Dynamical causal modelling of basal ganglia beta synchrony in Parkinson's Disease

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Overview

- Brief introduction to Dynamical causal modelling (DCM)

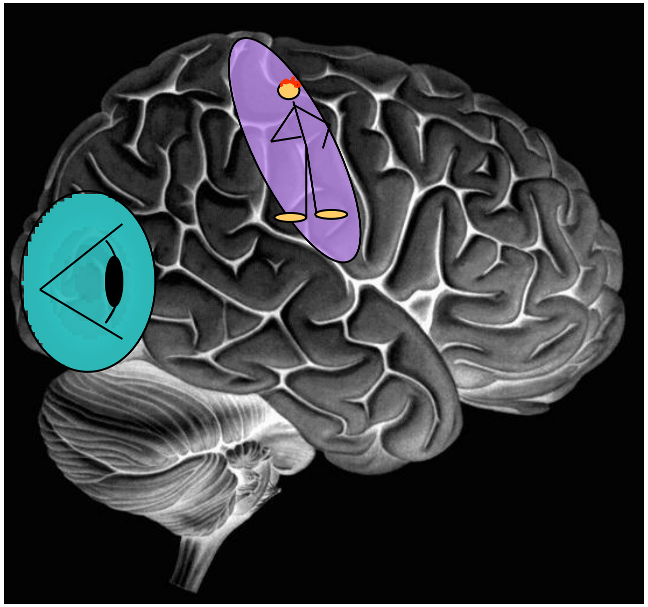
- Brief introduction to DCM for steady state responses (SSR)

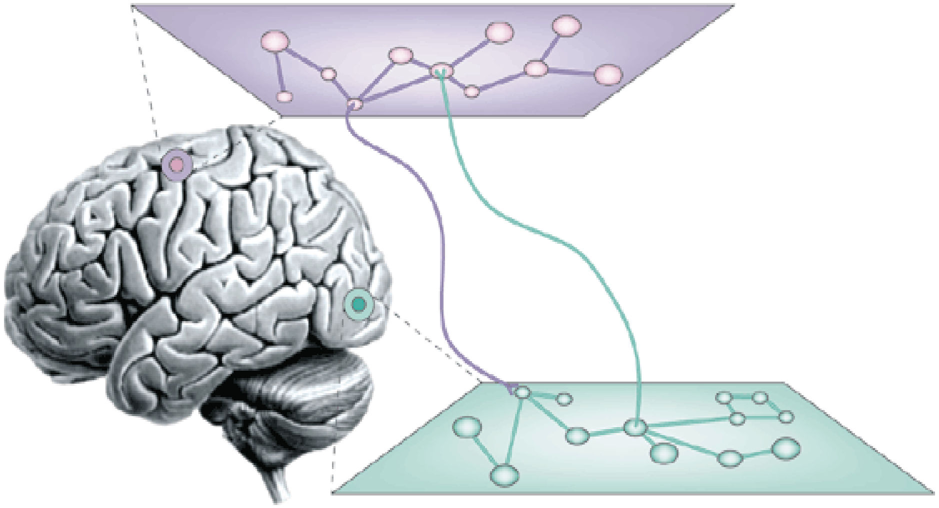
- DCM for SSR application to beta synchrony in parkinsonian networks

Principles of Organization

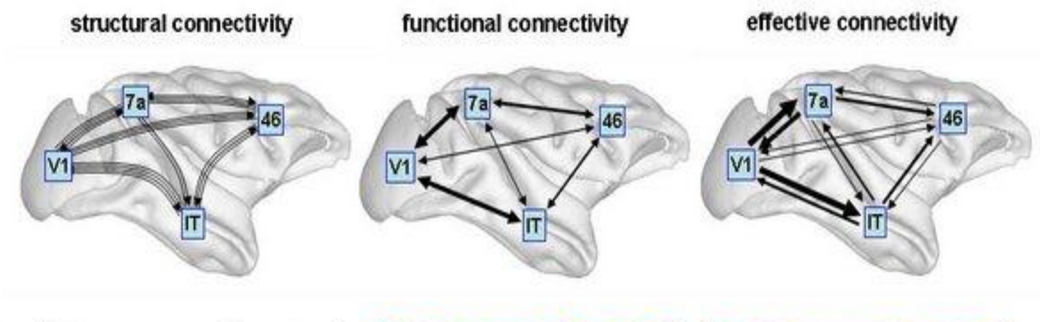
Functional specialization

Functional integration





Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

- **anatomical/structural connectivity**
  = presence of axonal connections

- **functional connectivity**
  = statistical dependencies between regional time series

- **effective connectivity**
  = directed influences between neurons or neuronal populations

Some models of effective connectivity

- Structural Equation Modelling (SEM)
  McIntosh et al. 1991, 1994; Büchel & Friston 1997; Bullmore et al. 2000

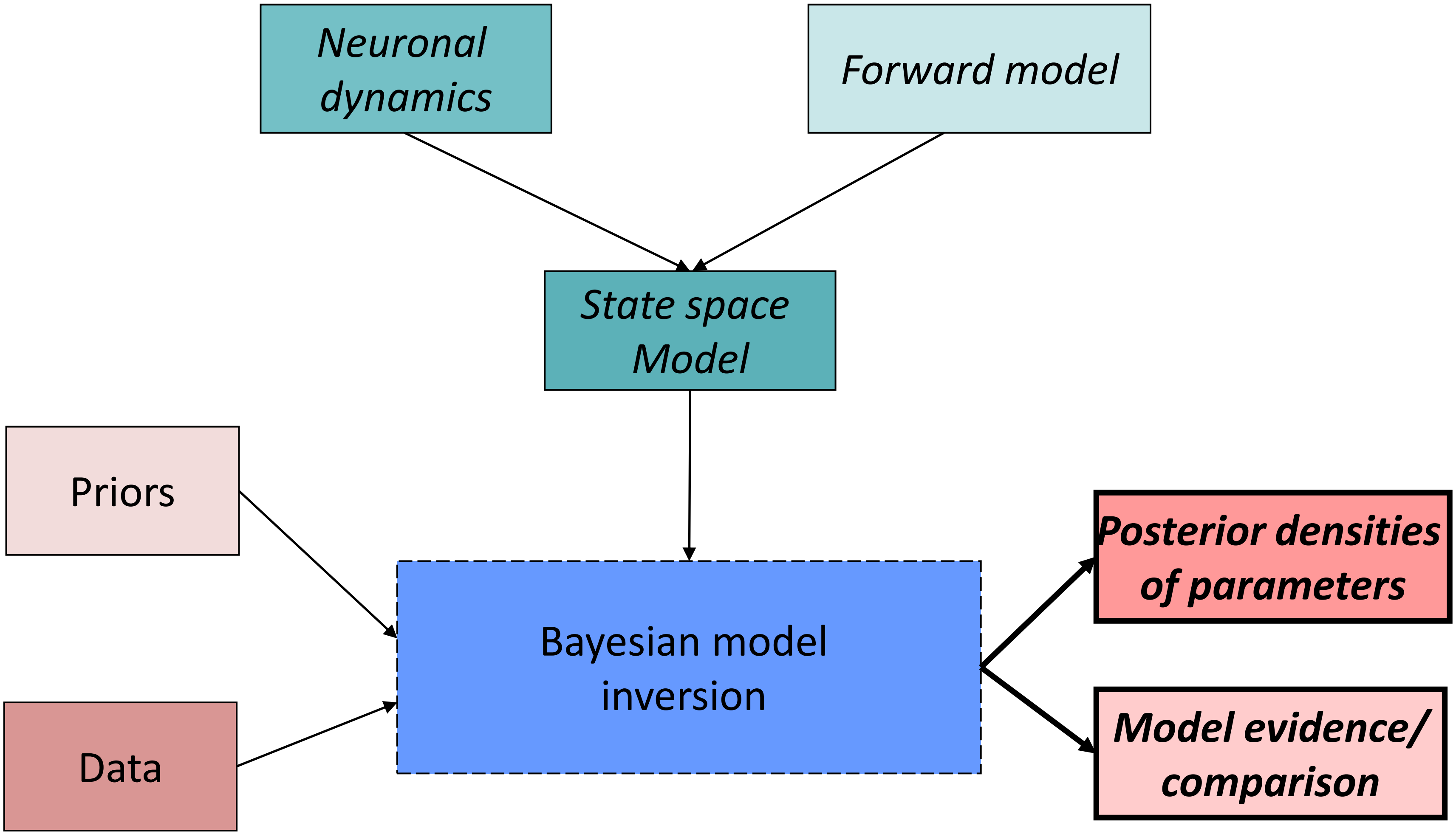
- regression models
  (e.g. psycho-physiological interactions, PPIs)
  Friston et al. 1997

- Volterra kernels
  Friston & Büchel 2000

- Time series models (e.g. MAR/VAR, Granger causality)
  Harrison et al. 2003, Goebel et al. 2003

- Dynamic Causal Modelling (DCM)
  fMRI: Friston et al. 2003; *MEEG:* David et al. 2006

DCM map

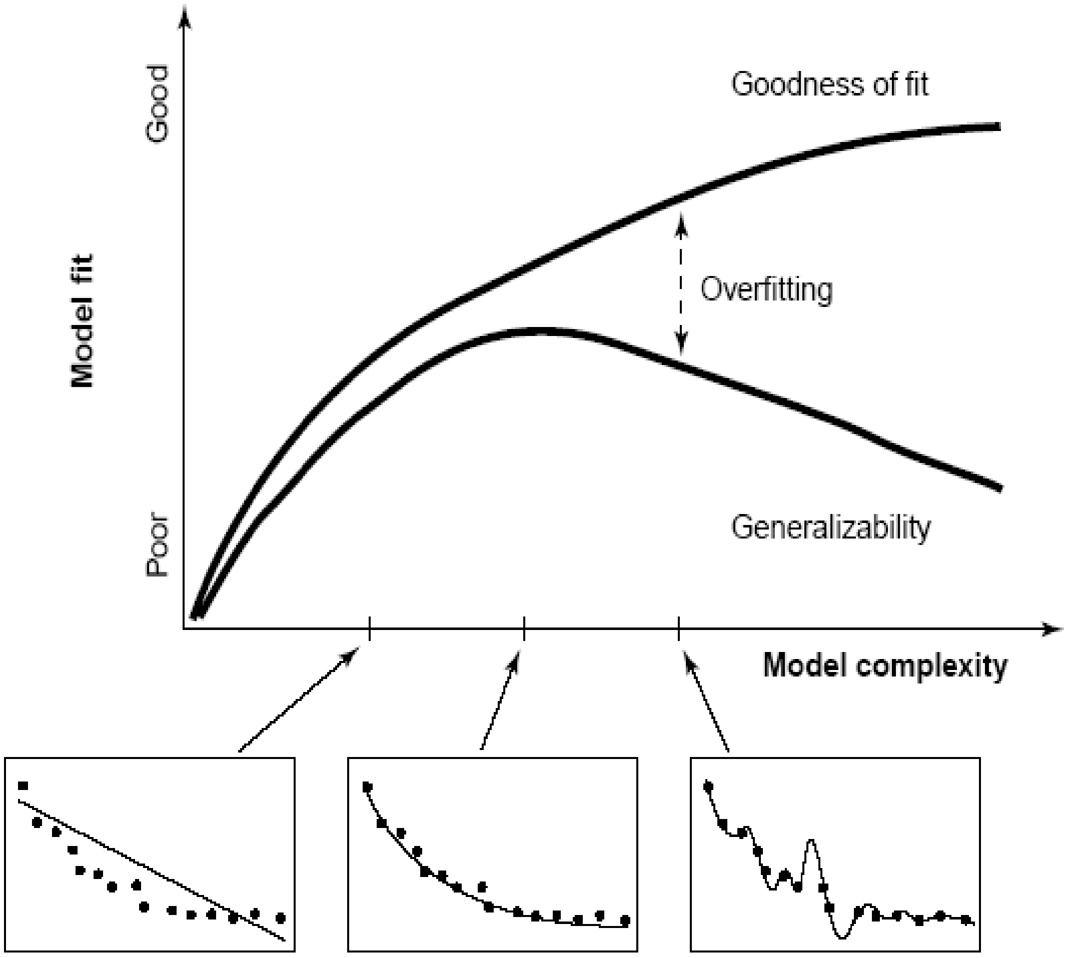

Neuronal dynamics
Forward model
State space Model
Priors
Data
Bayesian model inversion
Posterior densities of parameters
Model evidence/ comparison

Model comparison and selection

Given competing hypotheses on structure & functional mechanisms of a system, which model is the best?

Which model represents the best balance between model fit and model complexity?

For which model m does $p(y|m)$ become maximal?

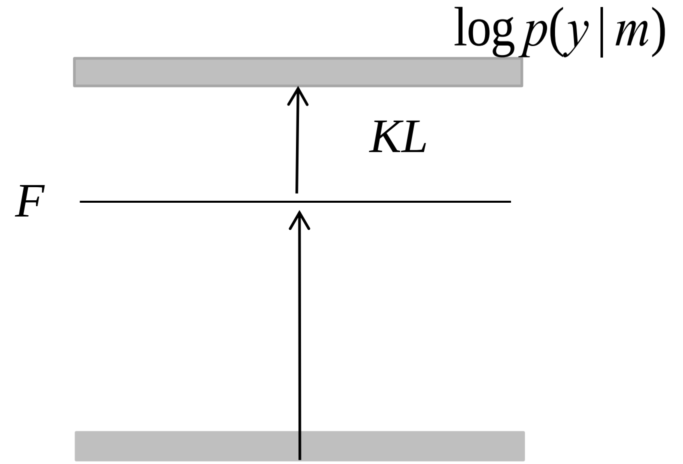


Pitt & Miyung (2002) *TICS*

Baysian model selection

The negative free energy approximation

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



balance between fit and complexity = accuracy - *complexity*

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

Deviation of posterior mean from prior mean

Independent Priors

$$KL_{Laplace} = \frac{1}{2}\ln\left|C_\theta\right| - \frac{1}{2}\ln\left|C_{\theta|y}\right| + \frac{1}{2}\left(\mu_{\theta|y} - \mu_\theta\right)^T C_\theta^{-1}\left(\mu_{\theta|y} - \mu_\theta\right)$$

Dependent Posteriors

Bayes factors

For a given dataset, to compare two models, we compare their evidences.

positive value, [0; ∞[

$$B_{12} = \frac{p(y \mid m_1)}{p(y \mid m_2)}$$

Kass & Raftery classification:

B_{12}	$p(m_1 \mid y)$	Evidence
1 to 3	50-75%	weak
3 to 20	75-95%	positive
20 to 150	95-99%	strong
$\geq$ 150	$\geq$ 99%	Very strong

or their log evidences

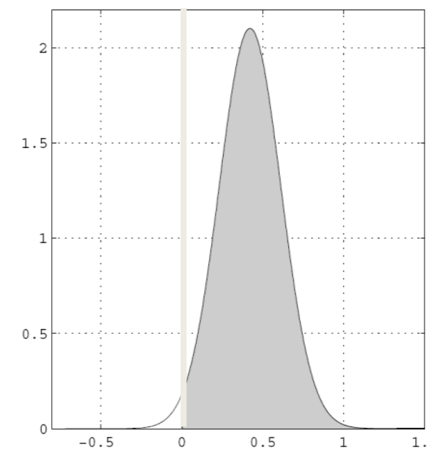
$$\ln(B_{12}) \approx F_1 - F_2$$

Kass & Raftery 1995, *J. Am. Stat. Assoc.*

Inference about DCM parameters

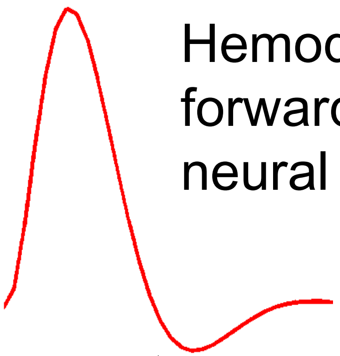
- Gaussian assumptions about the posterior distributions of the parameters
- posterior probability that a certain parameter (or contrast of parameters $c^T \eta_{\theta|y}$) is above a chosen threshold γ:

$$p = \phi_N \left(\frac{c^T \eta_{\theta|y} - \gamma}{\sqrt{c^T C_{\theta|y} c}} \right)$$



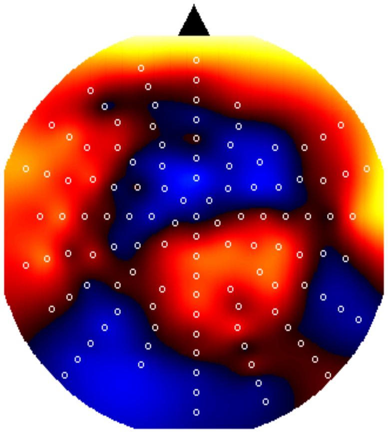
- By default, γ is chosen as zero ("does the effect exist?").

