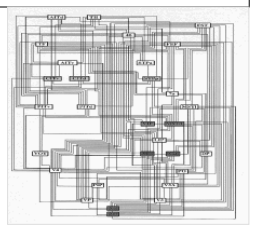
Connectivity in fMRI



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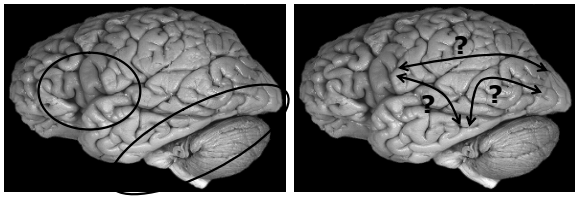
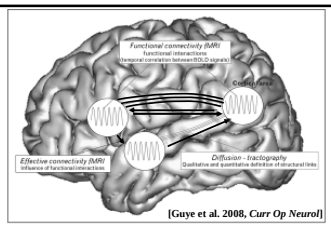
Systems analysis in functional neuroimaging

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

Functional integration:
How do regions influence each other?
→ Brain Connectivity





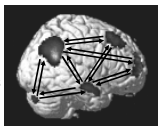
[Guye et al. 2008, *Curr Op Neurol*]

[Sporns 2007, *Scholarpedia*]

- **anatomical/structural connectivity**
  = 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]

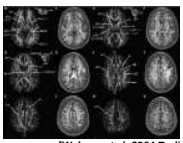
DSI: diffusion spectrum imaging

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

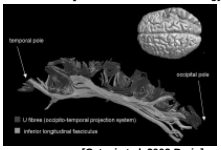
- **Identify structural connector hubs;**
  [Hagmann et al. 2008 PLoS Biol]

Structural connectivity

DTI: diffusion tensor imaging



[Wakana et al. 2004 Radiology]

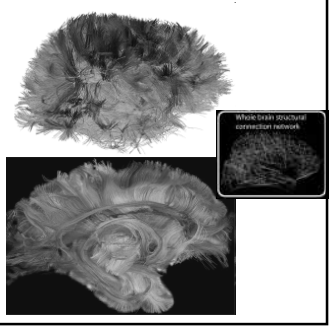


[Catani et al. 2003 Brain]

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

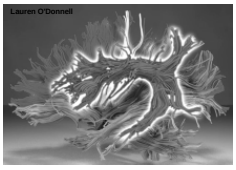
DSI: diffusion spectrum imaging

[Hagmann et al. 2008 PLoS Biol]



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.

(➔ a rationale suggested also for DCM; [Stephan et al. 2009 Neuroimage])

Functional connectivity

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

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

♣ Context or task-related connectivity

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

♣ Intrinsic/endogenous task-unrelated connectivity

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

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

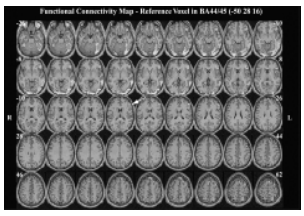
- **♦ Hypothesis-driven, using seed regions;** [Biswal et al. 1995 MRM]
- **♦ Data-driven (ICA, FCM), over all voxels;** [Damoiseaux et al. 2006 PNAS]

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

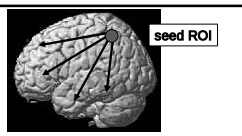
[Hasson et al. 2004 *Science*; Seghier et al. 2008 *Neuroimage*]

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

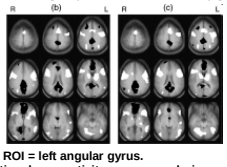
♦ Controlled task:
reading words, pseudowords, letter strings.
[Bokde et al. 2001 *Neuron*]



Seed ROI = left inferior frontal gyrus.
Functional connectivity maps vary when reading different words type.



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

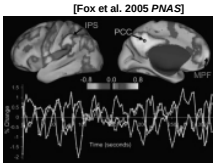


Seed ROI = left angular gyrus.
Functional connectivity maps vary during (natural) reading of sentences.

E.g. watching movies / Sleep / Hallucinations

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

[Fox et al. 2005 *PNAS*]

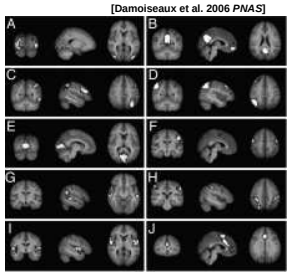


With seed ROIs (hypothesis-driven)

- 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 and colleagues work

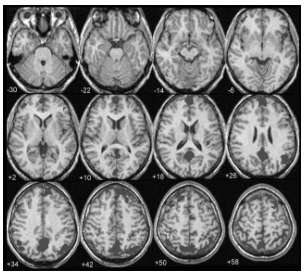
Flexibility of the GLM in SPM:

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.

[Fransson 2005 *HBM*]



Does functional connectivity not simply correspond to co-activation in SPMs?

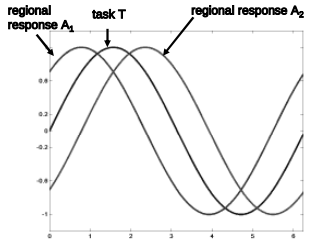
(for task-related functional connectivity)

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
$r(A_1,A_2) = 0$!

