Dynamic causal models of dementia

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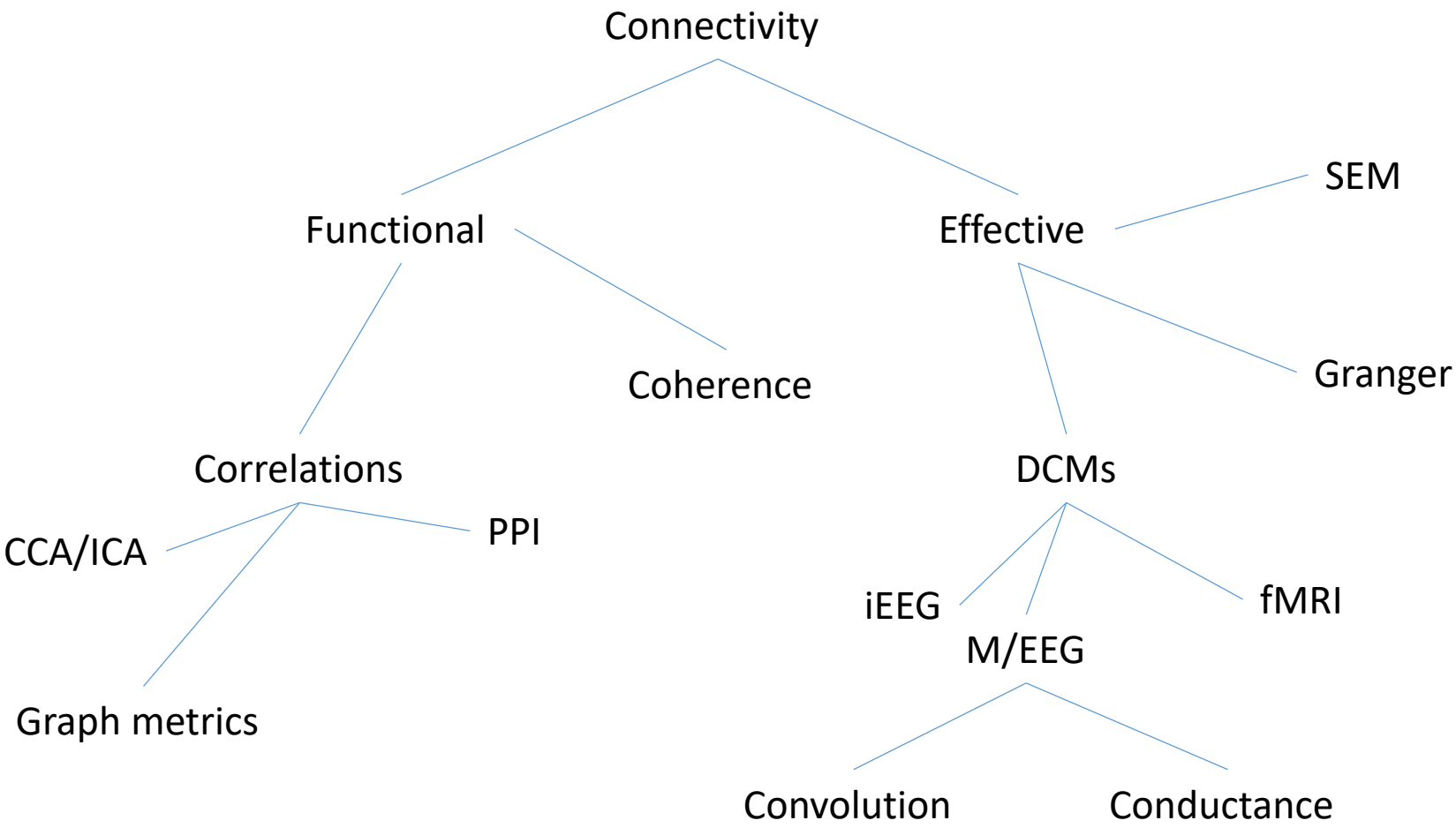
Disclosures

- Research grants from Janssen, Lilly, AstraZeneca
- Consultancies/advisory board for Asceneuron, Astronautx, Biogen, Curasen, SVHealth, ICG, WAVE, Astex, Prevail, UCB
- Chief Scientific Adviser to Alzheimer Research UK
- Chief Investigator CNS101 (CumulusNeuro)

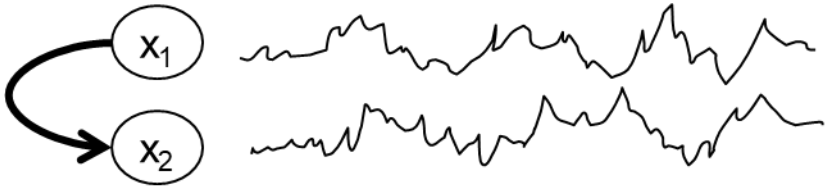
The pharmacology studies described today are unrelated to the above; and represent research only, not clinical advice.