Dynamical Causal Modelling: Generic Framework



Hemodynamic
forward model:
neural activity→BOLD

Electromagnetic
forward model:
neural activity→EEG
MEG
LFP



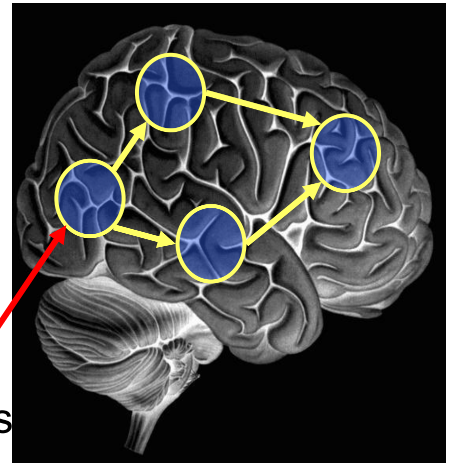
Neural state equation:

$$\frac{dx}{dt} = F(x,u,\theta)$$

fMRI

EEG/MEG

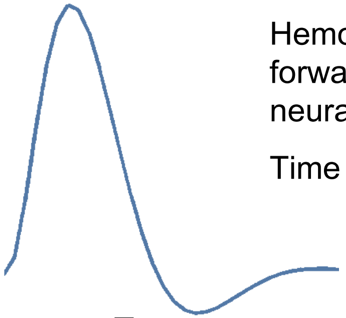
simple neuronal model
complicated forward model



inputs

complicated neuronal model
simple forward model

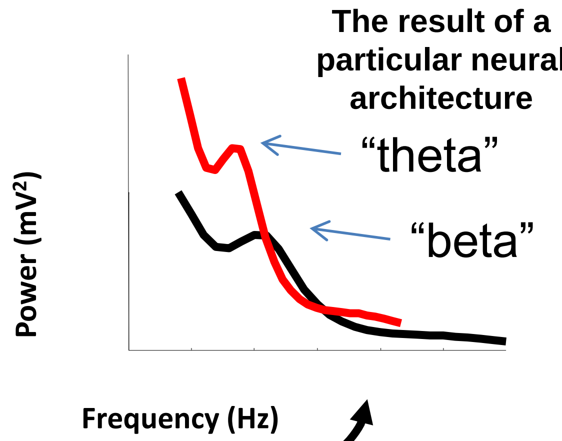
Dynamical Causal Modelling: Generic Framework



Hemodynamic
forward model:
neural activity→BOLD

Time Domain Data

Electromagnetic
forward model:
neural activity→EEG
MEG
LFP
Steady State Frequency Data



$$\frac{dx}{dt} = F(x, u, \theta)$$

Neural state equation:

fMRI

simple neuronal model

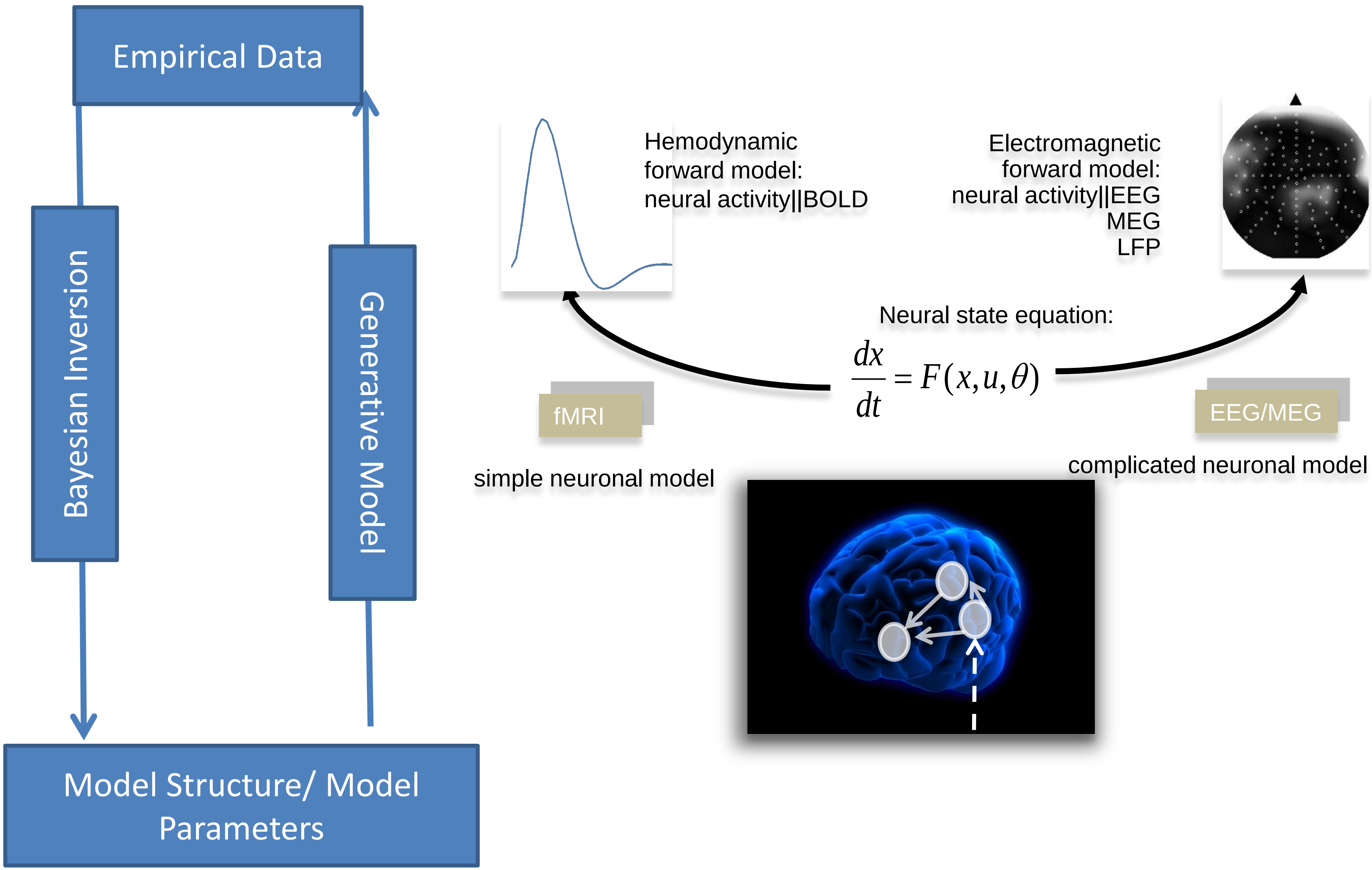
Slow time scale

EEG/MEG

complicated neuronal model

Fast time scale

Dynamical Causal Modelling: Generic Framework



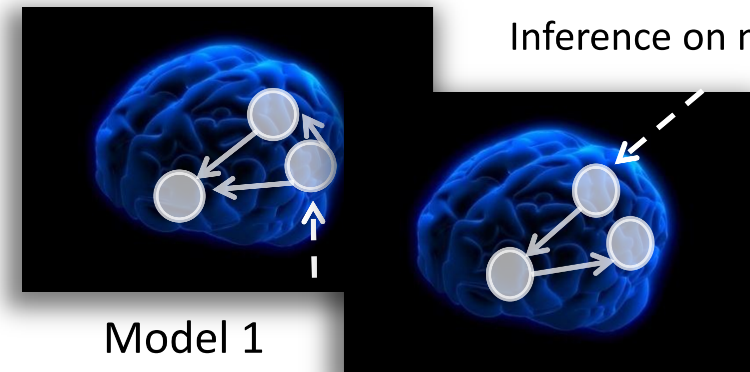
Dynamical Causal Modelling: Generic Framework

Bayesian Inversion

Bayes' rules: $$p(\theta \mid y, m) = \frac{p(y \mid \theta, m)\, p(\theta \mid m)}{p(y \mid m)}$$

Free Energy: $$\underset{\max}{F} = \boxed{\ln p(y|m)} - \boxed{D(q(\theta) \| p(\theta|y,m))}$$

Inference on models



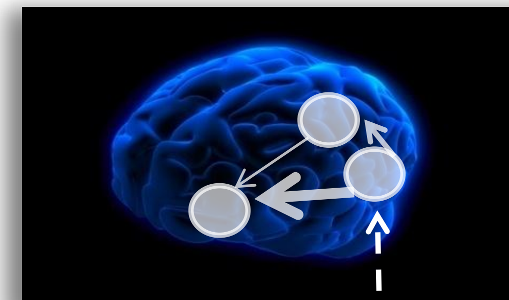
Model 1

Model 2

Model comparison via Bayes factor:

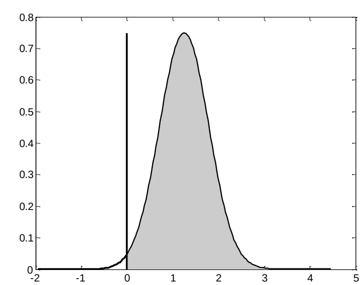
$$BF = \frac{p(y \mid m_1)}{p(y \mid m_2)}$$

Inference on parameters



Model 1

$$q(\theta) \approx p(\theta|y,m)$$



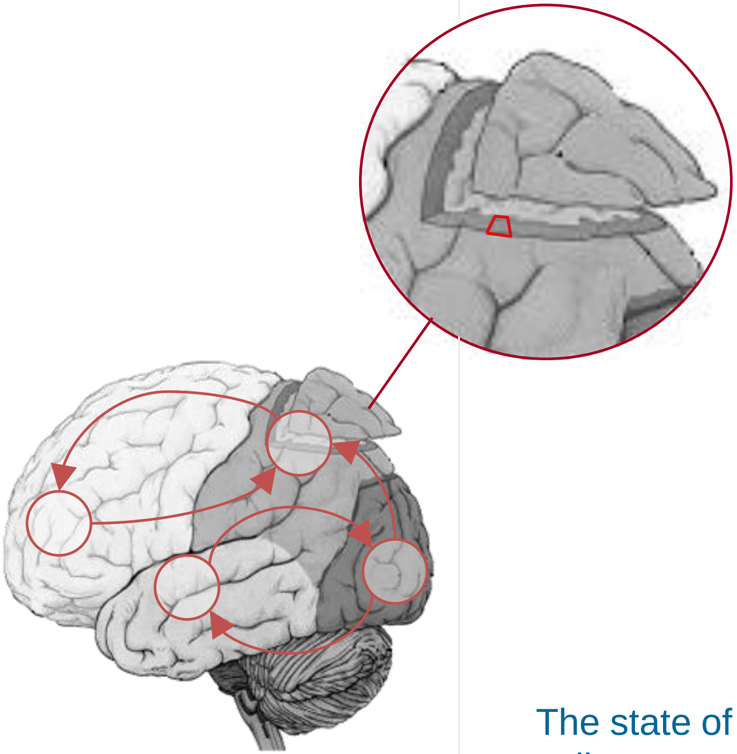
$$p(conn > 0 \mid y) = 99.1\%$$

- accounts for <u>both</u> accuracy and complexity of the model
- allows for inference about structure (generalisability) of the model

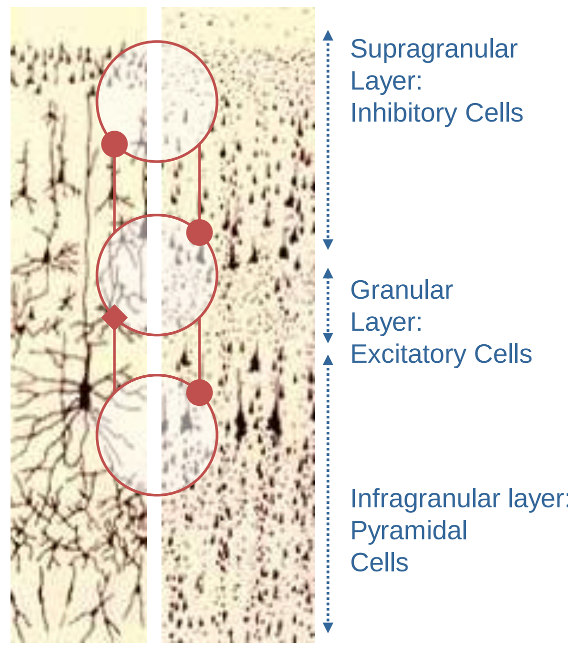
Stephan, Penny, Daunizeau, Moran, Friston (2009)

One Source

macro-scale



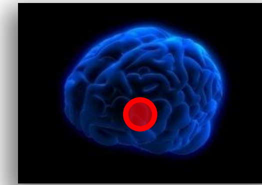
meso-scale



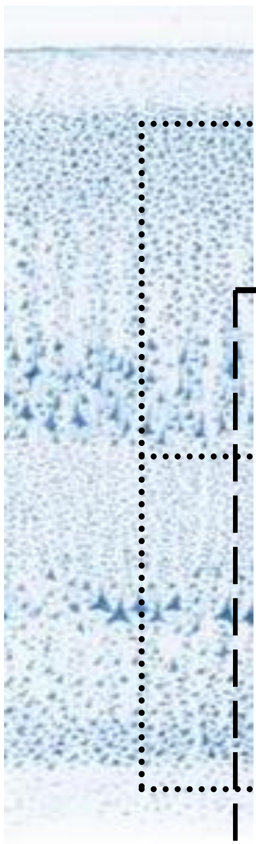
The state of a neuron comprises a number of attributes, membrane potentials, conductances etc. Modelling these states can become intractable. Mean field approximations summarise the states in terms of their ensemble density. Neural mass models consider only point densities and describe the interaction of the means in the ensemble

micro-scale

Neural Mass Model



Intrinsic connections



γ_5

Inhibitory cells in agranular layers

$$\dot{x}_7 = x_8$$
$$\dot{x}_8 = \kappa_e H_e (A^B + A^L + \gamma_3) S(x_9) - 2\kappa_e x_8 - \kappa_e^2 x_7$$
$$\dot{x}_{10} = x_{11}$$
$$\dot{x}_{11} = \kappa_i H_i \gamma_5 S(x_{12}) - 2\kappa_i x_{11} - \kappa_i^2 x_{10}$$
$$\dot{x}_{12} = x_8 - x_{11}$$

γ_4 γ_3

Excitatory spiny cells in granular layers

$$\dot{x}_1 = x_4$$
$$\dot{x}_4 = \kappa_e H_e ((A^F + A^L + \gamma_1) S(x_9) + Cu) - 2\kappa_e x_4 - \kappa_e^2 x_1$$

γ_1 γ_2

Excitatory pyramidal cells in agranular layers

$$\dot{x}_2 = x_5$$
$$\dot{x}_5 = \kappa_e H_e ((A^B + A^L) S(x_9) + \gamma_2 S(x_1)) - 2\kappa_e x_5 - \kappa_e^2 x_2$$
$$\dot{\mu}_3 = x_6$$
$$\dot{x}_6 = \kappa_i H_i \gamma_4 S(x_{12}) - 2\kappa_i x_6 - \kappa_i^2 x_3$$
$$\dot{x}_9 = x_5 - x_6$$

Extrinsic Connections:

Forward $\longrightarrow$

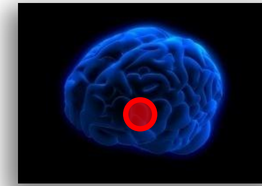
Backward $- - \rightarrow$

Lateral $\cdots\rightarrow$

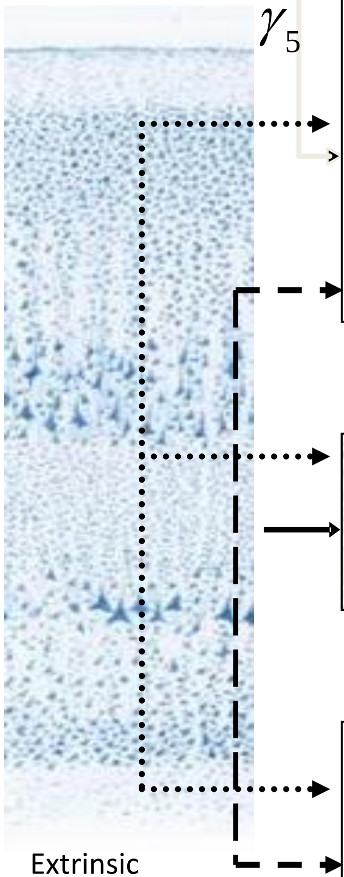
$$\dot{x} = f(x, u)$$

Moran, Kiebel, Stephan, Reilly, Daunizeau, Friston (2007)

Neural Mass Model



Intrinsic connections



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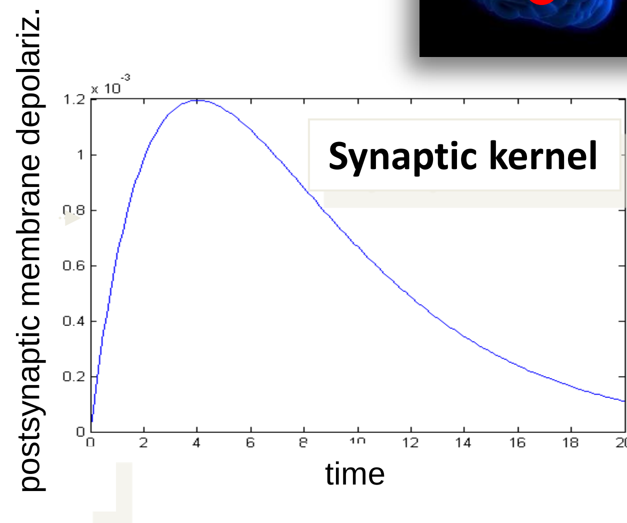
Extrinsic Connections:

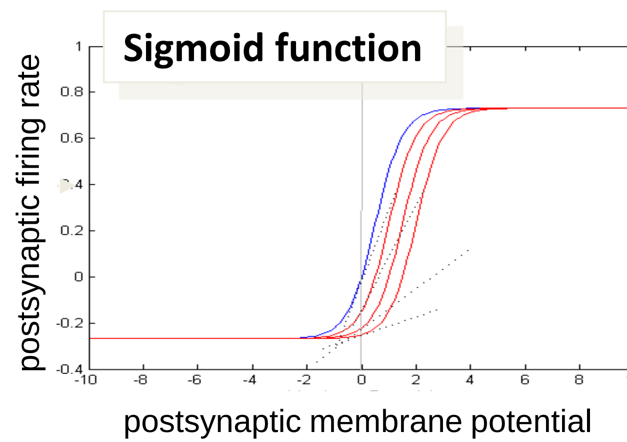
Forward →

Backward - - →

Lateral ····→

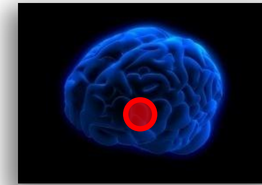
$$\dot{x} = f(x, u)$$





Moran, Kiebel, Stephan, Reilly, Daunizeau, Friston (2007)

Neural Mass Model



Intrinsic connections

γ_5

Inhibitory cells in agranular layers

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γ_4 γ_3

Excitatory spiny cells in granular layers

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γ_1 γ_2

Excitatory pyramidal cells in agranular layers

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$$\dot{x}_9 = x_5 - x_6$$

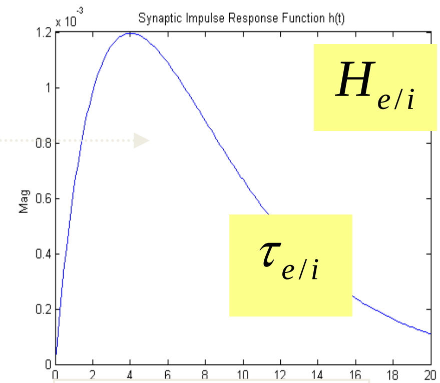
$$\dot{x} = f(x,u)$$

Extrinsic Connections:

