

Functional connectivity in fMRI

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Studying networks

- fMRI can be used for studying both, *functional segregation* and *functional integration*.
- Functional localization corresponds to localize in the brain a function. This was the approach advocated by the phrenologists and long discarded.
- ‘Traditional’ mass-univariate fMRI analyses allow investigating functional segregation, that is the specialization of brain regions for some aspect(s) of a function.

Studying networks

- fMRI can be used for studying both, *functional segregation* and *functional integration*
 - Functional integration is the study of connected processes.
 - Methods for functional integration can be broadly divided into functional connectivity (~ finding statistical patterns) and effective connectivity (~ model how regions interacts).

Definitions

- Connectivity analyses refer to methods aiming at identifying and quantifying inter-regional relationships (Friston, 1994, HBM, 20, 56-78).
- Functional connectivity is defined as the statistical association or dependency among two or more anatomically distinct time-series (Friston 1994, HBM 20, 56-78 & Friston et al., 1996, Cereb Cortex, 60 156-164). Measures of FC are agnostic regarding causality or direction of connections.

Functional Connectivity: what for?

- In FC analyses, there is no inference about coupling between regions; that is it does not tell *how* regions are coupled! Because it only test some form of correlation against the null hypothesis.
- FC is however useful to discover patterns (*which* regions are coupled), and compare patterns, especially between groups (e.g. define endophenotypes).

Functional vs. Effective Connectivity

- Showing that correlations between 2 regions differ between conditions means that the neural activity differed between conditions but the underlying coupling can still be the same: (i) it could relate to changes in coupling via a 3rd area (ii) could reflect changes in the noise (iii) could reflect changes in the amplitude of fluctuations.
- If one wants to examine how 1 region influences another, one needs (most of times) experimental changes studied via EC (PPI or DCM) methods.

Suitable designs for FC

- FC from resting-state assume stationarity of time-series (no change in the probability of signal properties over time)
- FC from event-related design is most often based on trials (no stationarity required)
- FC from block designs may be considered locally stationary, most often based in the block durations.
- http://en.wikipedia.org/wiki/Stationary_process
- The joint probability distribution does not change when shifted in time or space. Consequently, parameters such as the mean and variance, if they exist, also do not change over time or position.

Methods

- Connectivity can be based on occasions (time-series, trials, blocks) or on variables (voxels, ROI).
 - FC on occasions rely on statistical dependencies between time-series (e.g. time-series correlations).
 - FC on variables attempt to cluster voxels or regions based on the latent time-series (e.g. ICA).

FC between regions

i.e. how time-series between
regions are correlated

Dependencies of time-series

- *Correlations and cross-correlation* of time series
([Biswal et al., 1995, Mag Res Med., 34, 537-541](#))
- *Cross-coherence*
([Sun et al., 2004, NeuroImage, 21, 647-658](#))
- *Mutual information*
([Jeong et al., 2001, Clin Neurophysiol, 112, 827-835](#))
- *Canonical correlation*
([Worsley et al., 2005, IEEE international joint conference on neural networks, 3 1534-1541](#))

Resting state analysis

- **Cross correlation** between regions 1 and 2 with a time delay t (of course region 1 and 2 can be voxels, and then iteratively correlate every-voxels to each other)
- $r(t) = \text{cov}(s1, s2+t) / \text{sqrt}(\text{var}(s1) + \text{var}(s2+t))$
- Often cross-correlations are subtended by low frequency oscillations (less than 0.1Hz)

Resting state analysis

- **Cross coherence** between regions 1 and 2
- Equivalent to cross-correlation but in the frequency domain (thus account for any time delay)
- $$Coh(f) = \frac{abs(Cross-spectral\ density)^2}{(spectral\ density(s1(f)) * spectral\ density(s2(f)))}$$
- Coh(f) varies between 0 and 1 and is defined for different frequency bands f

Resting state analysis

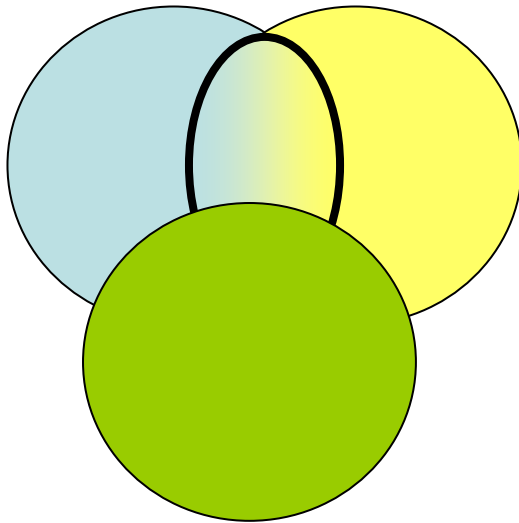
- **Mutual information** between regions 1 and 2
- Allows to measure non linear relationships, in the time or frequency domains

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

- The shared information relates to the joint probability distribution of s1 (x) and s2 (y)

