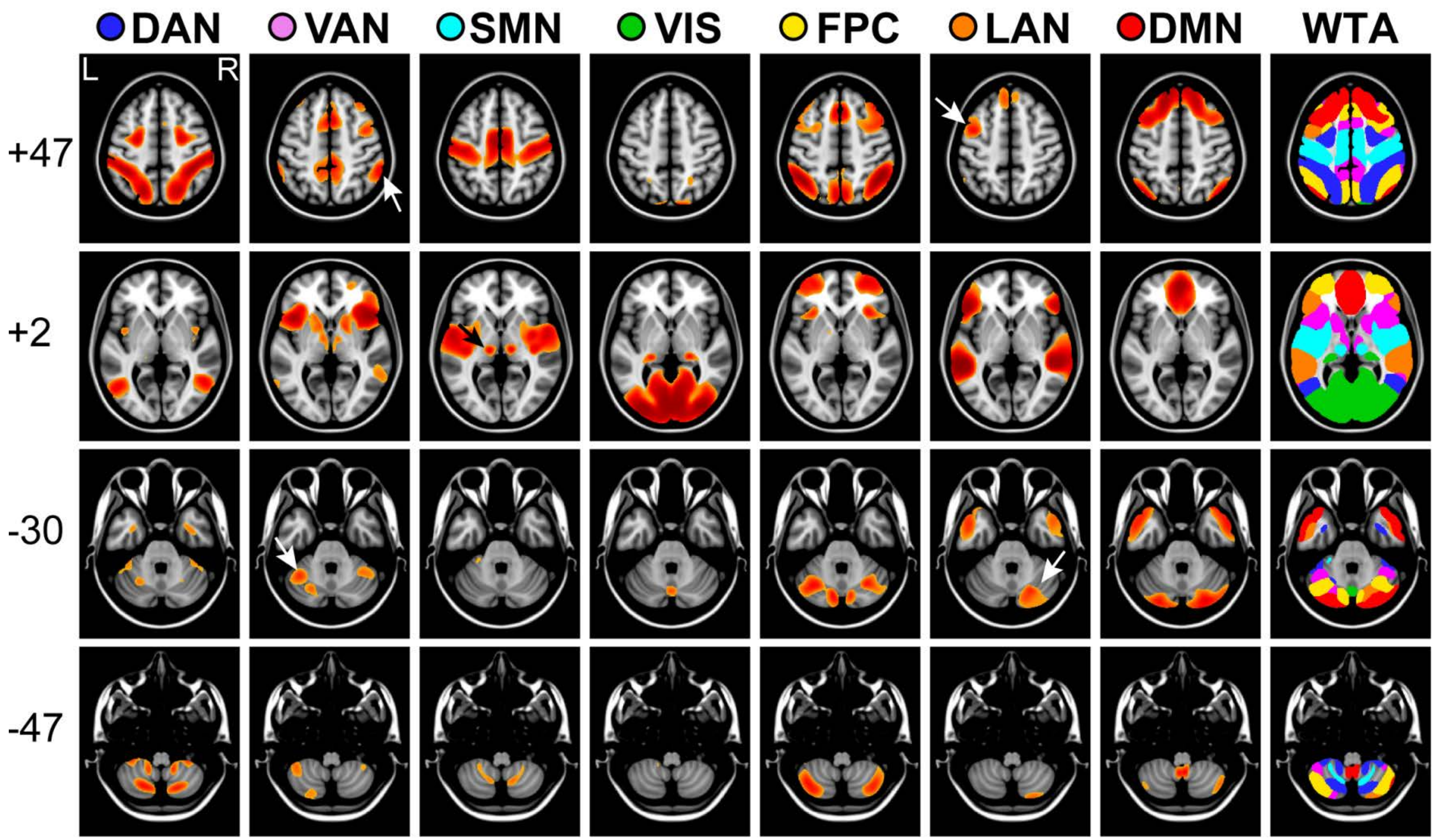
- Does function vary appropriately with structure across subjects?
  - Motor RSN estimates conform to gyral morphology
  - Motor RSN centroid covaries with central sulcus



Hacker et al., NeuroImage (2013)

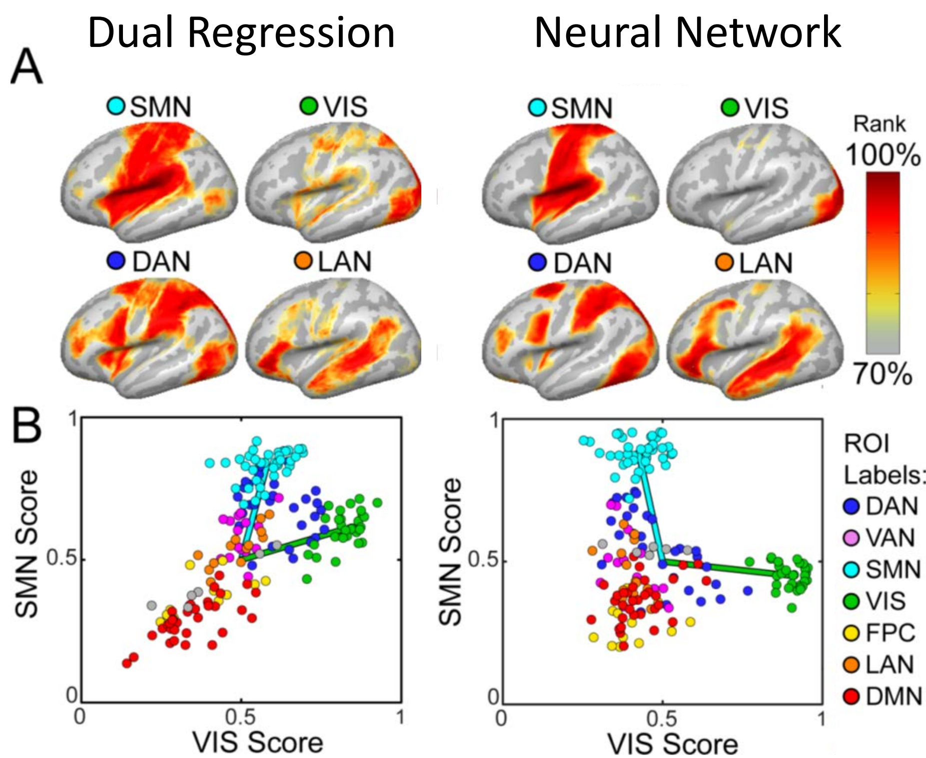
Generalizability to Untrained Brain Regions