Forward ⟶

Backward – – →

Lateral ·····→



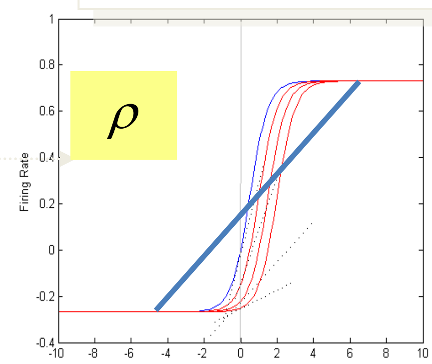
$H_{e/i}$: Receptor Density

$\tau_{e/i}$

Synaptic kernel

$$v = r \otimes h$$

Sigmoid function



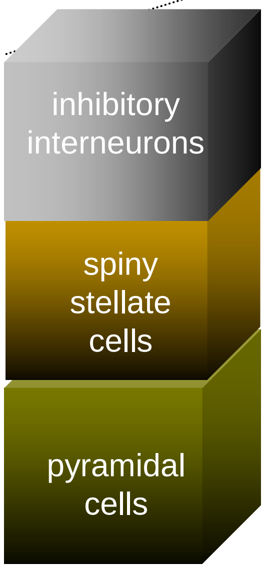
ρ : Firing Rate

$$r = S(v)$$

Moran, Kiebel, Stephan, Reilly, Daunizeau, Friston (2007)

State Equations

$$\dot{x} = f(x, u, \theta)$$



$$\dot{x}_7 = x_8$$

$$\dot{x}_8 = \frac{H_e}{\tau_e}((A^B + A^L + \gamma_3 I)S(x_0)) - \frac{2x_8}{\tau_e} - \frac{x_7}{\tau_e^2}$$

γ_4 γ_3

$$\dot{x}_1 = x_4$$

$$\dot{x}_4 = \frac{H_e}{\tau_e}((A^F + A^L + \gamma_1 I)S(x_0) + Cu) - \frac{2x_4}{\tau_e} - \frac{x_1}{\tau_e^2}$$

γ_1 Intrinsic connections γ_2

$$\dot{x}_0 = x_5 - x_6$$

$$\dot{x}_2 = x_5$$

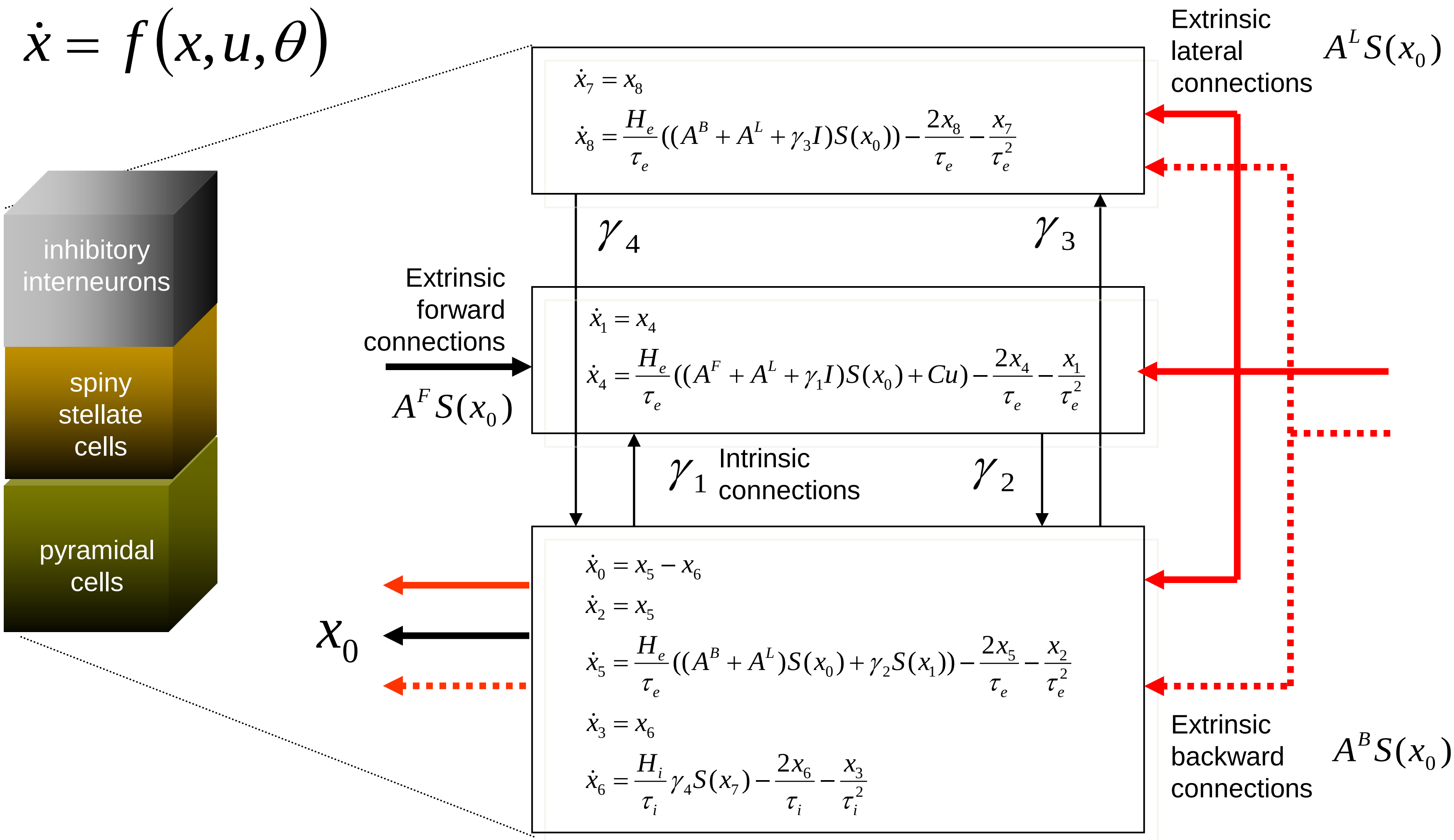
$$\dot{x}_5 = \frac{H_e}{\tau_e}((A^B + A^L)S(x_0) + \gamma_2 S(x_1)) - \frac{2x_5}{\tau_e} - \frac{x_2}{\tau_e^2}$$

$$\dot{x}_3 = x_6$$

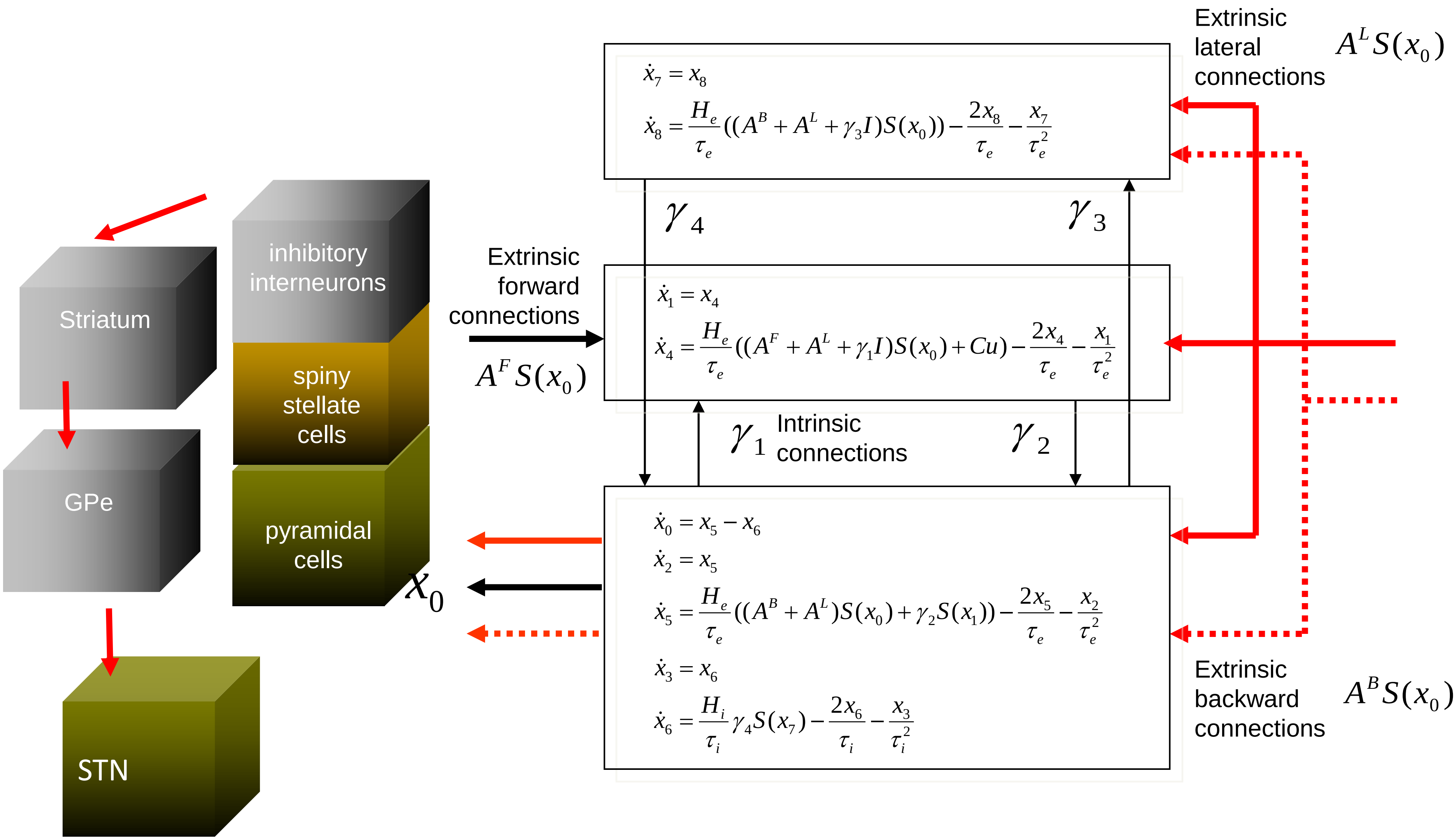
$$\dot{x}_6 = \frac{H_i}{\tau_i}\gamma_4 S(x_7) - \frac{2x_6}{\tau_i} - \frac{x_3}{\tau_i^2}$$

State Equations

$$\dot{x} = f(x,u,\theta)$$



State Equations in BG



Beta synchrony in parkinsonian networks

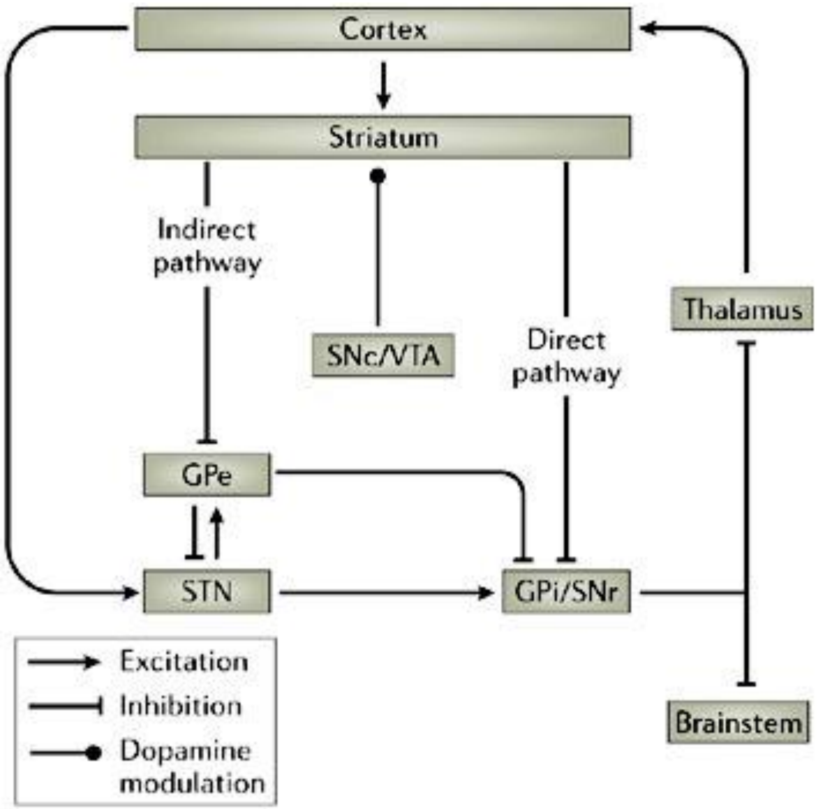
- Parkinson's disease (**PD**) is associated with abnormally **synchronized** oscillations in the **beta** frequency band in the ***cortical-basal ganglia-thalamocortical*** **network**. Amplitude changes in these oscillations correlate with variations in motor impairment.

- To study effective connectivity in this network, we use a dynamic causal model (**DCM**) of steady-state responses (**SSR**), which summarizes electrophysiological data in terms of their ***cross-spectral density***. These spectral features are generated by biologically plausible, **neural-mass models** of coupled electromagnetic sources.

- Our ultimate **goal** is to use such models, once validated, to **identify novel therapeutic targets** in patients with PD.

Pathologic Beta Rythm in Parkinson`s

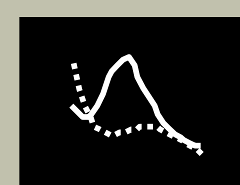
Chronic loss Dopamine innervations in the Striatum



Traditional theory of negative motor symptoms induced by an unbalance in the striatal outputs of direct (↓) /indirect (↑) pathways

Newer theory focused on pathological synchrony: STN

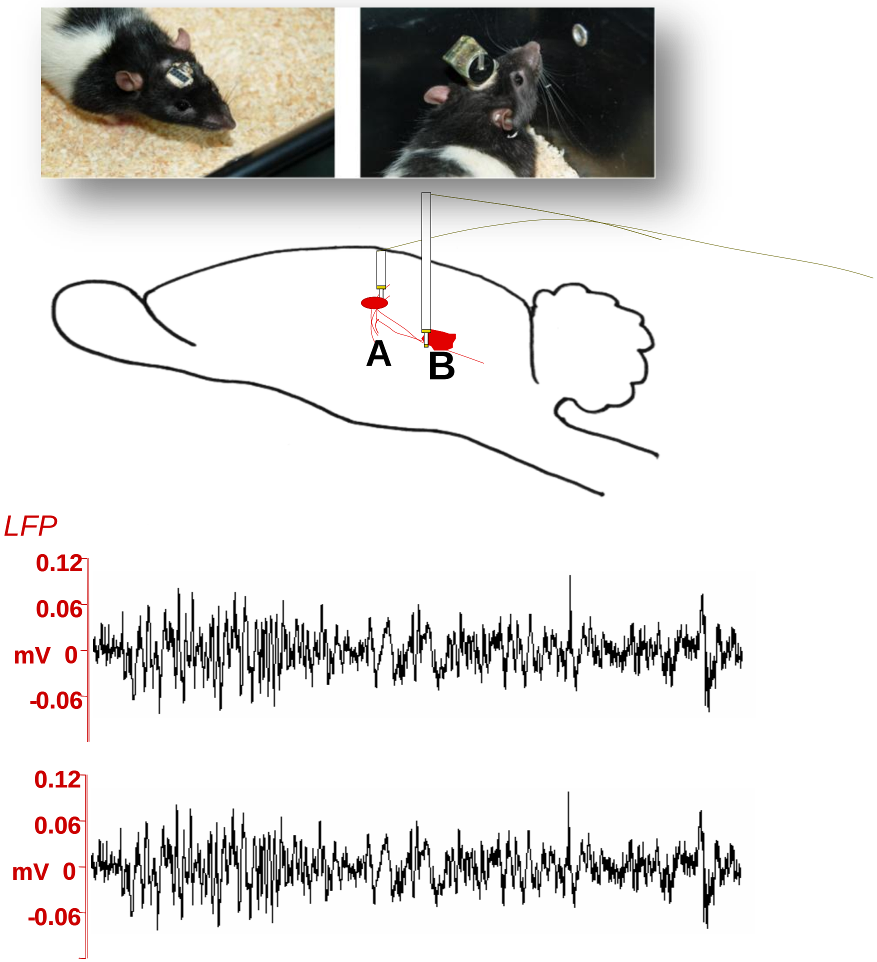
Beta oscillations correlate to disease state



20 Hz

Pathologic Beta Rythm in Parkinson`s

Alterations in Brain Connectivity Underlying Beta Oscillations in Parkinsonism
PLOS computational Biology
Moran et al., 2011

