



Functional connectivity for 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 on occasions

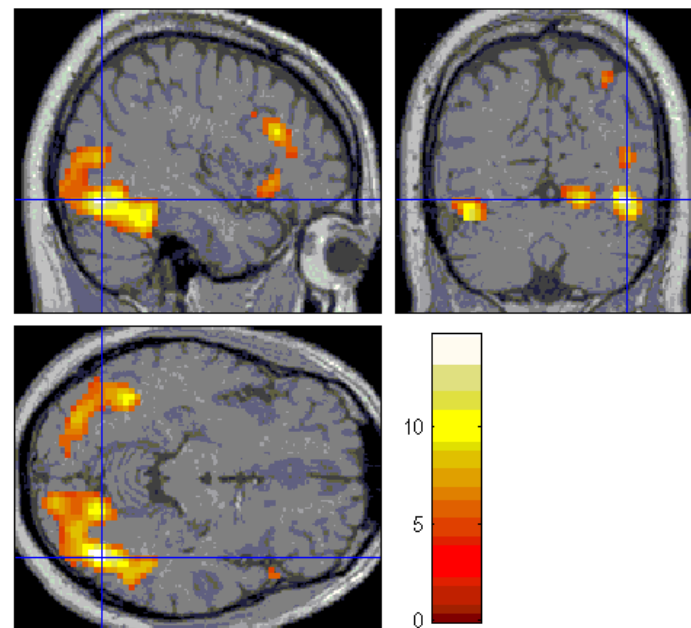
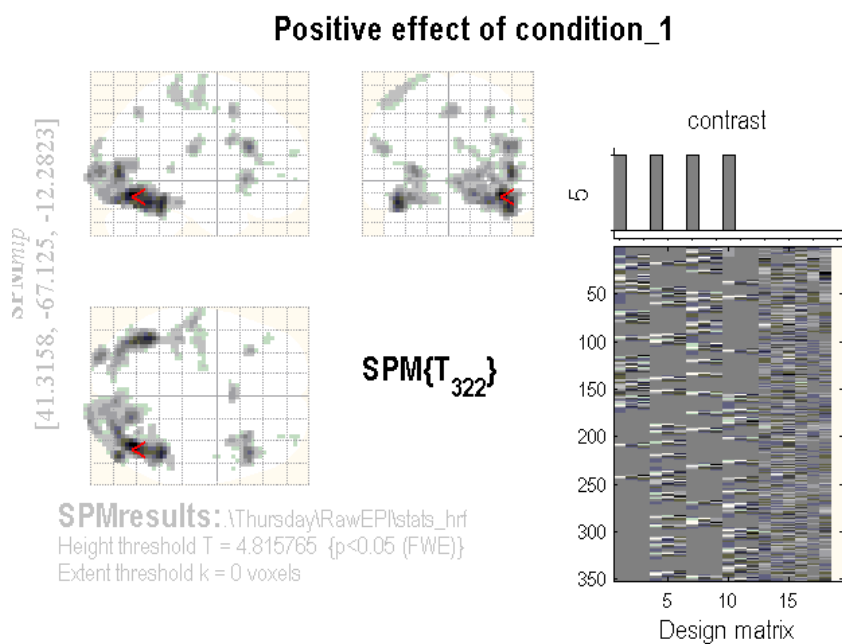
i.e. how time-series between
regions are correlated

Dependencies of time-series

- Extract (compute) one or several time series and look at the correlations.
- **GLM based:** enter 1 time course and regress on all other voxels
- **ROI – Parcellation based:** define ROI and extract time series ; then compute the correlation between all pairs (statistical thresholding must be for the whole matrix not pair-wise).

Famous Faces example

- SPM dataset famous/non famous x repetition



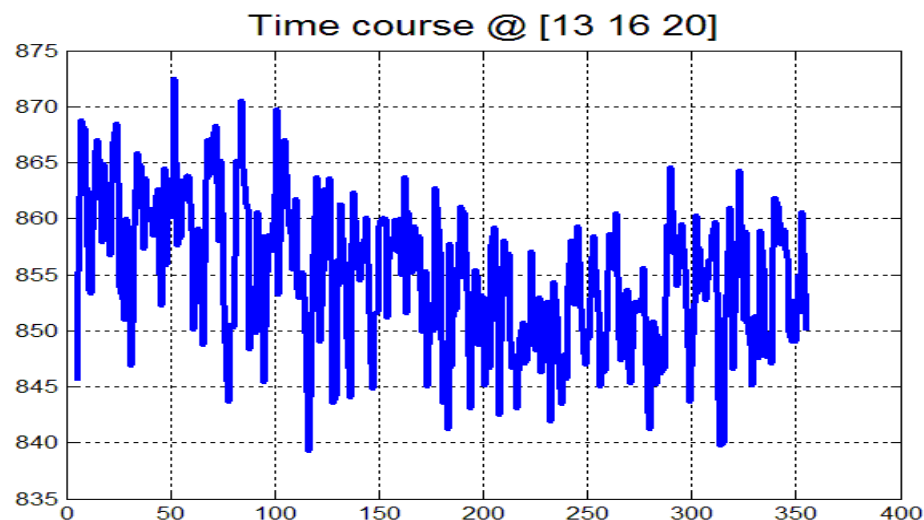
Famous Faces example

- Connectivity from the right fusiform gyrus.

```
Files = spm_select(Inf, 'image', 'select  
contrasts images');
```

```
V = spm_vol(Files);
```

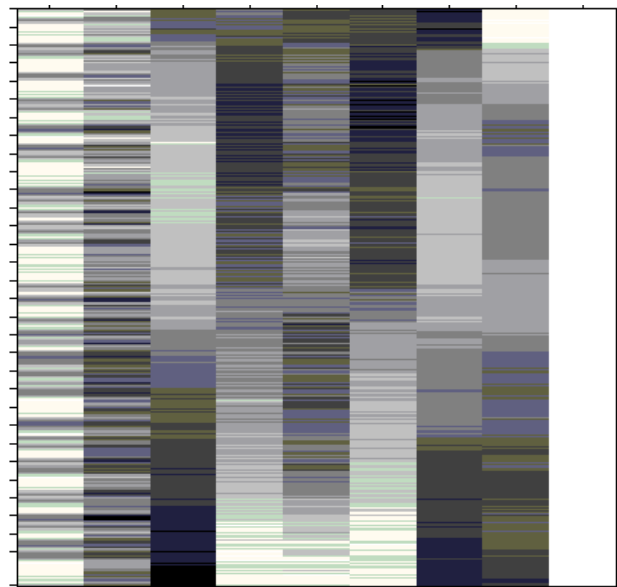
```
[Y, xY] = spm_summarise(V, [39 -70 -13]');
```



