Anatomical Background of Dynamic Causal Modeling and Effective Connectivity Analyses

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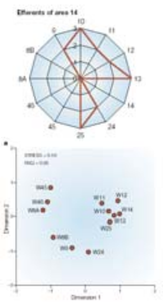
Outline

- Relation between structure and function
- Effective connectivity
- Dynamic causal modeling (DCM)

Connectional fingerprints determine local function

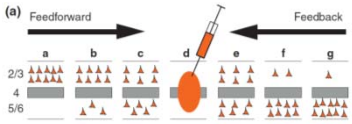
- Unique anatomical connectivity patterns (connectional fingerprints) for cortical areas
- “Families” of cortical areas (clusters) with similar patterns
- Analogous results for electrophysio-logical response patterns

Anatomical connectivity is the major determinant for the response profile of neuronal ensembles.

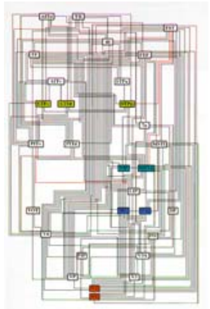


Passingham et al., *Nat Rev Neurosci,* 2002

Anatomical connections define processing hierarchies



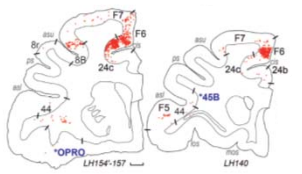
Markov & Kennedy, *TICS*, 2014



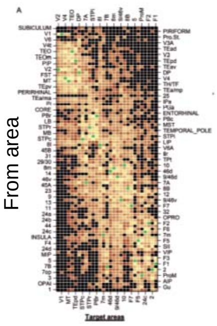
Literature based database:
http://cocomac.g-node.org/
Stephan et al., *Phil. Trans. B,* 2001;
Kötter, *Neuroinformatics,* 2004

Felleman & Van Essen, *Cereb Cortex,* 1991
Hilgetag et al, *Phil Trans. B,* 2000

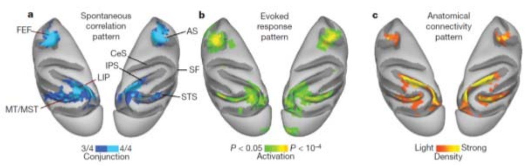
Weighted and directed connectivity matrix in macaque



Fraction of labeled neurons per area
→ weight
Markov et al., *Cereb Cortex,* 2012; *J Comp Neurol* 2014;



Activation, intrinsic functional connectivity and anatomy



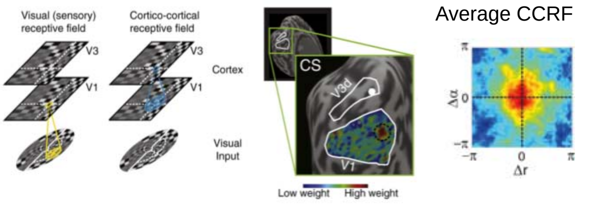
Spontaneous correlation pattern

Evoked response pattern: eye movement task

Anatomical connectivity pattern

Vincent et al, *Nature*, 2007

Tight link between functional and anatomical connectivity - human fMRI



Intrinsic functional connectivity in humans is visuotopically organized → matches monkey anatomy!

Heinzle et al, *Neuroimage*, 2011

Some naming conventions

- Anatomical connectivity
  - Fibre bundles, Close Contacts, Synapses
- Functional connectivity
  - Statistical relation, e.g. Correlation, Mutual information
- Effective connectivity
  - Directed influence, e.g. DCM, Transfer Entropy, Granger Causality

Outline

- Relation between structure and function
- Effective connectivity
- Dynamic causal modeling (DCM)

Why effective connectivity?

Anatomical connectivity is critical for understanding brain function …

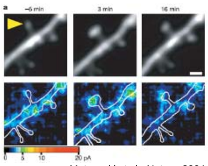
… but not sufficient on its own.