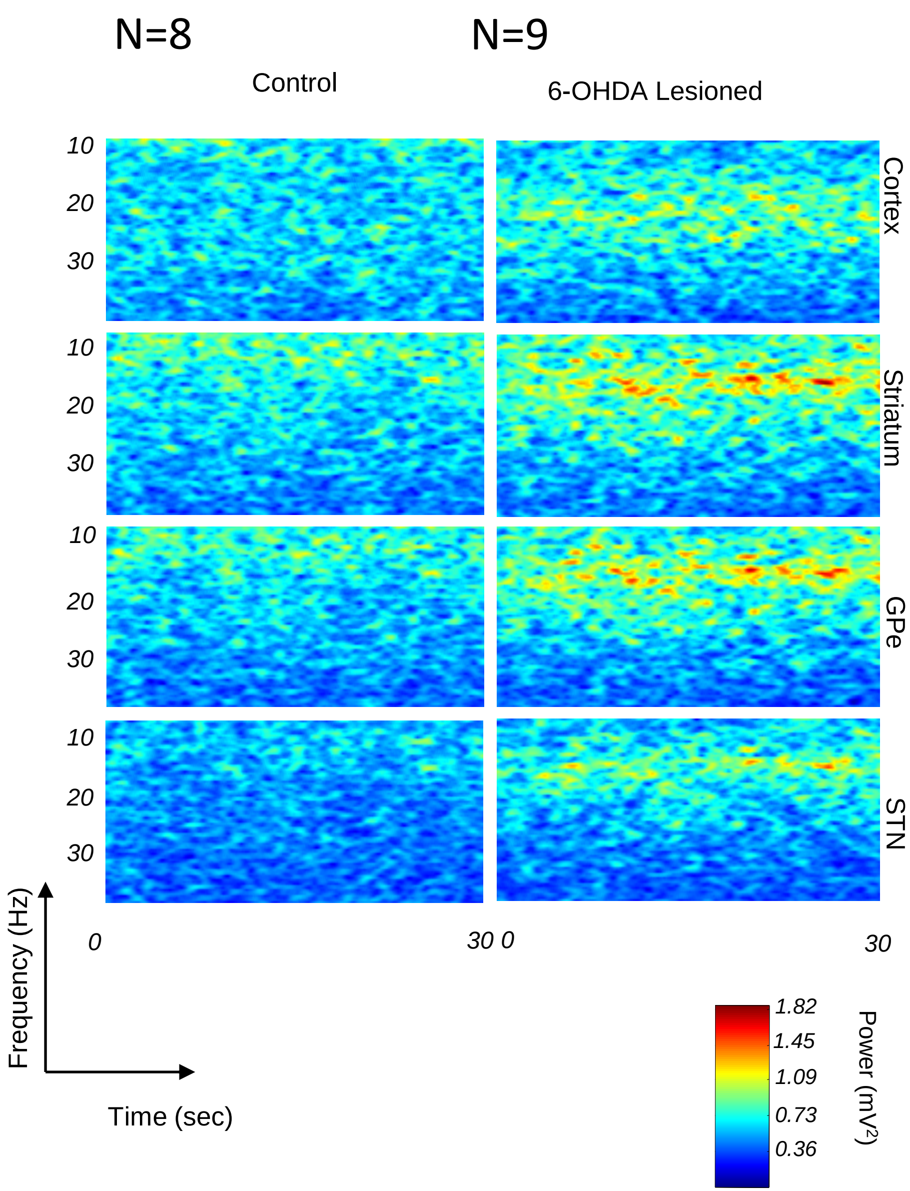


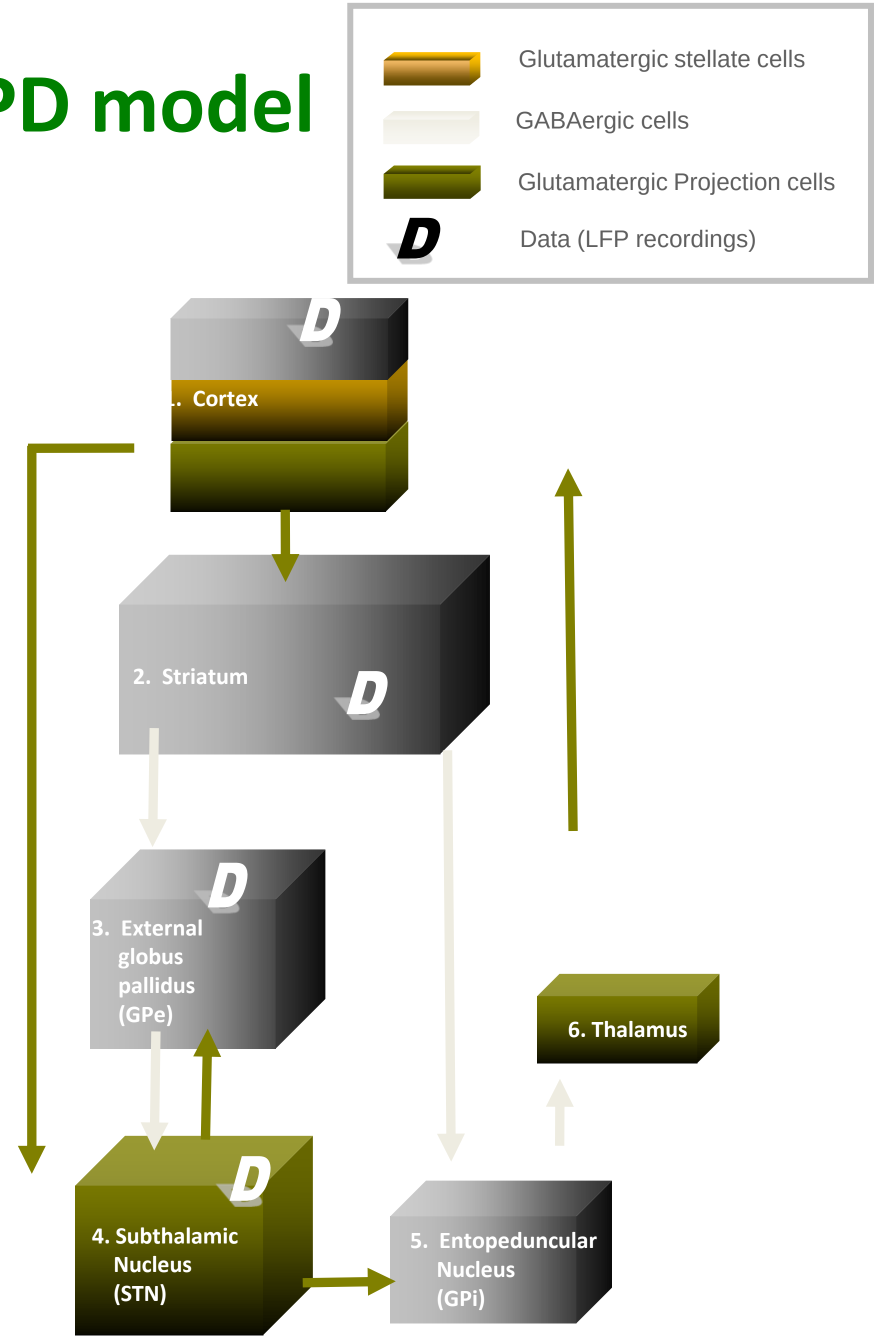
Cortico-basal ganglia-thalamocortical circuits are disrupted by the dopamine depletion of Parkinson's disease (PD), leading to pathologically exaggerated beta oscillations.

Used 6-hydroxydopamine-lesioned rat model of PD to examine the effective connectivity underlying these spectral abnormalities.

Local field potential recordings made simultaneously in the frontal cortex, striatum, GPe and STN.

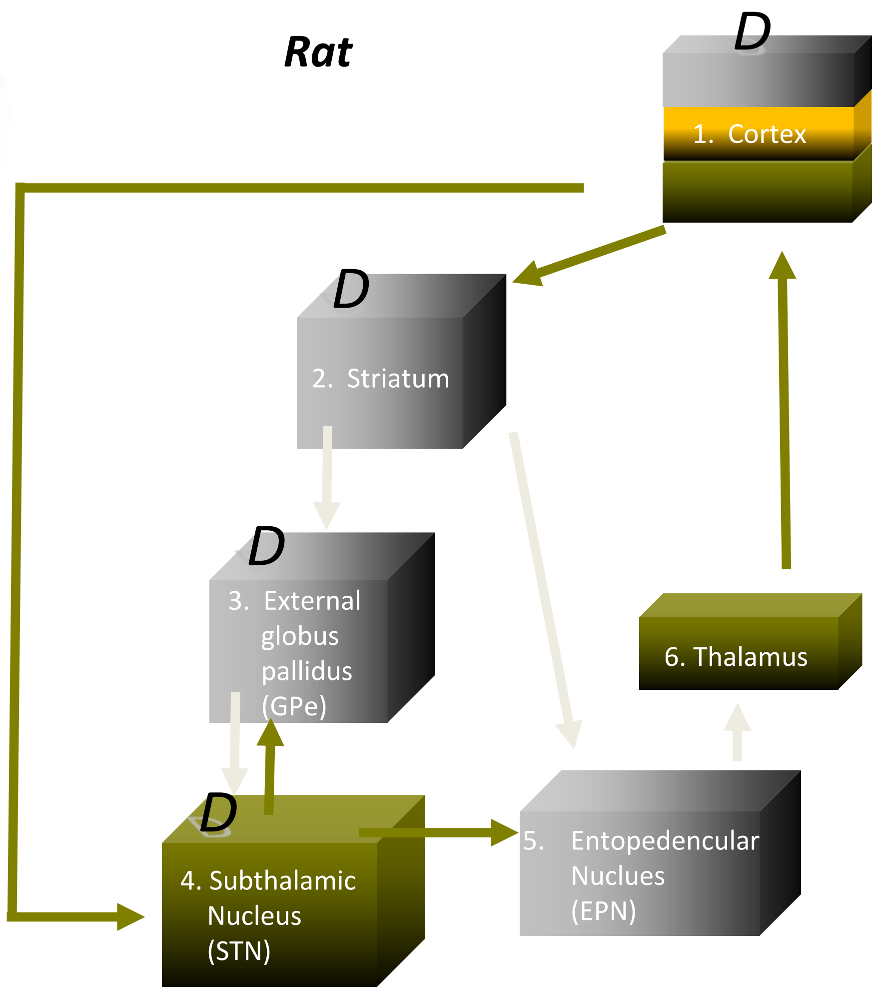
DCM of Beta in 6-OHDA rat PD model





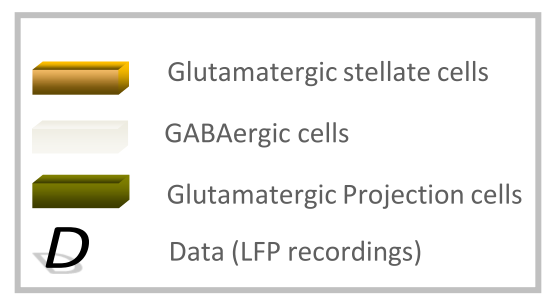
Structure of the Dynamical Causal Model

Rat

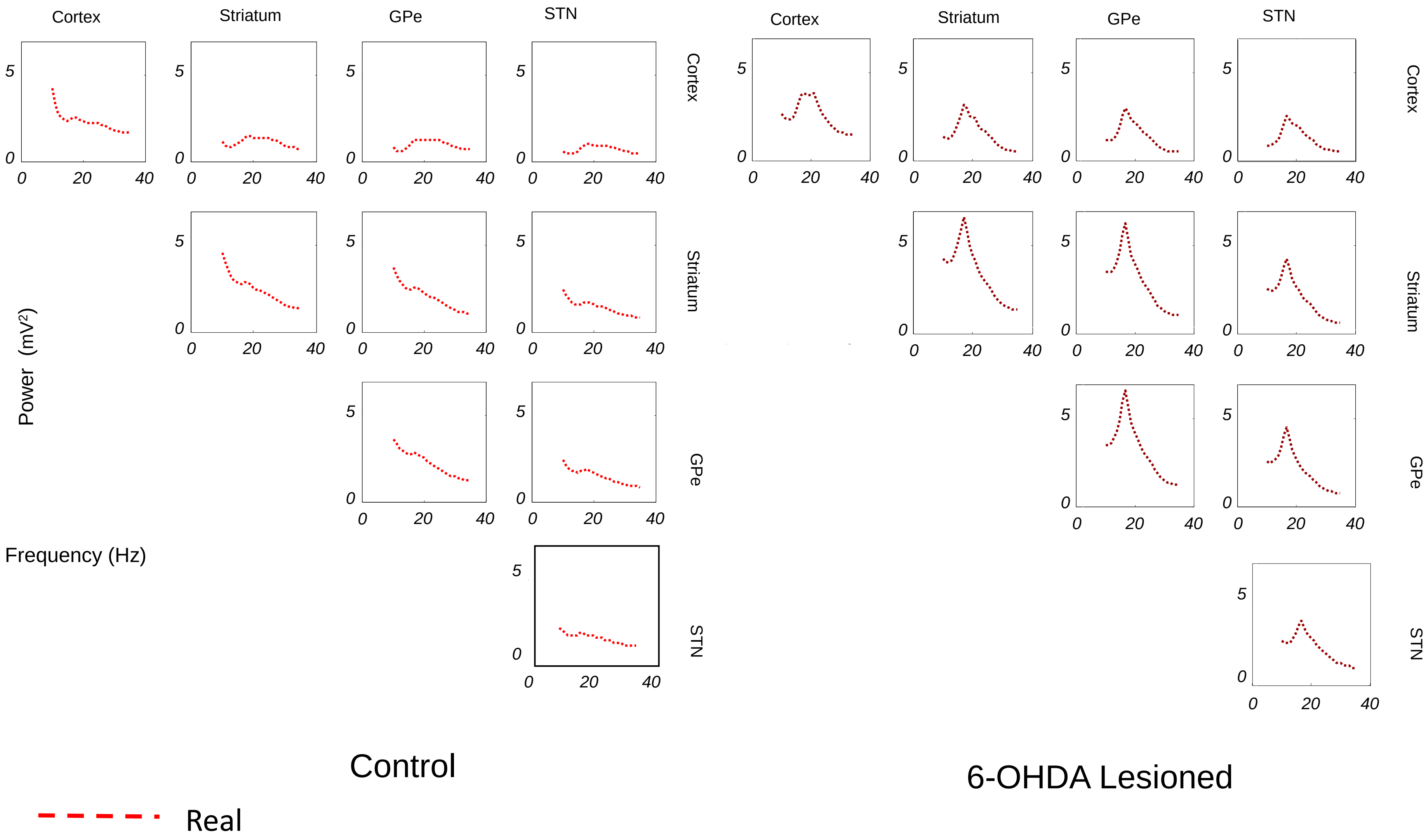


Limited network sampling in rodents

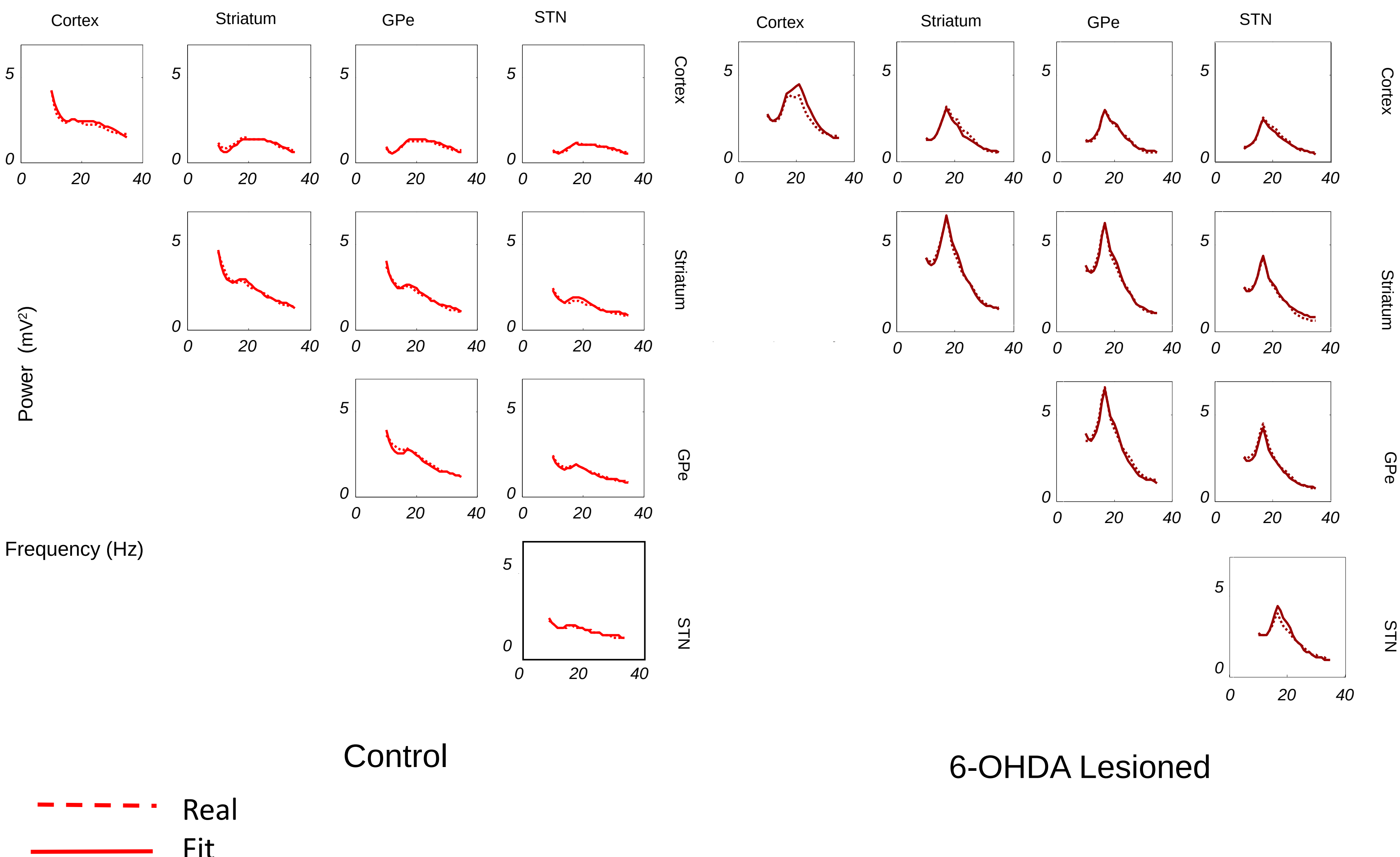
Even with reduced circuit model & LFP recordings with EEG we have at least 2 hidden sources