For Event related designs

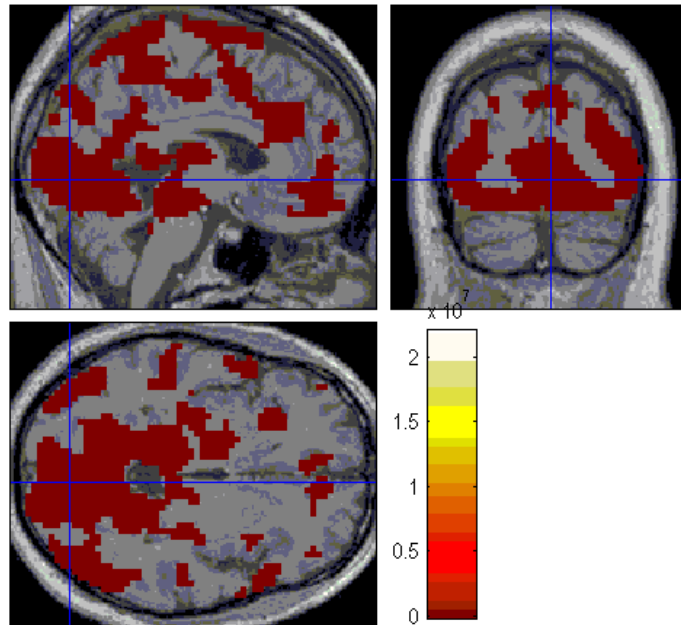
- **Partial correlations, coherence and MI**
- Usually, the stimulus waveform across condition is entered as covariate to (linearly) remove associations due to the stimulation. This can be the modelled waveform or inputs from other ROI.
- Only partial analyses make sense because the correlations are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

Famous Faces example



time course FFA

All stimuli



Then proceed as usual, 2nd level using con images

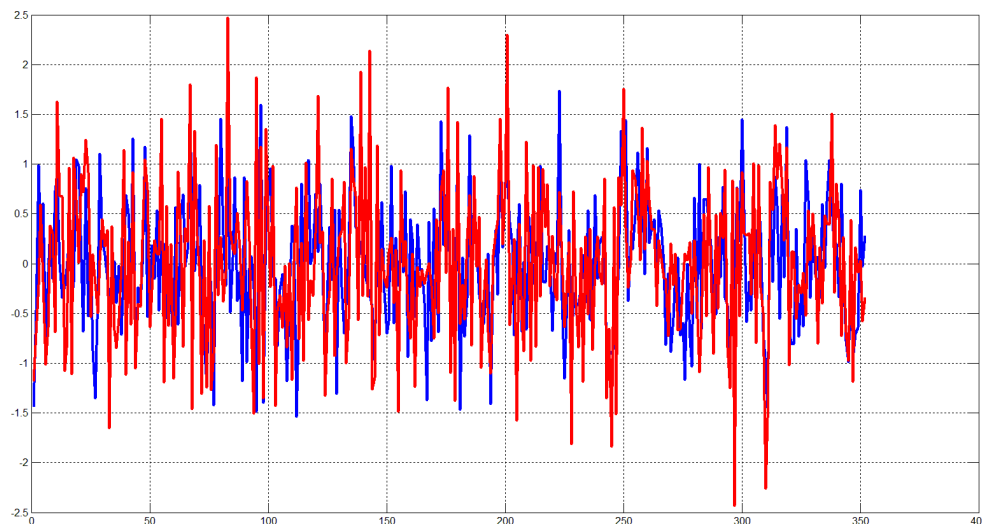
Dependencies of time-series

- Extract (compute) one or several time series and look at the correlations.
- **From the residuals**, assuming linearity, shows underlying coupling (\approx resting state in term of coupling but quantities varies and thus not recommended to compare groups – [Fair et al. 2007, NeuroImage 35](#))

Famous Faces example

- Connectivity between left/right fusiform gyri

```
Files = spm_select(Inf, 'image', 'select  
contrasts images'); V = spm_vol(Files);  
Y1 = spm_summarise(V, [39 -70 -13]');  
Y2 = spm_summarise(V, [-39 -70 -16]');
```



Dependencies of time-series

- *Cross-correlations in time:*

$$r(t) = \text{cov}(s1, s2+t) / \text{sqrt}(\text{var}(s1) + \text{var}(s2+t))$$

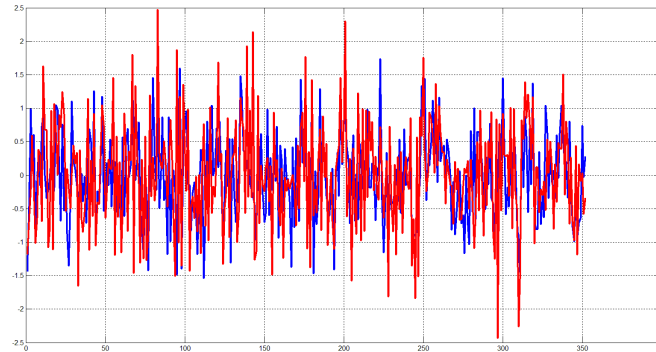
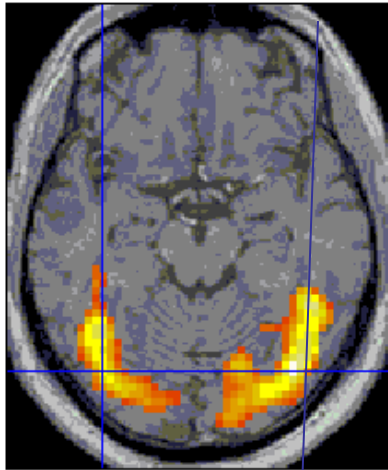
- *Cross-coherence in frequency*

$$\text{Coh}(f) = \text{abs}(\text{Cross-spectral density})^2 / (\text{spectral density}(s1(f)) * \text{spectral density}(s2(f)))$$

- *Mutual information*

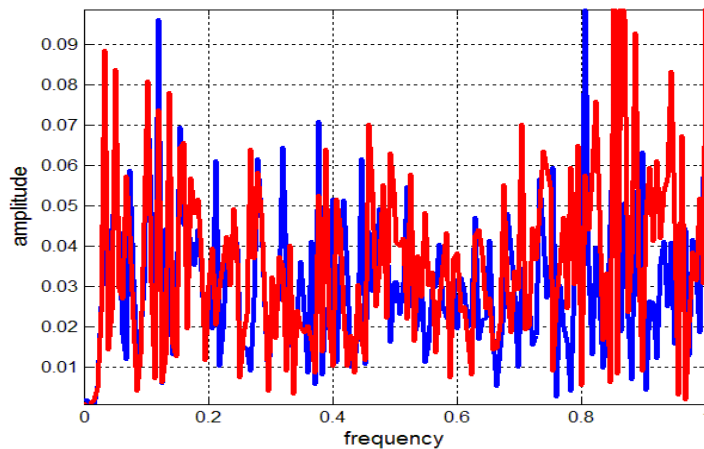
$$I(X; Y) = \sum_{y \in Y} \sum_{x \in X} p(x, y) \log \left(\frac{p(x, y)}{p(x) p(y)} \right),$$

