Resting state functional Connectivity

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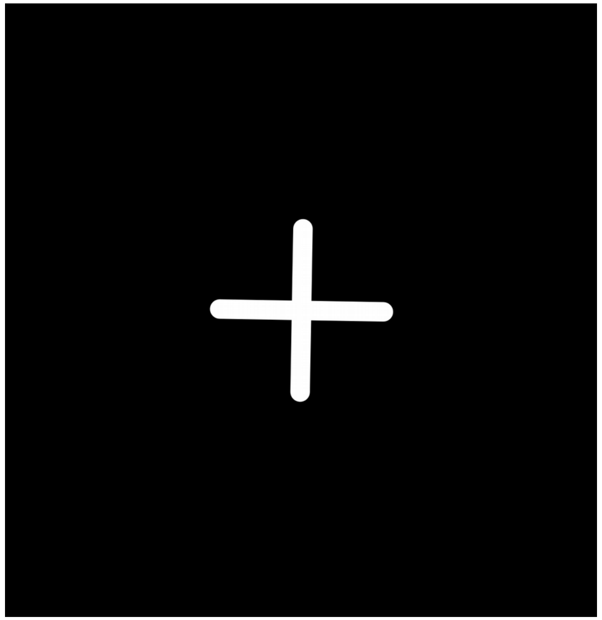
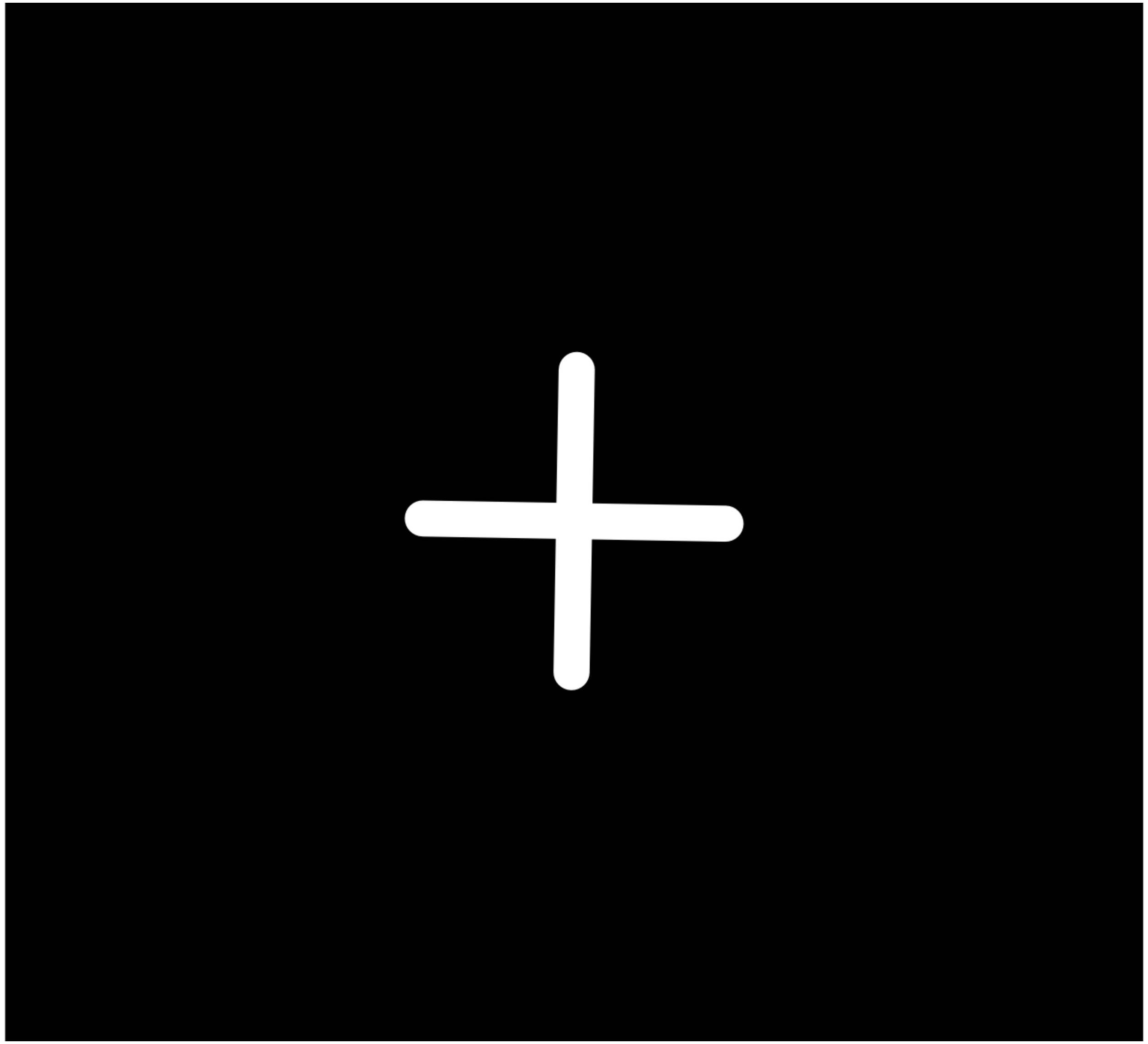
Overview



- Resting state fMRI: how does it inform us?
- Popular methods to study FC in Resting State
- Resting state networks and functional architecture

Resting state

- Eyes open with fixation cross or eyes closed
  - differences are observed (Agcaoglu et al., 2019)
- Versus Task: no cognitive constrain
- So why looking at it?



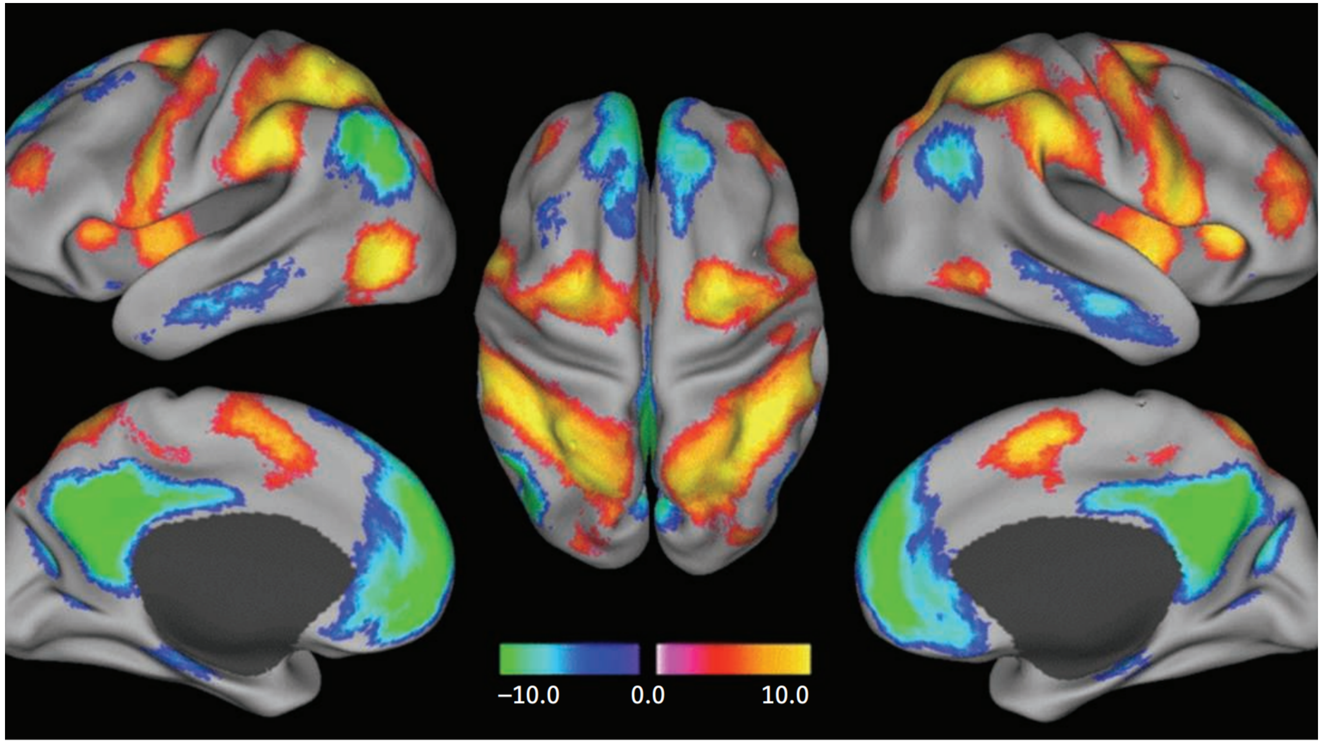
Energy argument

The brain is far from at rest

- Internal signal: ongoing, spontaneous thoughts
- external signal

Raichle, Science 2006

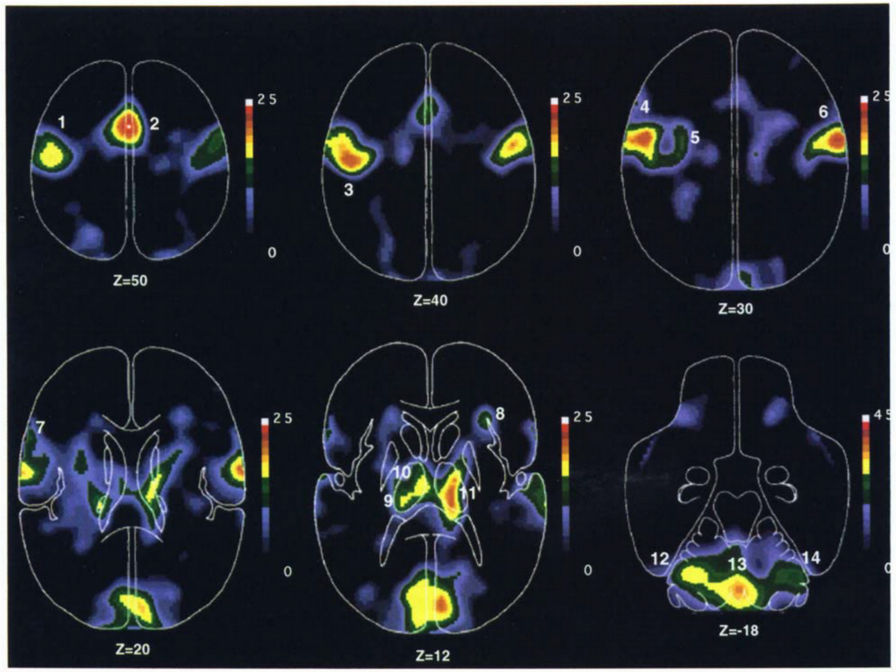
- Brain < 2% body weight but consumes ~20% of total energy
- estimated 60-80% of this energy used to support communication between cells
- task-evoked activity accounts for ~1%



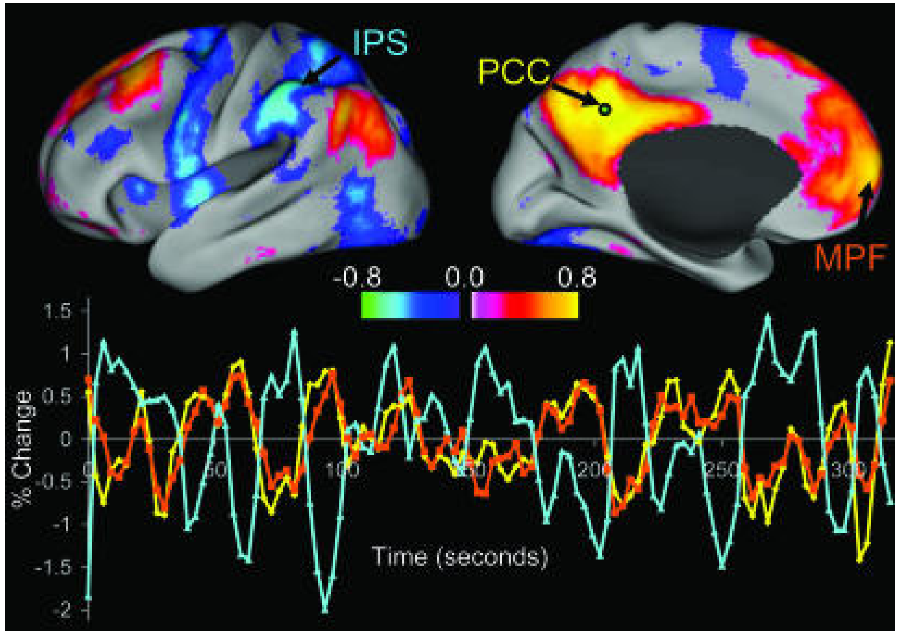
Fox et al. 2005

Default mode network

- Historically, meta-analysis of visual tasks in PET reveals a "task negative network"
- Anticorrelating with "task positive network": attention-demanding or goal-directed task
- DMN: Default Mode Network



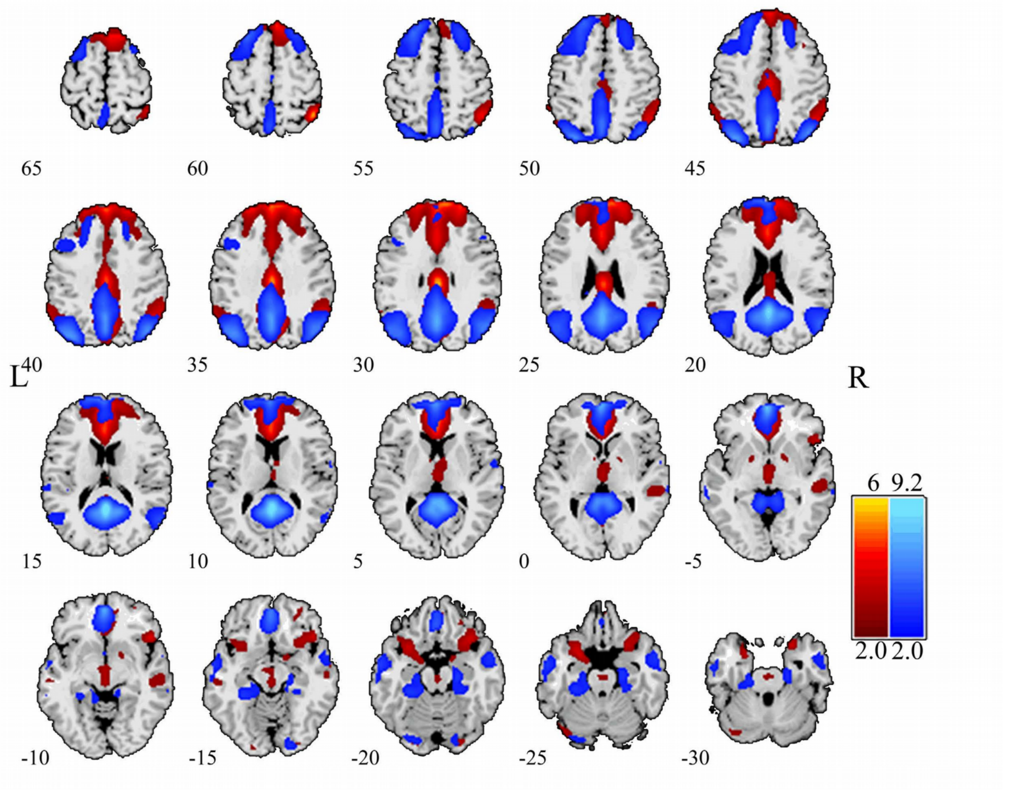
Shulman et al. 1997

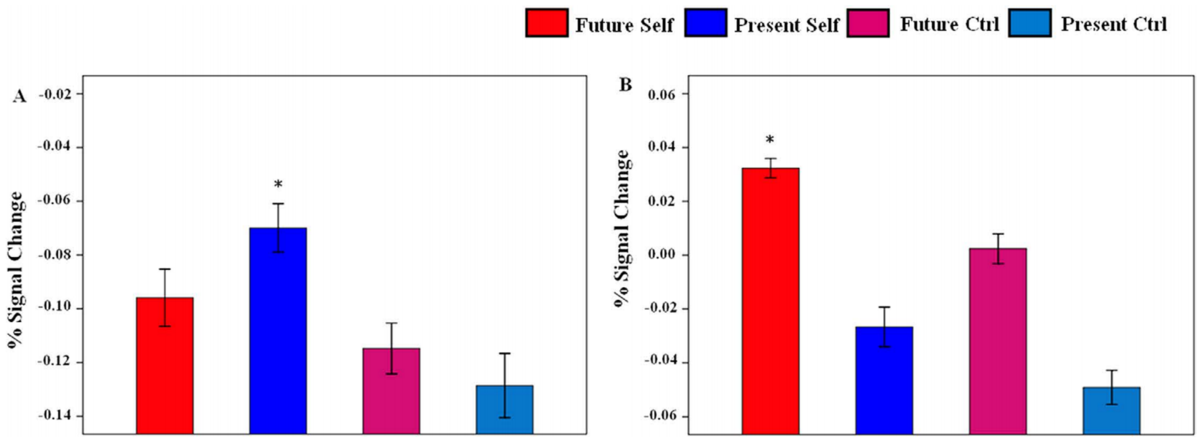


Fox et al. 2005

Default mode (?) network

- Far from a default mode
  - E.g. Greicius et al. 2004: introspection and Alzheimer
- Related to (Andrews-Hanna 2012):
  - autobiographical information,
  - thinking about others,
  - thinking about the present, the past
- Not homogeneous activity across nodes (e.g. future-oriented thoughts)