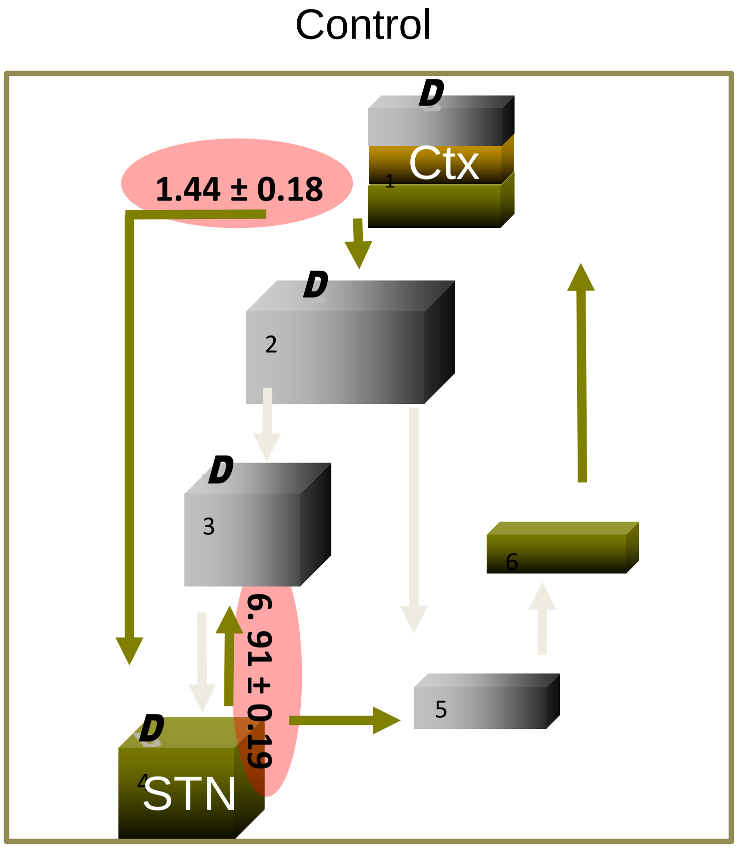
Model Inversion



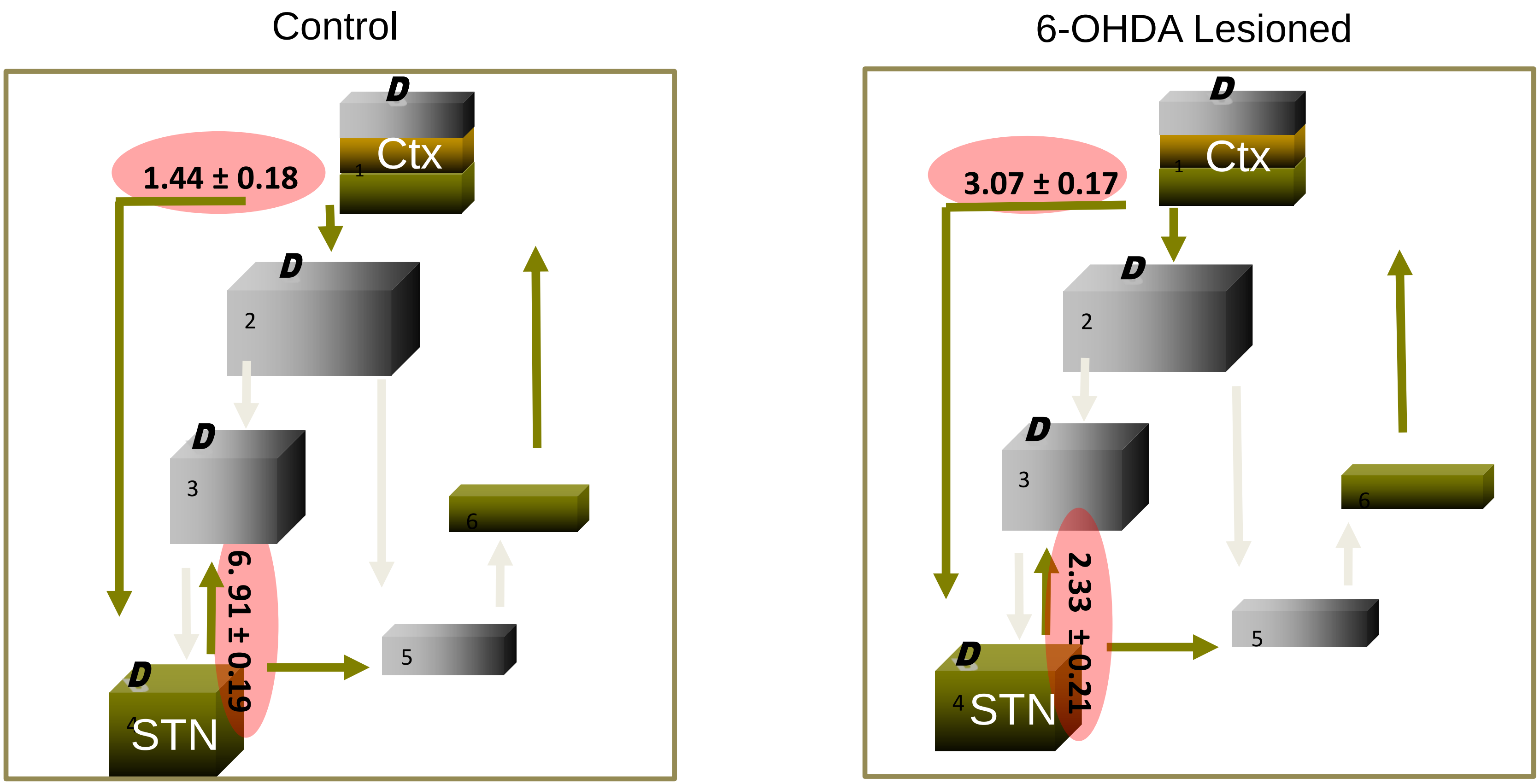
Model Inversion



Connectivity Changes



Connectivity Changes



Contribution Analysis

In the Parkinsonian Network which connections exacerbate the problem oscillation?

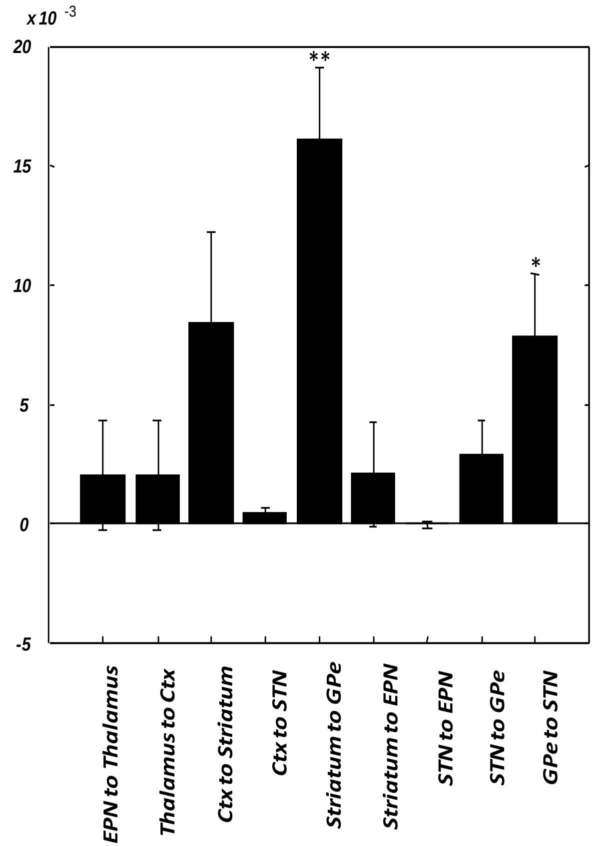
What leads to an increase in beta overall when particular synapses are perturbed?

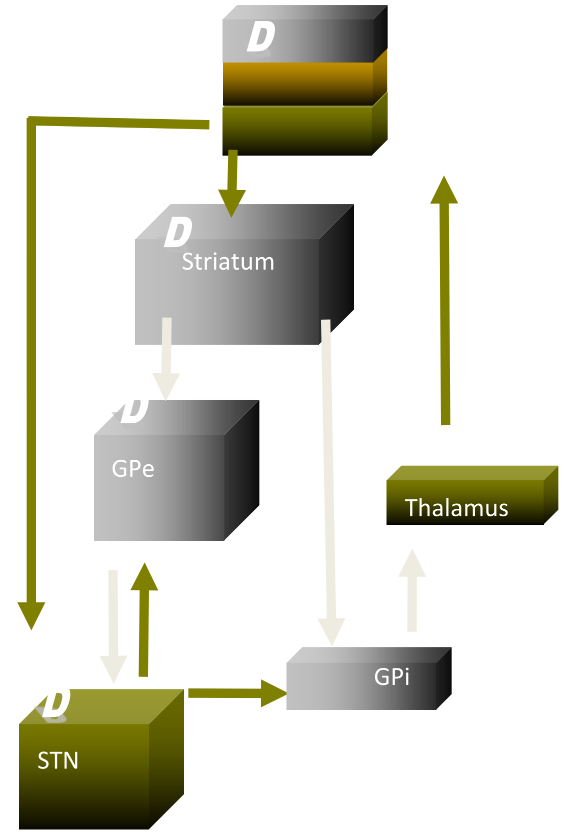
$$\frac{d\beta_{peak}}{dc}$$

Contribution Analysis

In the Parkinsonian Network which connections exacerbate the problem oscillation?

$$\frac{d\beta_{peak}}{dc}$$





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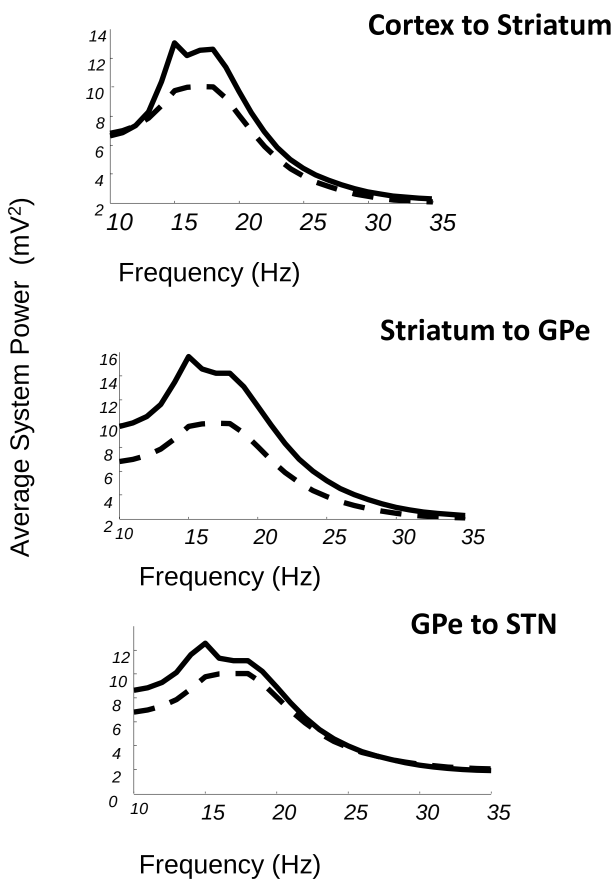

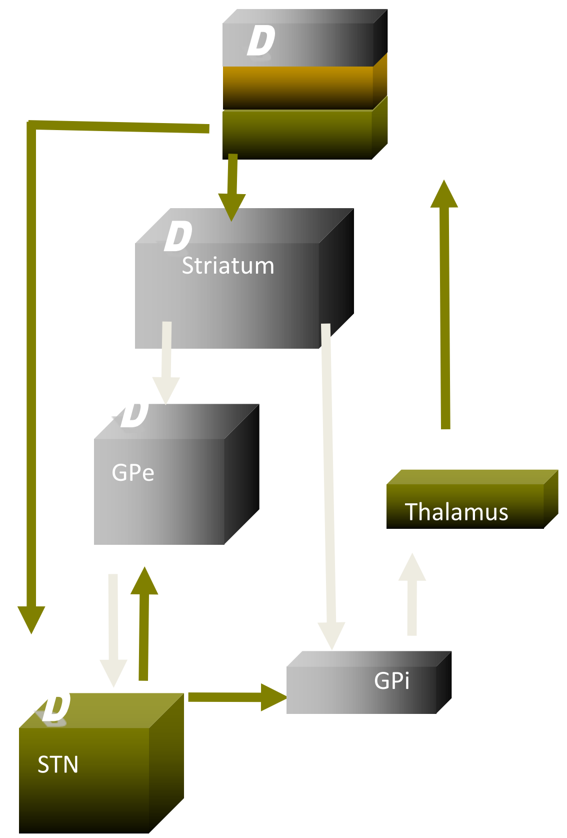

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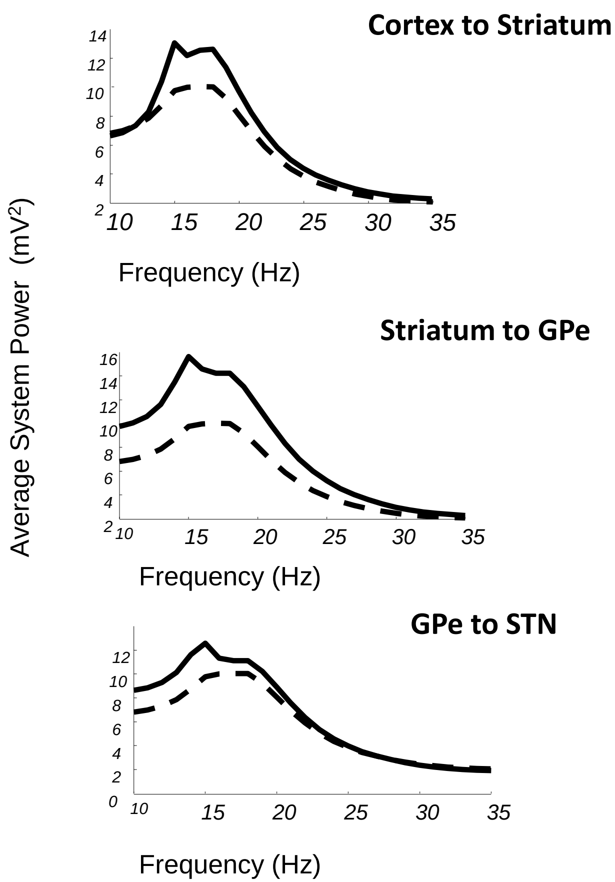
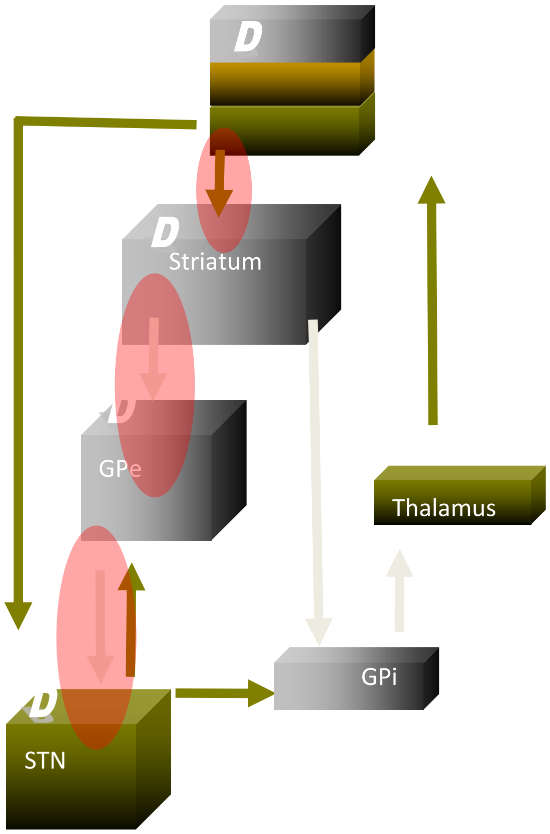
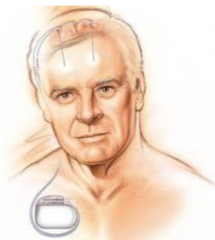
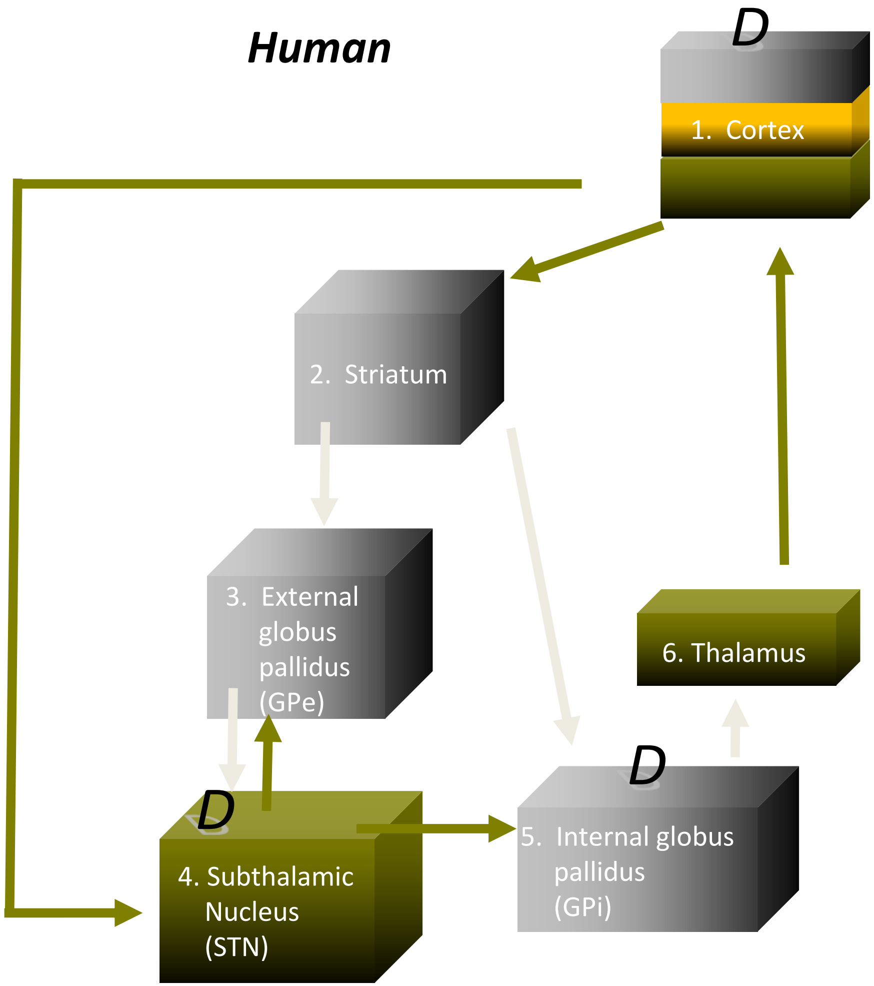