- Correct extrapolation to regions not in the training data (cerebellum, thalamus in this example) indicates learning of an underlying function



Hacker et al., NeuroImage (2013)

Algorithm Comparison



- Linear method retains covariance between correlated RSNs
  - Overlap in topographies
- Non-linear methods can orthogonalize RSN estimates
  - Greater spatial specificity

Hacker et al., NeuroImage (2013)

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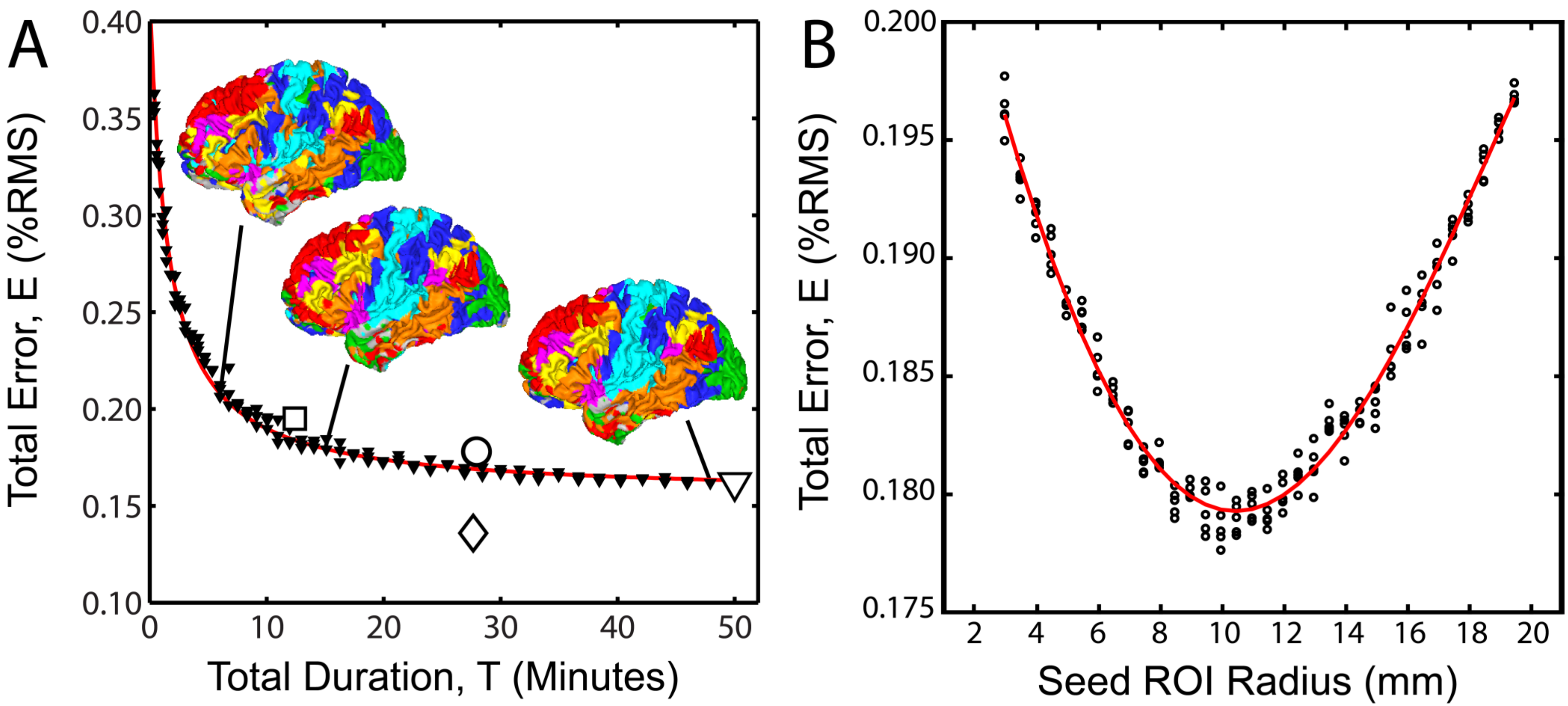
Methodological Optimization

- Supervised learning performance can objectively optimize methodological parameters with respect to RSN mapping quality:



Hacker et al., NeuroImage (2013)

Design considerations !

- What RSNs to define?
  - Must be well represented in training data
  - E.g. seed regions must cover all networks of interest
- Generalizability
  - Are the subjects used in training matched to those in the experimental dataset?
  - Similar acquisition parameters?
- Choices in preprocessing must be consistent
  - Head motion correction
  - Temporal / spatial censoring and/or blurring
  - Nuisance signal regression

Key Points

- A variety of unsupervised approaches have produced similar sets of canonical RSNs.
- Hierarchically organized data makes comparable solutions across subjects challenging.
- Supervised learning can be used to generate reliable solutions in individual subjects.

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