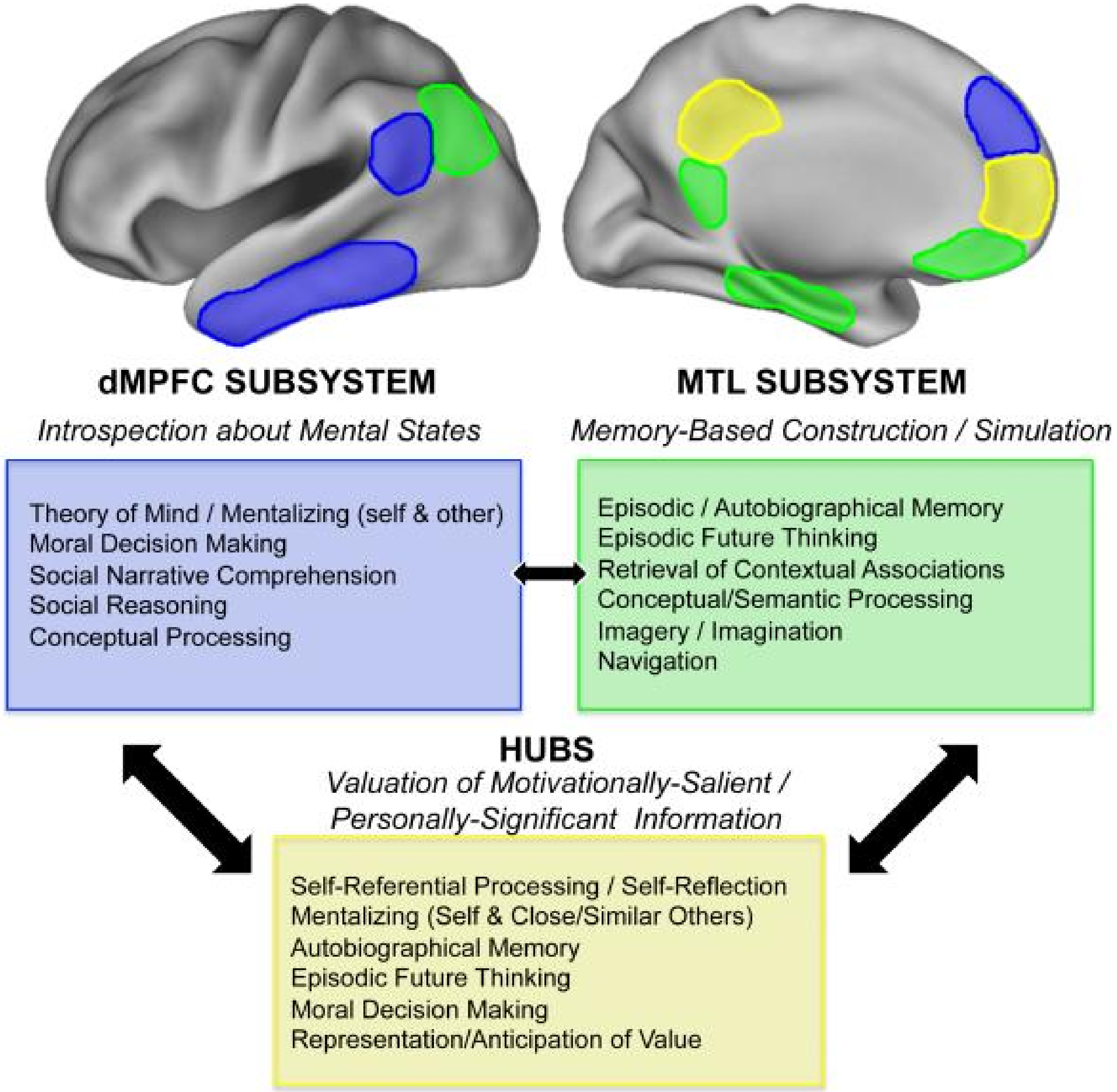
Anterior DMN

Posterior DMN

Xu et al. 2015

Default mode (?) network

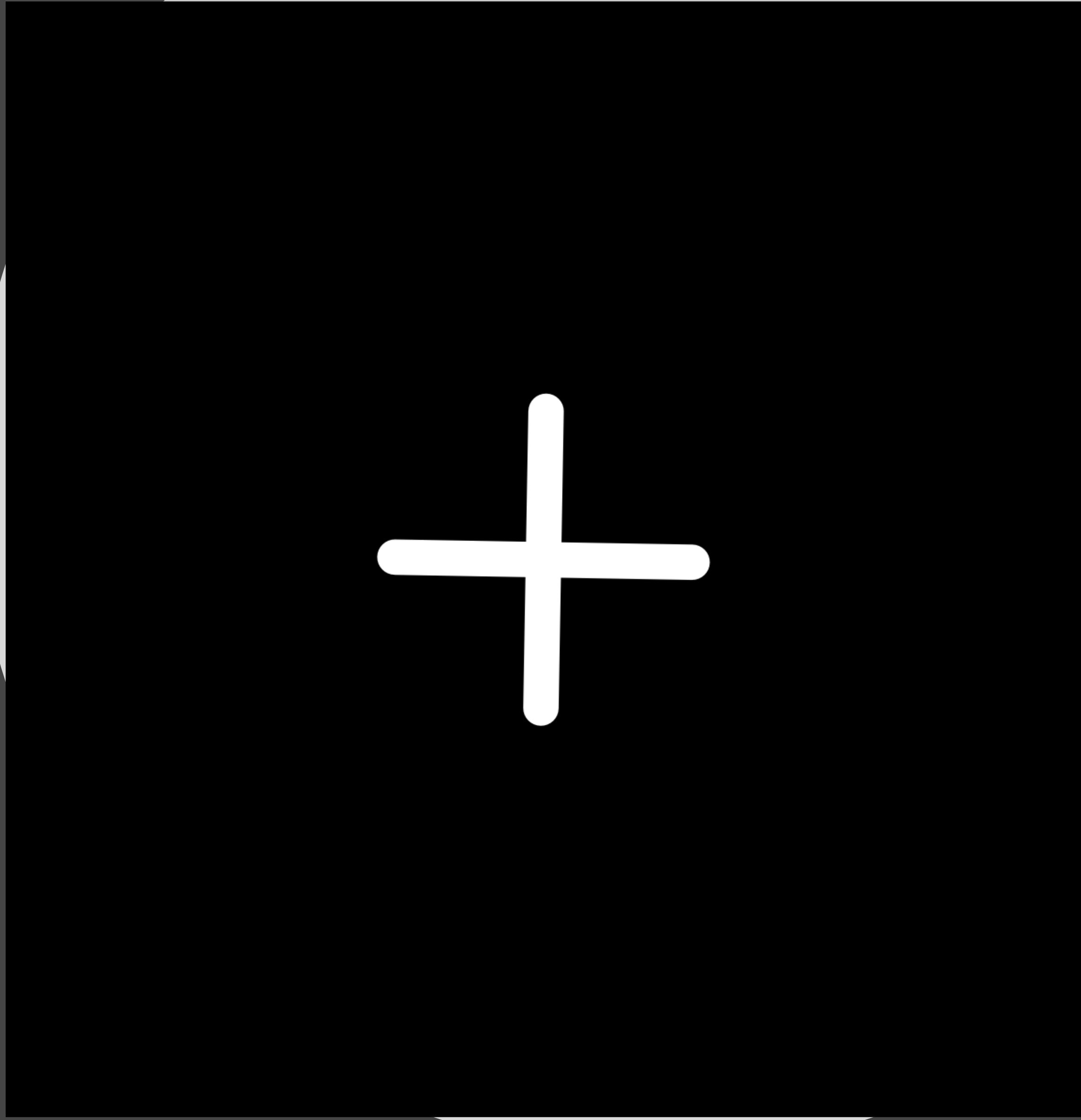
- Key to integrate information
- Co-activating in task:
  - Memory / working memory
  - processing of emotionally-salient stimuli
  - Interplay between emotional processing and cognitive functions
  - …



Andrews-Hanna 2012

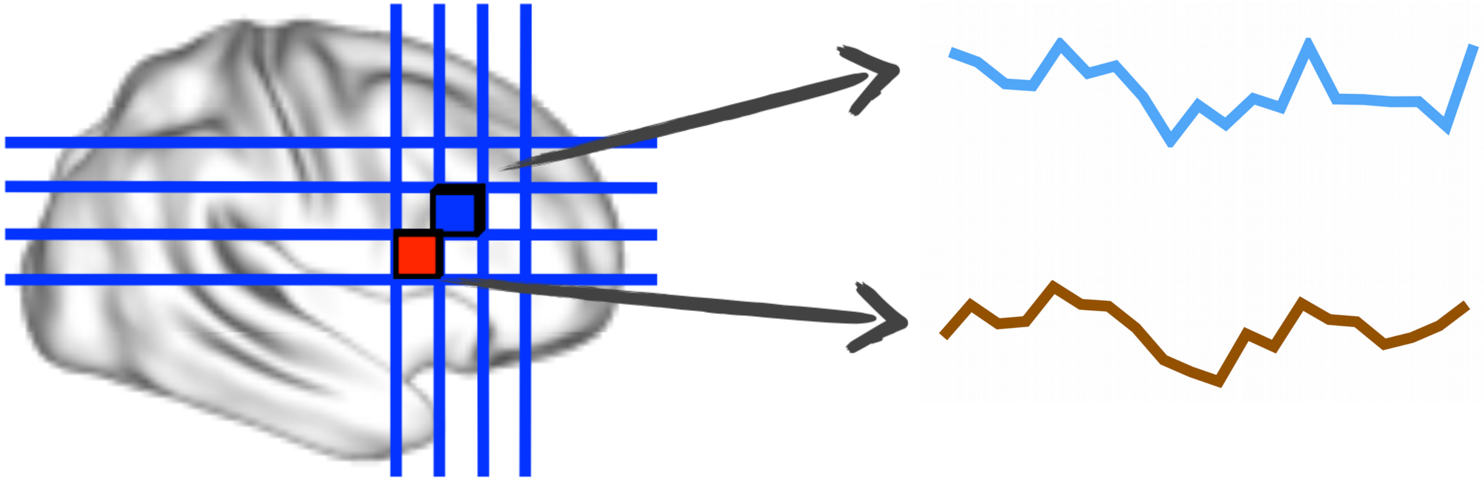
Resting state is not a noisy baseline

- How to study it?
  - Co-activation in time of area: Functional connectivity
- What popular methods?
  - Connectivity matrices
  - Seed-based correlation (Biswal, Raichle/Fox)
  - PCA/ICA (Kiviniemi, Beckmann, Calhoun)
- What did we learned so far?
  - Resting state networks
  - Functional baseline architecture



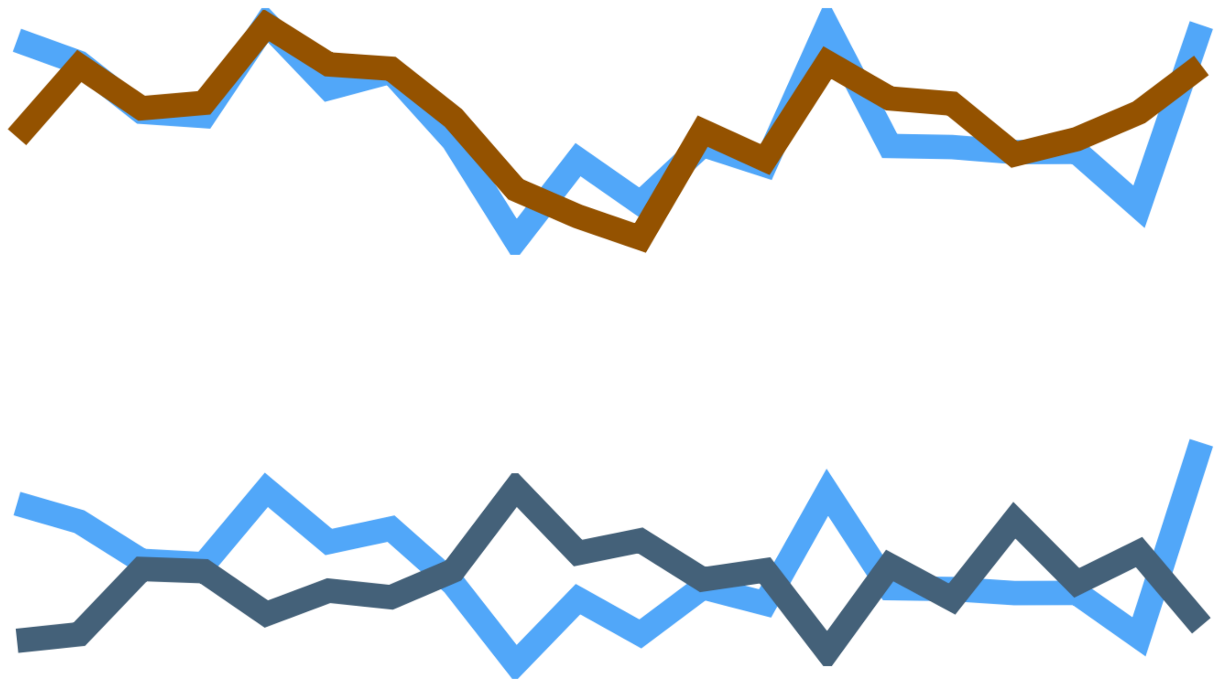
How to disentangle activity without design?

- Based on co-activation of areas/voxels in time: correlation
- Extracting time series :
  - **average,**
  - weigthed average,
  - PCA



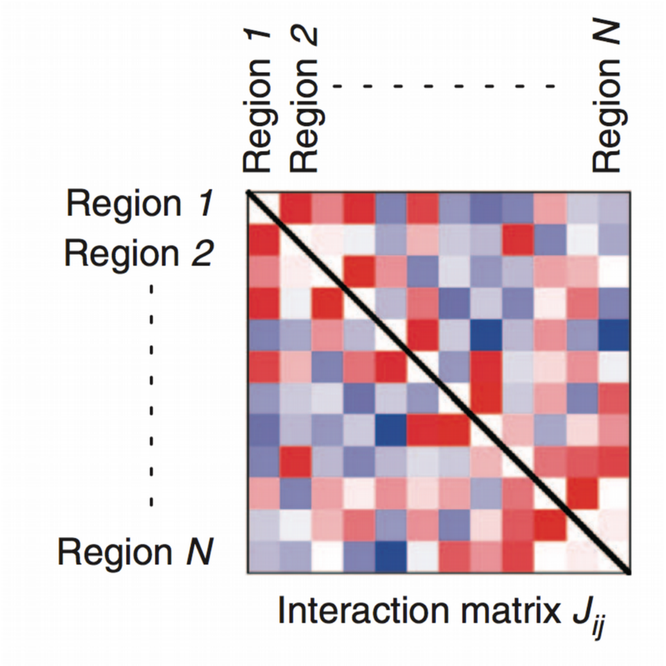
How to disentangle activity without design?

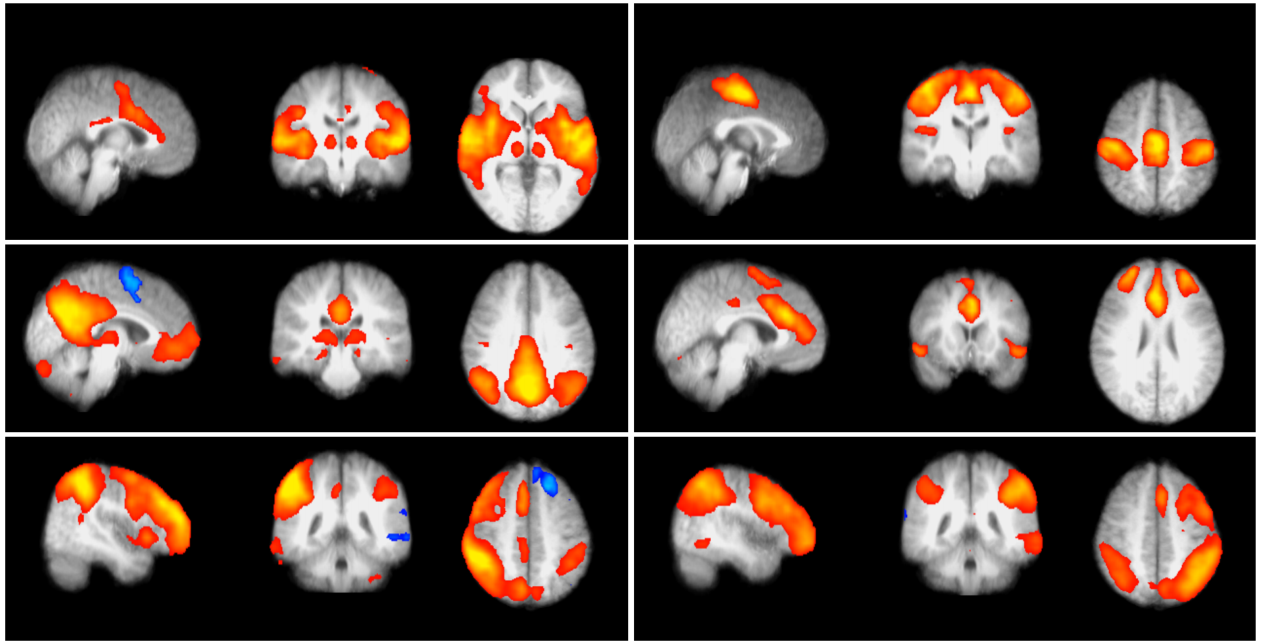
- Based on co-activation of areas/voxels in time: correlation
- Extracting time series :
  - **average,**
  - weigthed average,
  - PCA
- correlated or anti - correlated



How to disentangle activity without design?

