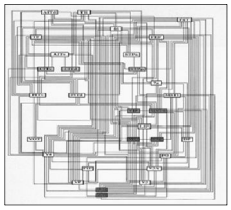
Connectivity in fMRI:
a brief overview



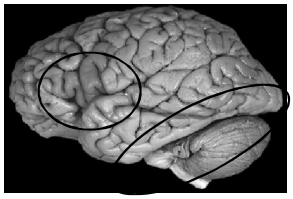
Mohamed Seghier

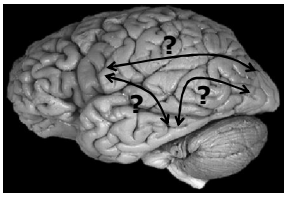
Wellcome Trust Centre for Neuroimaging,
University College London, UK

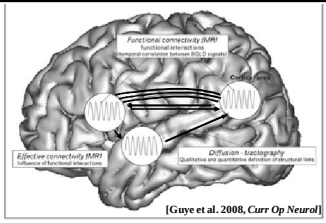
Systems analysis in functional neuroimaging

Functional segregation:
What regions respond to a particular experimental input?

Functional integration:
How do regions influence each other?
→ Brain Connectivity [Friston 1994, *HBM*]





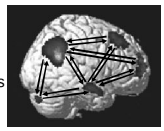


[Guye et al. 2008, *Curr Op Neurol*]

- **anatomical/structural connectivity** [Sporns 2007, *Scholarpedia*]
  = presence of axonal connections
- **functional connectivity**
  = statistical dependencies between regional time series
- **effective connectivity**
  = causal (directed) influences between neurons or neuronal populations

For understanding brain function **mechanistically**, we need **models of effective connectivity**,

i.e. **models of causal interactions** among neuronal populations to explain regional effects in terms of interregional connectivity



An overview:

1- anatomical/structural connectivity
- **anatomy is not enough?**

2- functional connectivity
- **methods and types.**
- **a limited inference?**

3- effective connectivity
- **methods (PPI, SEM).**
- **limitations.**

Structural connectivity

DTI: diffusion tensor imaging

-**Anisotropy analyses on RA or FA images;**
[Basser and Pierpaoli 1996 JMR]
+ in SPM: - correlations with behaviour
- group comparisons.

-**Tractography techniques:**
(e.g. seed/target/crossing regions)
+ deterministic
[Mori et al. 1999 Ann Neurol]

+ probabilistic
[Parker et al. 2002 IEEE TMI]

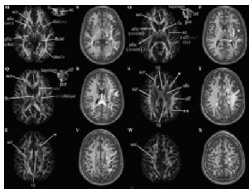
DSI: diffusion spectrum imaging

-**Fibers orientation at high definition (6D-space);**
+ Resolving fibers intersections
[Wedeen et al. 2005 MRM]

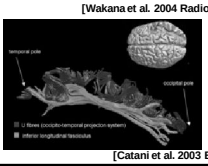
-**Identify structural connector hubs;**
[Hagmann et al. 2008 PLoS Biol]

Structural connectivity

DTI: diffusion tensor imaging

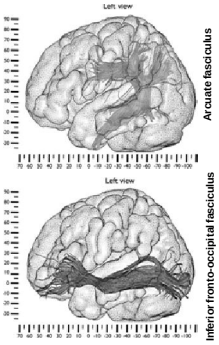


[Wakana et al. 2004 Radiology]



[Catani et al. 2003 Brain]

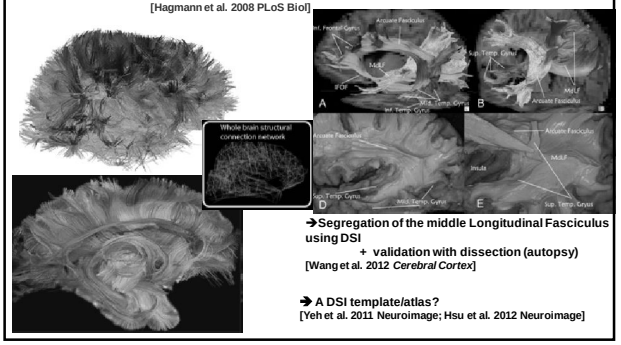
➔ An atlas of white matter tracts in MNI
[Catani and Thiebaut de Schotten 2008 Cortex]