Functional connections → synapses

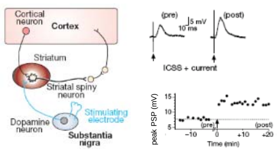
Context dependent *modulation of connection strengths*, *synaptic plasticity*, *neuronal adaptation* mechanisms, etc. …

Synaptic connections show plasticity

- Numerous mechanisms at different time scales (ms to days) → incl. very rapid changes!
- Regulated in several ways (e.g. modulatory effects of DA)

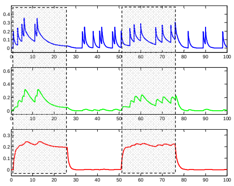


Matsuzaki et al., *Nature*, 2004



Reynolds et al., *Nature*, 2001

Connections are recruited in a context-dependent fashion



Synaptic strengths are context-sensitive: They depend on the spatio-temporal distribution of presynaptic inputs and post-synaptic events.

To understand brain (dys)function ...

… we need models of effective connectivity that:

- incorporate anatomical and physiological principles
- connect these to computational mechanisms
- allow for inference on neuronal mechanisms (e.g., synaptic plasticity) from measured brain responses

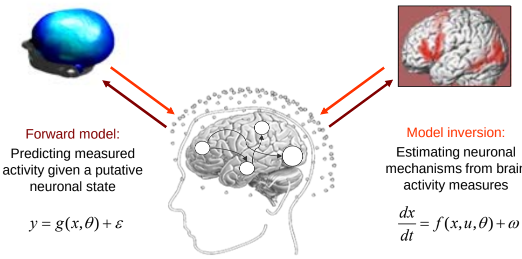
Outline

- Relation between structure and function
- Effective connectivity
- Dynamic causal modeling (DCM)

Dynamic causal modeling (DCM)

EEG, MEG

fMRI



Forward model:
Predicting measured activity given a putative neuronal state

$$y = g(x, \theta) + \varepsilon$$

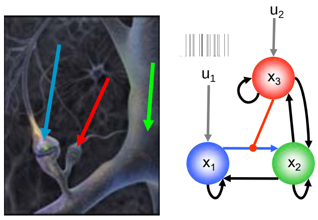
Model inversion:
Estimating neuronal mechanisms from brain activity measures

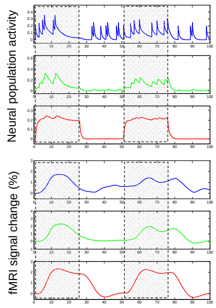
$$\frac{dx}{dt} = f(x, u, \theta) + \omega$$

David et al., *Neuroimage,* 2006
Moran et al., *NeuroImage,* 2008

Friston et al., *Neuroimage,* 2003
Stephan et al., *Neuroimage,* 2008
Stephan et al., *Neuroimage,* 2010

Nonlinear DCM for fMRI – neural model



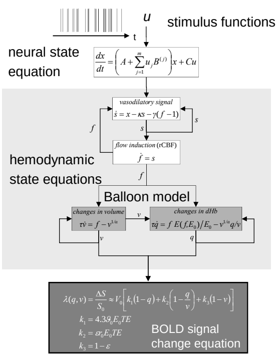


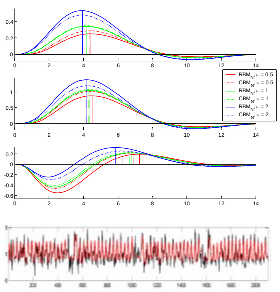
$$\frac{dx}{dt} = \left(A + \sum_{i=1}^{m} u_i B^{(i)} + \sum_{j=1}^{n} x_j D^{(j)} \right) x + Cu$$

Weights are constrained / reflect by anatomy

Stephan et al., *Neuroimage,* 2008

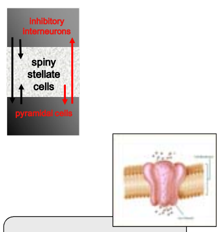
Hemodynamics DCM – forward model





Stephan et al., *Neuroimage,* 2007

Conductance-based DCMs (for EEG)



$$C\dot{V} = \sum g_i \left(V_i^0 - V_i \right)$$

$$C\dot{V}^{(2)} = g_L(V_L - V^{(2)}) + g_E^{(2)}(V_E - V^{(2)}) + g_{NMDA} f_{Mg}(V^{(2)})(V_E - V^{(2)}) + \Gamma_V$$
$$\dot{g}_E^{(2)} = \kappa_E(\gamma_{2,3}^{(E)}\sigma(\mu_V^{(3)} - V_R, \Sigma^{(3)}) - g_E^{(2)}) + \Gamma_E$$
$$\dot{g}_{NMDA}^{(2)} = \kappa_{NMDA}(\gamma_{2,3}^{(I)}\sigma(\mu_V^{(3)} - V_R, \Sigma^{(3)}) - g_{NMDA}^{(2)}) + \Gamma_{NMDA}$$