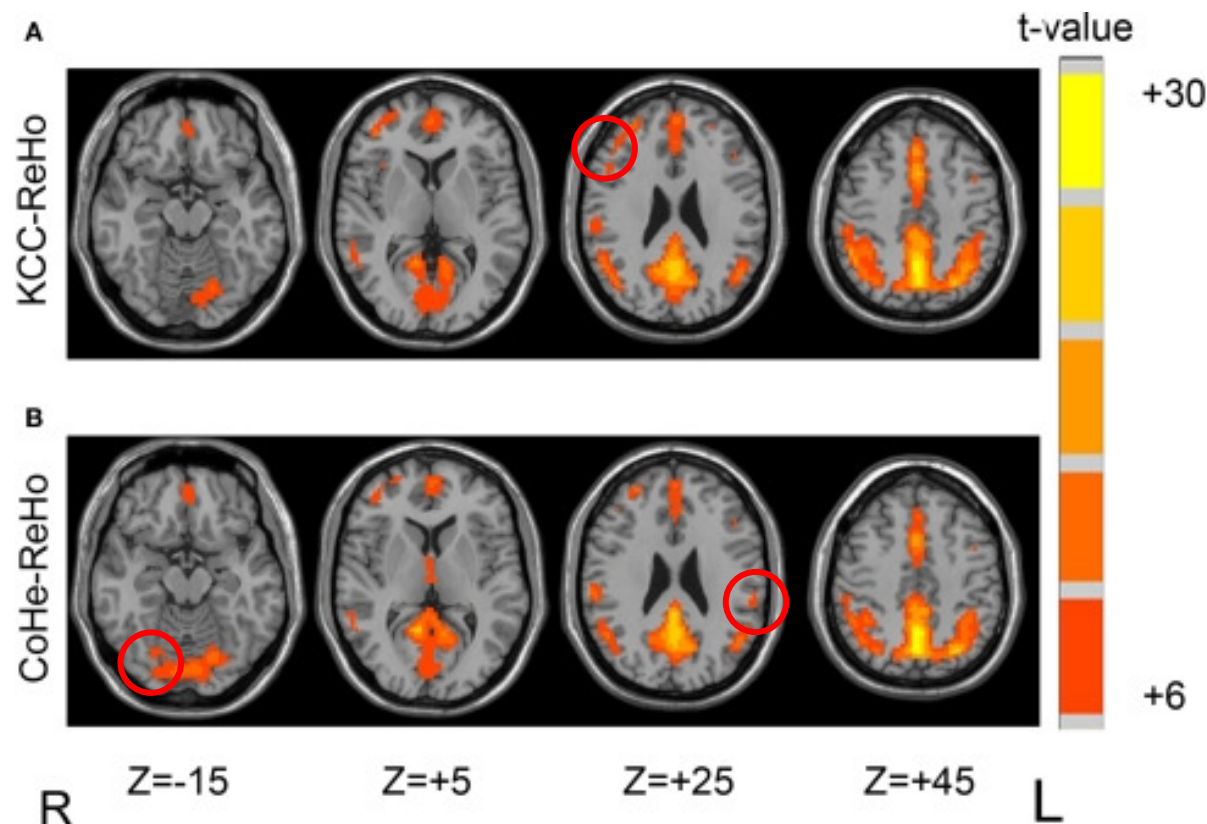
Resting state analysis

- **Partial analyses**
- Compute the dependencies between s_1 and s_2 accounting for s_3 (conditional dependence)



Which method to choose?

- Probably good idea to try them all, will inform on the type of relationship

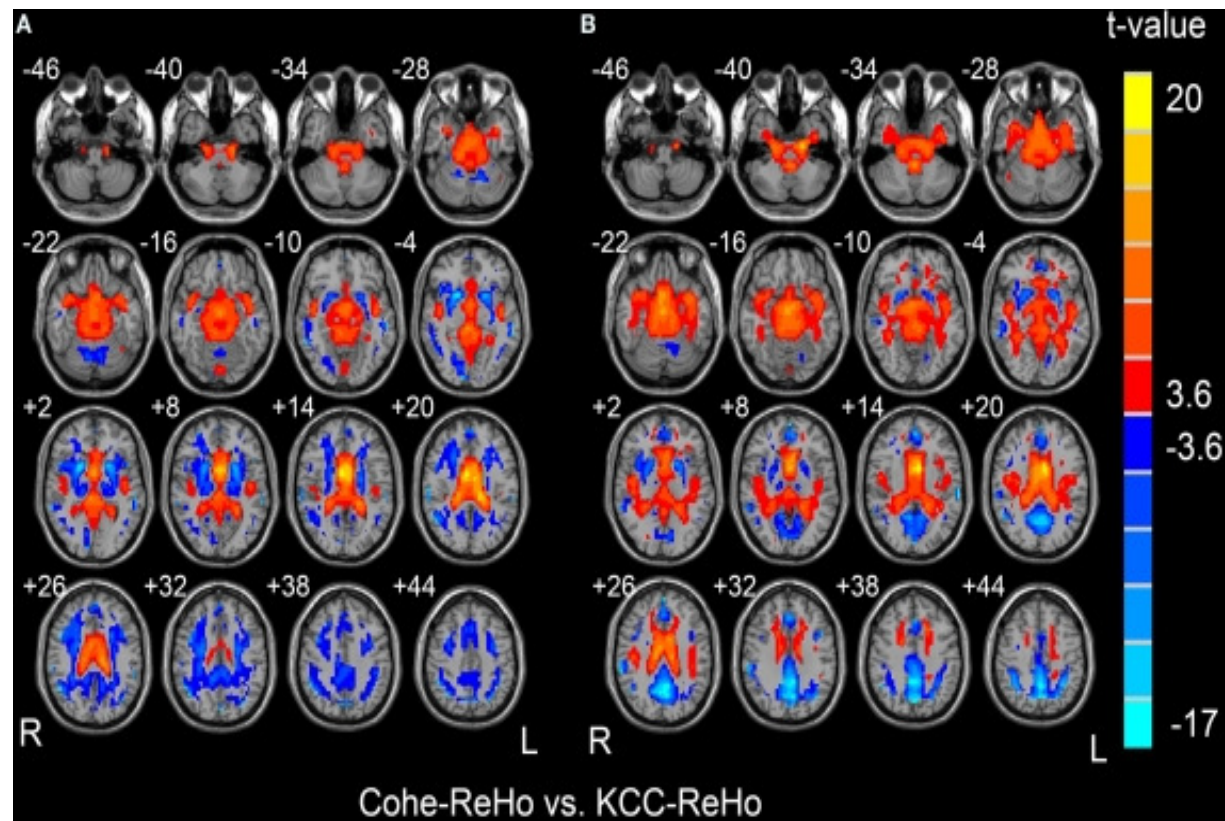


[Liu et al. 2010 Front Syst Neurosc 4, 24.](#)

One-sample *t*-test results of Kendall's coefficient of concordance and Coherence showed that major regions of DMN had higher KCC-ReHo (A) and CoHe-ReHo (B) than the global mean

Which method to choose?

- Probably good idea to try them all, will inform on the type of relationship



[Liu et al. 2010 Front Syst Neurosc 4, 24.](#)

Paired t-test showed differences in various areas

Event related designs

- **Partial cross-correlation, cross-coherence and MI**
- Usually, the stimulus waveform across condition is entered as covariate to (linearly) remove associations due to the stimulation. This can be the modelled waveform or inputs from other ROI.
- Partial analyses make more sense because the correlations are high/low due to the presence/absence of stimulus evoked responses.