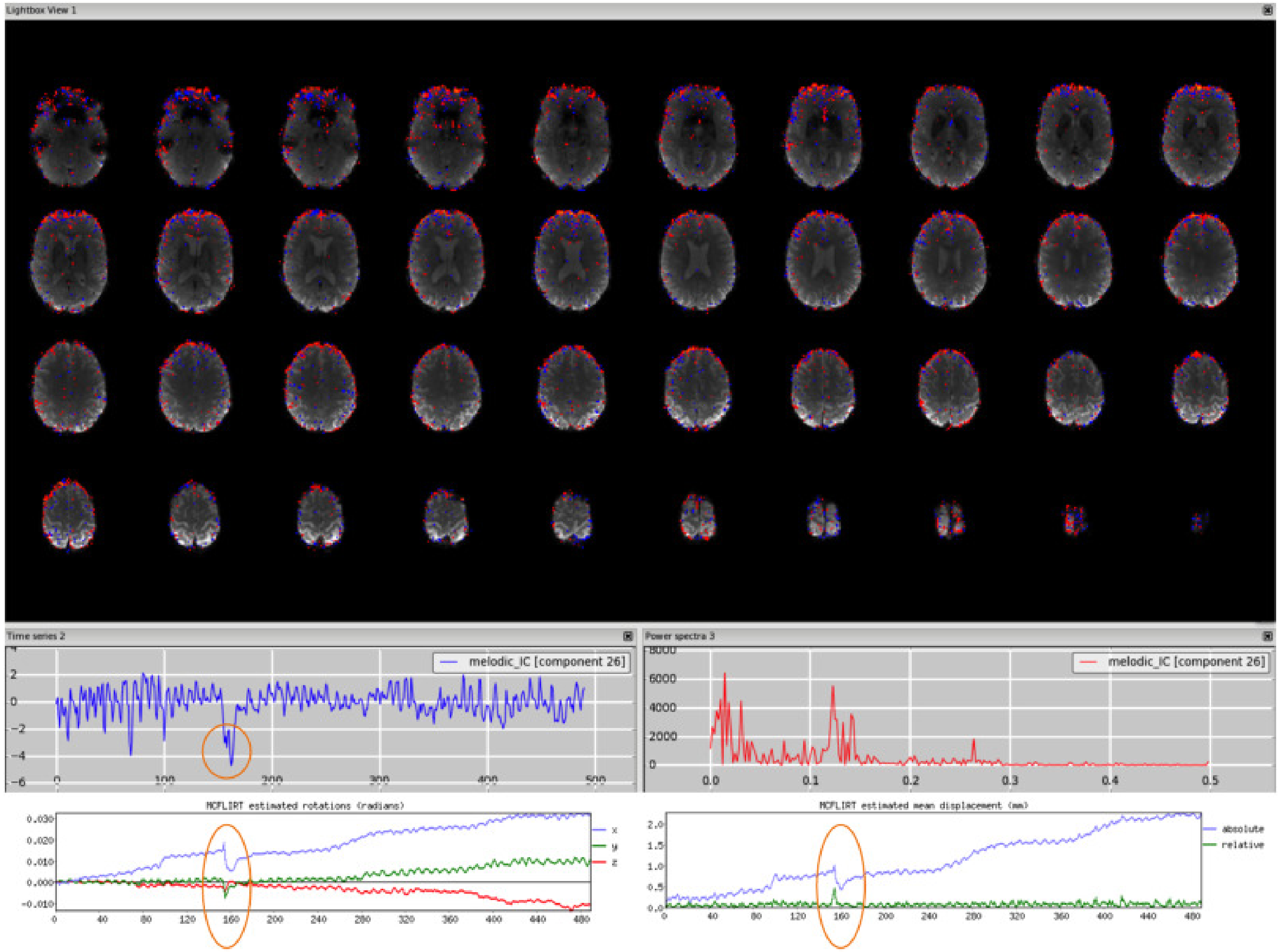
- Matrices or brain maps
- No design to control for unrelated signal, pre-processing is key





Pre-processing is key

- **Head movement**
- Cardiac rhythm
- Respiration
- Cerebro-spinal fluid
- MRI sequence/scanner
- …



Griffanti et al., 2017

Pre-processing is key

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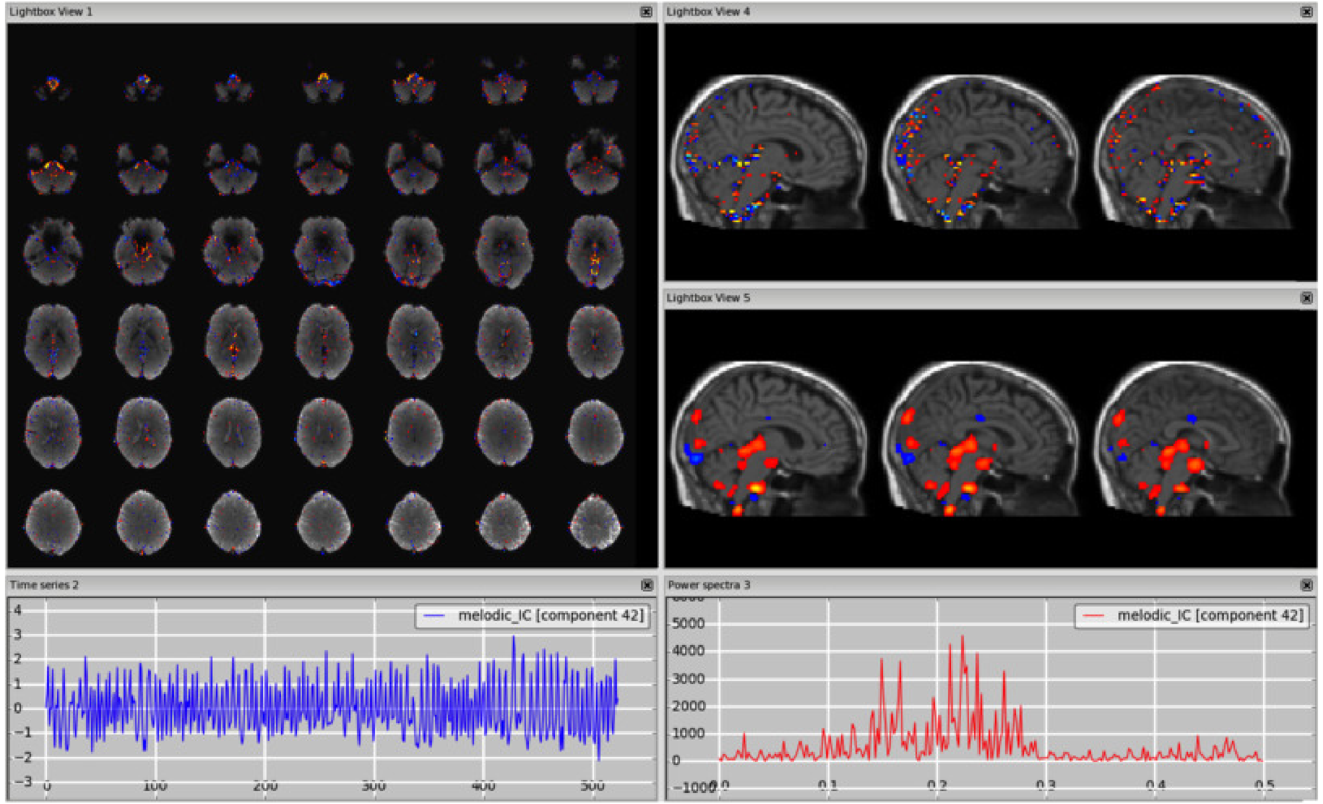

Griffanti et al., 2017

Pre-processing is key

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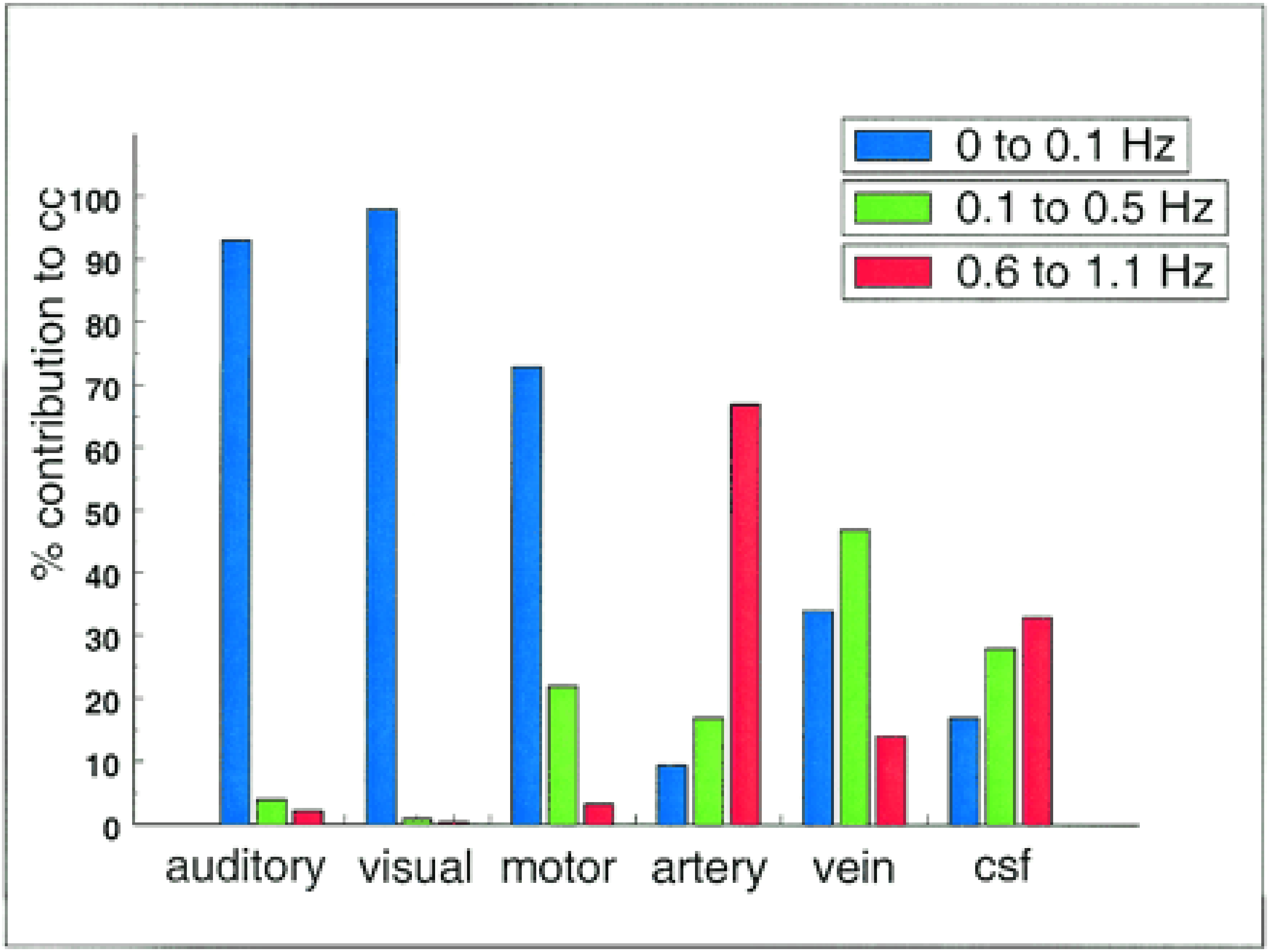
Physiological noise is high frequency heavy

low band filtering ?



Cordes et al., 2001

Pre-processing is key

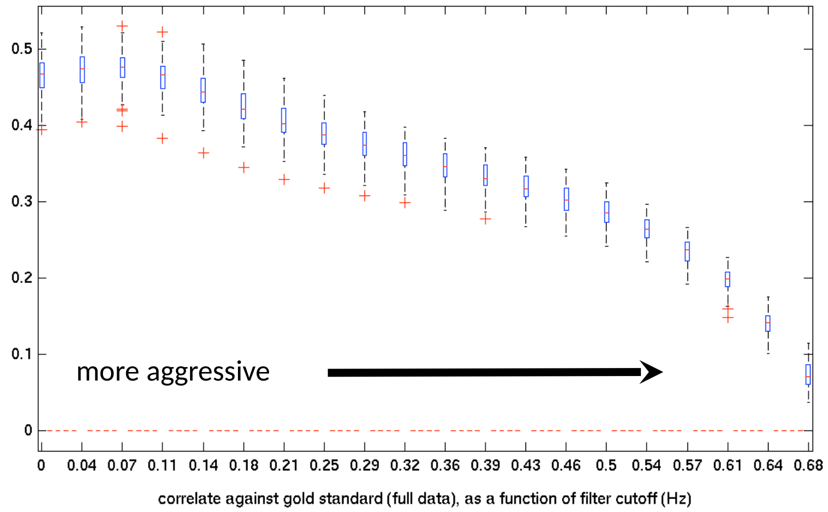
Physiological noise is high frequency heavy

low band filtering ?

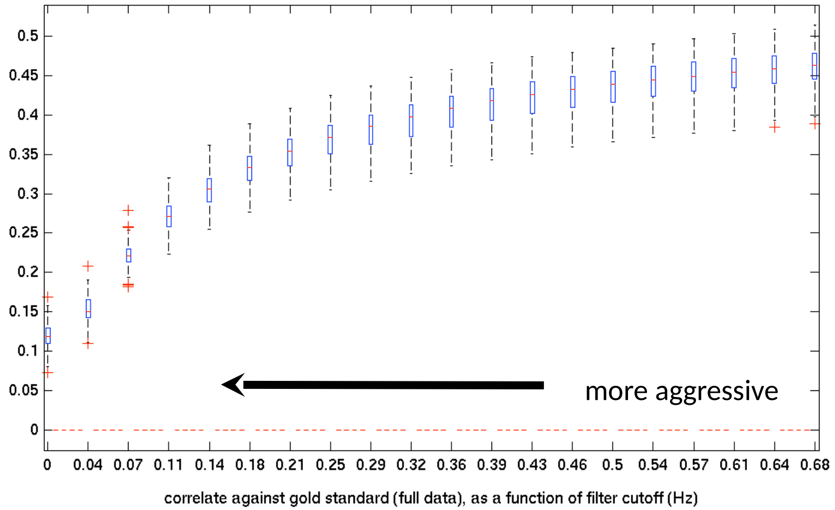
- (!) high frequency is not only physiological noise
- Loss of signal, (van Oort 2014)
- better to clean the signal

similarity to full dataset partial correlation netmat

Highpass filtering



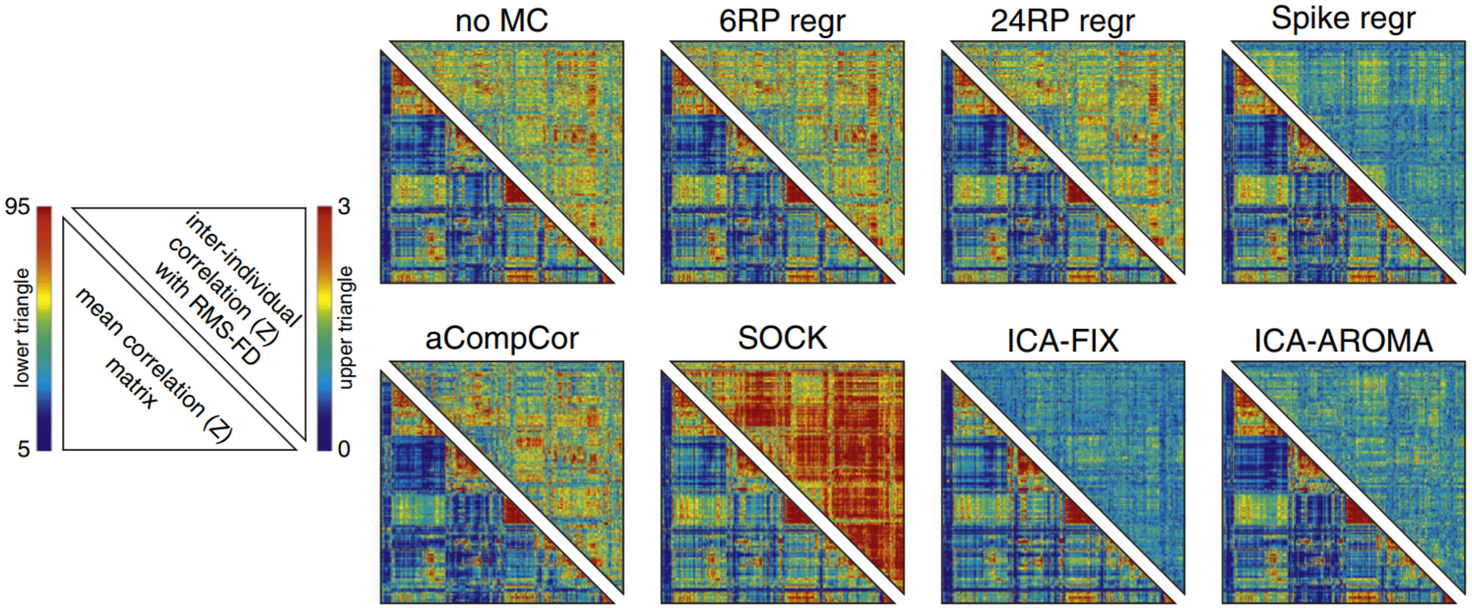
Lowpass filtering



van Oort et al. HBM 2014

Pre-processing is key

- motion correction
- spatial smoothing (1.5x voxelsize)
- temporal filtering (highpass only!) for scanner drift
- nuisance regression (CSF, WM, other, ~~Global signal regression~~)
- **secondary motion correction** (ICA-AROMA, ICA FIX, spike regression)



Pruim et al. 2015

Co-activation: Dependencies between time series

- Correlations and cross-correlation of time series (Biswal et al., 1995)
- Cross-coherence (Sun et al., 2004)
  - Correlation in frequency domain
- Mutual information (Jeong et al., 2001)
  - Based on probability distribution
  - Non linear relationship

$$\mathrm{cov}_{XY} = \sigma_{XY} = E[(X - \mu_X)(Y - \mu_Y)]$$

$$\mathrm{corr}_{XY} = \rho_{XY} = E[(X - \mu_X)(Y - \mu_Y)]/(\sigma_X \sigma_Y)$$