A family of brain connectivity methods



Dynamic Causal models

- Dynamic



$$x(t) = \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

overall system state represented by state variables

$$\frac{dx}{dt} = \dot{x} = \begin{bmatrix} \dot{x}_1 \\ \vdots \\ \dot{x}_n \end{bmatrix}$$

change of state vector in time

*System **dynamics*** = change of state vectors in time

Connectivity as time constants

Dynamic Causal models

- Dynamic
- Causal

Causal *effects* in the system:

interactions between elements

events in the world *u*

system parameters θ

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

Including connectivity x1 → x2 versus x2 → x1

Dynamic Causal models

- Dynamic
- Causal
- Models

$$\dot{\boldsymbol{z}} = f\left(\boldsymbol{z}, \boldsymbol{U}, \boldsymbol{\theta}^{(n)}\right)$$

$$\boldsymbol{y} = g\left(\boldsymbol{z}, \boldsymbol{\theta}^{(h)}\right) + \boldsymbol{X}_0\boldsymbol{\beta}_0 + \varepsilon$$

$$\begin{aligned} \dot{\boldsymbol{z}} &= \boldsymbol{J}\boldsymbol{z} + \boldsymbol{C}\boldsymbol{u}(t) \\ \boldsymbol{J} &= \left(\boldsymbol{A} + \textstyle\sum_k \boldsymbol{B}^{(k)}\, \boldsymbol{u_k}(t)\right) \end{aligned}$$

$$\boldsymbol{J} = \underbrace{-0.5 \cdot \exp\left(\boldsymbol{A_I}\right) \cdot \exp\left(\sum_k \boldsymbol{B_I^{(k)}}\, \boldsymbol{u_k}(t)\right)}_{Intrinsic\ (self-inhibition)} + \underbrace{\left(\boldsymbol{A_E} + \sum_k \boldsymbol{B_E^{(k)}}\, \boldsymbol{u_k}(t)\right)}_{Extrinsic\ (between-region)}$$

A – baseline connectivity
B – task modulation
C - Driving inputs
U – task events

Dynamic Causal models

- Dynamic
- Causal
- Models

$$\dot{\boldsymbol{z}} = f\left(\boldsymbol{z}, \boldsymbol{U}, \boldsymbol{\theta}^{(n)}\right)$$
$$\boldsymbol{y} = g\left(\boldsymbol{z}, \boldsymbol{\theta}^{(h)}\right) + \boldsymbol{X}_0\boldsymbol{\beta}_0 + \varepsilon$$

hypotheses tested in terms of parameters
hypotheses tested in terms of model comparison

Historical comparison: AIC, BIC, GBF, BRFX, ….
Now free energy F ~ log(model_evidence)
= accuracy – complexity

Estimating the parameters….

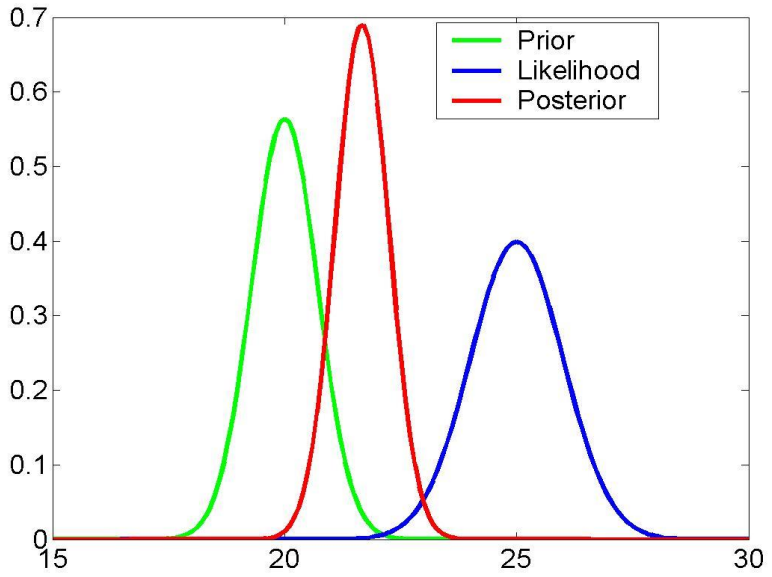
- Priors used to inform Bayesian parameter estimation
- express prior knowledge (belief) about parameters of the model
- Update beliefs according to the new evidence (and precision)
- hemodynamic parameters and connectivity parameters