Structure of the Dynamical Causal Model

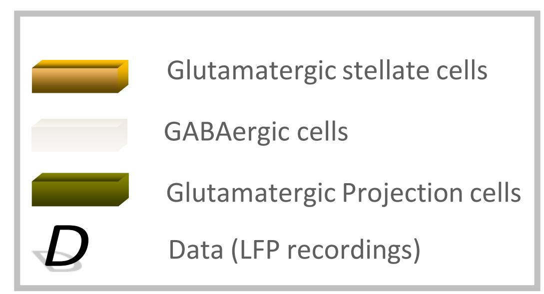


Human

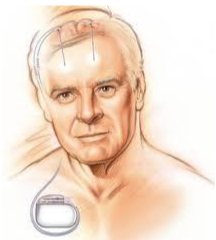


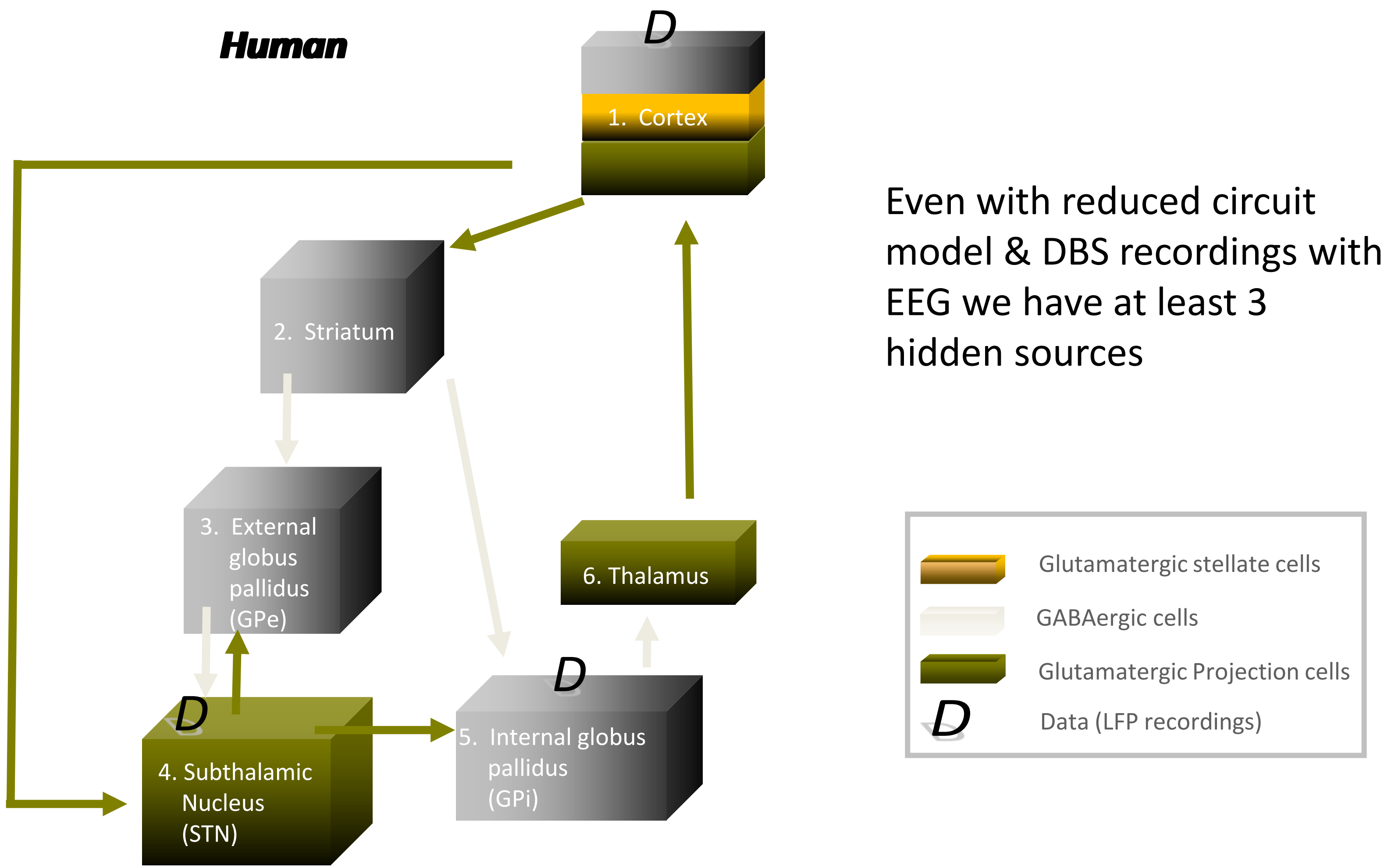
Limited network sampling in patients

Even with reduced circuit model & DBS recordings with EEG we have at least 3 hidden sources



The problem: limited network sampling in patients





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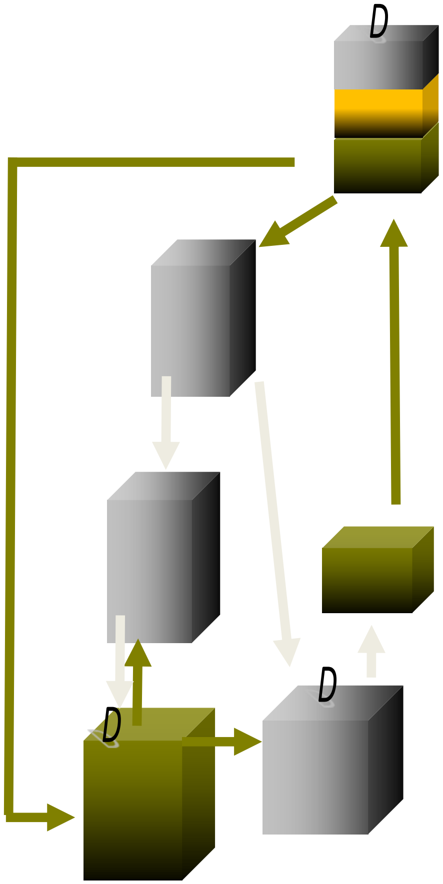