Famous Faces example



```
[r,lag]=xcorr(Y1,Y2,'coef');  
[value,position]=max(r)  
Lag = lag(position)
```

value = 0.4055
Lag = 0



```
sampling_rate = 1/TR  
L = nb_scans / 2;  
[coh,freq]=mscohere(Y1,Y2,hanning(round  
(L)),round(L/2),round(L),1/sampling_rate)
```

Max coh = 0.9

Event related designs

- **Beta-series correlation analysis**

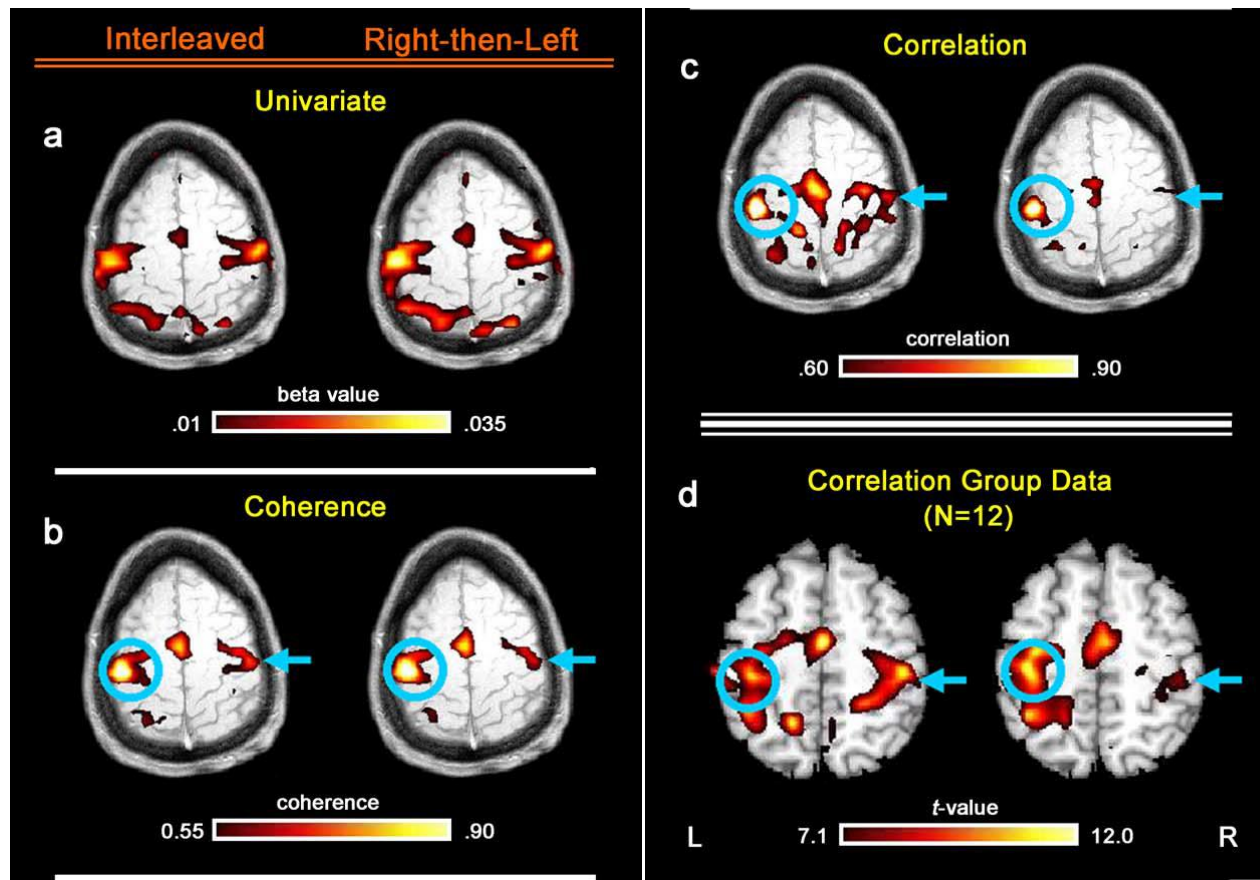
[\(Rissman et al., 2004 NeuroImage 23, 752-763\)](#)

- 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.
- Best is to use many models each time with one trial and all of the others (Mumford et al., 2012).