Bayes Theorem

$$p(\theta \mid y) \propto p(y \mid \theta) \cdot p(\theta)$$

posterior $\propto$ likelihood $\cdot$ prior

updated belief $\propto$ new data $\cdot$ old belief



Bayesian Model Selection

Bayes theorem:

$$p(\theta \mid y, m) = \frac{p(y \mid \theta, m)\, p(\theta \mid m)}{}$$

Model evidence:

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

Bayes factor B:

compare two models i and j by the ratio of probabilities

$$B_{ij} = \frac{p(y \mid m = i)}{p(y \mid m = j)}$$

$$F \approx \log p(y \mid m) = accuracy(m) - complexity(m)$$

$$\Delta F_{ij} = F_i - F_j$$

Bayesian Model Selection

Bayes theorem:

$$p(\theta \mid y, m) = \frac{p(y \mid \theta, m)\, p(\theta \mid m)}{}$$

Model evidence:

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Bayes factor B:

compare two models i and j by the ratio of probabilities

$$B_{ij} = \frac{p(y \mid m = i)}{p(y \mid m = j)}$$

B_{12}	$p(m_1 \mid y)$	Evidence	ΔF
1 to 3	50-75%	weak	
3 to 20	75-95%	positive	>1.1
20 to 150	95-99%	strong	>3
≥ 150	≥ 99%	Very strong	>5

$$\Delta F_{ij} = F_i - F_j$$

Group studies

Historical AIC, BIC, group-Bayes-factor (sum over individuals)… but vulnerable to outliers

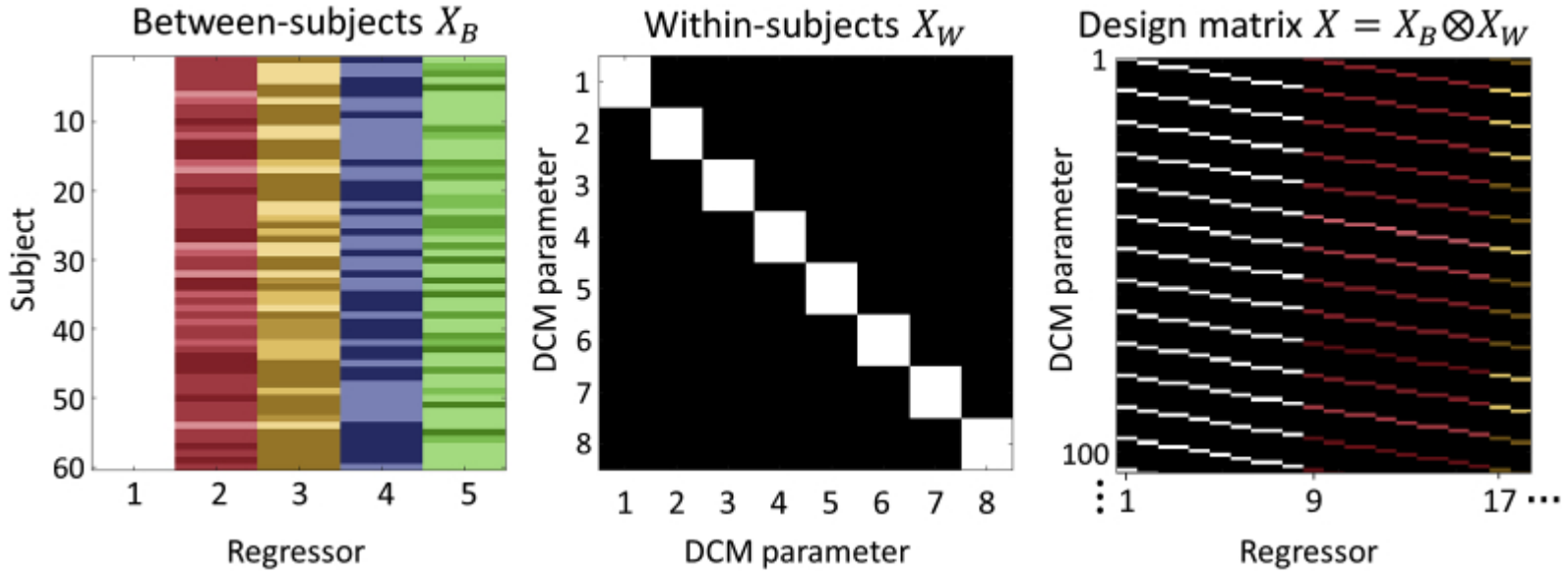
Then “Random Effects” models selection

specify multiple DCMs per subject then estimate the relative probability that any randomly selected person from the population would have had their data generated by each model (ie random effect over models)

Parametric Empirical Bayes (PEB)

Random effects on parameters rather than models. All subjects have the same basic architecture, but differ in terms of connection strength in that model

PEB



If mean-centred, then the first column of ones corresponds to mean experiment-related changes in connectivity over subjects, and between-subject effects add to this.