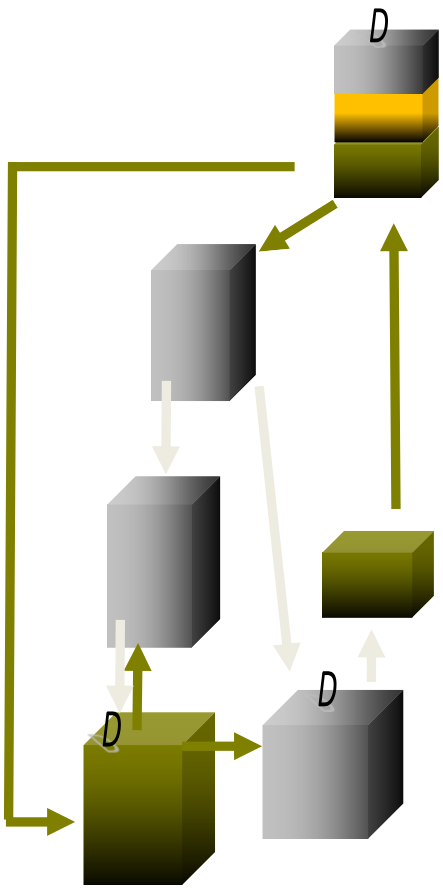
Data spectral density

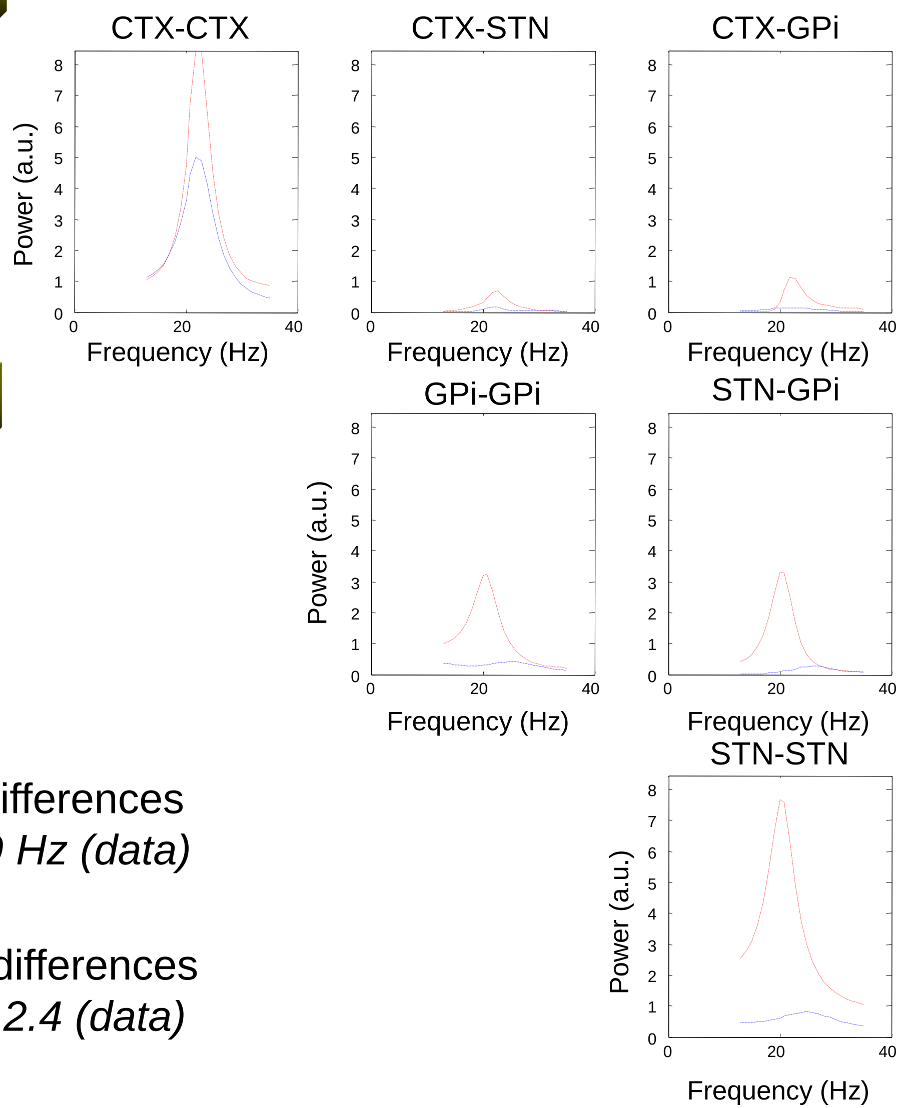
2 trials
DCM

Levedopa

OFF
ON

Data spectral density





2 trials
DCM

Levedopa

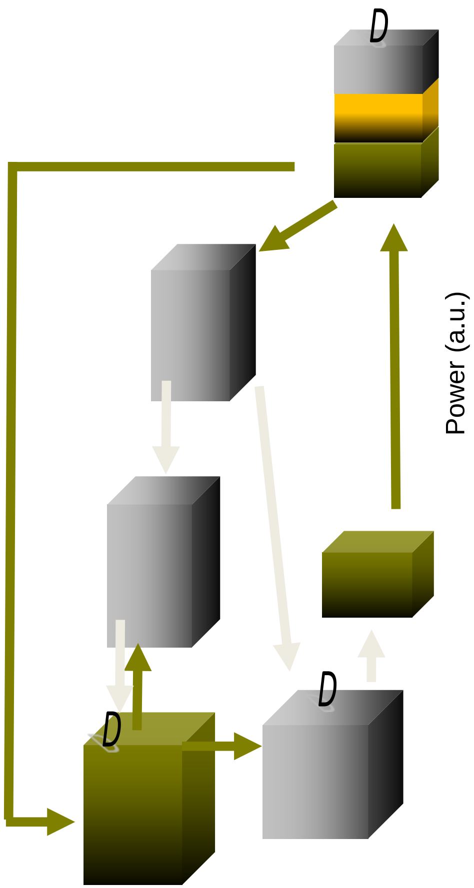
OFF
ON

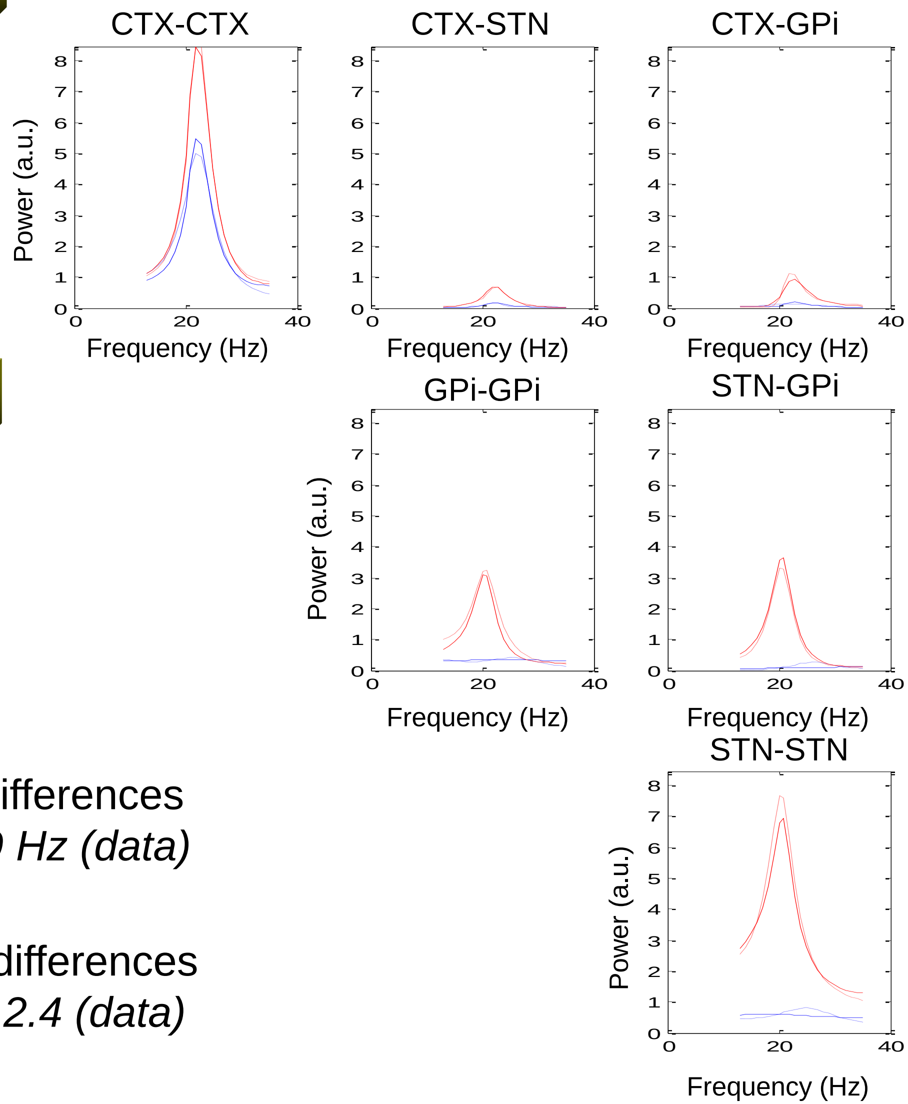
- - - - Dotted line: *data*

Modelling frequency differences
mean STN peak ≠: *6.9 Hz (data)*

Modelling amplitude differences
mean STN power ≠: *2.4 (data)*

Data spectral density





2 trials
DCM

Levedopa

OFF
ON

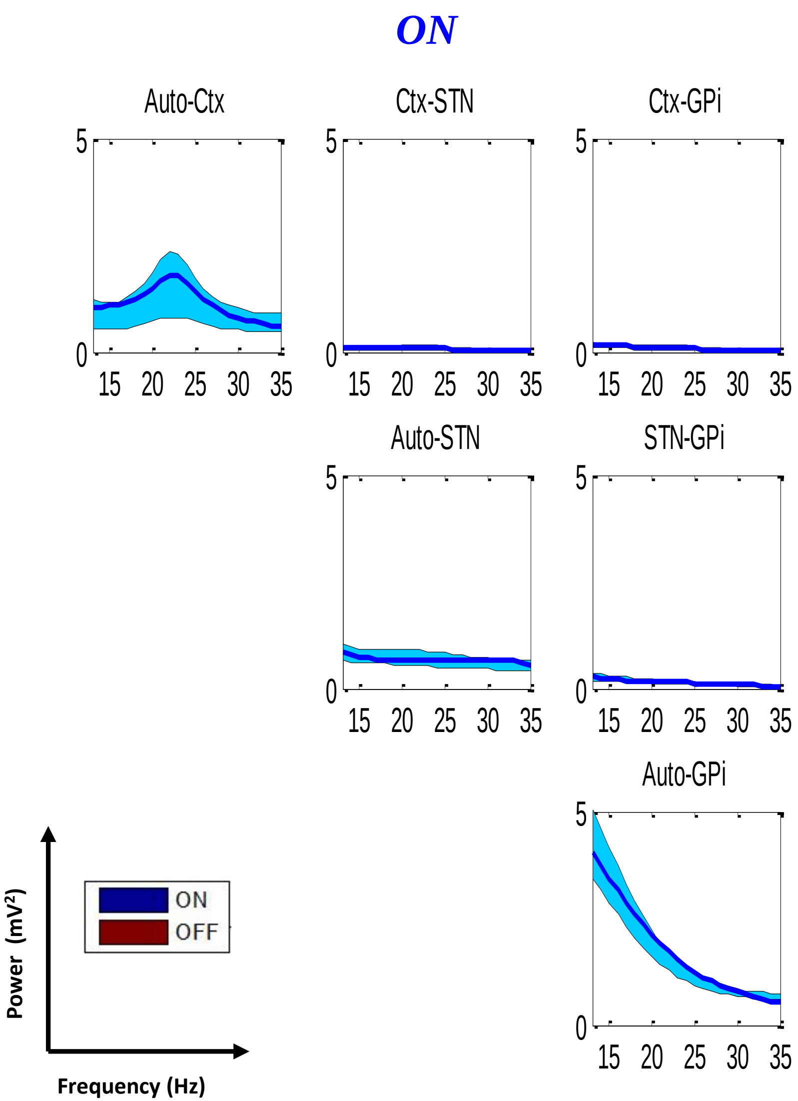
—— **Full line:** *model fit*

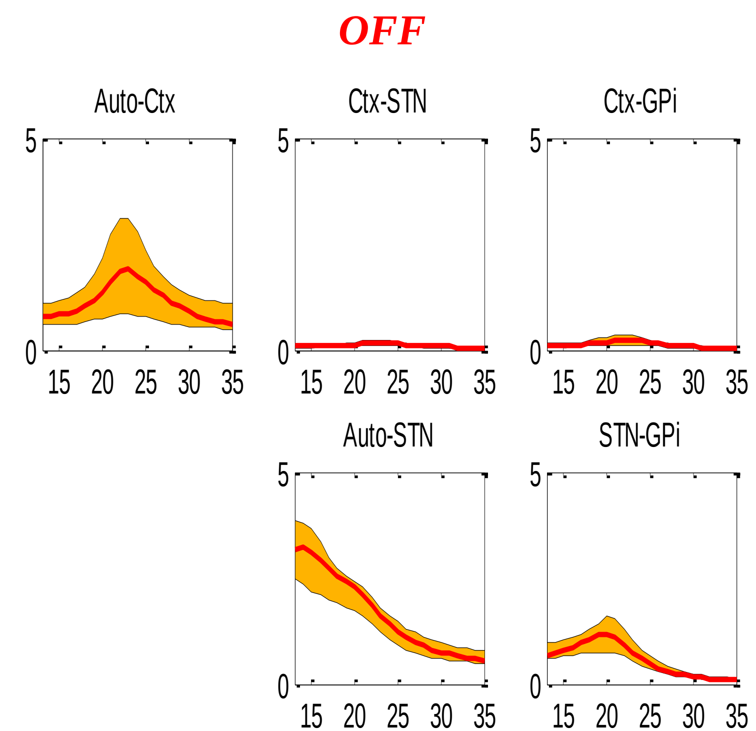
- - - - **Dotted line:** *data*

Modelling frequency differences
mean STN peak ≠: *6.9 Hz (data)*

Modelling amplitude differences
mean STN power ≠: *2.4 (data)*

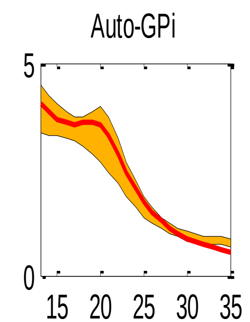
Model fit and Data means



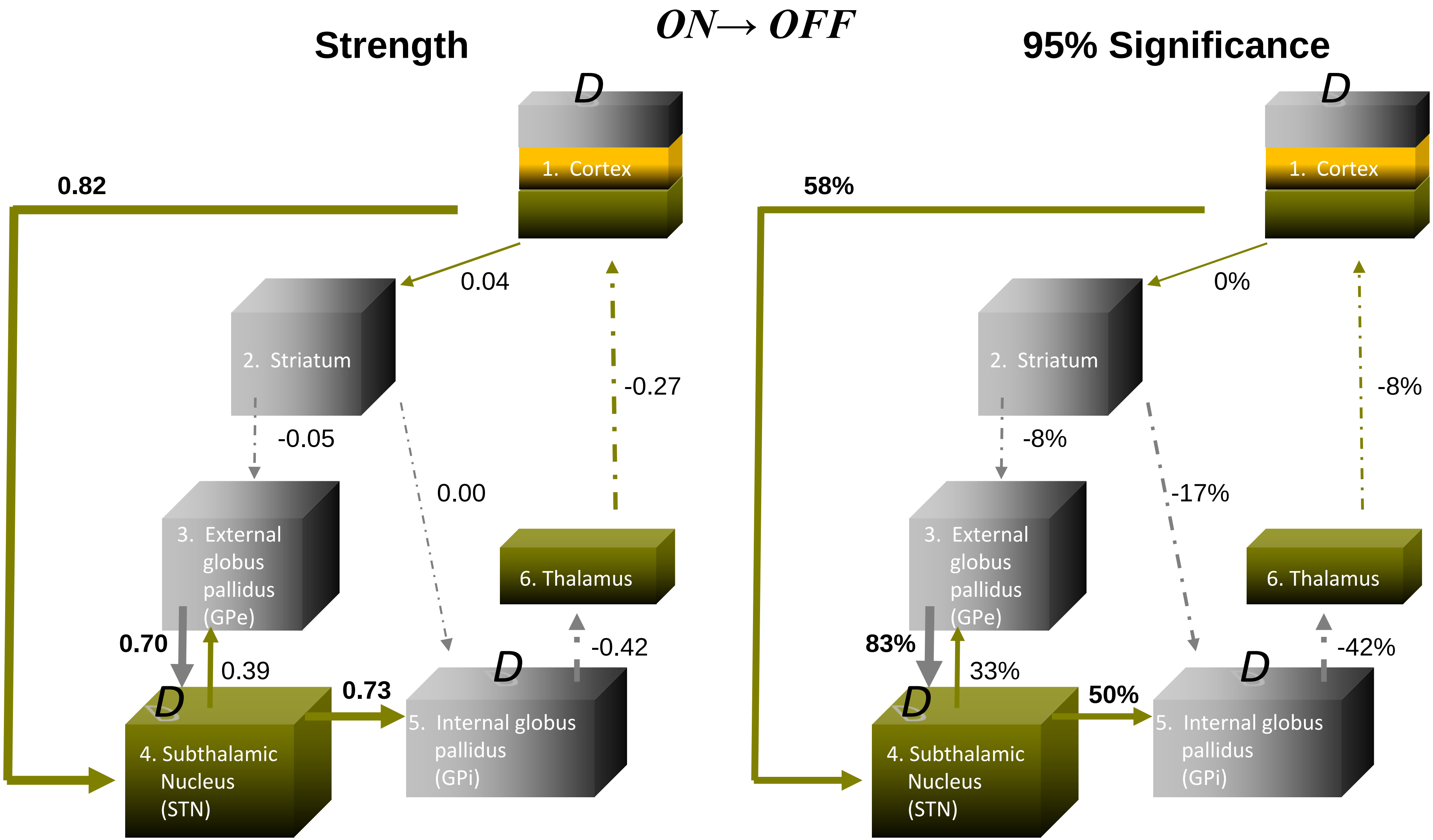


Full line: *average data*

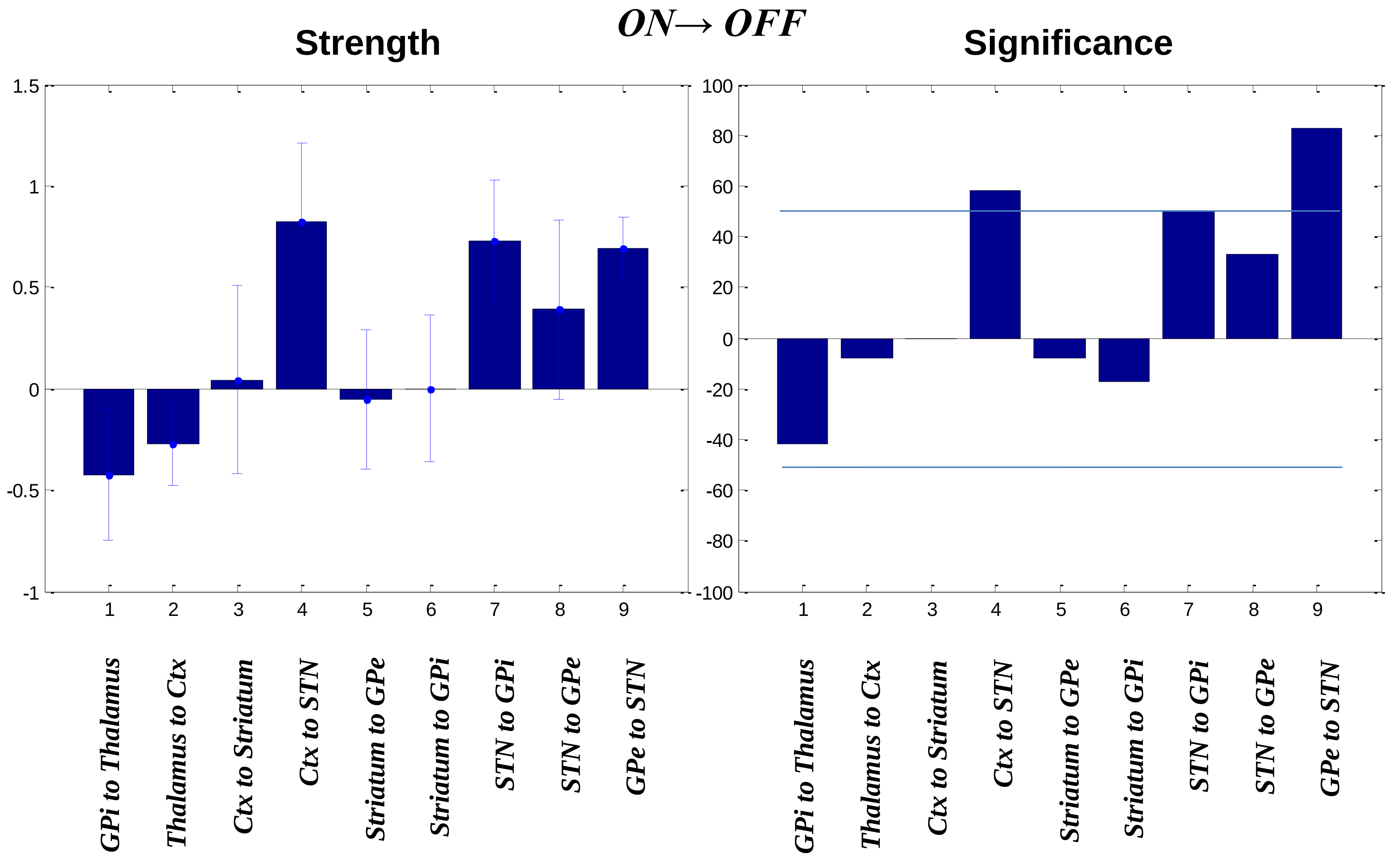
Shaded area: *model fit w/ 95% C.I..*



Group connectivity significance

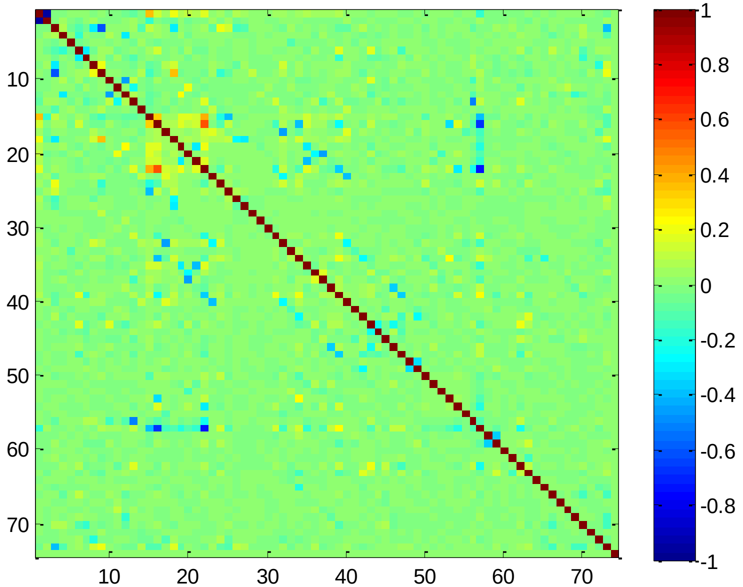


Group connectivity significance



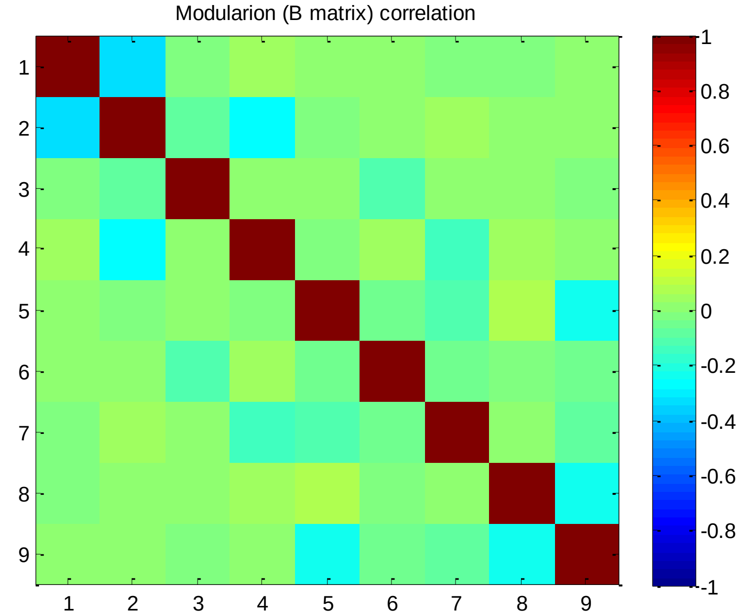
Posterior correlations and parameter identifiability

Correlation for all parameters



B modulation
between (41:49, 41:49)

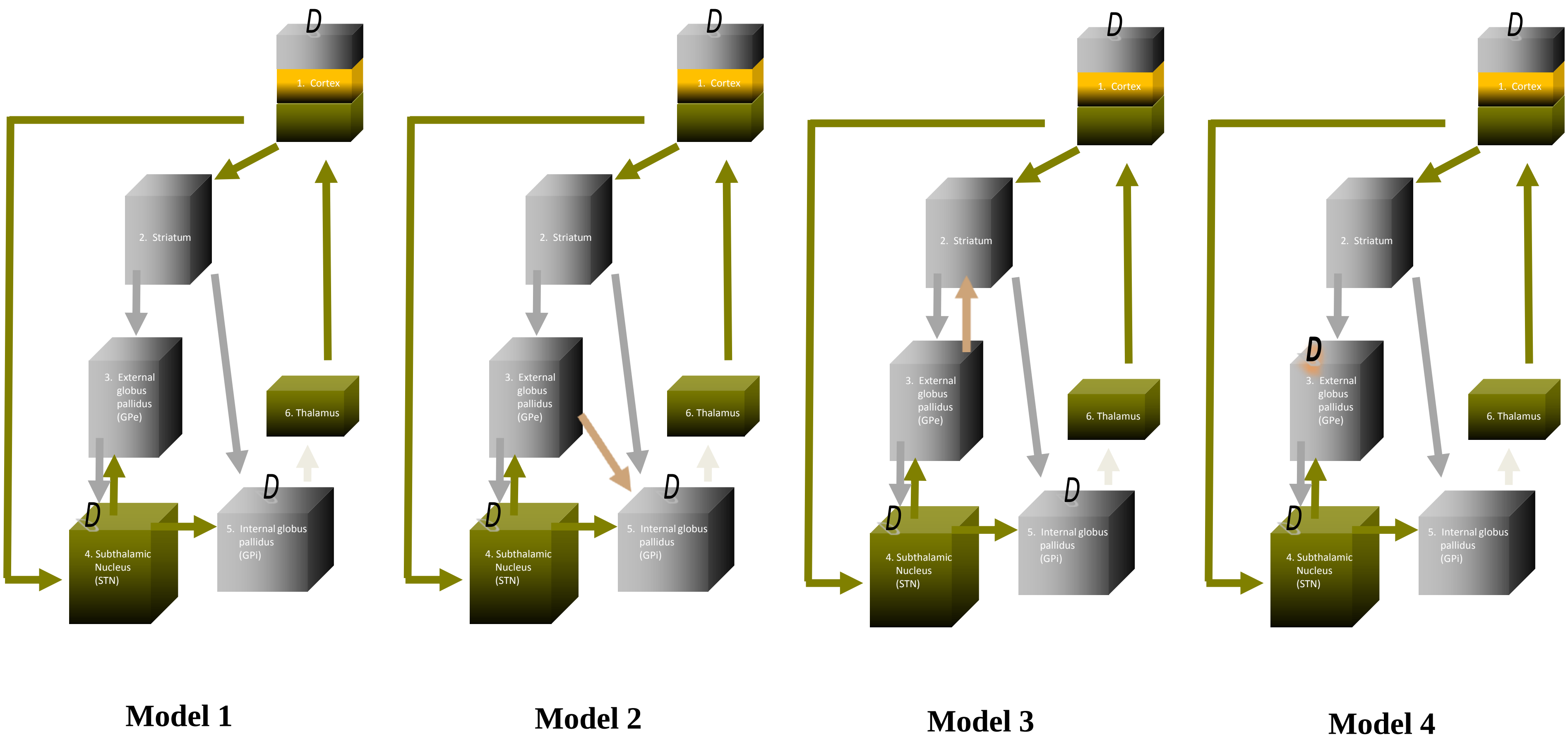
Correlation for modulation parameters



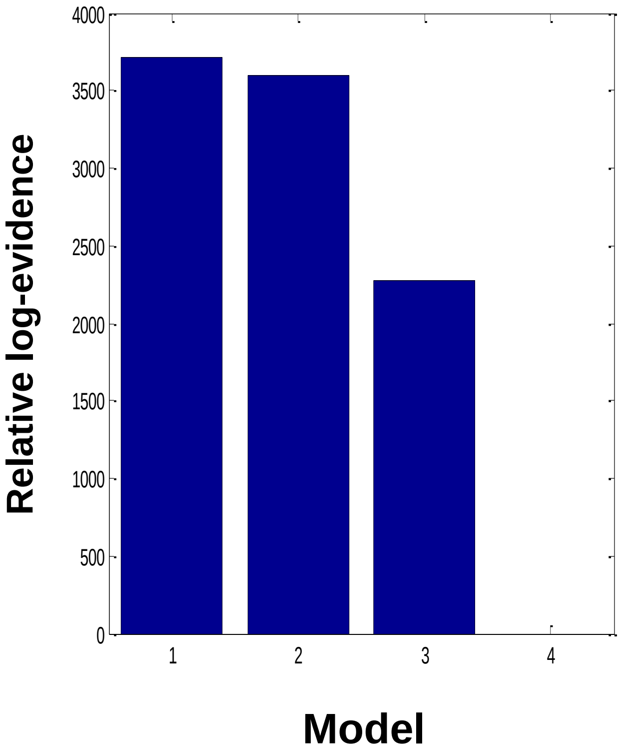
Among our parameters of interest (modulation connectivity measures) where, on average, **only small correlations (~0.05)**