Event related designs

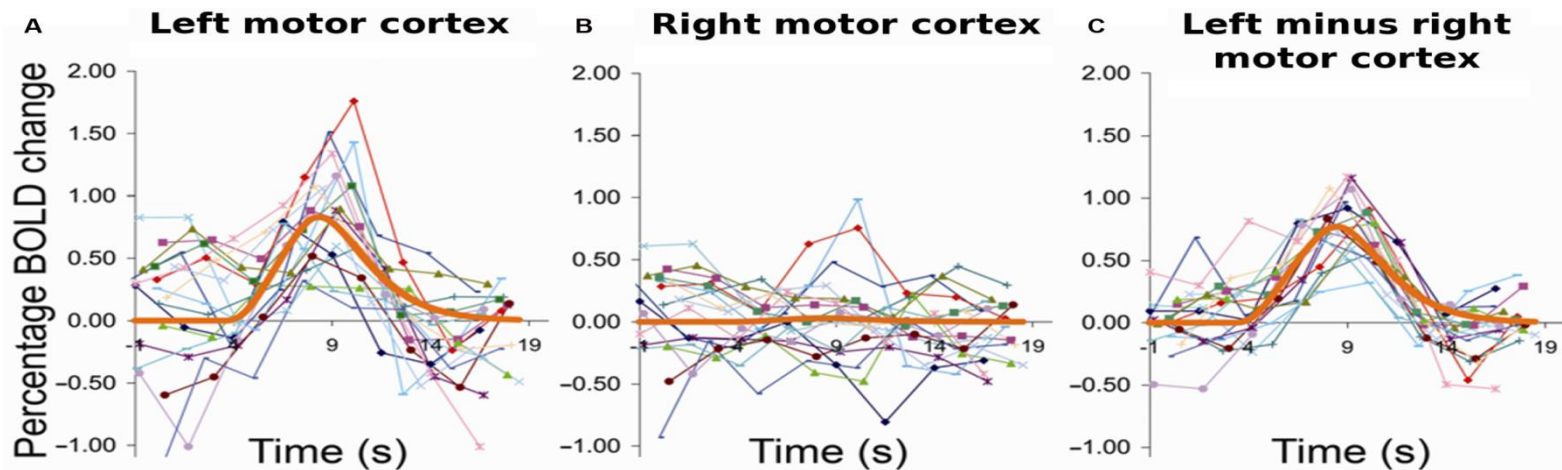
- **Beta-series correlation analysis**

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



Event related designs

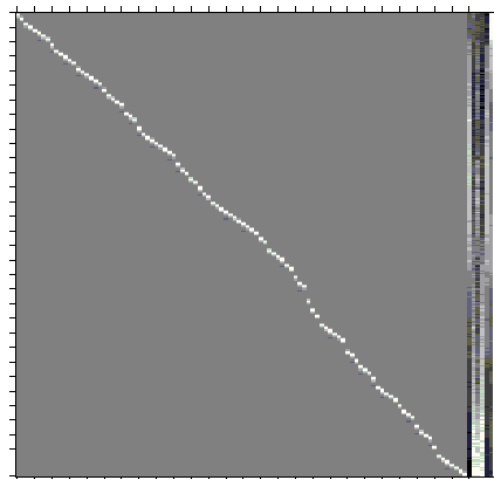
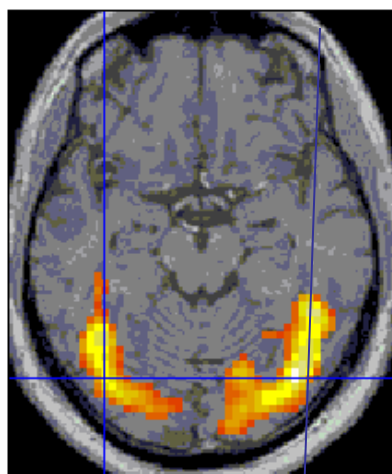
- **Peak correlation**
- Based on an estimate of the peak values of the BOLD responses in regions s1 and s2 for each trial
 - relates to trial to trial variance



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

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

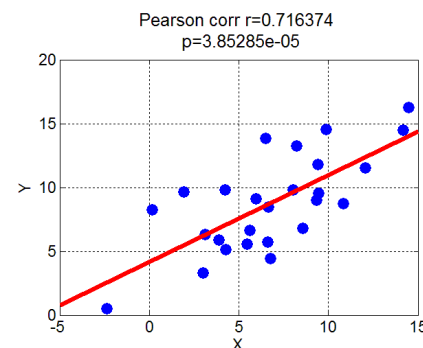
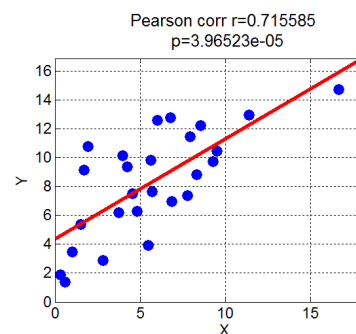
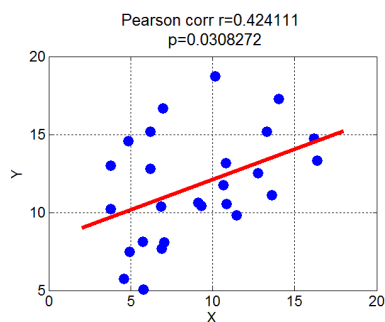
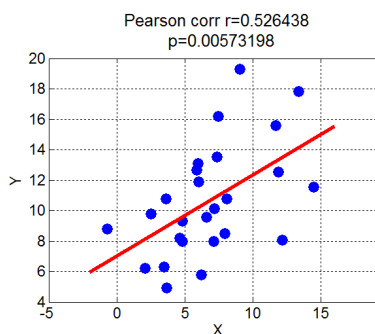
Famous Faces example



1 Beta per trial

Reorganize beta value per condition for left and right fusiform and correlate

Can also do full brain using beta maps (Y) and a seed region (X)



Non Famous 1

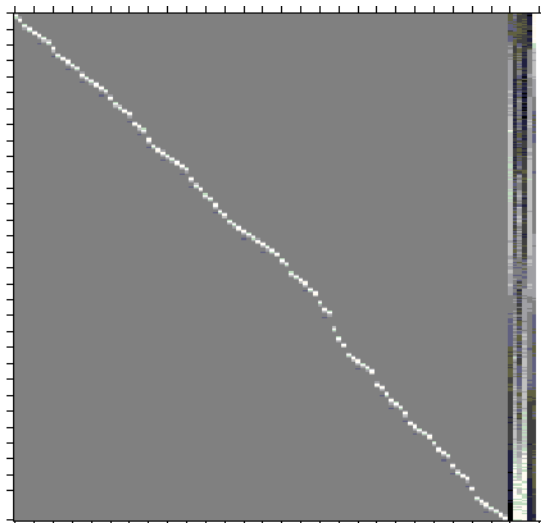
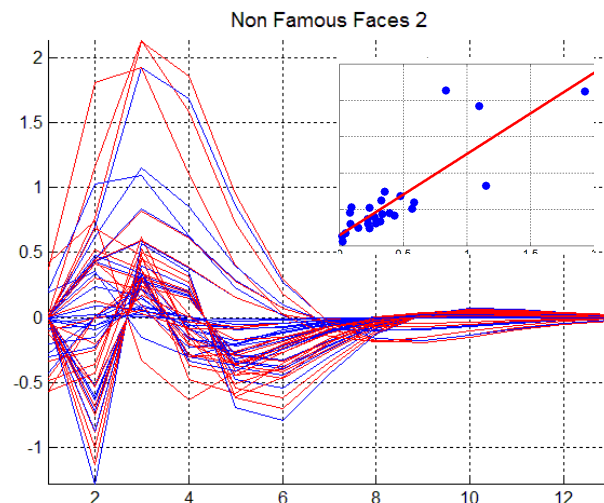
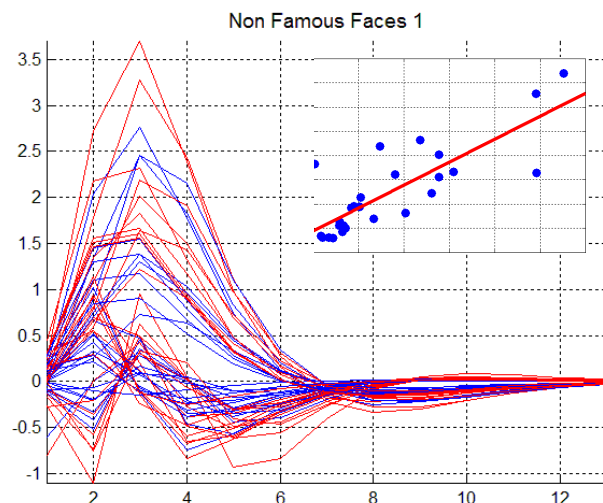
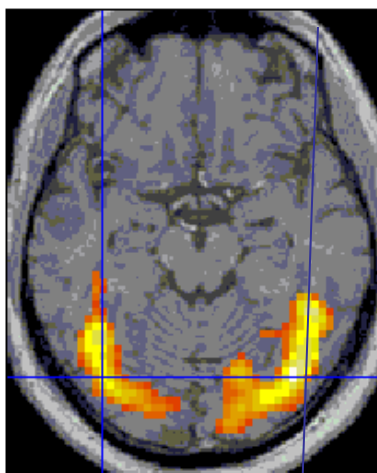
Famous 1

< Non Famous 2

Famous 2

Repetition enhances connectivity between left/right FFA

Famous Faces example



$$X(:,1) * \text{Beta}(1) = 1^{\text{st}} \text{ trial}$$

-
-

We can reconstruct each trial
and get the peak, time to peak,
etc ..