Structural connectivity

DSI: diffusion spectrum imaging

[Hagmann et al. 2008 PLoS Biol]



→Segregation of the middle Longitudinal Fasciculus using DSI
+ validation with dissection (autopsy)
[Wang et al. 2012 *Cerebral Cortex*]

→ A DSI template/atlas?
[Yeh et al. 2011 Neuroimage; Hsu et al. 2012 Neuroimage]

Knowing anatomical connectivity is not enough...

- Connections are recruited in a context-dependent fashion:
  - Local functions depend on network activity
- Connections show plasticity
  - Synaptic plasticity = change in the structure and transmission properties of a synapse
  - Critical for learning
  - Can occur both rapidly and slowly

→ **Need to look at functional/effective connectivity.**

Anatomo-functional connectivity: combine functional with structural connectivity.
→ **explain function by anatomy: RSNs and WM tracts;** [van den Heuvel et al. 2009 *HBM*]
→ **link to brain dynamics;** [Baria et al. 2013 Neuroimage; Pinotsis et al. 2013 Neuromimage]
→ **constrain priors in DCM by DTI tractography;** [Stephan et al. 2009 *Neuroimage*]

Functional connectivity

= statistical dependencies (temporal correlations) between activations. [Friston et al. 1993 *JCBFM*]

- **Seed-based correlation analysis (in SPM)**
- **Eigen-decomposition (e.g. PCA, SVD)**
- **Independent component analysis (ICA)**
- **Coherence analysis**
- **Clustering (e.g. FCM)**

[Li et al. 2009 *CMGI*]

♣ **Task-related connectivity**

- **Controlled stimulations (known inputs)**
- **Uncontrolled conditions (free-model inputs)**

[Cordes et al. 2000 AJNR]
[McKeown et al. 1998 HBM]

♣ **Intrinsic/endogenous task-unrelated connectivity**

- **"rest" (external stim. = 0)**
- **passive fixation.**

[Biswal et al. 1995 MRM]
[Damoiseaux et al. 2006 PNAS]

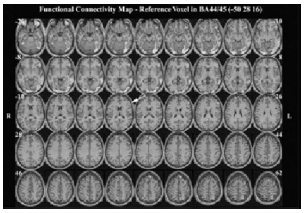
- **Hypothesis-driven, using seed regions;**
- **Data-driven (ICA, FCM), over all voxels;**

- **Within-subject: inter-regional temporal dependencies;**
- **Across-subject: second-level covariance or inter-subject synchronisation.**

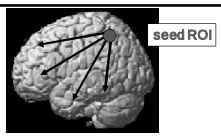
[Hasson et al. 2004 *Science*; Seghier et al. 2008 *Neuroimage*]

♣ **Whole-brain regression with seed regions:**
➔ **functional connectivity maps (SPM)**

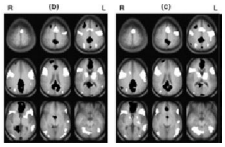
♦ **Controlled task:**
reading words, pseudowords, letter strings.
[Bokde et al. 2001 *Neuron*]



Seed ROI = left inferior frontal gyrus.
Functional connectivity maps vary with word type.



♦ **Uncontrolled task (= unlocked onsets):**
continuous sentence reading.
[Hampson et al. 2006 *Neuroimage*]



Seed ROI = left angular gyrus.
Functional connectivity maps vary during (natural) reading of sentences.

E.g. watching movies / sleep / hallucinations

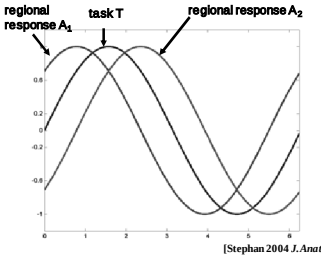
Does functional connectivity not simply correspond to co-activation in SPMs?
(for task-related functional connectivity)

Seed ROI A1 selected from task T

No !