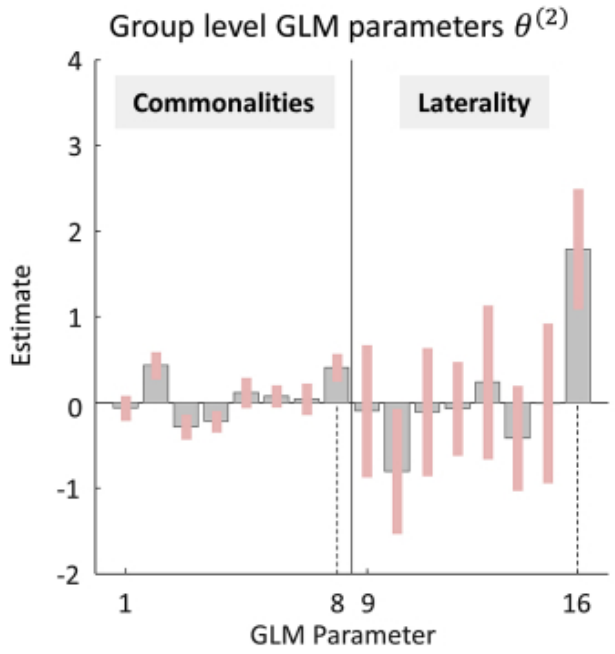
Ie the first regressor represents group mean effective connectivity.

which DCM connectivity parameters can receive between-subject effects

what the experimental (between-subject) effects act on; ie. which (within-subject) parameters

PEB

invert the PEB model (**spm_dcm_peb.m**) to get two useful quantities:
the estimated group-level parameters
and the group-level free energy



$F^2 \sim \text{Log } p(Y|m)$

F ~ log of the probability of observing the neuroimaging data (from all subjects) given the entire hierarchical model m.
Sum of all subjects' DCMs accuracies, minus the complexity induced *and the second-level GLM*.
Can compare free energy of PEB models with different sets of parameters switched on and off to find the optimal explanation for the dataset as a whole.

PEB

invert the PEB model (**spm_dcm_peb.m**) to get two useful quantities:
the estimated group-level parameters
and the group-level free energy

Where multiple factors are subject to multiple covariates the number pf models of very large – so consider to reduce to model "families" (cf standard DCM)

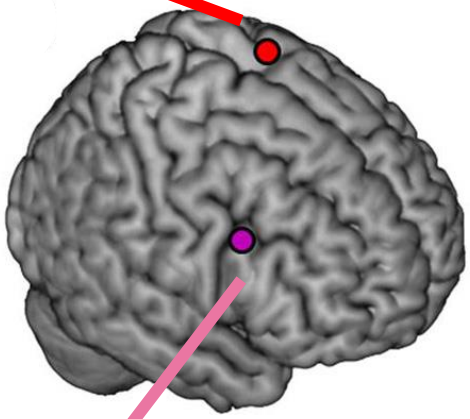
Or Bayesian Model Reduction (BMR): free energy and parameters for 'reduced' models are computed analytically. The difference between a full and reduced models is their priors (eg. some connections switched off, spm_log_evidence_reduce.m)

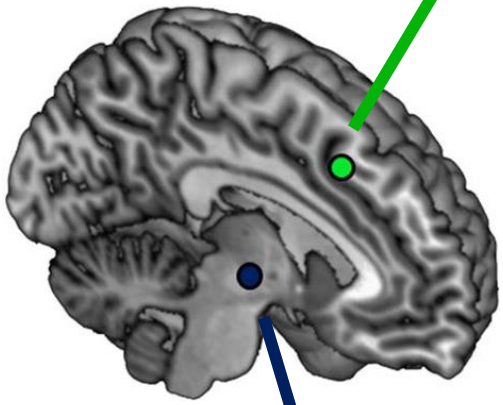
fMRI

How to stop what you are doing?