Beyond FC using 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

Beyond FC using PPI

- **Functional connectivity:**

(1) $Y = X\beta_1 + R\beta_2 + \varepsilon$ (GLM with X the stimulus onsets + times series + confounds)

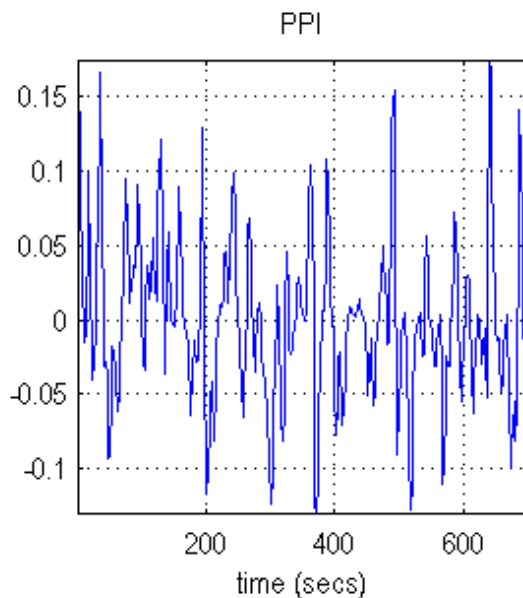
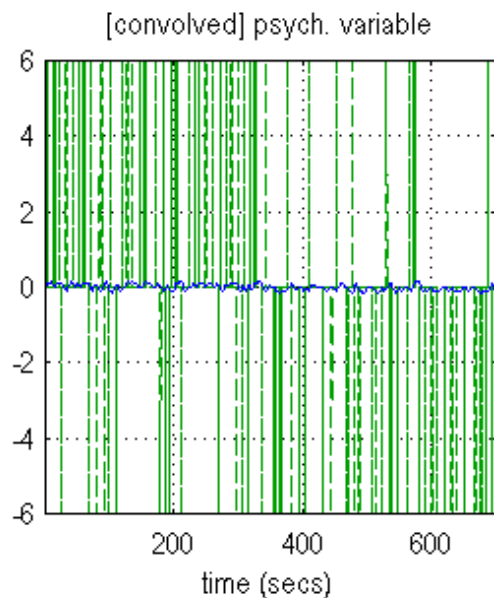
- **Effective connectivity:**

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

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

Famous Faces example

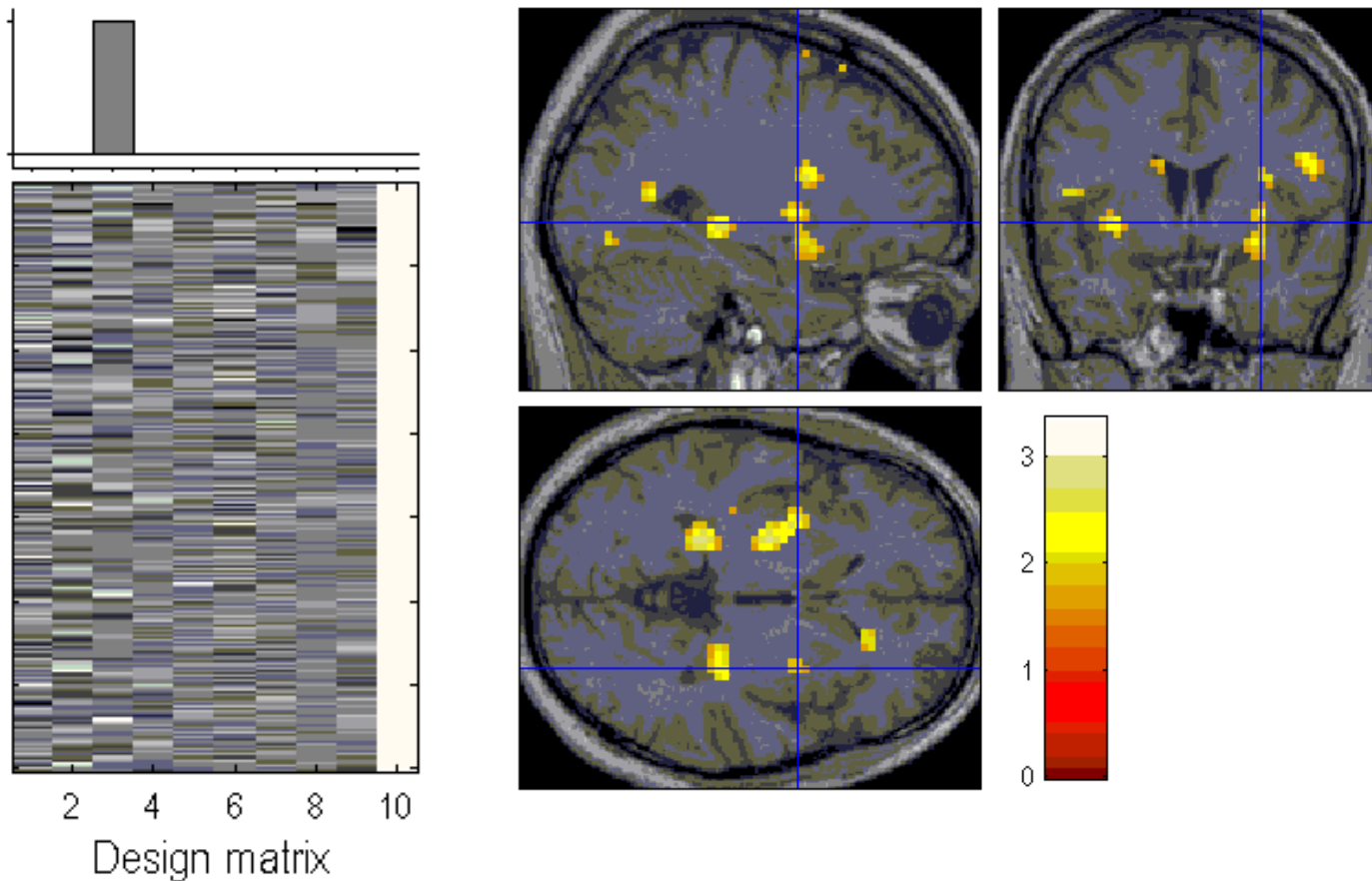
- Define an effect of interest (eye zeros)
- Create a PPI regressor adjusting for that effect
- Set up a new GLM with the ROI time course (PPI.Y), trials (PPI.P), and interaction (PPI.ppi)