The maximum correlation is -0.32 between connections 1 and 2

Bayesian Model Comparison

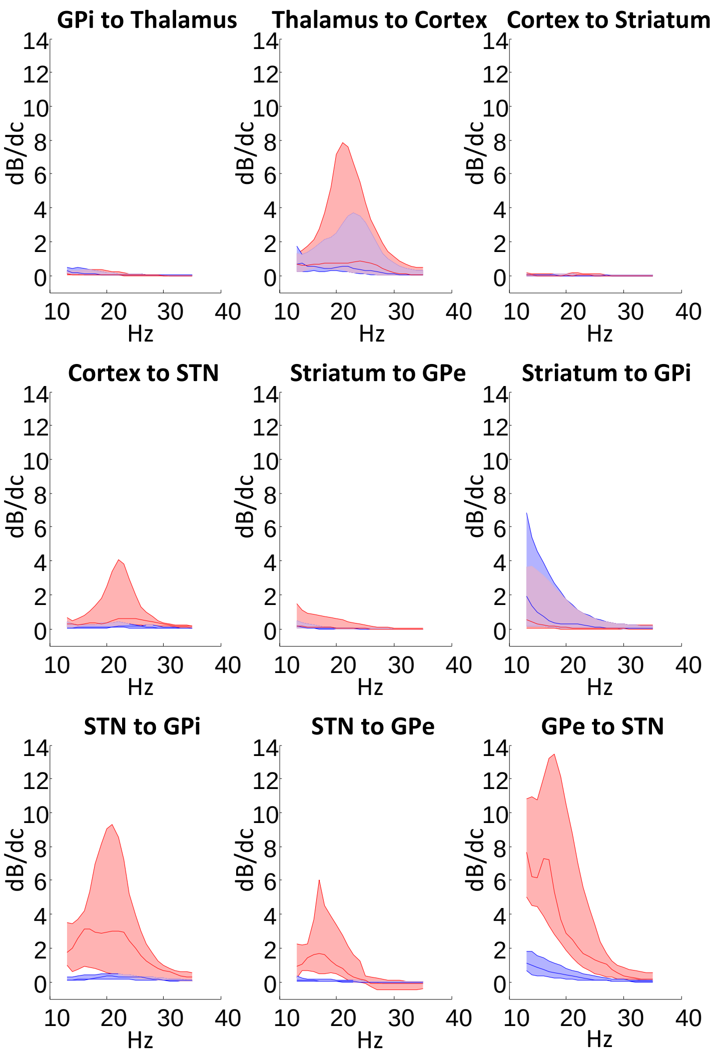


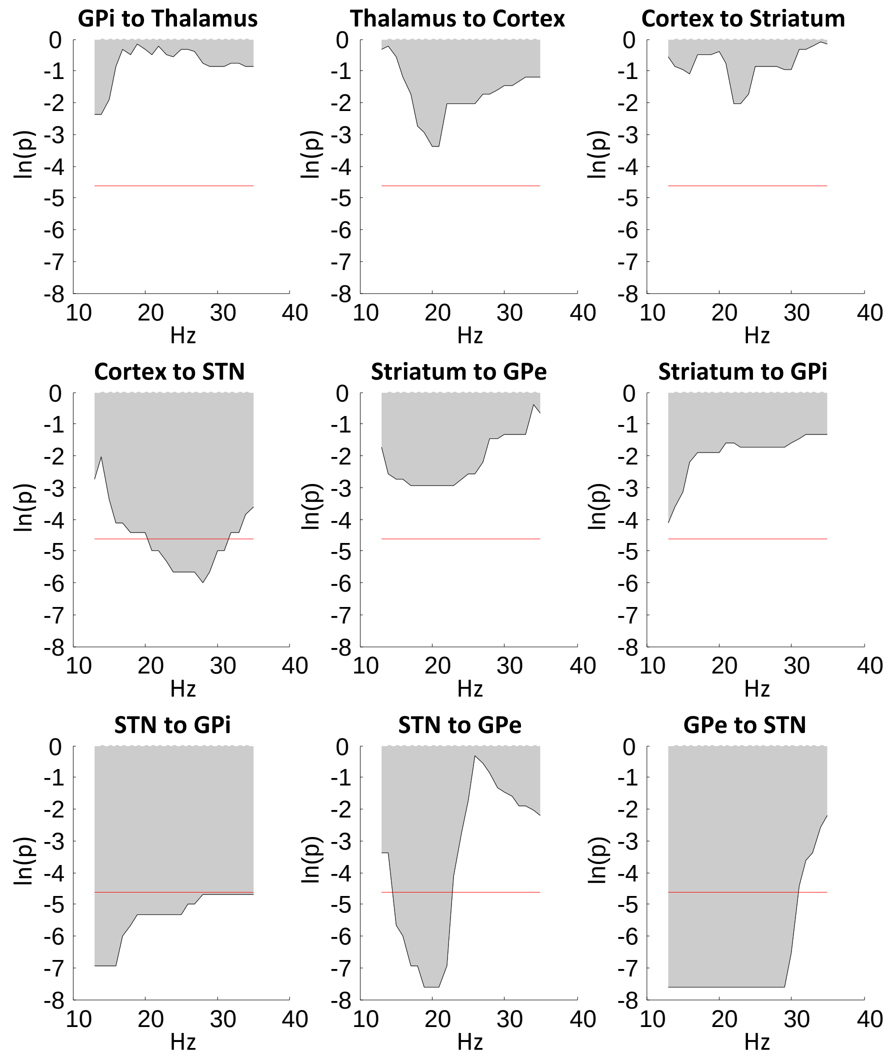
Bayesian Model Comparison



$$\Delta logGBF_{1,2} = 109$$

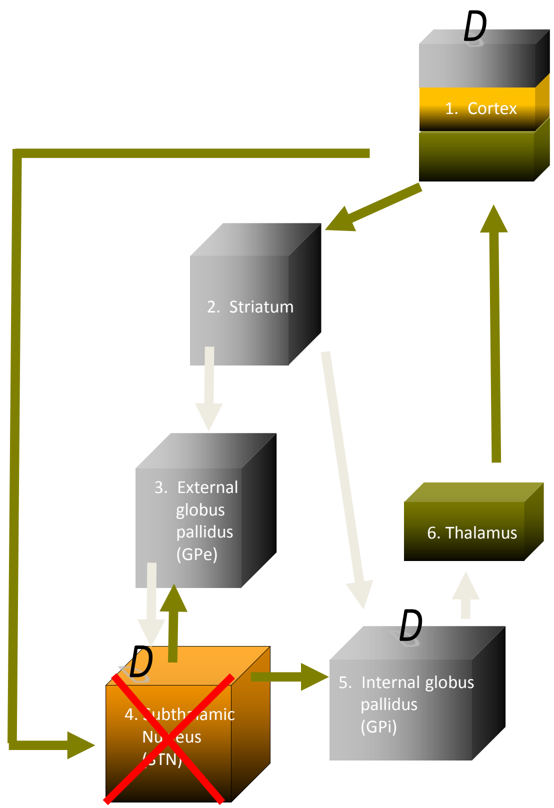
Contribution analysis



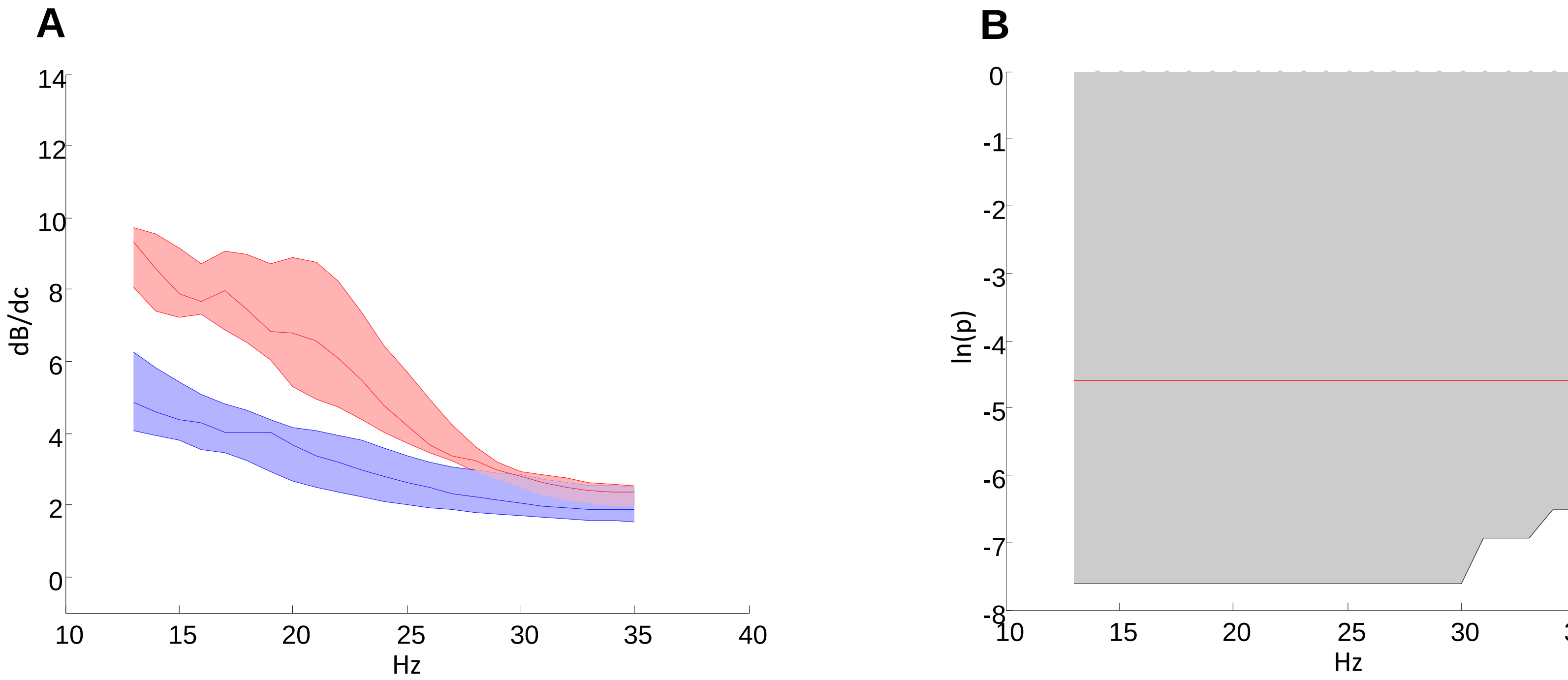


Lesioning Simulation

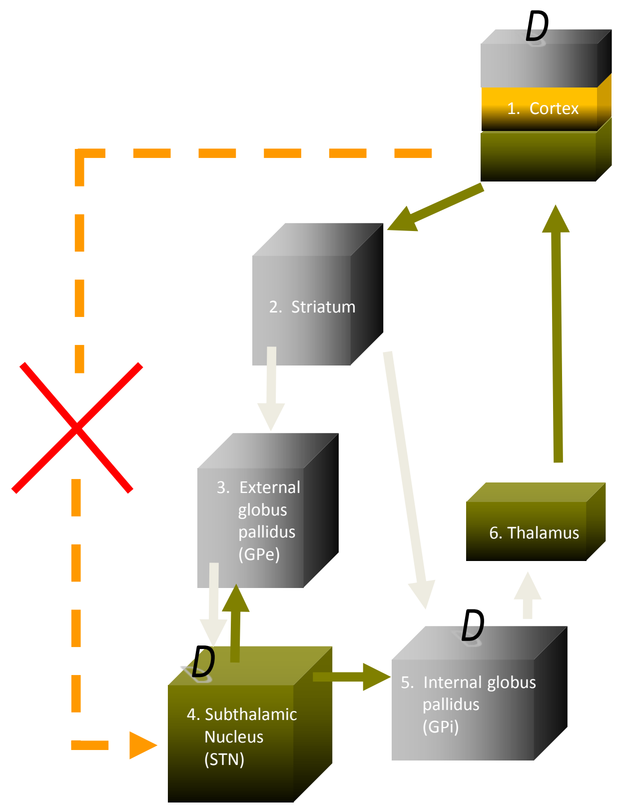
STN source



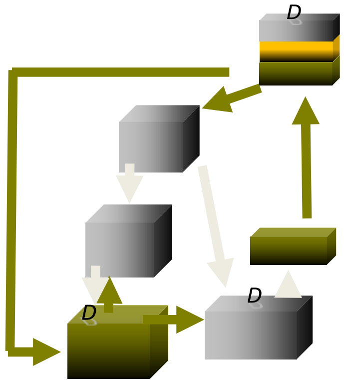
Lesioning STN

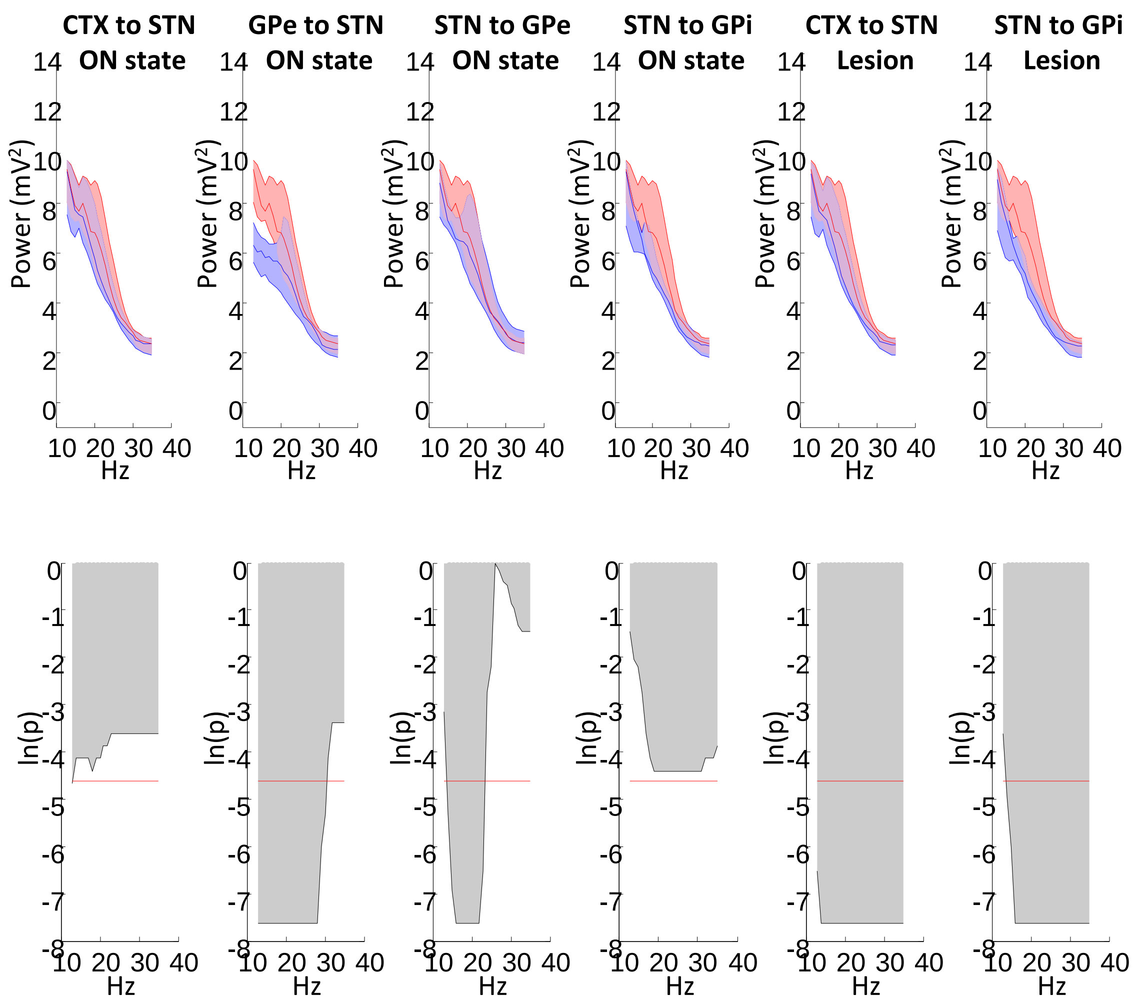


Lesioning connections to STN

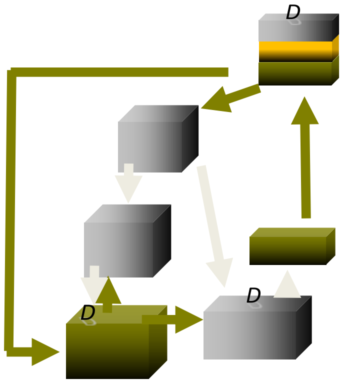


Lesioning connections to STN





Comparison between PD patients with 6OHDA midbrain lesion rodents



	PD Patients	6OHDA midbrain lesioned rodents
Change in Connection **strength** from ON to OFF in PD or from healthy to lesioned in rodents	Ctx-STN strengthened STN-GPi strengthened GPe- STN strengthened	Ctx-STN strengthened STN-GPe weakened
Change in Connection **contribution** from ON to OFF in PD or from healthy to lesioned in rodents	Ctx-STN increased GPe-STN increased STN-GPe increased STN-GPi increased	Striatum-GPe increased GPe-STN increased

Both models showed strengthening of the hyperdirect pathway in the Parkinsonian state and increased beta promoting potency in the GPe to STN pathway.

Conclusions

- Our results indicate that one can use DCM for SSR to estimate network connection strengths within network models of Rat and Human PD, using LFPs.
- Using real data, we found good agreement on optimal model architecture and connectivity parameter estimation when compared with previous studies in human and rat.
- This model was further validated through the prediction of the effects of standard therapeutic procedures aimed at the STN.
- We are able to explore the effects of candidate therapeutic interventions through safe, cheap and valid simulations.

Thank you

for your attention!

Acknowledgements

Peter Brown
Karl Friston
Rosalyn Moran
Hayriye Cagnan