Here both areas A_1 and A_2 are correlated identically to task T, yet they have zero correlation among themselves:

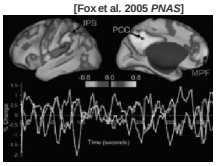
$r(A_1,T) = r(A_2,T) = 0.71$
but
$r(A_1,A_2) = 0$!



[Stephan 2004 *J. Anat.*]

♠ **Intrinsic (resting-state) networks**
➔ **fMRI during "rest" or passive fixation.**
➔ **Spontaneous fluctuations of fMRI signal (LF: 0.01-0.1 Hz)**

[Fox et al. 2005 *PNAS*]

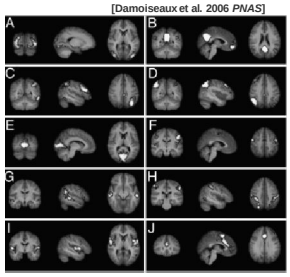


With seed ROIs (hypothesis-driven)

- Widely used in normal subjects and patients: e.g. looking for abnormal/altered intrinsic connectivity in diseased populations.

[Broyd et al. 2009 *Neurosci Biobehav Rev*]
[Fox and Greicius 2010 *Front Syst Neurosci*]

[Damoiseaux et al. 2006 *PNAS*]



Data-driven, using ICA.
e.g. see Calhoun et al. // Smith et al.

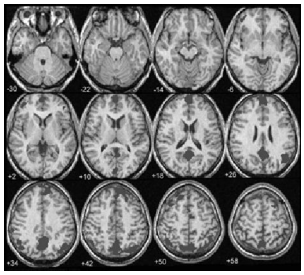
Flexibility of the GLM in SPM:

[Fransson 2005 *HBM*]

Resting-networks with a GLM analysis (without seed ROIs)

Regressors = a discrete cosine basis set containing 120 regressors that together spanned the frequency range of 0–0.1 Hz.

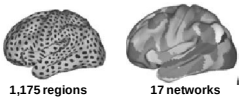
➔ identify any signal change as a linear combination of the individual basis functions.



Large-scale network analysis:

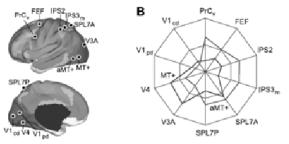
[Yeo et al. 2011 *J Neurophysiol*]

Resting-state fMRI data from 1000 subjects.



1,175 regions **17 networks**

➔ Functional connectivity profile as a fingerprint

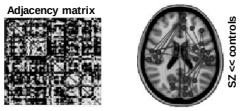


Examine local vs. distributed networks.
➔ Dissociate different brain areas.

[Fornito et al. 2012 *Neuroimage*]

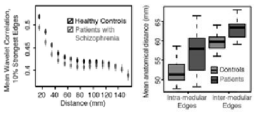
Schizophrenia = a disorder of brain connectivity.

Adjacency matrix



The use of graph theory:
Local/global statistics on edges and nodes
➔ Define topological measures of connectivity

See Sporns and Bullmore work.

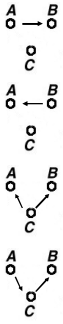


[Alexander-Bloch et al. 2013 *Cereb Cortex*]

Pros & Cons of functional connectivity analysis

- Pros:
  - useful when we have no experimental control over the system of interest and no model of what caused the data (e.g. sleep, hallucinations, natural vision)
- Cons:
  - interpretation of resulting patterns is difficult / arbitrary;
  - no mechanistic insight;
  - operates at the level of BOLD time series;
  - usually suboptimal for situations where we have a priori knowledge / experimental control

→ **Effective connectivity**



Effective connectivity

fMRI experiment;
GLM, task contrasts

Can we go beyond this "static" picture?
➔ Dynamics or interactions between regions…

= causal (directed) influences between neurons or neuronal populations.

= explain *regional* effects in terms of *interregional* connectivity.

➔ Hypotheses constrained by the main effects or interactions from the GLM.