Resting and event related designs

- **Seed based analysis**: regress (i.e. linearly correlate) the time-course of one voxel or ROI over the whole brain.
- For event related design, this can be performed on residuals, i.e. 1st fit a model with the stimulus time course (usually \otimes hrf and derivatives) and other confounds (e.g. motion) to obtain residuals and 2nd fit a model with the ROI residual time course on all residuals (allows to account for spurious correlations due to the stimulus evoked response)

Resting and event related designs

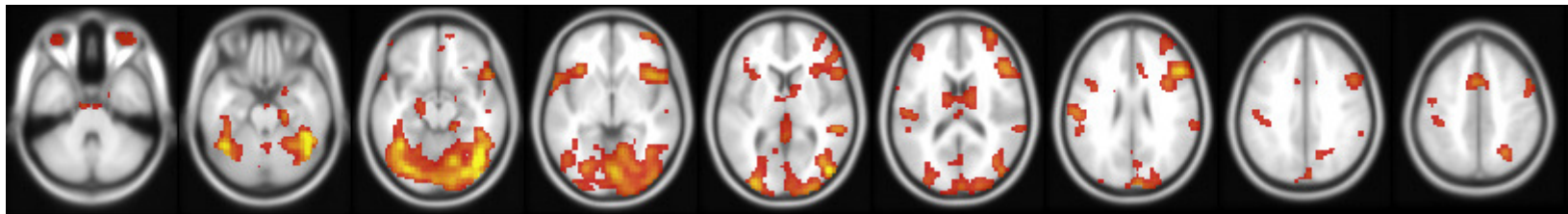
- **Seed based analysis:**
- Extract time-course (eigenvariate button for instance or any data extraction tool like e.g. EasyROI)
- Set-up a model with this time course as regressor (+ other confounds if one raw data)

Note: generate residuals when fitting the model: set defaults.stats.maxres to Inf (spm_defaults – also impacts smoothness estimation) and comment lines 940 to 943 in spm_spm (i.e. do not delete residuals).

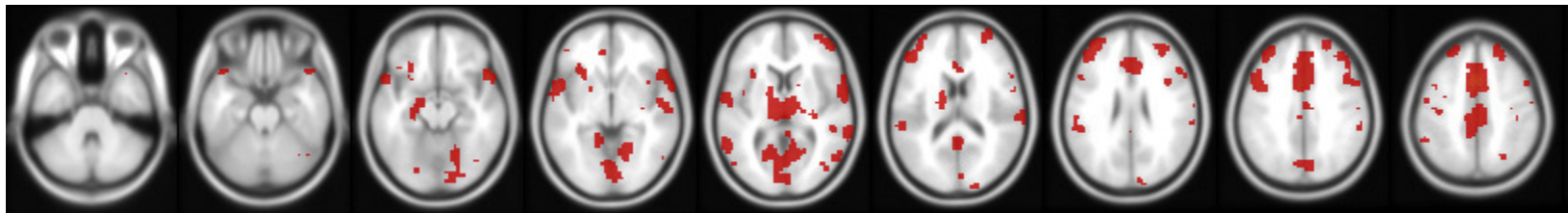
Example from the Single Subject data set

- N1/N2/F1/F2

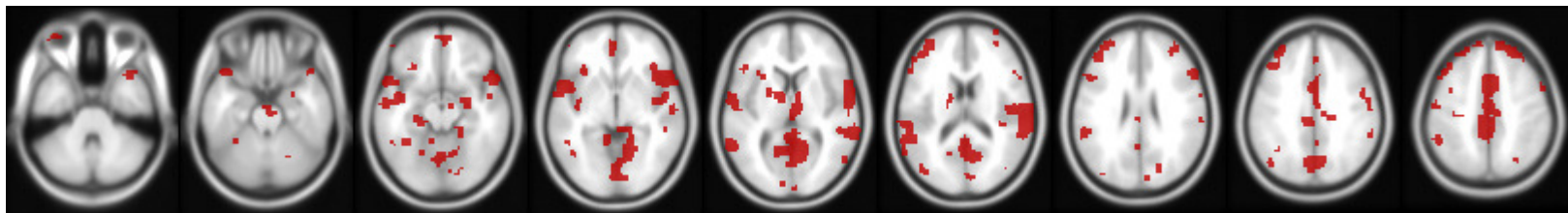
Activations



Seed from ACC on Raw data (+ filters & motion)