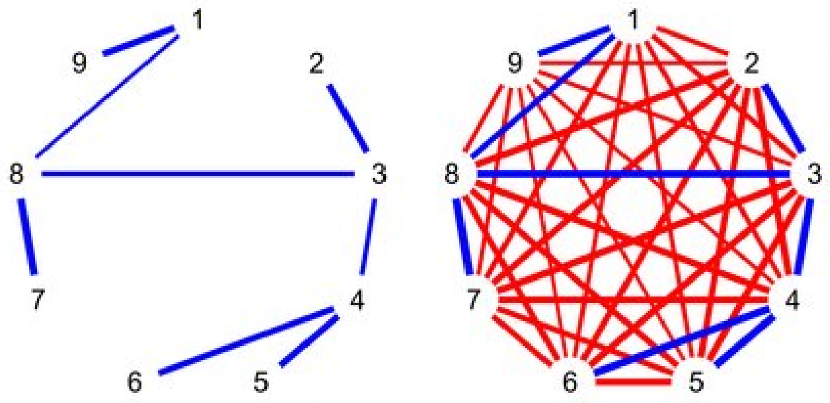
$$\mathrm{Coh}_{xy}(\lambda) = | R_{xy}(\lambda) |^2 = \frac{| f_{xy}(\lambda) |^2}{f_{xx}(\lambda) f_{yy}(\lambda)}$$

*Coh(f) = abs(Cross-spectral density)² / (spectral density(X) * spectral density(Y))*

$$I(X;Y) = \sum_{y \in Y} \sum_{x \in X} p(x,y) \log\left(\frac{p(x,y)}{p(x)\,p(y)}\right),$$

Connectivity matrices

- Partial analysis / precision matrix
- Controlling for redundancy in multiple correlation
- Reverse correlation + adjusting for diagonal OR Reverse covariance
- Have to be whole brain or control for residual

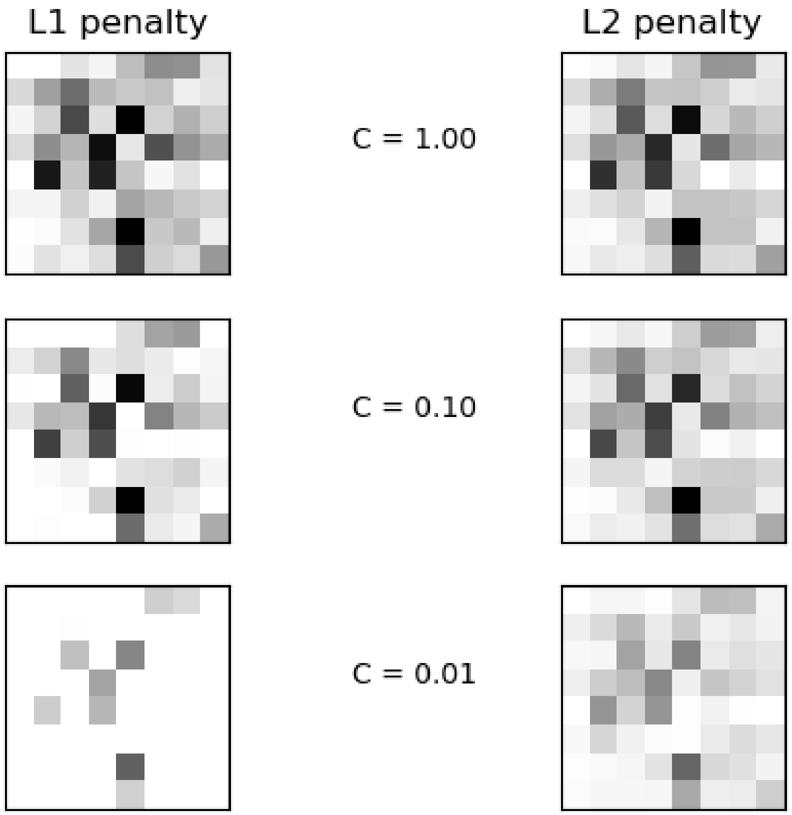


Schmittmann et al. 2015

Connectivity matrices

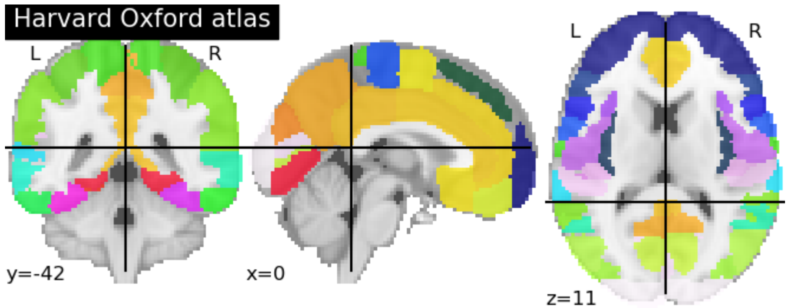
- The power issue
  - one correlation = min 3 points
  - 3 x N*(N-1)/2 for one matrix
    - N number of nodes
- Sparsity
  - Assumed that most edges are zero
- Enforced by estimating correlation/covariance, e.g.
  - Inverse matrix is the support to optimize the matrix
  - L1-regularization
  - Ledoit-Wolf (L2-shrinkage estimator)

See Smith et al. 2011

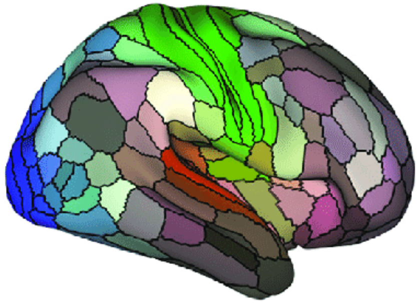


Connectivity matrices

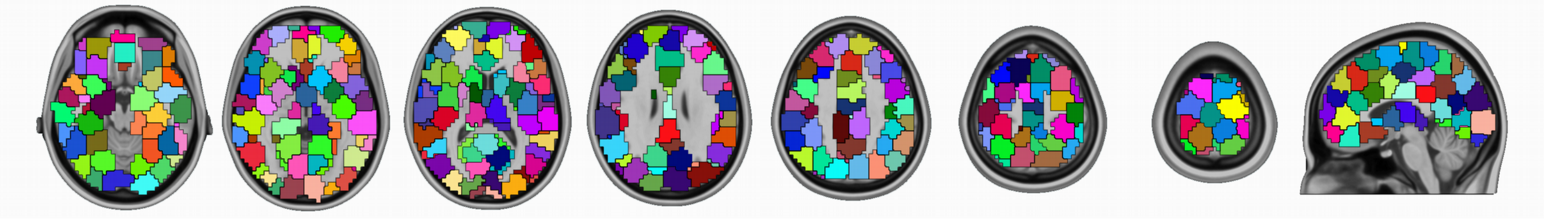
- Can be bring to subject space (Kashyap et al. 2019)
- Choice of the atlas
  - Not appropriate boundaries= “Blured” time series
  - shape and exact location interact strongly with the modelling of connectivity (Bijsterbosch et al., 2018)
- Anatomical
  - AAL
  - Harvard oxford
- **Functional**
  - Glasser: multimodal and multiscale
  - Craddock: spatially constrained spectral clustering
  - ICP: hierarchical instantaneous connectivity parcellation



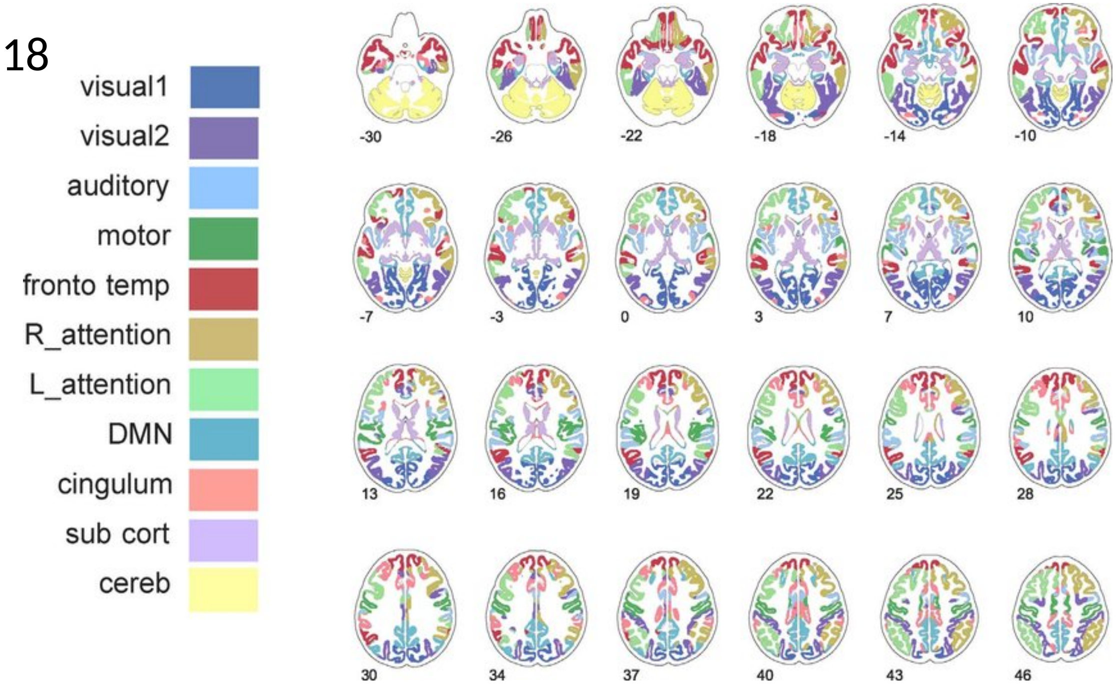
Glasser et al. 2016



Craddock et al. 2012

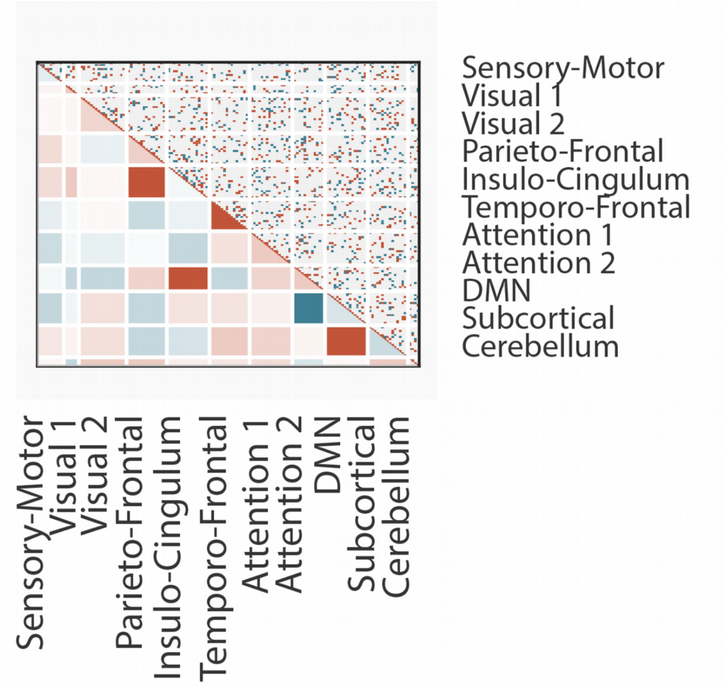


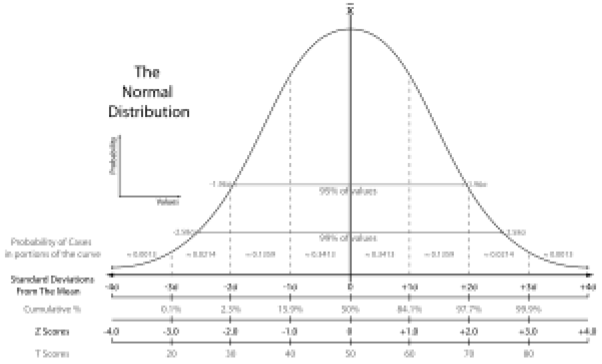
Van Oort et al. 2018

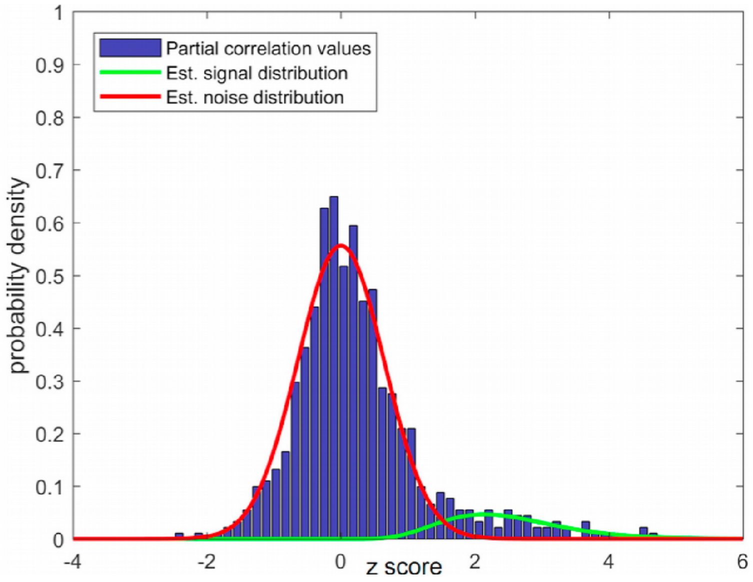


Connectivity matrices

- Look at average per network (within- and between-networks)
- Look at differences between groups (lower correction for multiple comparison)
- Selecting the signal against the noise: thresholding on group average matrix
  - Z score
  - Mixture modelling (Byelczik et al., 2018)



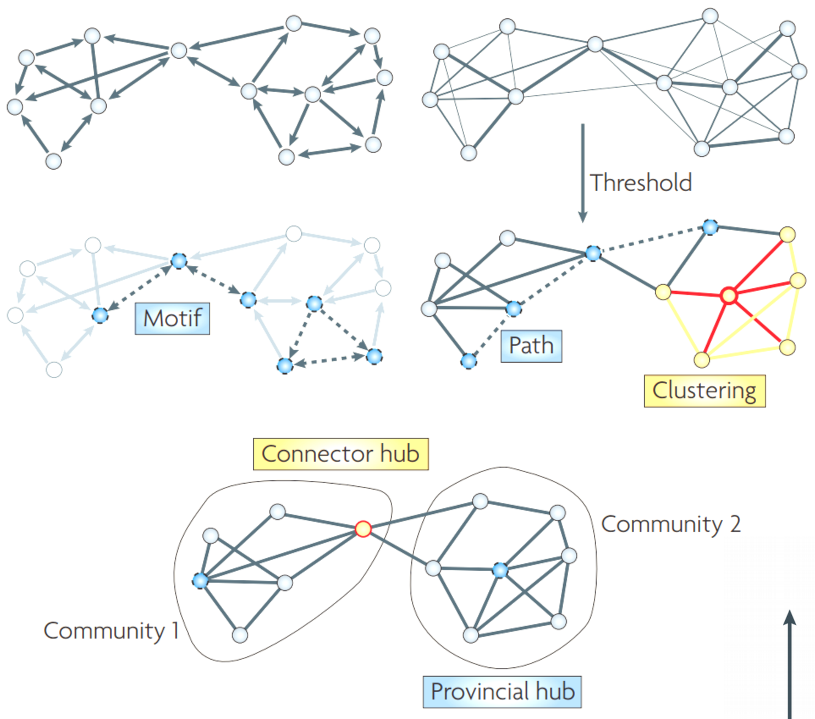


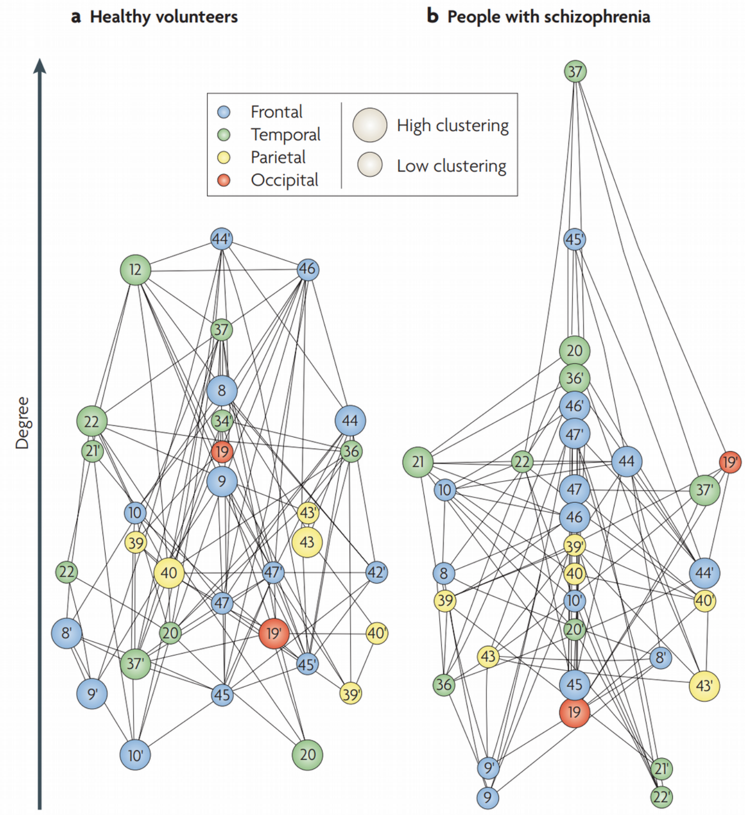


Bielczyk et al., 2018

Connectivity matrices

- Graph theory (Bullmore and Sporns, 2009)
  - Node degree, degree distribution and assortativity
  - Clustering coefficient and motifs
  - Path length and efficiency
  - Connection density or cost
  - Hubs, centrality and robustness
  - Modularity
- Appropriate region definition is key