Some models for computing effective connectivity from fMRI data

Structural Equation Modelling (SEM)
[McIntosh and Gonzalez-Lima 1991, 1994]

Volterra kernels
[Friston and Büchel 2000]

Dynamic Causal Modelling (DCM)
[Friston et al. 2003]

Dynamic Bayesian networks (DBN)
[Rajapakse and Zhou 2007]

Psycho-Physiological Interactions (PPI)
[Friston et al. 1997]

Multivariate Autoregressive Model (MAR)
[Harrison et al. 2003]

Granger causality
[Goebel et al. 2003]

Nonlinear system identification
[Li et al. 2010]

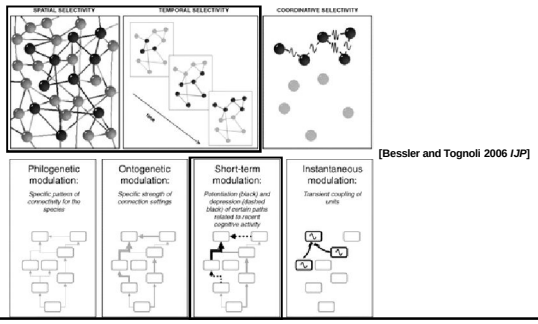
Types of analysis to assess effective connectivity:

PPI – psychophysiological interactions
SEM – structural equation modeling
DCM – dynamic causal model

STATIC MODELS

DYNAMIC MODEL

See Appendix A1 in [Friston et al. 2003 *Neuroimage*]



[Bessler and Tognoli 2006 *IJP*]

Psycho-physiological interaction (PPI)

- bilinear model of how the psychological context A changes the influence of area B on area C :

$$B \times A \rightarrow C$$

➔ PPI corresponds to differences in regression slopes for different contexts.

Psycho-physiological interaction (PPI)

Task factor

Stimulus factor	Task A	Task B
Stim 1	A1	B1
Stim 2	A2	B2

GLM of a 2x2 factorial design:

$$y = (T_A - T_B)\beta_1 + (S_1 - S_2)\beta_2 + (T_A - T_B)(S_1 - S_2)\beta_3 + e$$

main effect of task; main effect of stim. type; interaction

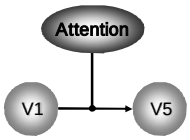
We can replace one main effect in the GLM by the time series of an area that shows this main effect.

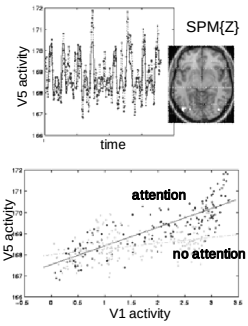
$$y = (T_A - T_B)\beta_1 + V1\beta_2 + (T_A - T_B)V1\beta_3 + e$$

main effect of task; V1 time series ≈ main effect of stim. type; psycho-physiological interaction

[Friston et al. 1997, *NeuroImage*]

Example PPI: Attentional modulation of V1→V5





[Friston et al. 1997, *NeuroImage*]
[Büchel & Friston 1997, *Cereb. Cortex*]

Pros & Cons of PPIs

- Pros:
  - given a single source region, we can test for its context-dependent connectivity across the entire brain;
  - easy to implement (in SPM);
- Cons:
  - only allows to model contributions from a single area;
  - operates at the level of BOLD time series;
  - ignores time-series properties of the data;
  - can have multiple interpretations.

➔ **Dynamic Causal Models**

Some models for computing effective connectivity:

Structural Equation Modelling (SEM) [Mcintosh and Gonzalez-Lima 1991, 1994]	Psycho-Physiological Interactions (PPI) [Friston et al. 1997]
Volterra kernels [Friston and Büchel 2000]	Multivariate Autoregressive Model (MAR) [Harrison et al. 2003]
Dynamic Causal Modelling (DCM) [Friston et al. 2003]	Granger causality [Goebel et al. 2003]
Dynamic Bayesian networks (DBN) [Rajapakse and Zhou 2007]	Nonlinear system identification [Li et al. 2010]

Conclusion: **For effective connectivity:**

Each method has its advantages and weaknesses and its use should be motivated by the question of interest, level of inference, paradigm design, data acquisition and analysis.

➔ An alternative method = DCM (next talk!).