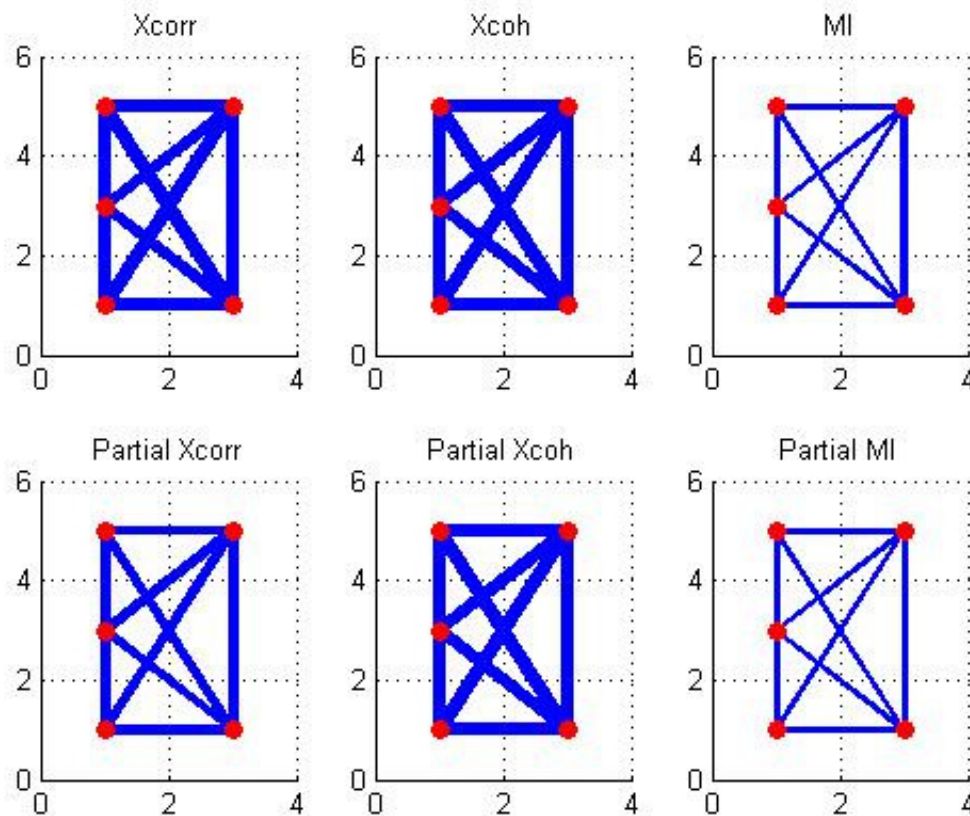


Seed from ACC on residuals data



Example from the Single Subject data set

- Analysis of time series ACC / Insulae / Fusiform



Strong links ACC / Insulae
= seed based

Also shows link ACC /
Fus and Insulae / Fus
→ $r=.9$ on raw data and
 $r=.7$ and $.8$ removing hrf,
both as 0 order
→ $r=.9$ using coherence
but at very low frequency
(which is removed by
filters in my seed based
analysis)

Event related designs

- ***Beta-series correlation analysis***

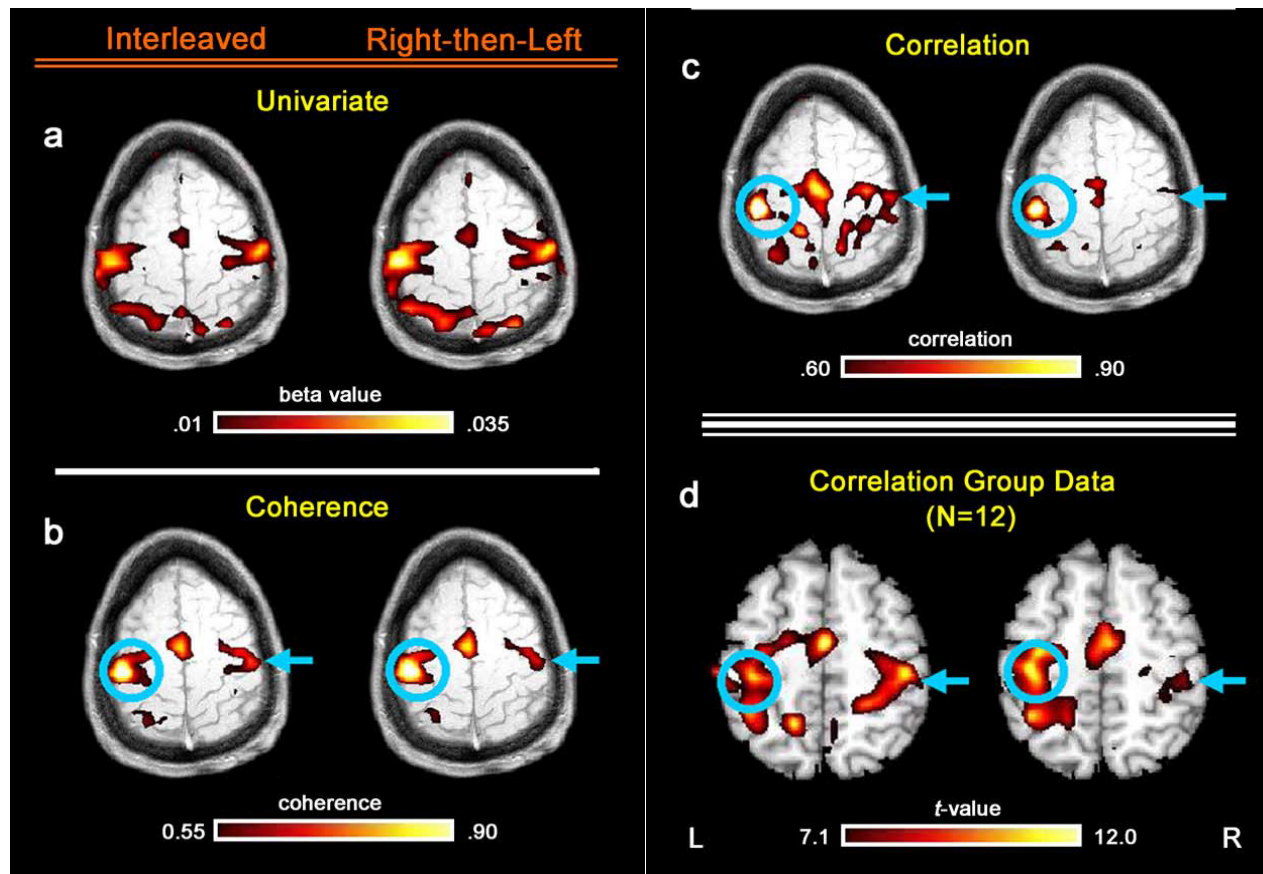
[\(Rissman et al., 2004 NeuroImage 23, 752-763\)](#)

- Fit a model with as many regressors as trials to obtain trial-to-trial variations and assess to correlations between ROIs within subject and then across subjects.
- Only works for slow-event related designs