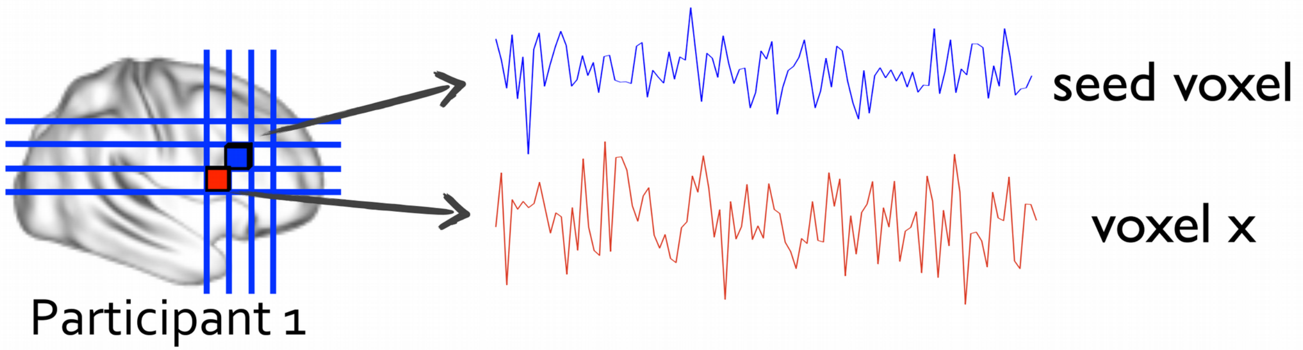




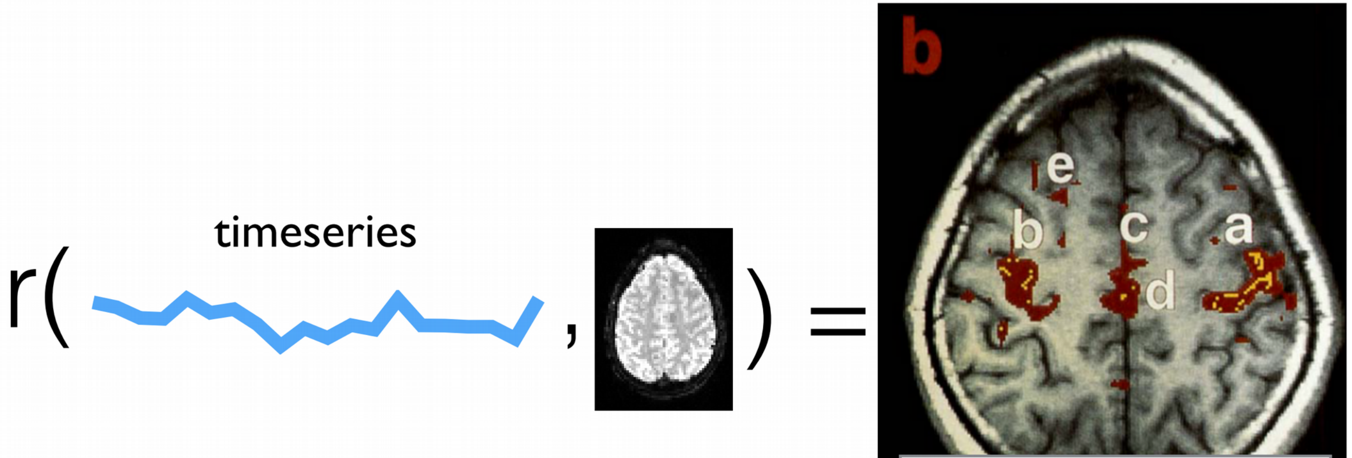
Bullmore and Sporns, 2009

Spatial maps: seed correlation

- One region: from atlas or maps to the rest of the brain
- How to: regression
    - take into account amplitude differences
    - enter seed time series as regressor in GLM.
- Group analysis:
    - 1 spatial map per subject
    - like a second level in activation study
- (!) Seed selection bias
    - Model sensitive to within subject artefact, secondary effect
    - Need to define a seed that mean the same across subjects



for xi... xn:
SBFC = r(seed voxel, voxelxi)



Correlation map from a resting state experiment

Biswal et al. (1995) MRM

Spatial maps: PCA

- PCA: Principal component analysis
- Creates a set of components which are linear combinations of the original data
- Components are orthogonal and uncorrelated = all of the covariance is explained

$$X = USV' \rightarrow X'X = (VS'U')(USV') = V(S'S)V'$$

X n scans
& p voxels

voxel x voxel
covariance

Eigen vectors
(contribution of
each voxel per
component ->
eigen image)

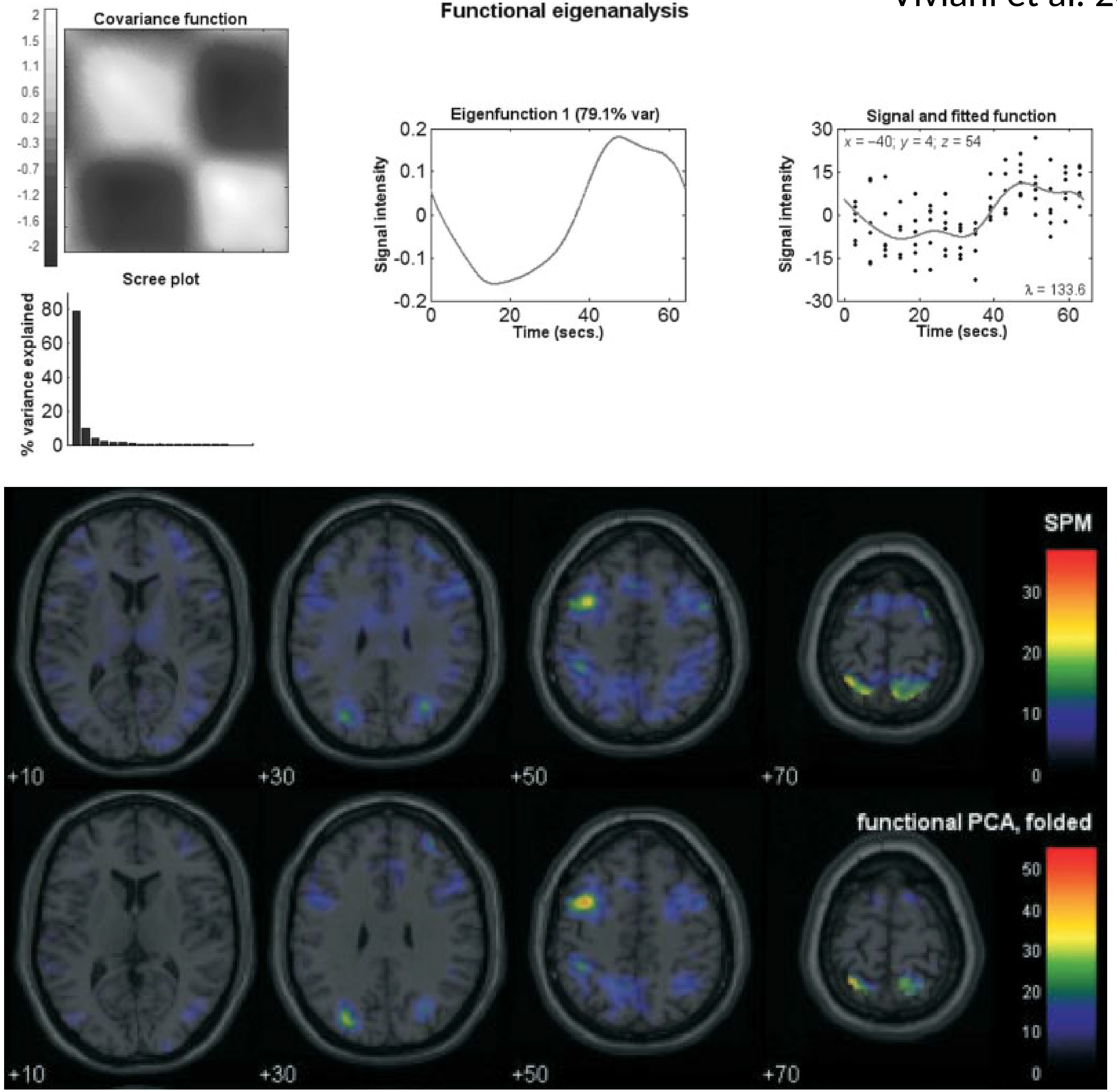
Singular values
→ diag(S'S) are the
eigen values =
proportion of variance
accounted for

Friston, 1993 JCBF, 13, 5-14

Spatial maps: PCA to FDA

- Can be improved using smooth function over voxels rather than raw data
- FDA: functional data analysis (Ramsay and Silverman, 1997)
  - to represent and transform the data in ways that aid further analysis,
  - to display the data so as to highlight various characteristics,
  - to study important sources of pattern and variation among the data, and
  - to explain variation in an outcome or dependent variable by using input or independent variable information.

Viviani et al. 2005

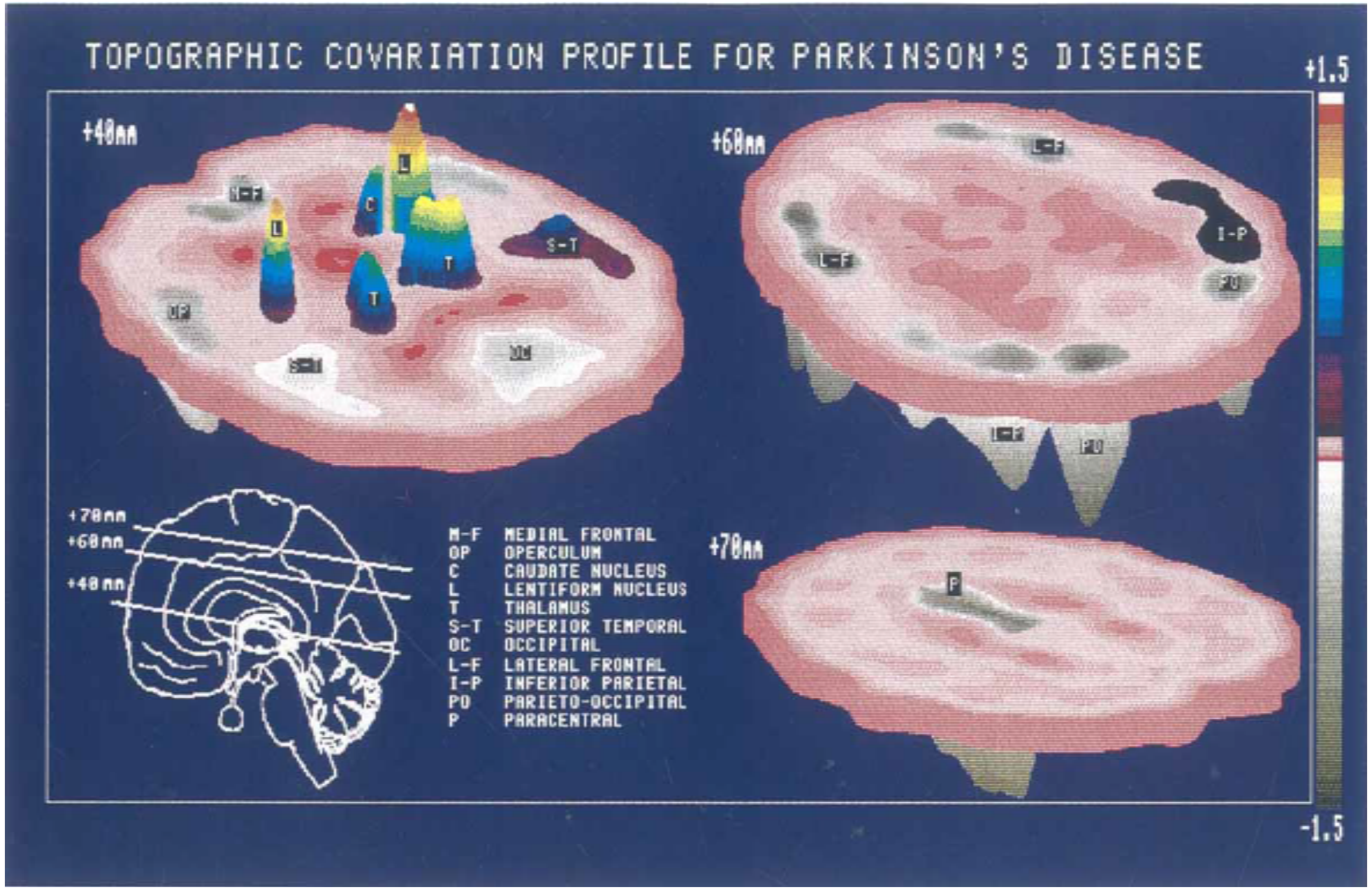


Spatial maps: SSM

- Scaled Subprofile Model (Alexender & Moller 1994)
- Like PCA but data are scaled to find group differences, i.e. Xnp
  - n subjects
  - p voxels
- PCA: X=X-mean(X,1)
  - center columns (subjects) ensuring comp. are uncorrelated across voxels
- SSM: X=(ln(X)-mean(ln(X),1))-mean(ln(X),2)
  - log transform, center columns and center rows

$X'X=V(S'S)V'$ ✉ V eigen images – group invariant

$XX'=U(SS')U'$ ✉ U = Subject Scaling Factor (weights)



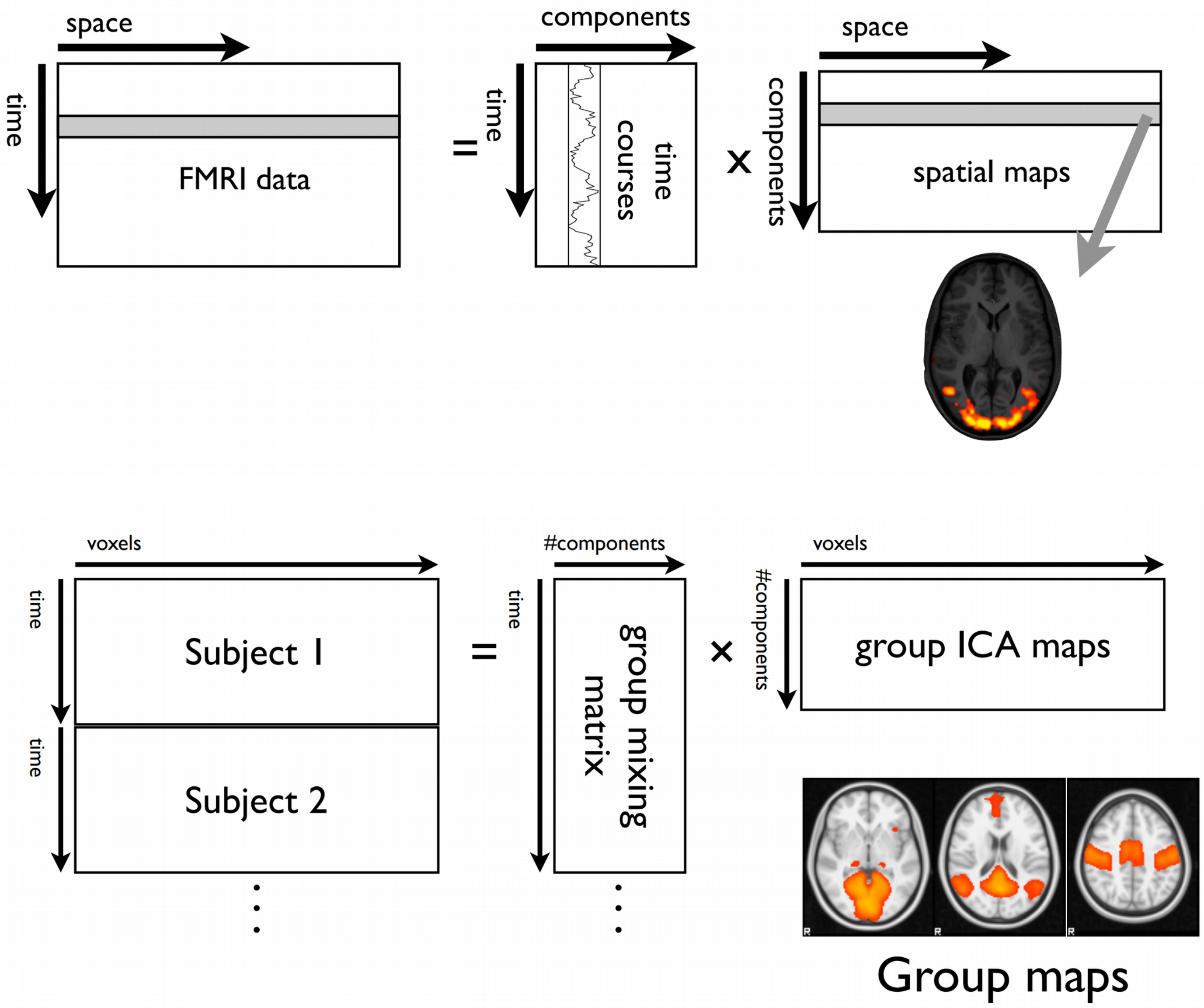
V ✉ find pattern of correlation between voxels

U ✉ find the relative weight of each subject (here show diff. in disease gp)

Spatial maps: ICA

- ICA: Independent component Analysis
- data driven multivariate analysis
- Algorithm converge to a set of independent basis that explain the data

- Can’t be done for each subject separately:
  - Small changes in data change the results,
  - correspondence problem between ICs
- Combining subject: concat-ICA or group ICA