$\gamma_{1,2}^{(I)}$ $\gamma_{2,3}^{(E)}$

$$C\dot{V}^{(1)} = g_L(V_L - V^{(1)}) + g_E^{(1)}(V_E - V^{(1)}) + g_I^{(1)}(V_I - V^{(1)}) + u + \Gamma_V$$
$$\dot{g}_E^{(1)} = \kappa_E(\gamma_{1,3}^{(E)}\sigma(\mu_V^{(3)} - V_R, \Sigma^{(3)}) - g_E^{(1)}) + \Gamma_E$$
$$\dot{g}_I^{(1)} = \kappa_I(\gamma_{1,2}^{(E)}\sigma(\mu_V^{(2)} - V_R, \Sigma^{(2)}) - g_I^{(1)}) + \Gamma_I$$

$\gamma_{3,2}^{(I)}$ $\gamma_{1,3}^{(E)}$ $\gamma_{3,1}^{(E)}$

$$C\dot{V}^{(3)} = g_L(V_L - V^{(3)}) + g_E^{(3)}(V_E - V^{(3)}) + g_I^{(3)}(V_I - V^{(3)}) + g_{NMDA} f_{Mg}(V^{(3)})(V_E - V^{(3)}) + \Gamma_V$$
$$\dot{g}_E^{(3)} = \kappa_E(\gamma_{3,1}^{(E)}\sigma(\mu_V^{(1)} - V_R, \Sigma^{(1)}) - g_E^{(3)}) + \Gamma_E$$
$$\dot{g}_I^{(3)} = \kappa_I(\gamma_{3,2}^{(I)}\sigma(\mu_V^{(2)} - V_R, \Sigma^{(2)}) - g_I^{(3)}) + \Gamma_I$$
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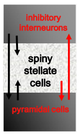
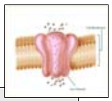
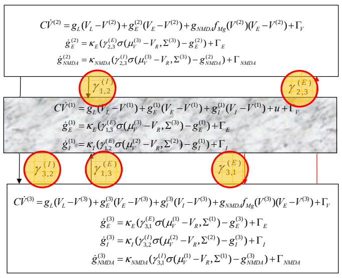
Marreiros et al., *Neuroimage,* 2010
Moran et al., *Neuroimage,* 2011

Conductance-based DCMs (for EEG)





$$C\dot{V} = \sum g_i \left(V_i^0 - V_i\right)$$



$$C\dot{V}^{(2)} = g_L(V_L - V^{(2)}) + g_E^{(2)}(V_E - V^{(2)}) + g_{NMDA} f_{Mg}(V^{(2)})(V_E - V^{(2)}) + \Gamma_V$$
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$$C\dot{V}^{(3)} = g_L(V_L - V^{(3)}) + g_E^{(3)}(V_E - V^{(3)}) + g_I^{(3)}(V_I - V^{(3)}) + g_{NMDA} f_{Mg}(V^{(3)})(V_E - V^{(3)}) + \Gamma_V$$
$$\dot{g}_E^{(3)} = \kappa_E(\gamma_{3,1}^{(E)}\sigma(\mu_V^{(1)} - V_R, \Sigma^{(1)}) - g_E^{(3)}) + \Gamma_E$$
$$\dot{g}_I^{(3)} = \kappa_I(\gamma_{3,2}^{(I)}\sigma(\mu_V^{(2)} - V_R, \Sigma^{(2)}) - g_I^{(3)}) + \Gamma_I$$
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Weights are constrained by anatomy

Marreiros et al., *Neuroimage,* 2010
Moran et al., *Neuroimage,* 2011

Generative models, model selection and model validation

Any given DCM = a particular **generative model** of how the measured data (may) have been caused

Model selection = hypothesis testing = comparing competing models (i.e. different ideas about mechanisms underlying observed data)

→ Evaluate the relative plausibility of competing explanations for an established effect (e.g., activation)

→ Careful definition of model (hypothesis) space crucial!

model selection ≠ model validation!