Event related designs

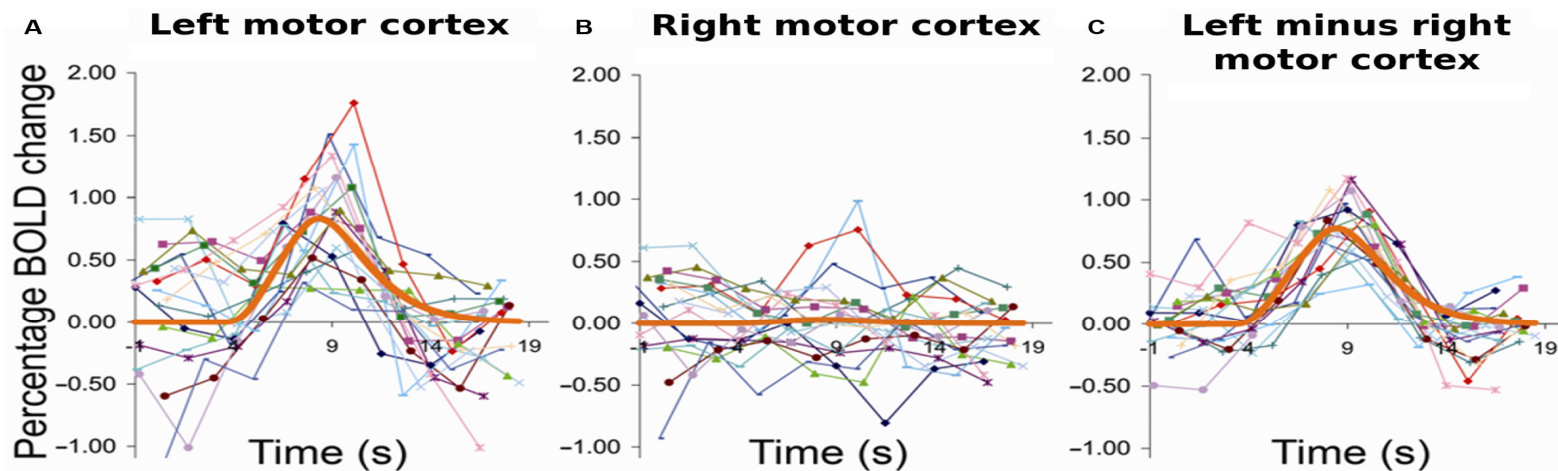
- **Beta-series correlation analysis**

(Rissman et al., 2004 NeuroImage 23, 752-763)



Event related designs

- **Peak correlation**
- Based on an estimate of the peak values of the BOLD responses in regions s1 and s2 for each trial
 - relates to trial to trial variance



Sadaghiani et al. 2010 *Front. Syst. Neurosci.* 4:20

http://www.frontiersin.org/systems_neuroscience/10.3389/fnsys.2010.00020/full

Event related designs

- **Functional canonical correlation:** relate the multivariate pattern of activation of p ROI to the experimental design (general method – special cases are Canonical Variate Analysis, Linear Discriminant Analysis, MANCOVA)

$$(X'X)^{-1/2} X'Y (Y'Y)^{-1/2} = USV'$$

Covariance in X
X with p ROI

Covariance in Y
Y with q conditions

Covariance between X and Y

Covariance(XY) adjusted for within covariance

Singular Value Decomposition

U p patterns of neural activity
V q classes / groups for U
S q*q corr between X and Y
= mode of correlation between ROI

Quick look at PPI

- **Seed based analysis**: regress (i.e. linearly correlate) the time-course of one voxel or ROI *experimental design, over the whole brain.
- Look for changes in the correlation between brain regions under experimental change = PsychoPhysiological Interaction
- PPI reflects the physiological effect of a ROI processing stimuli on other regions, it is an index of Effective Connectivity

Quick look at PPI

- **Functional connectivity:**

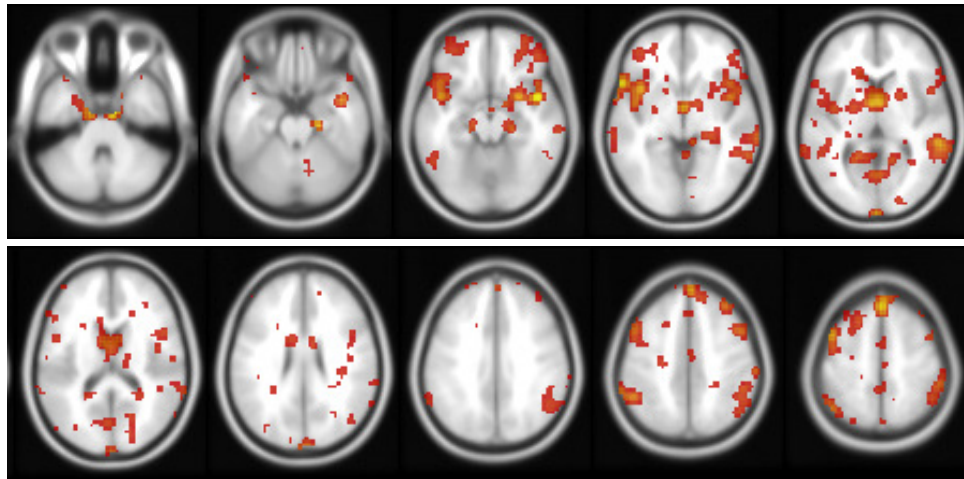
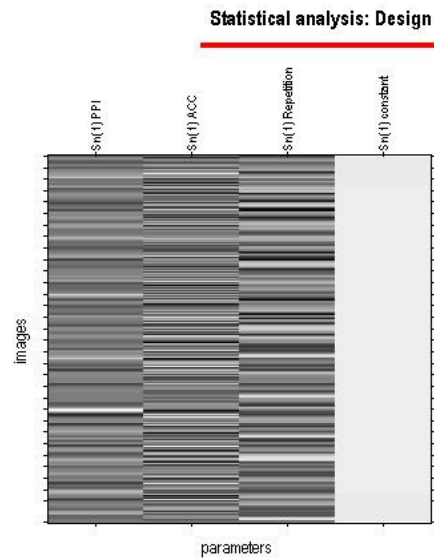
(1) $Y = X\beta_1 + \varepsilon$ (GLM with X the stimulus onsets + confounds) and (2) $e = R\beta_2 + \varepsilon$ (GLM with ROI residual time course)

- **Effective connectivity:**

$$Y = X\beta_1 + R\beta_2 + XR\beta_3 + \varepsilon$$

GLM with X, R and XR (interaction) but high correlations can make the model unstable – better assessed using semi-partial coef.