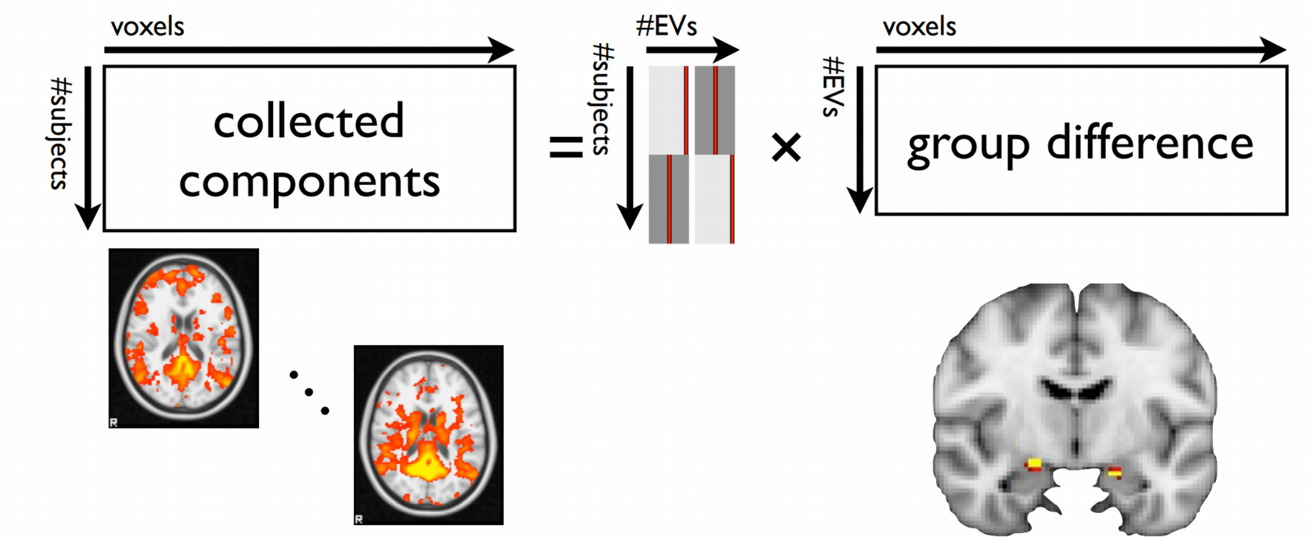


Cole et al. 2010

Spatial maps: analysis

- dual regression
  - regress spatial maps into each subject's 4D data to find subject-specific timecourses
  - regress these back into the 4D data to find subject specific spatial maps associated with the group maps

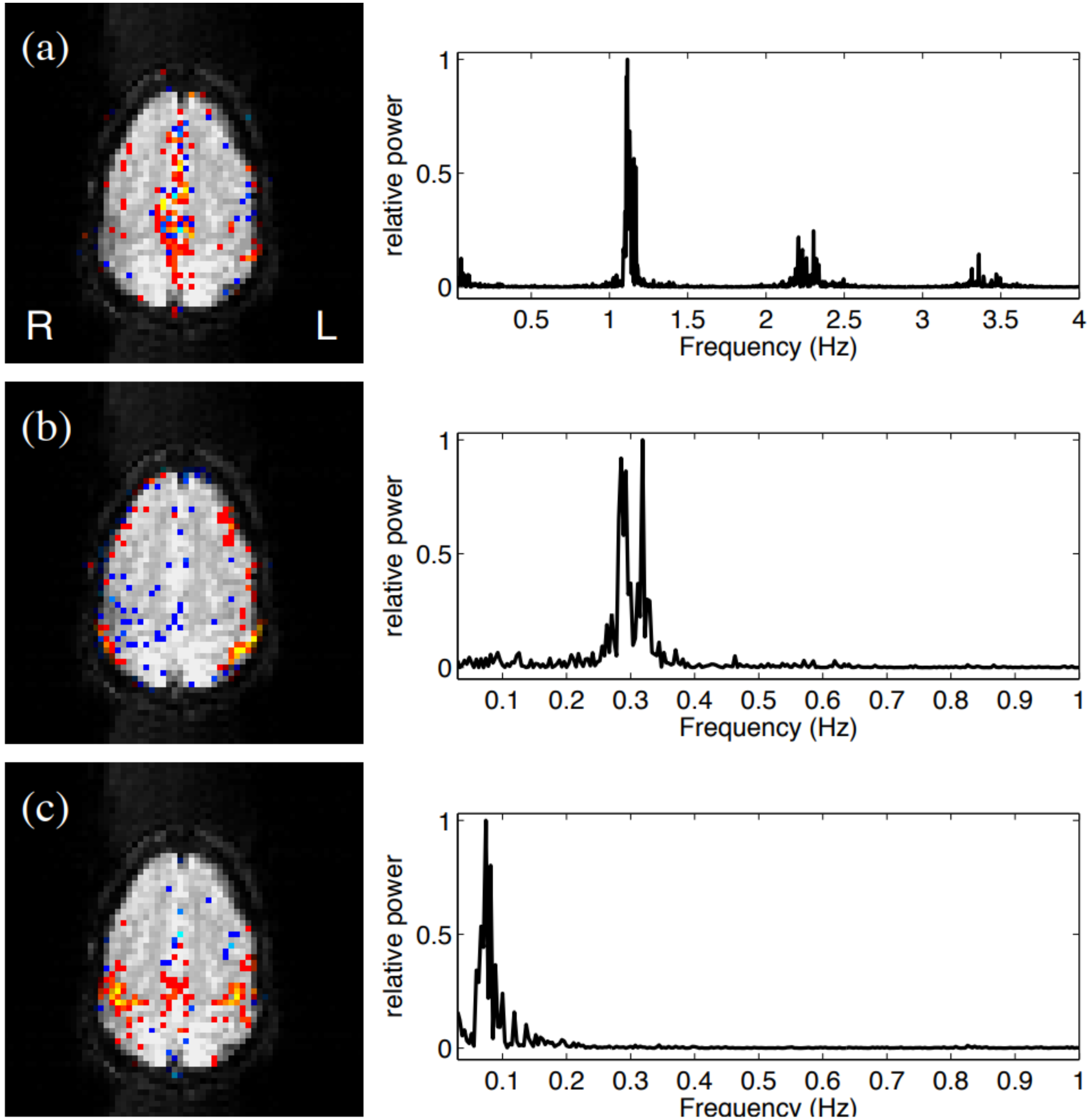
- to compare maps across participants
  - group differences at the voxel level
  - relationship with a continuous variable



Nickerson et al. 2017

Spatial maps: analysis

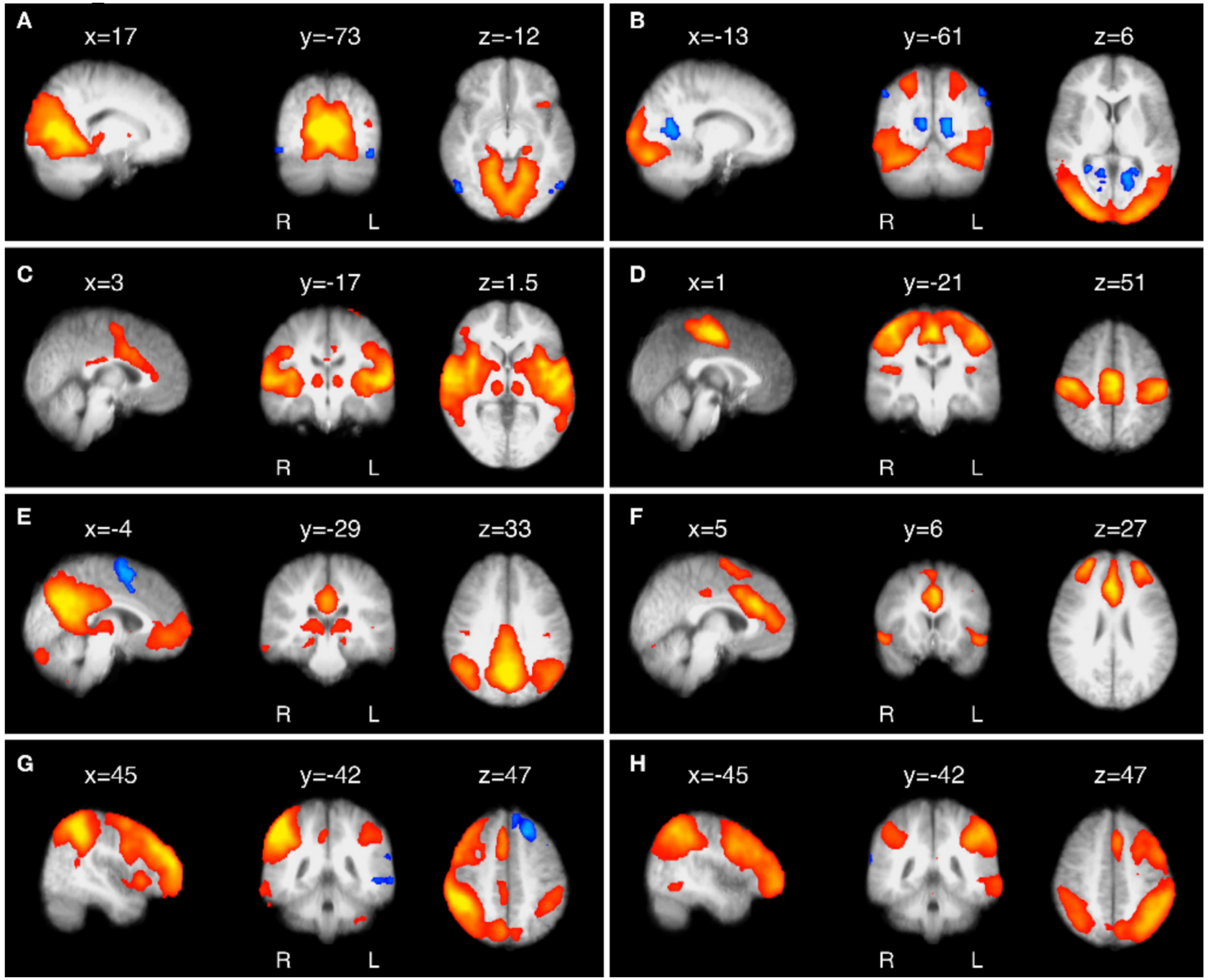
- Multiple maps:
  - regression in time
  - we can then look at their connectivity (second level)
- (!) extract relevant maps:
  - see frequency domain
  - E.g. noise component
  - E.g. visual



Beckmann et al., 2005

Resting state networks: functional architecture

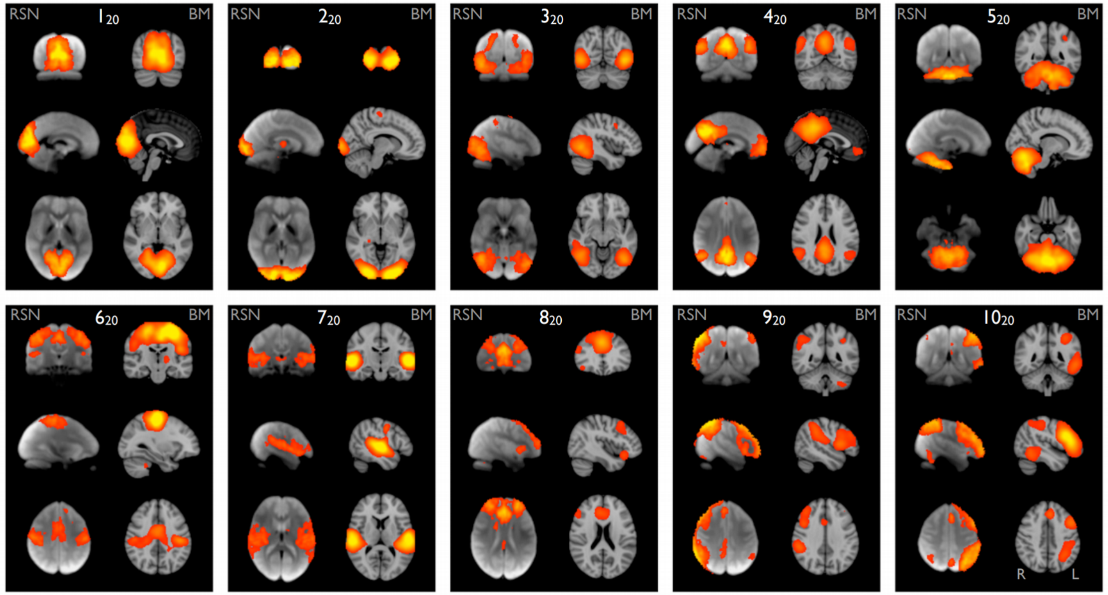
- From seed-based or from IC analyses, we obtain a set of spatial maps
- Resting state networks (RSN)
- Very consistently



Beckmann et al., Philos Trans R Soc Lond, B, Biol Sci 2005

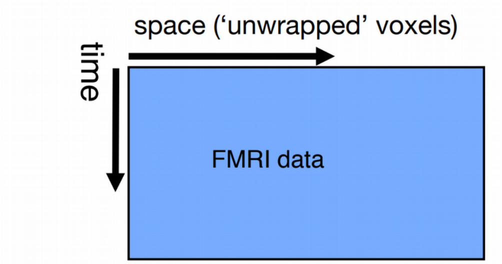
Resting state networks: functional architecture

- Correspondence of RSN with task meta-analysis (Smith et al., 2009)
- Pairings between RSN maps and BrainMap maps at ICA dimensionality of 20
- Mapping the 10 paired maps back onto BrainMap “Behavioural Domains”

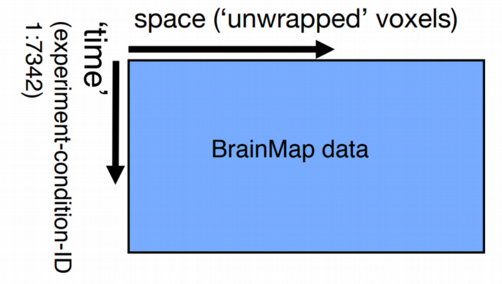


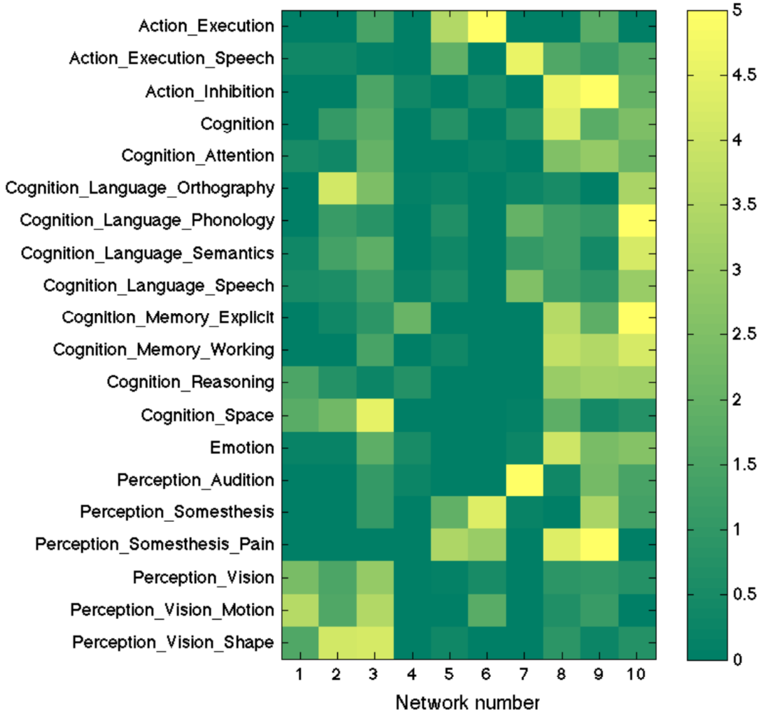
Smith et al., 2009

Resting FMRI data



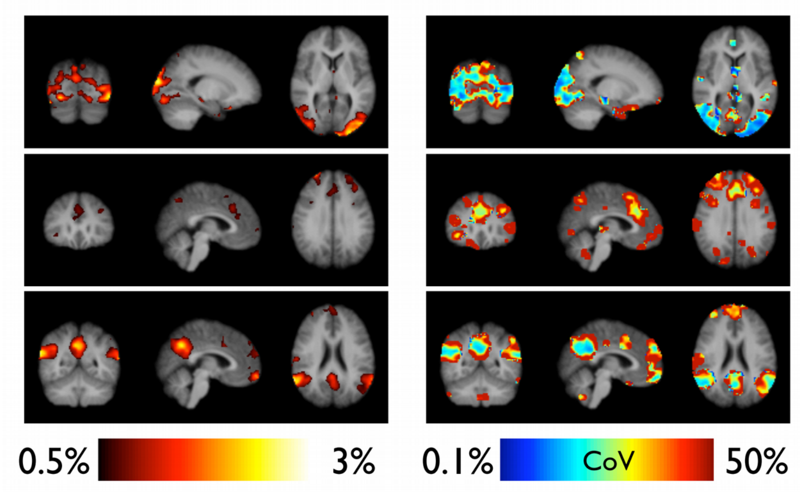
BrainMap, RIC, San Antonio



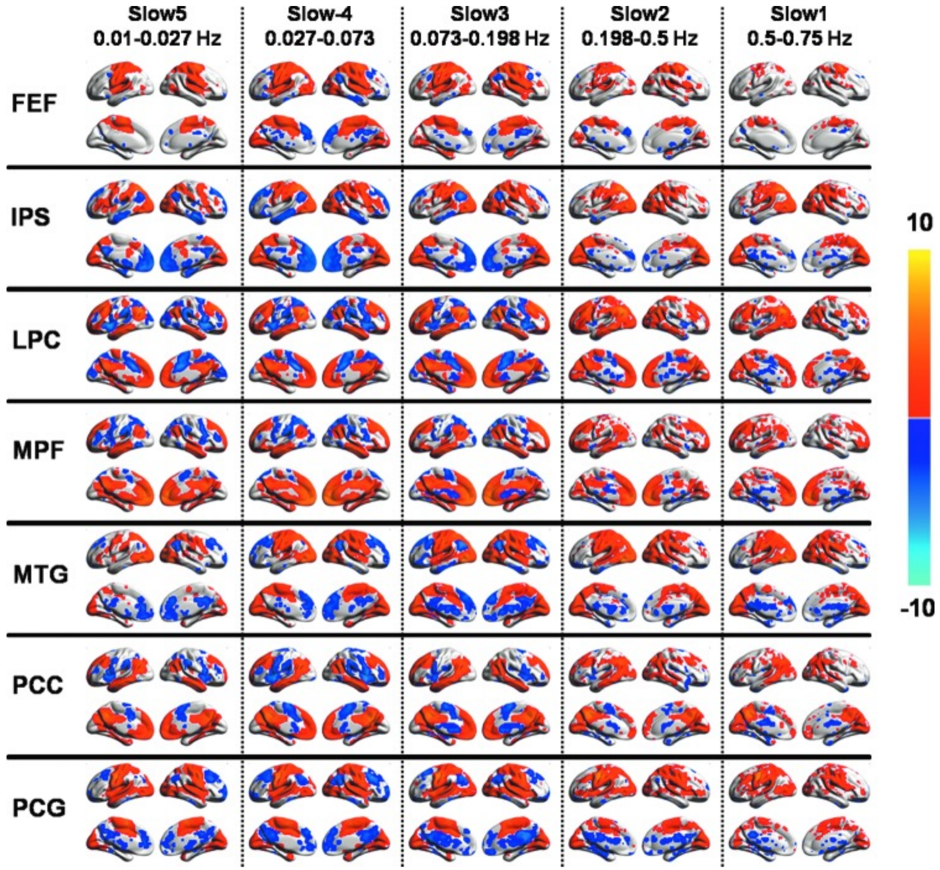


Resting state networks: consistency

- In healthy subjects (Damoiseaux et al., PNAS 2006)
  - Coefficient of variation across participants
- Different frequency (Gohel et al., Brain connect 2015)
  - **Seed based**
  - IC
  - (!) thresholded maps