Model validation requires external criteria (external to the measured data)

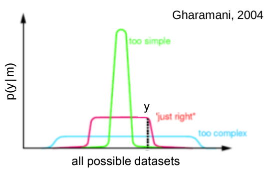
Bayesian model selection (BMS)

Model evidence:

$$p(y\,|\,m) = \int p(y\,|\,\theta, m)\, p(\theta\,|\,m)\, d\theta$$

$$\log p(y\,|\,m) = \langle \log p(y\,|\,\theta, m) \rangle - KL\left[q(\theta), p(\theta\,|\,m)\right] + KL\left[q(\theta), p(\theta\,|\,y, m)\right]$$

Gharamani, 2004



→ accounts for <u>both</u> accuracy and complexity of the model

→ a measure of how well the model generalizes

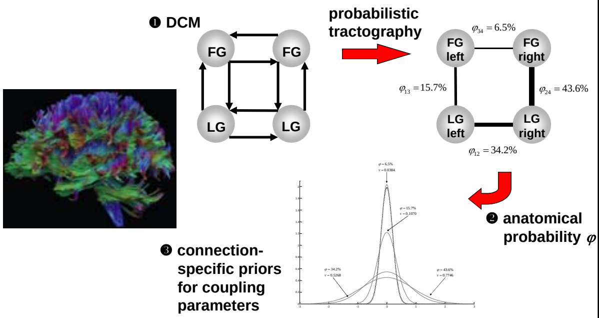
Various approximations, e.g.:
- negative free energy, AIC, BIC

McKay, *Neural Comp,* 1992
Penny et al., *Neuroimage, 2004*

Examples for the use of DCM

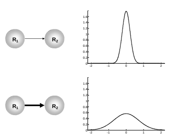
- Anatomical priors for DCM for fMRI
- Modulation of connectivity by prediction errors
- Conductance based DCM
- if time permits: DCM validation in patients or layered DCM

Anatomically informed priors



Stephan et al., *Neuroimage,* 2009

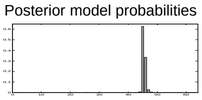
Anatomically informed priors

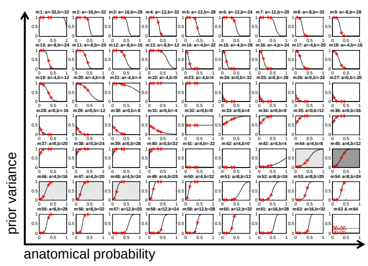


Models with anatomically informed priors were clearly superior :

Bayes Factor >10^9

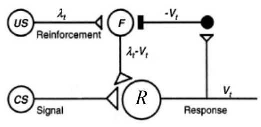
Posterior model probabilities



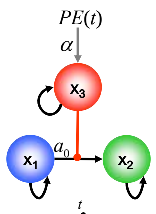


Stephan et al., *Neuroimage,* 2009

Prediction errors drive synaptic plasticity



McLaren 1989

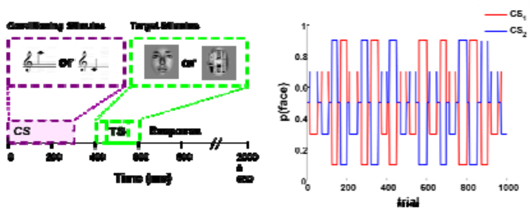


$$w_t = w_0 + \alpha \sum_{k=1}^{t} PE_k$$

$$w_t \approx a_0 + \alpha \int_0^t PE(\tau) d\tau$$

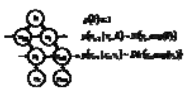
synaptic plasticity during learning = *f* (prediction error)

Learning of dynamic audio-visual associations



Model behavior with a hierarchical Bayesian Model → estimate of prediction errors PE