PPI testing if ACC modulates other regions based on repetition



Note how different this is from seed analysis

- If I wanted to look at repetition non-famous and repetition famous, I would need 2 PPI regressors
→ gPPI a toolbox by Donald McLaren

FC between time-series

i.e. how voxels/ROI are clustered
based on their time-series

Principal component analysis

- **Voxel-wise PCA** ([Friston, 1993 JCBF, 13, 5-14](#))
- 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

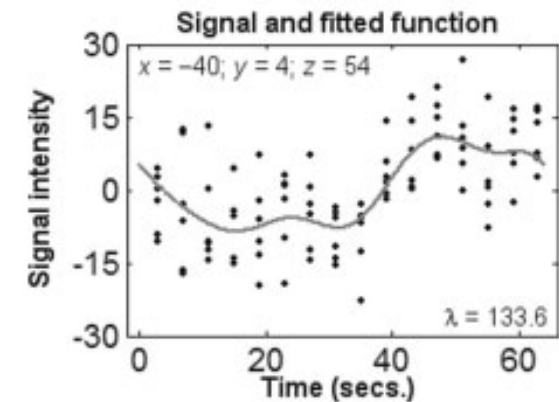
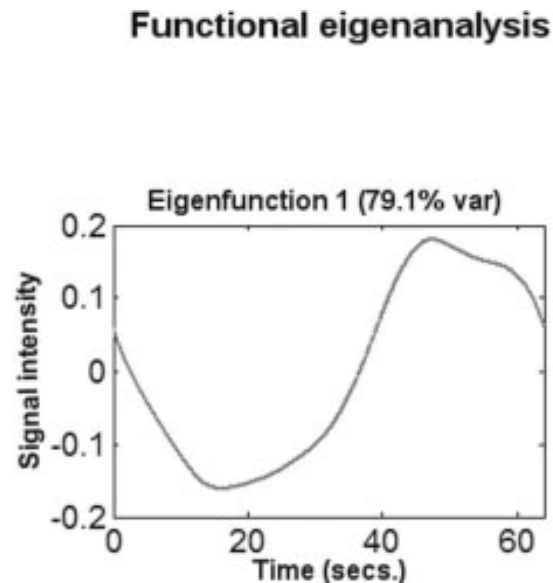
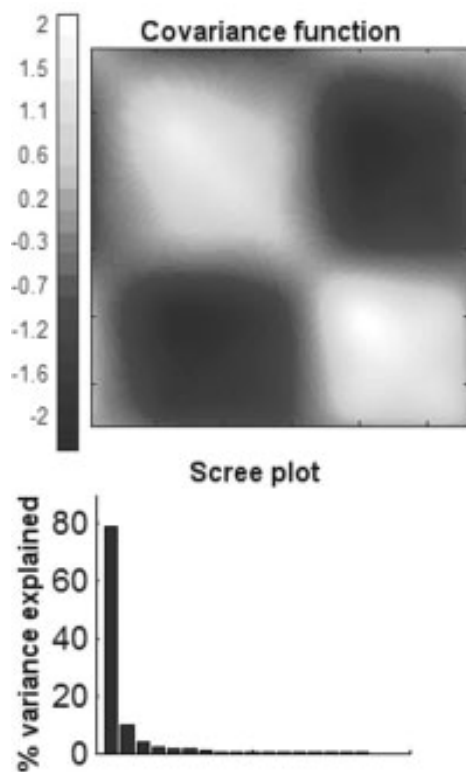
voxel x voxel
covariance

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

Singular values
→ $\text{diag}(S'S)$ are the
eigen values =
proportion of variance
accounted for

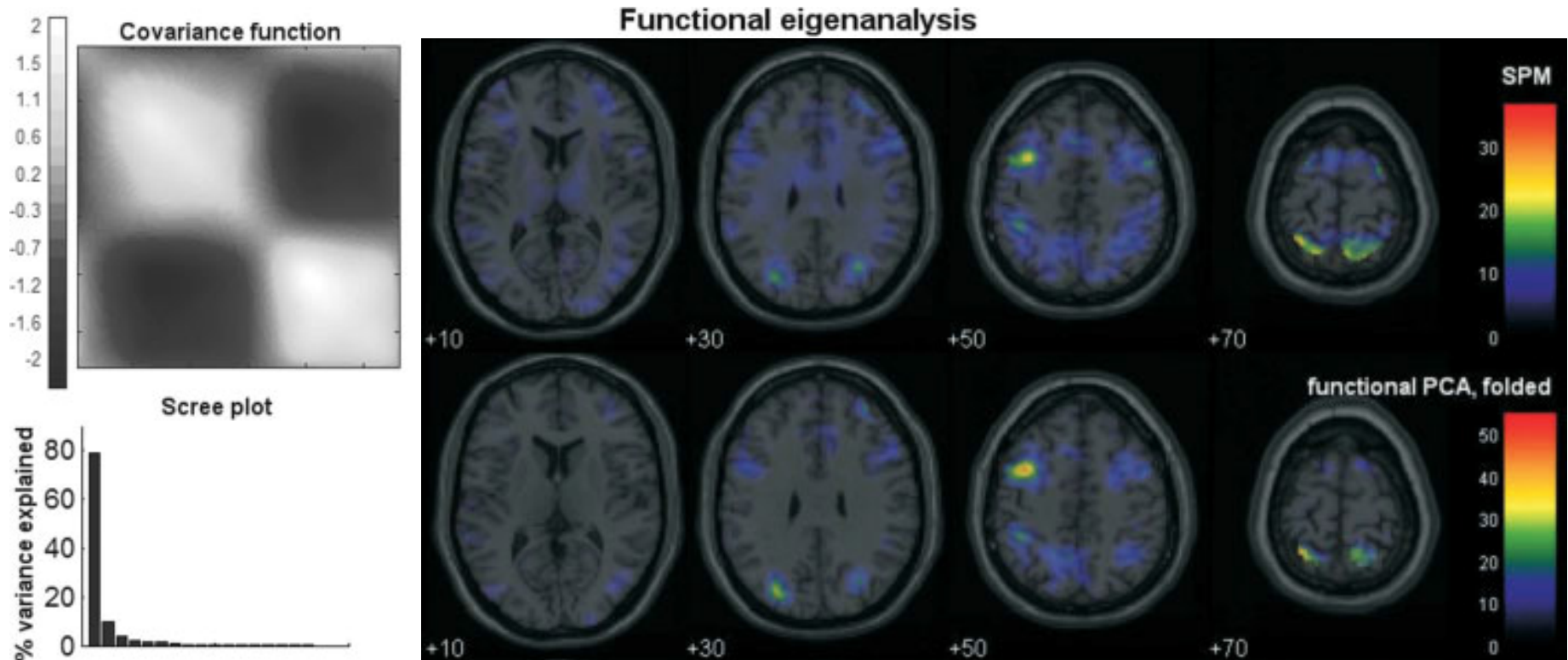
Principal component analysis

- Some improvement possible using smooth function over voxels rather than raw data ([Viviani et al. 2005 HBM 24, 109-129](#))