Damoiseaux et al., 2006

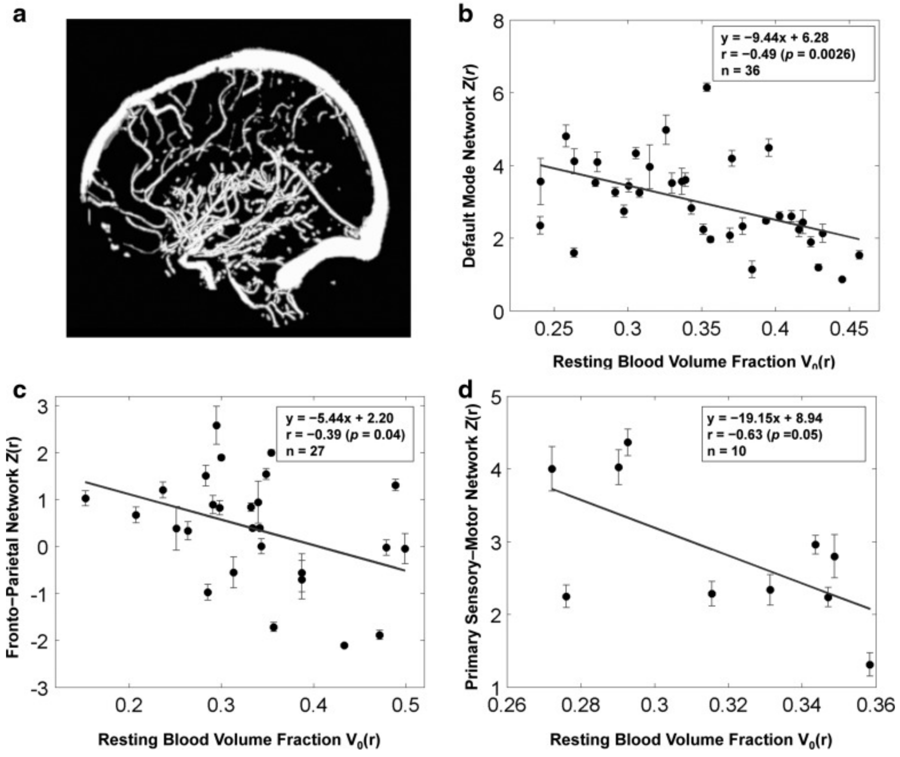


Gohel et al., 2015

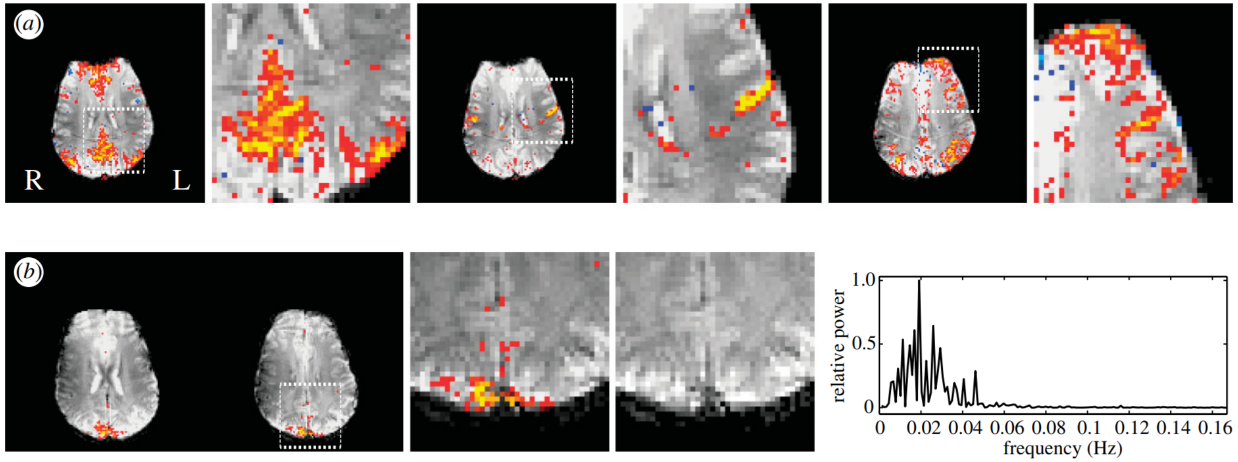
Resting state networks: underlying biology

- Could it be linked to some vascular organization ?

- Strong coupling within RSN with blood flow
- Inform on consumption (Tak 2015)
- IC maps of RSN are located in grey matter (a) and differ from IC maps of blood vessel networks capturing large vessels and surrounding tissue (Backmann 2005)



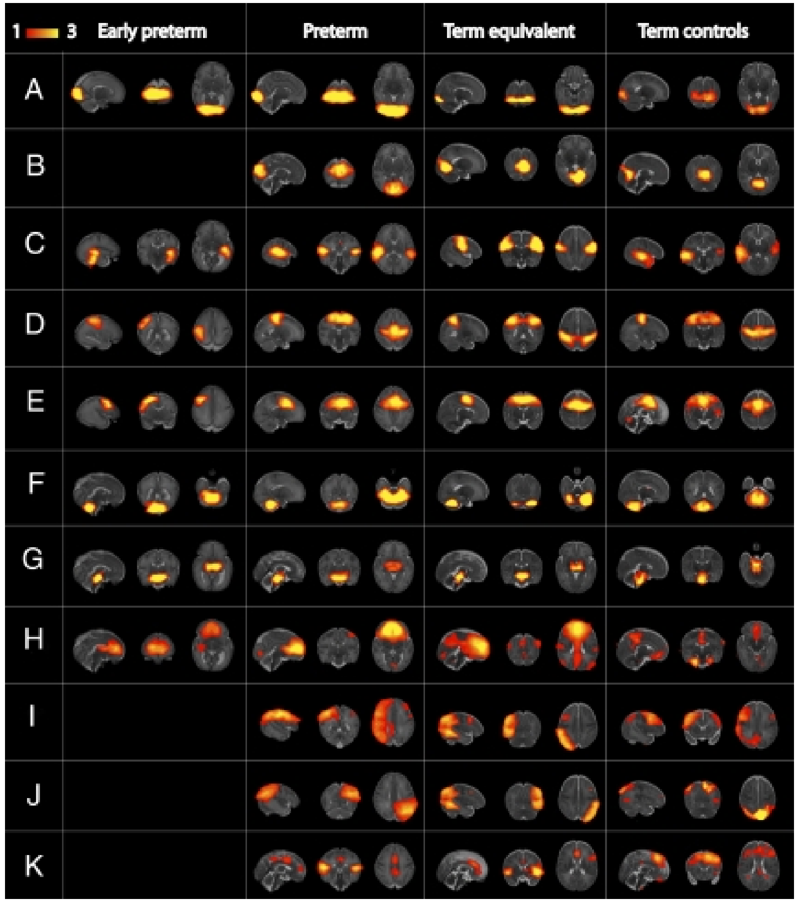
Tak et al, 2015

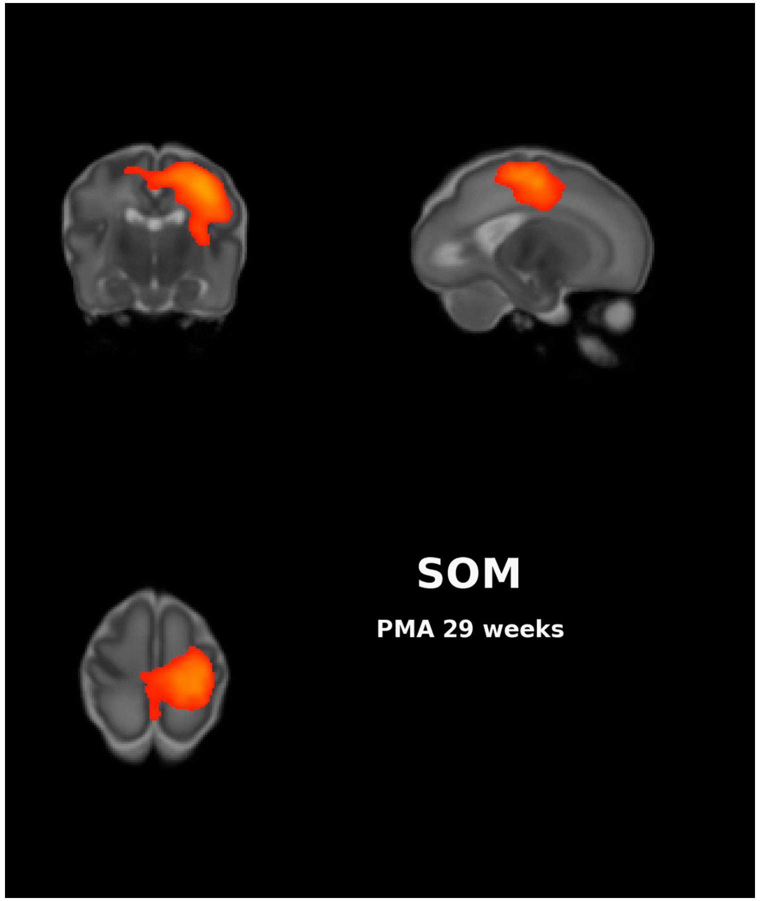


Beckmann et al, 2005

Resting state networks: underlying biology

- Could it be due to developmental constrains ?
- Neurons migrating according to gradient
- They can be detected early on (during gestation, Doria et al., 2010)
- They develop with age



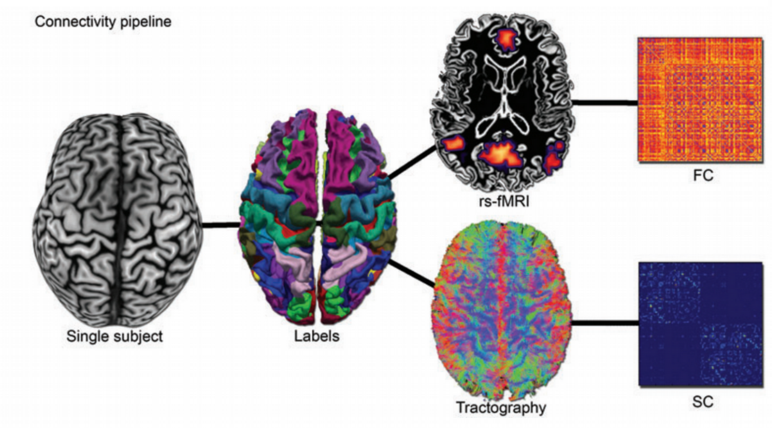


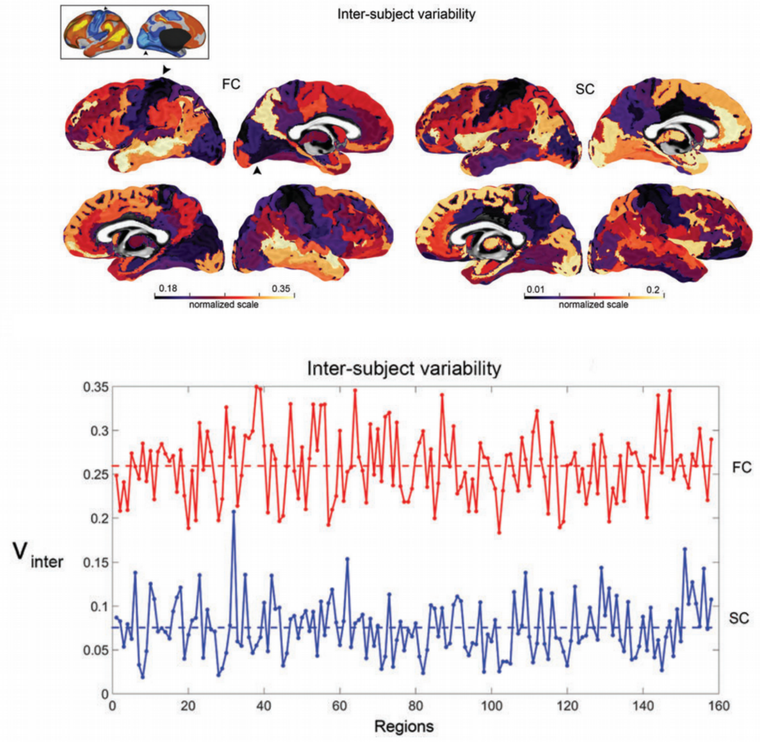
Doria et al., 2010

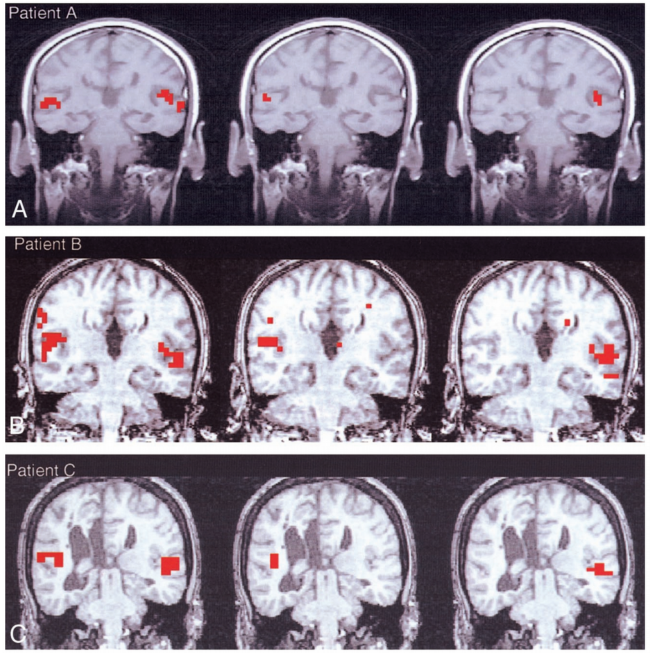
Resting state networks: underlying biology

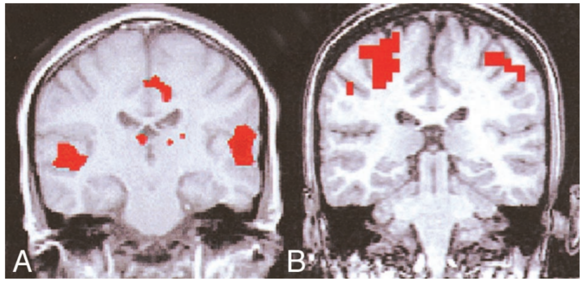
- Could they be emerging from the white matter tracts (structural connectivity)?
- Obviously a link
  - Quigley 2003 - auditory localization task: no auditory damage, seed correlation: lost lateral synchrony
  - Damage corpus callosum interrupt the FC of R/L auditory areas
- But not all can be explained:
  - Chamberland 2017: Weak relationship between FC and SC intersubject variability
  - (!) DTI only captures myelinated fibers, fail with crossing fibers

Chamberland et al, 2017





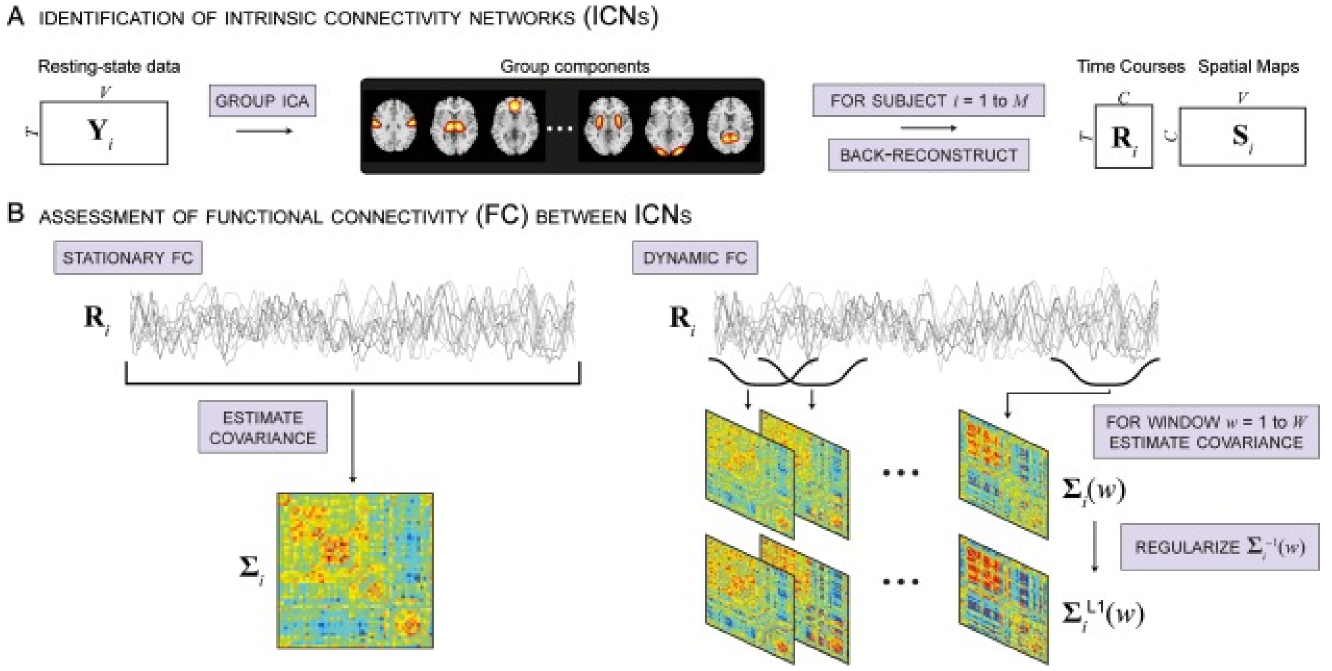




Quigley et al, 2003

Static versus Dynamic connectivity

- Why would the connectivity be static ?
- We can estimate dynamic connectivity by
  - time windows, sliding window
  - instantaneous correlation, MTD
- Apply smoothing