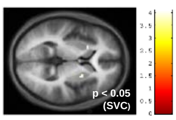
(Behrens et al., *Nat Neurosci*, 2007)



den Ouden et al., *J Neurosci*, 2010

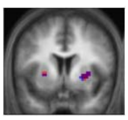
Prediction error (PE) activity in the putamen

PE during active sensory learning



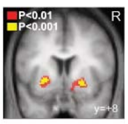
PE during incidental sensory learning

den Ouden et al., *Cereb Cortex*, 2009



PE during RF learning

O'Doherty et al., *Science*, 2004

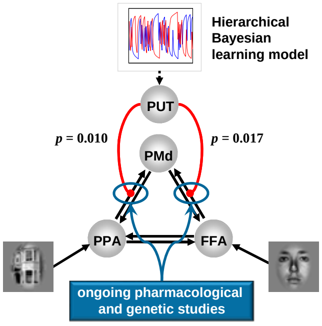


PE = "teaching signal" for synaptic plasticity during learning

Could the putamen be regulating trial-by-trial changes of task-relevant connections?

PE control plasticity during adaptive cognition

- Influence of visual areas on premotor cortex:
  - stronger for surprising stimuli
  - weaker for expected stimuli



den Ouden et al., *J Neurosci,* 2010

What is a good model?

"… essentially, all models are wrong, but some are useful."
George E.P. Box

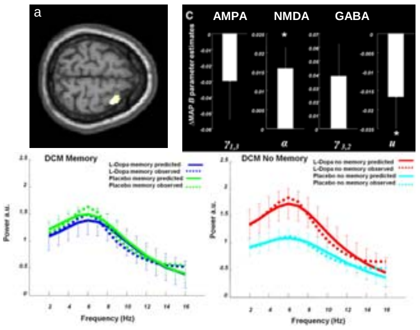
Strategies for model validation

1. in silico — **numerical analysis & simulation studies**
2. humans — **experiments of known cognitive/neurophys. processes**
3. animals & humans — **experimentally controlled system perturbations**
4. patients — **clinical facts**

Examples: Validation of DCM in animal studies:

- infers site of seizure origin (David et al. 2008)
- infers primary recipient of vagal nerve stimulation (Reyt et al. 2010)
- infers synaptic changes as predicted by microdialysis (Moran et al. 2008)
- infers fear conditioning induced plasticity in amygdala (Moran et al. 2009)
- tracks anaesthesia levels (Moran et al. 2011)
- predicts sensory stimulation (Brodersen et al. 2010)

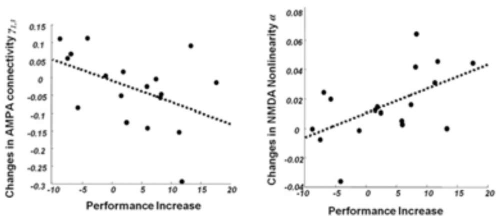
Dopaminergic modulation of AMPA/NMDA receptors



- ↓ exogenous inputs to layer IV
- ↑ NMDA inputs to layer III pyramidal cells and interneurons

Moran et al., *Curr Biol,* 2011

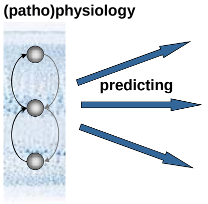
Estimates of AMPA/NMDA correlate with behaviour



Moran et al., *Curr Biol,* 2011

Validating models against clinical facts

model of neuronal (patho)physiology



individual diagnosis

individual outcome

individual therapeutic response

Brodersen et al., *PLoS Comp Biol,* 2011;
Brodersen et al, *Neuroimage Clin.* 2013

Summary

- Anatomical connectivity information is important, but not everything
- Models of effective connectivity → neural system mechanisms can be inferred from neuroimaging data
- DCM is one (not the only) method for this:
  - Neuronal interactions are modeled at the hidden neuronal level
  - Bayesian system identification method
  - Key role for model selection
  - Can be integrated with measures of anatomical connectivity
  - Can be integrated with computational models
- **Validation is critical** (for any modeling approach)

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Translational Neuromodeling Unit