Principal component analysis

- Some improvement possible using smooth function over voxels rather than raw data ([Viviani et al. 2005 HBM 24, 109-129](#))



Scaled Subprofile Model

- **SSM** ([Alexander & Moller 1994 HBM, 2, 79-94](#))

- Like PCA but data are scaled to find group differences, i.e. X_{np} with n subjects and p voxels

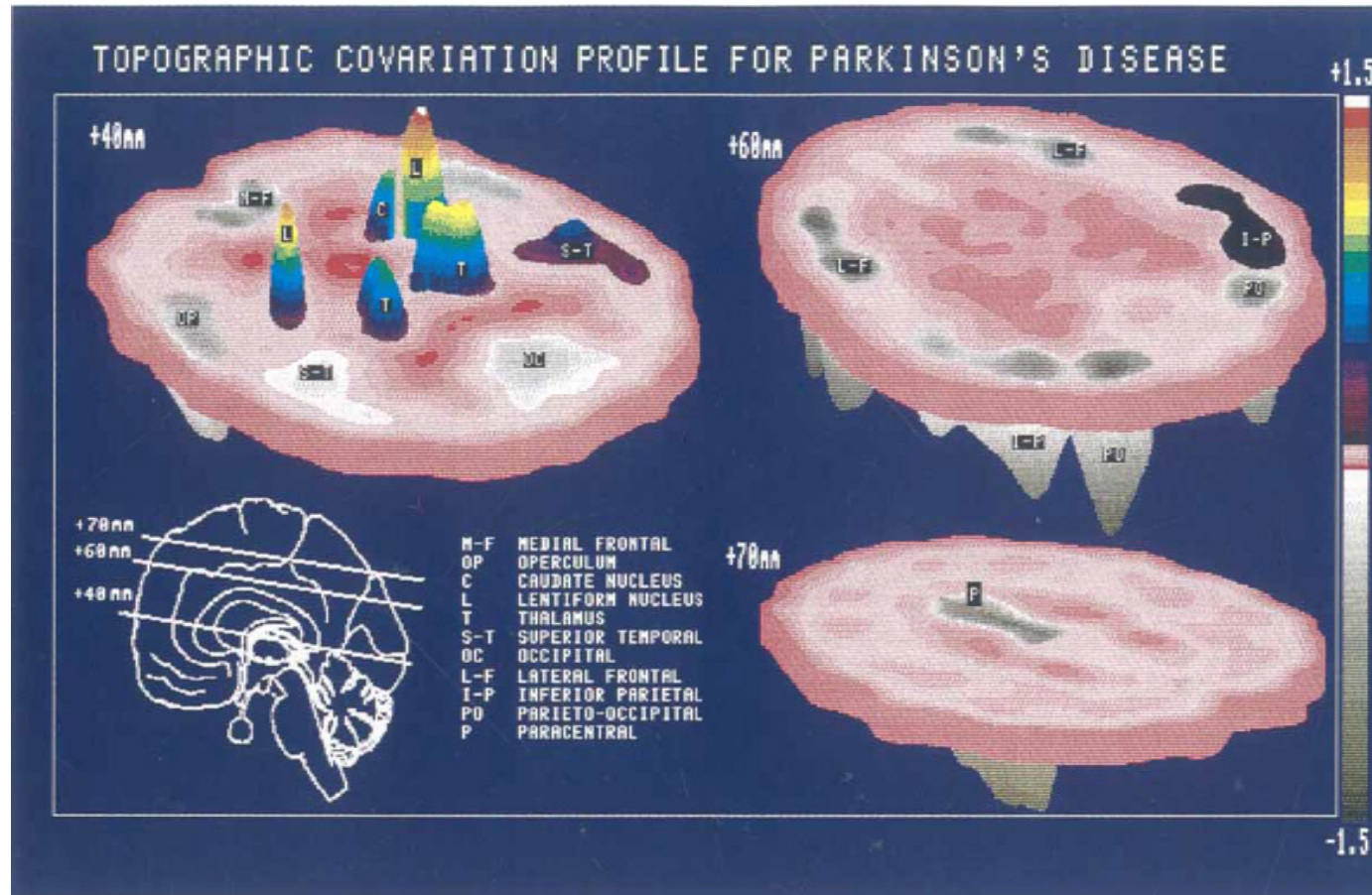
PCA: $X = X - \text{mean}(X, 1)$ → center columns (subjects)
ensuring comp. are uncorrelated across voxels

SSM: $X = (\ln(X) - \text{mean}(\ln(X), 1)) - \text{mean}(\ln(X), 2)$ → 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)

Scaled Subprofile Model



V → find pattern of correlation between voxels

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

Independent component analysis

- One issue with PCA is that ‘sources’ or components are necessarily spatially and temporally uncorrelated, orthogonal and Gaussian.
- ICA offers an alternative by finding components that are maximally independent (i.e. not necessarily orthogonal or Gaussian) in one domain only. Spatial ICA (fMRI) gives spatial maps (with overlapping temporal time-courses) and Temporal ICA (MEEG) gives temporal components (with overlapping spatial maps).