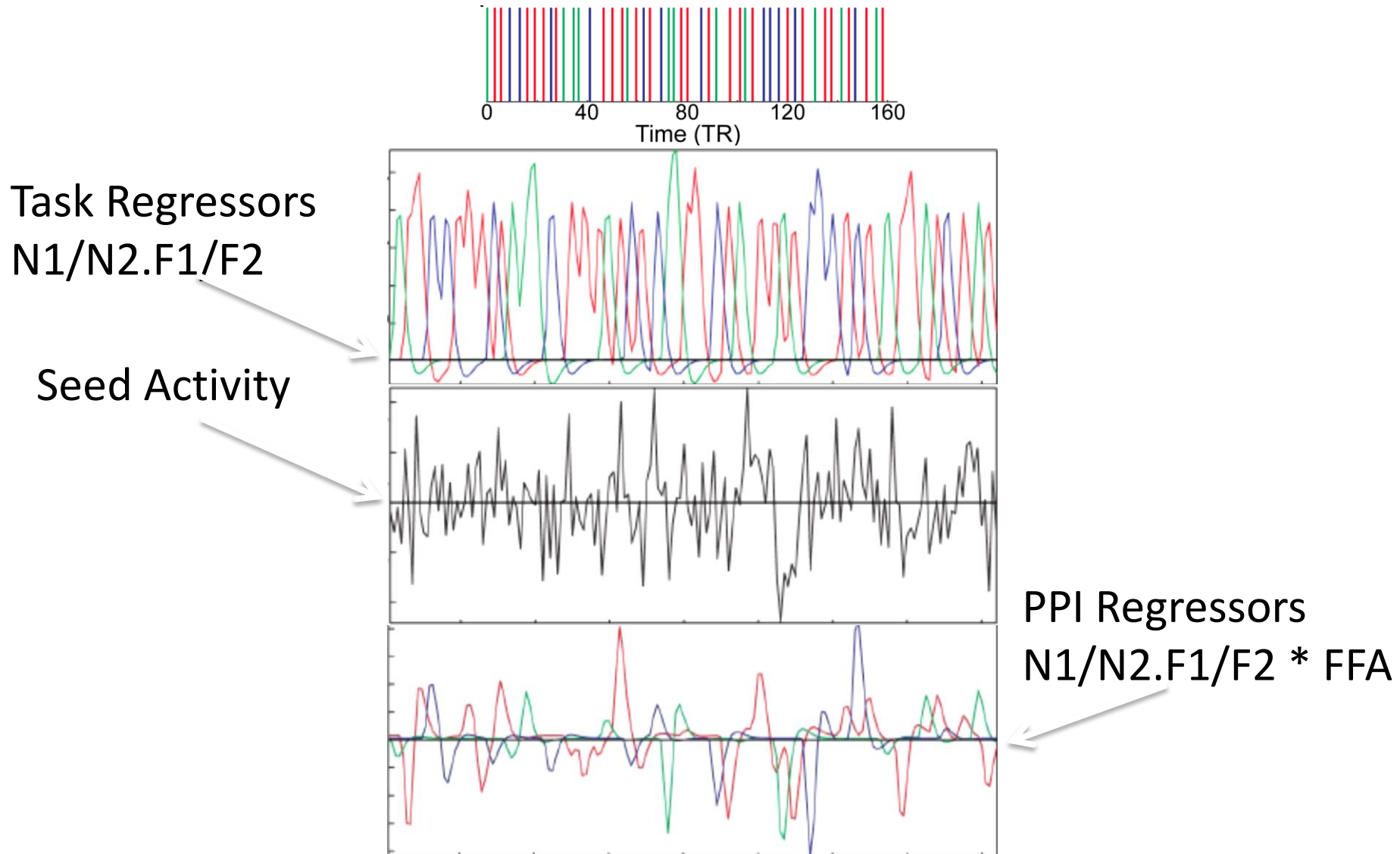
All trials treated equals
PPI use contrasts

Famous Faces example

- PPI: FFA * repetition effect



Generalized PPI



FC on variables

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

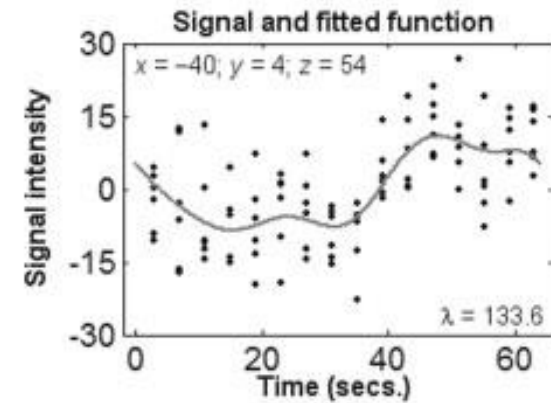
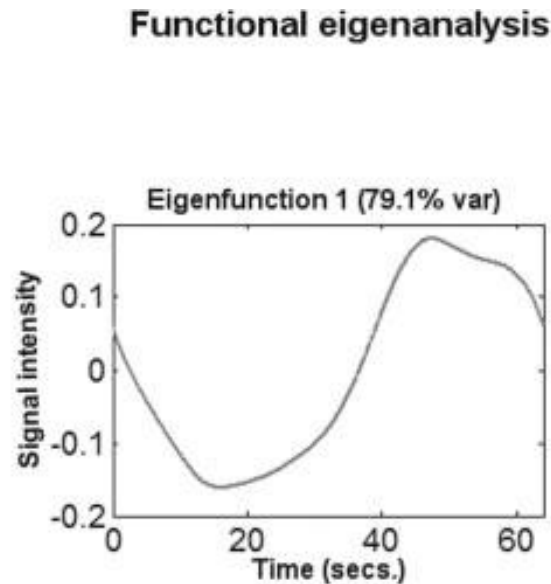
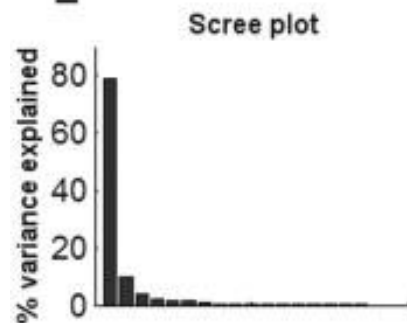
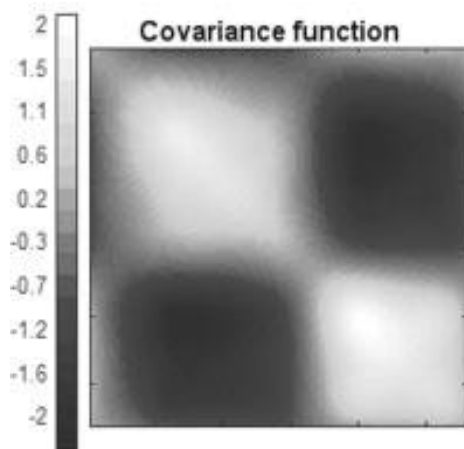
voxel x voxel covariance