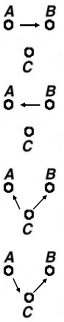


[Stephan 2004 *J. Anat.*]

Pros & Cons of functional connectivity analysis

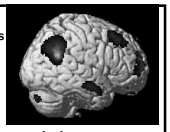
- Pros:
  - useful when we have no experimental control over the system of interest and no model of what caused the data (e.g. sleep, hallucinations, natural vision)
- Cons:
  - interpretation of resulting patterns is difficult / arbitrary;
  - no mechanistic insight;
  - operates at the level of BOLD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

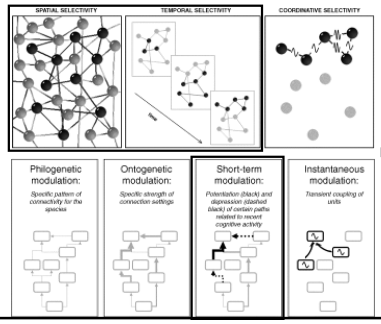
See Appendix A1 in [Friston et al. 2003 *Neuroimage*]

Types of analysis to assess effective connectivity:

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

STATIC MODELS

DYNAMIC MODEL



[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:

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

β_1: main effect of task; β_2: main effect of stim. type; β_3: interaction

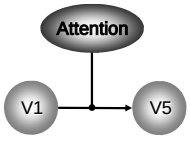
We can replace one main effect in the GLM by the time series of an area that shows this main effect.

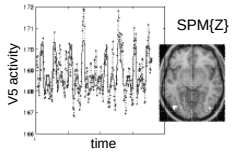
$$y = (T_A - T_B)\beta_1 + V1\beta_2 + \boxed{(T_A - T_B)V1\beta_3} + e$$

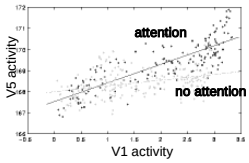
β_1: main effect of task; β_2: V1 time series ≈ main effect of stim. type; β_3: psycho-physiological interaction

[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**

structural equation modeling (SEM)

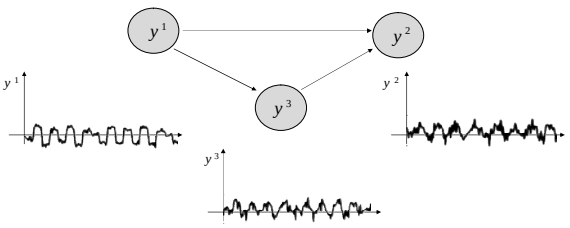
- Developed in economics (1920s);
- Introduced to imaging (PET) by McIntosh and Gonzalez-Lima (1991)

♣ **SEM (path analysis):**
multivariate tool that is used to test hypotheses regarding the influences among interacting variables.

- Connections between brain areas are based on known neuroanatomy.
- Causality is assumed a priori (not inferred from the data).
- Interregional covariances of activity are used to calculate the path coefficients representing the magnitude of the influence or directional path.

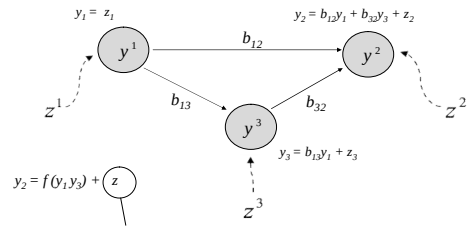
To start with…

Question: are these regions functionally related to each other?

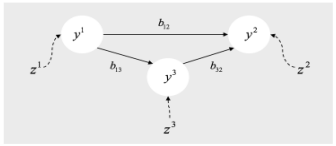


? how activity in one area is related to activity in other areas via a set of path coefficients.

To start with…



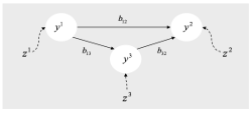
Innovations -
independent residuals, driving the region stochastically



$$y_t = y_t\beta + z_t$$

β includes only paths of interest

$$\begin{bmatrix} y_t^1 & y_t^2 & y_t^3 \end{bmatrix} = \begin{bmatrix} y_t^1 & y_t^2 & y_t^3 \end{bmatrix} \begin{bmatrix} 0 & b_{12} & b_{13} \\ 0 & 0 & 0 \\ 0 & b_{32} & 0 \end{bmatrix} + \begin{bmatrix} z_t^1 & z_t^2 & z_t^3 \end{bmatrix}$$



$$y_t = y_t\beta + z_t$$

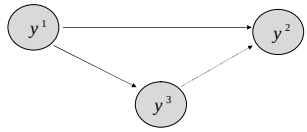
Estimate path coefficients ($b_{12,13,32}$) using a standard estimation algorithm

$$y_t(1-\beta) = z_t$$
$$y_t = z_t(1-\beta)^{-1}$$
$$\langle y_t^T y_t \rangle = (1-\beta)^{-1T} \langle z_t^T z_t \rangle (1-\beta)^{-1}$$

$\langle y_t^T y_t \rangle$ - *implied covariance*

$\langle z_t^T z_t \rangle$ - *assumed some value of the innovations*

Alternative models:



-To make inferences about changes in effective connectivity:
- "null model" (e.g. path coefficient are fix/common)
- "alternative model" (e.g. some coefficients can vary)

Model comparison: likelihood ratio (chi-squared test)

Limitations

- Static model (average effect)
- Inference about the parameters is obtained by iteratively constraining the model, nested models.
- Need to separate data
- The causality is inferred at the hemodynamic level
- No input to model (stochastic innovations)

[Penny et al. 2004 *Neuroimage*]

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!).

Thank you!