Independent component analysis

$$\text{Observations} = W * \text{IC Maps}$$

fMRI data (Gaussian)
scans x voxel

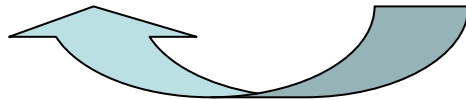
Mixing
Matrix

Underlying sources
components * scans

$$\text{IC Maps} = A^{-1} * \text{Observations}$$

Spatial independence
super-gaussian pdf

Unmixing Matrix
components * scans

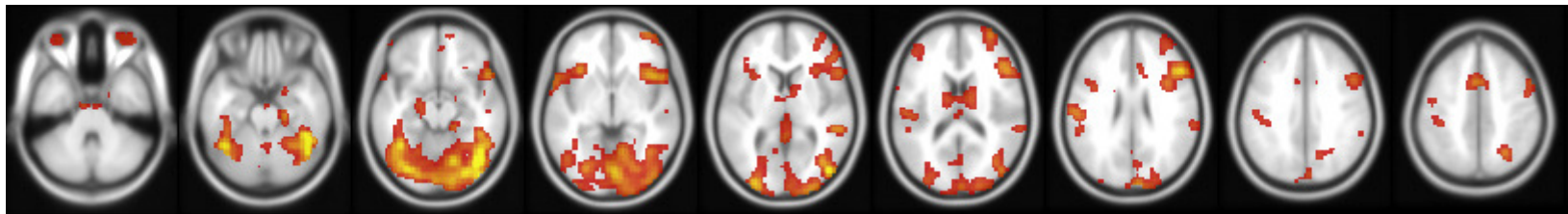


Iterate to maximize some properties
(e.g. entropy of the cdf = kurtosis of the pdf)

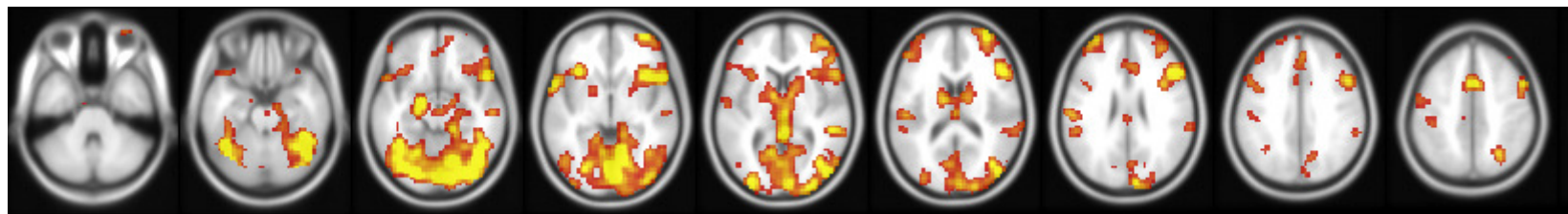
For group analysis, need to pool components extracted per subject: clustering (different IC per subject), group ICA (GIFT Toolbox: same IC but no within subject variance), Tensor ICA (FSL: both within and between subjects variance)

Independent component analysis

Activations



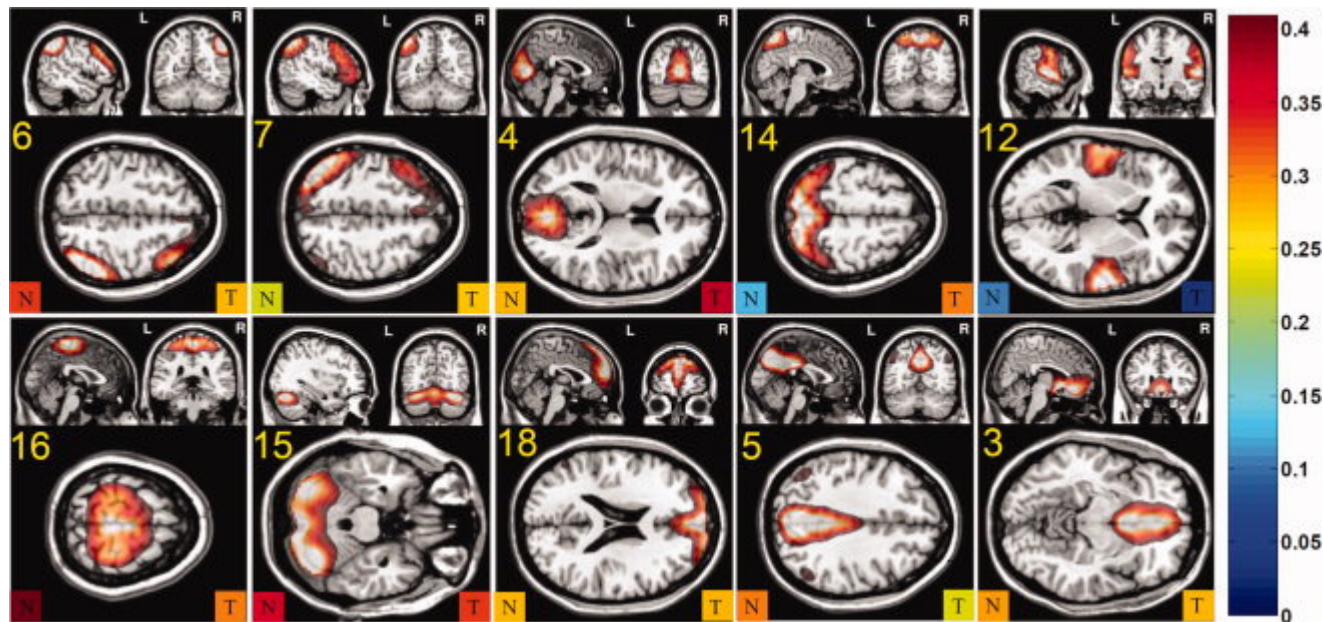
Component 5 – correlation with the design matrix .6



- One network for ACC / Fus / Insulae

Independent component analysis

- [Arbabshirani et al 2012 HBM](#)



ICA on resting state and auditory oddball on the same subjects

Comparison of the power of IC between sessions

Functional Network connectivity → Components time-courses correlates differently between rest and task (=task makes networks to change their relationships)

References

Friston 2011 *Functional and Effective Connectivity: A Review*. Brain Connectivity, 1, 13-36

Calhoun & Adali (2006) Unmixing fMRI with ICA. IEE Eng Med Bio 79-90

Zhou et al (2009) MATLAB *toolbox* for functional connectivity NeuroImage 47:1590-1607

McIntosh & Misisic, Multivariate Statistical analyses for Neuroimaging Data. Ann Rev Psy, 64, 499-525