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

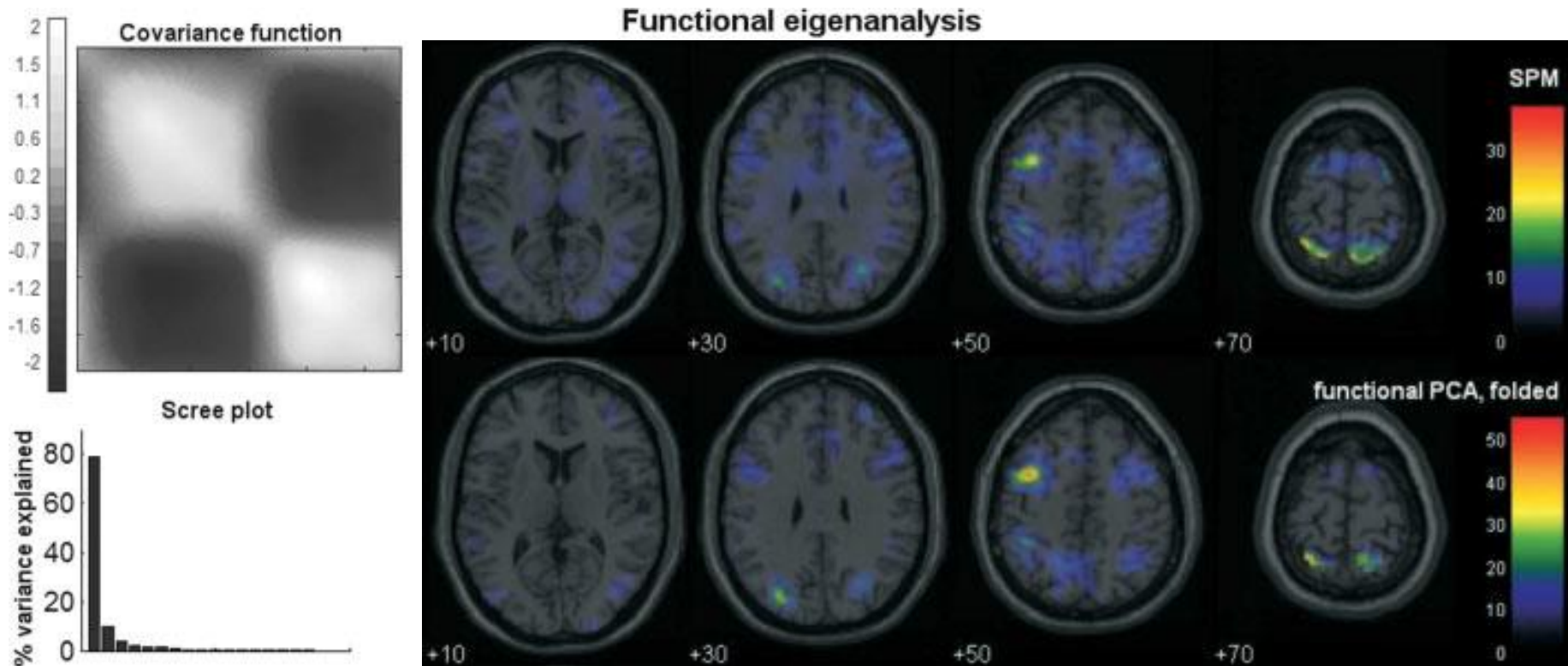
Principal Component Analysis

- 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

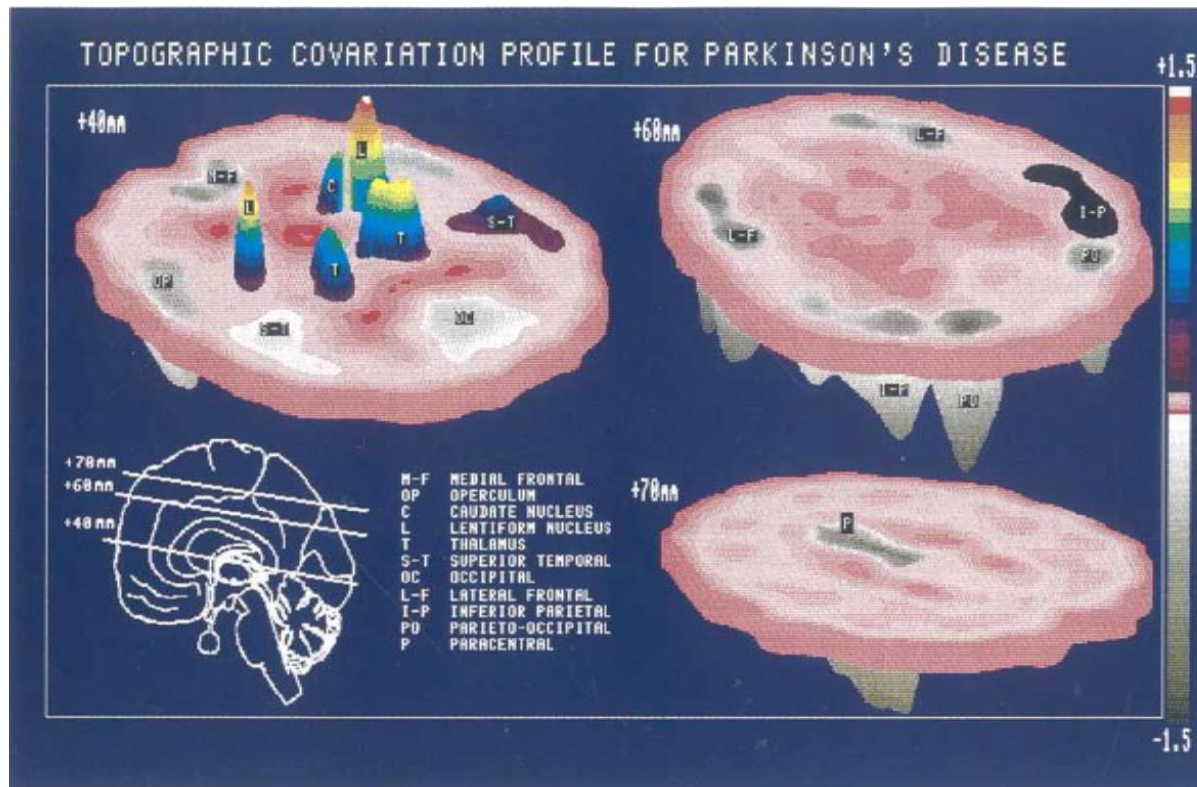
PCA: $X = X - \text{mean}(X, 1)$ → center columns (subjects)
ensuring comp. are uncorrelated across voxels

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)

SSMPCA toolbox ([Peng et al 2014 HBM, 35](#))