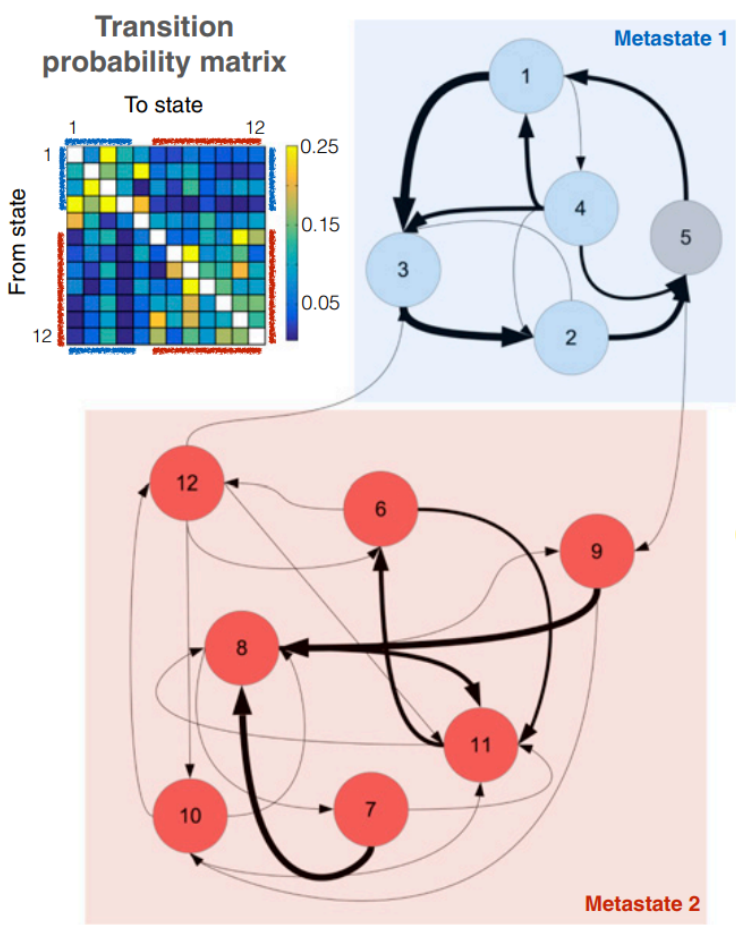
Allen et al., 2014

$$MTD_{ijt} = \frac{(dt_{it} \times dt_{jt})}{(\sigma_i \times \sigma_j)}$$

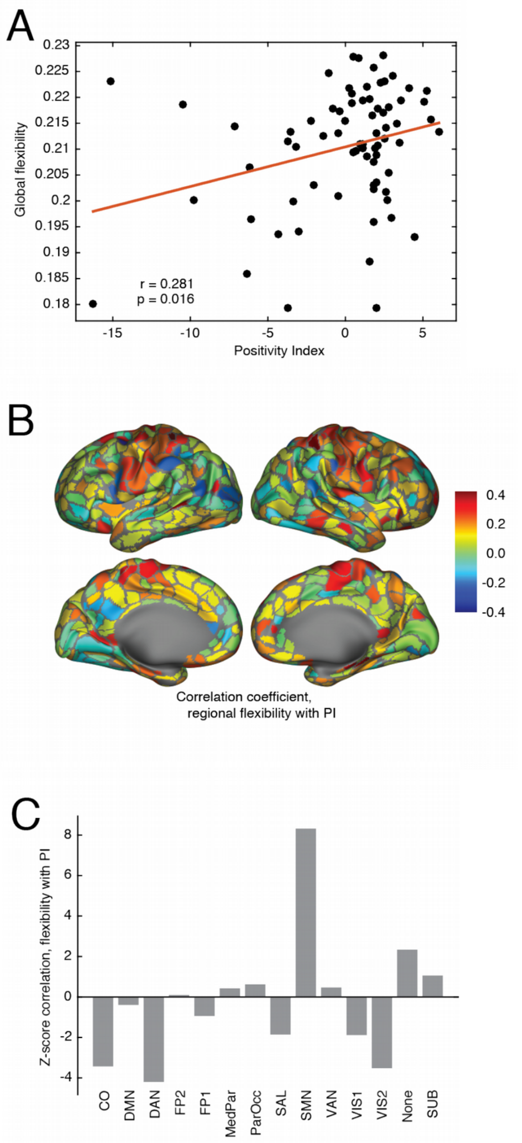
Shine et al., 2015

Static versus Dynamic connectivity

- Remember the power problem in estimating connectivity?
- These connectivity maps cannot by taken as ground truth.
- They are used to investigate:
  - emergent patterns, states using clustering or deep learning (e.g. Vidaurre)
  - rate of change / flexibility of the connectivity (e.g. relationship with mindset, Betzel)



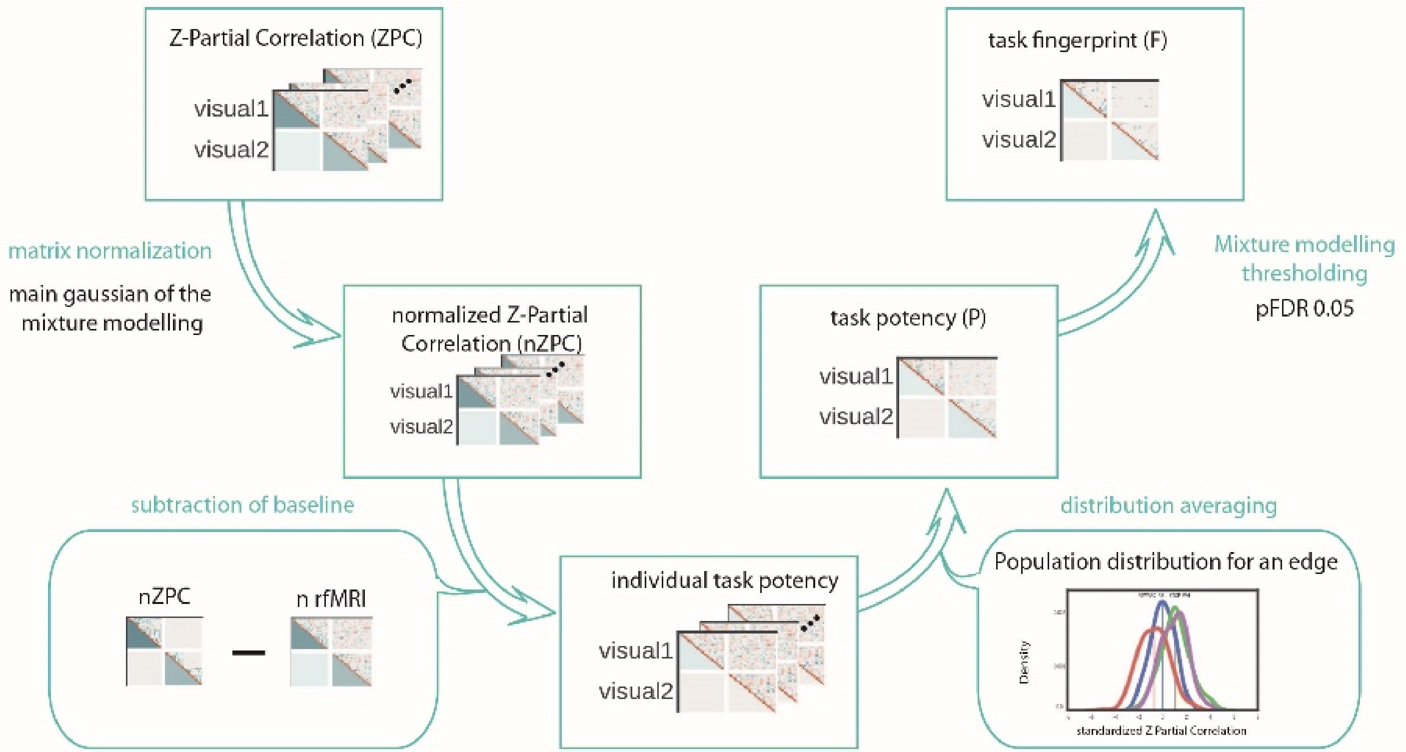
Vidaurre et al., 2017



Betzel et al., 2016

Flexibility between states: from a baseline functional network architecture to a task state

- Modulations away from this architecture to perform a task
  - cognitive processing building on top of the ongoing baseline connectivity
- Task potency
  - removing subject specific baseline
  - control for some individual differences
- How to:
  - a rest and a task for each subject,
  - same preprocessing,
  - normalization

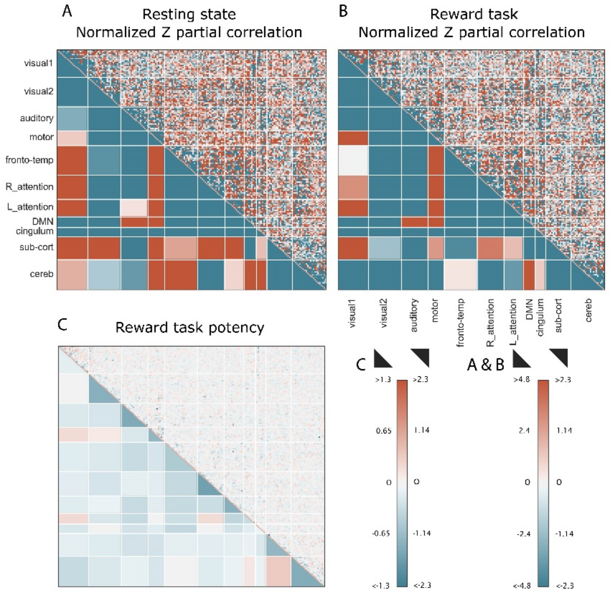


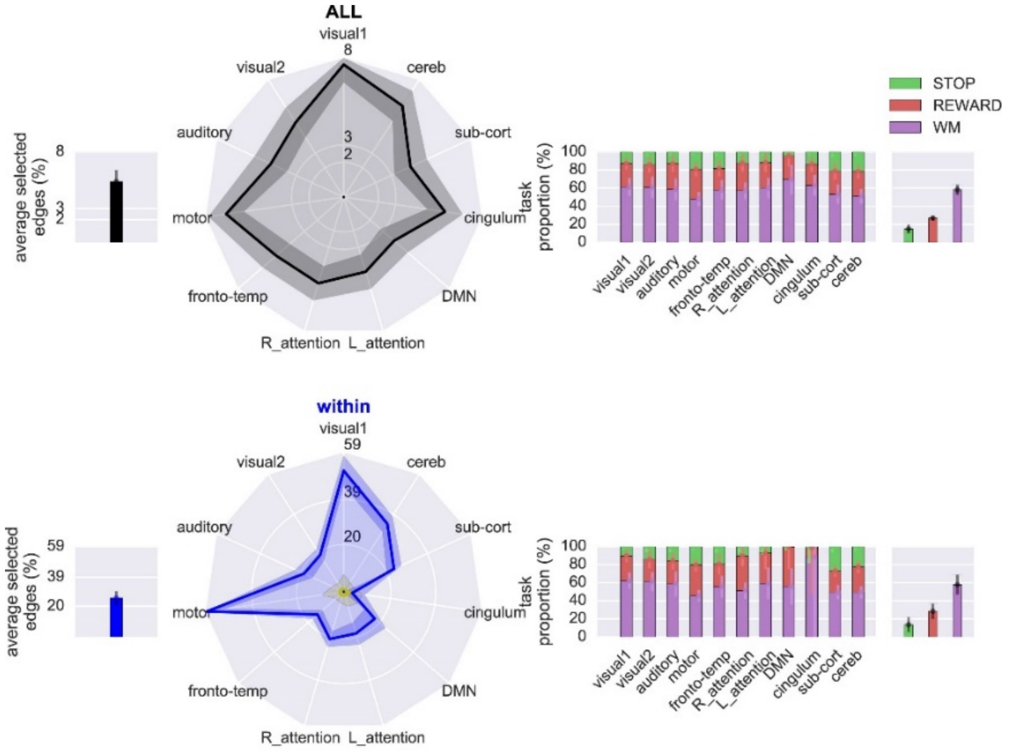
Chauvin et al. 2018

Flexibility between states: from a baseline functional network architecture to a task state

- Analysis :
  - Thresholding: task fingerprint
  - Comparison across tasks

- We learn that within RSN modulation is greater than between RSN
- RSNs are the core of cognitive processing

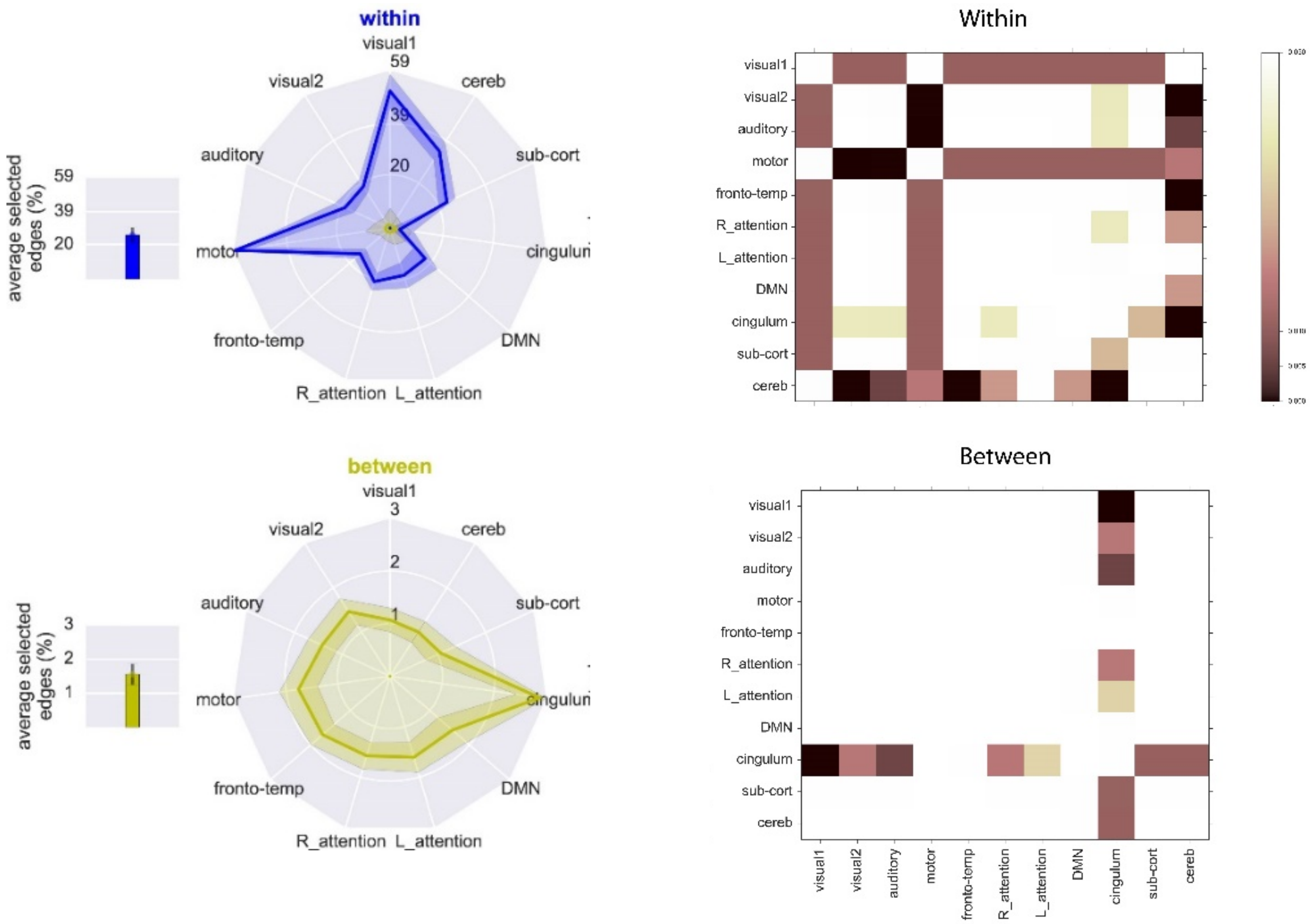




Chauvin et al. 2018

Flexibility between states: from a baseline functional network architecture to a task state

- Motor and visual networks show more within network modulation: greater segregation across tasks
- Cingulum networks show less within network and more between networks modulations: active role in integration of information during task



Take home message

- Functional architecture
  - Resting state networks
  - Integrating rest and task analysis is key to understand the brain networks activity
- Multiple ways of studying the RS FC
  - Based on extracting information from time series of brain area
  - Multiple metrics that depend on your question
  - Leading to multiple possible analysis
- Multiple bias possible
  - Don’t underestimate the value of preprocessing