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

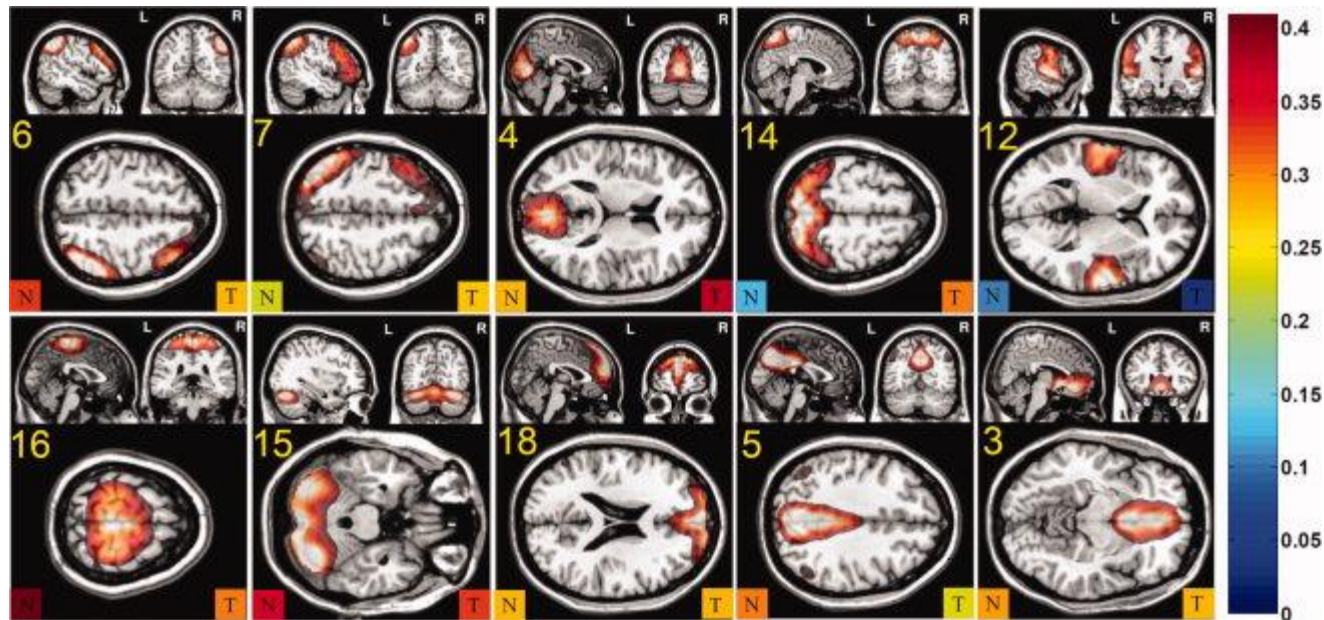


Iterate to maximize some properties
(e.g. entropy of the cdf = kurtosis of the pdf)

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

- [Arbabshirani et al 2012 HBM](#)

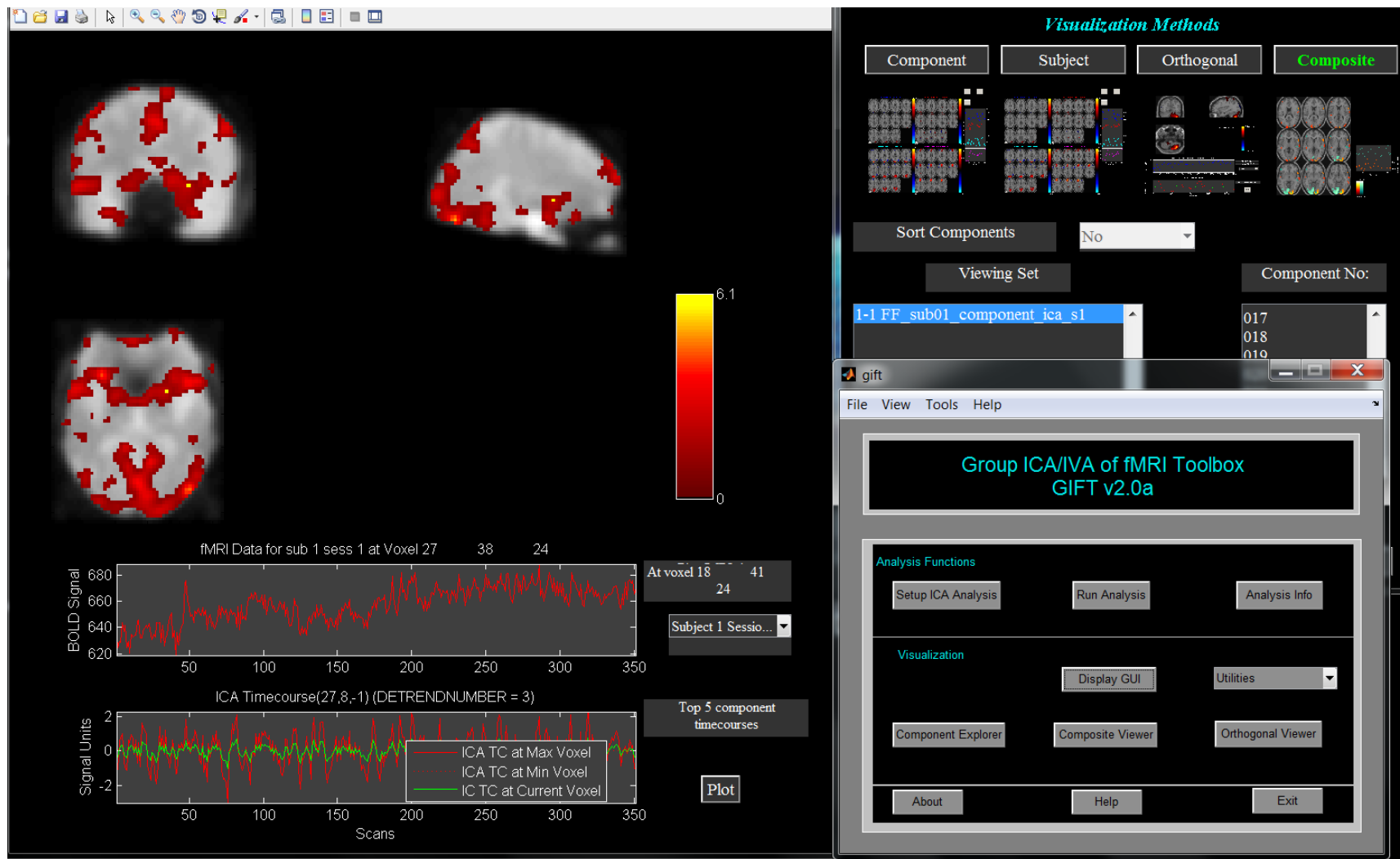


ICA on resting state and auditory oddball on the same subjects

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)

Famous Faces example



References

- See in text references

- See also

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

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References

- *Correlations and cross-correlation*
(Biswal et al., 1995, Mag Res Med., 34, 537-541)
- *Cross-coherence*
(Sun et al., 2004, Neurolmage, 21, 647-658)
- *Mutual information*
(Jeong et al., 2001, Clin Neurophysiol, 1120, 827-835)
- *Canonical correlation*
(Worsley et al., 2005, IEEE international joint conference on neural networks, 3 1534-1541)