Motor cortex (M1)
Source of corticospinal projections for motor control

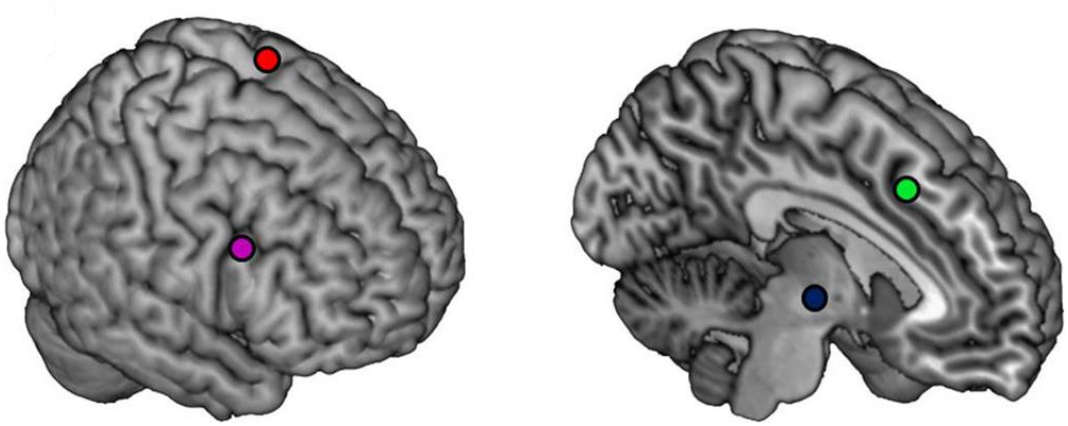
preSMA
(i) Selection of action
(ii) For inhibition of action, prior to IFG (Husain)

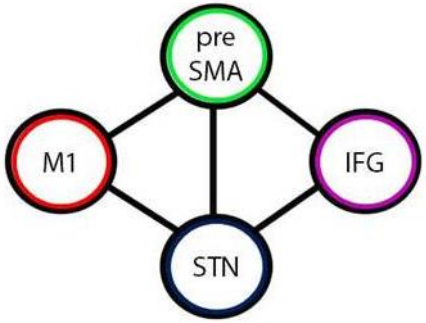




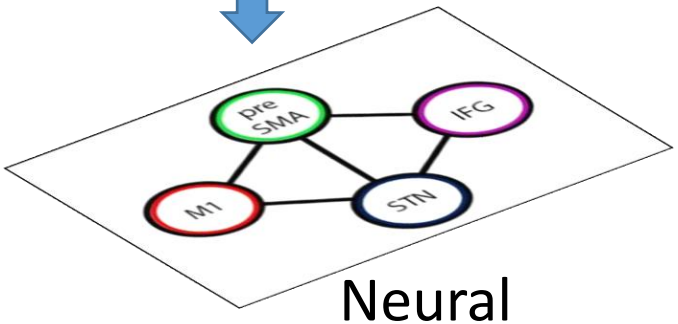
Inferior frontal gyrus (rIFG)
(i) Inhibiting actions (Aron, Poldrack, Neurbert)
(ii) orienting to relevant events (Sharp, Hampshire)

Subthalamic nucleus (STN)
brakes the thalamic outputs of the basal ganglia
(Frank, Strafella, Forstmann)



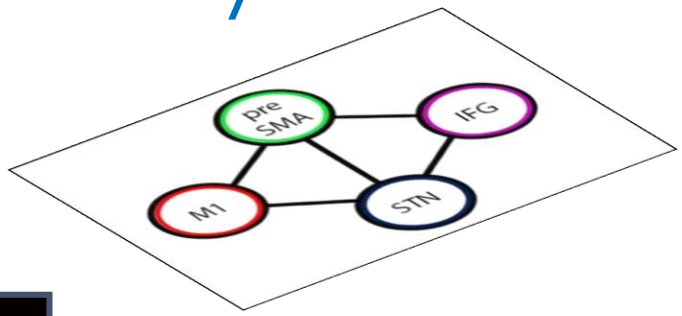

pre
SMA
M1
IFG
STN

Dynamic causal modelling (DCM) to study connectivity of the stopping network

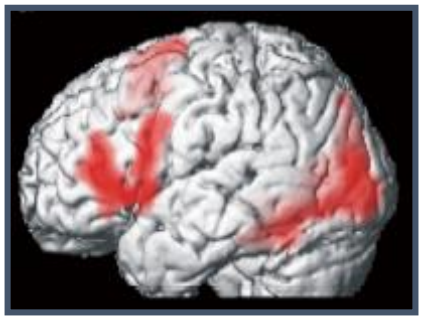


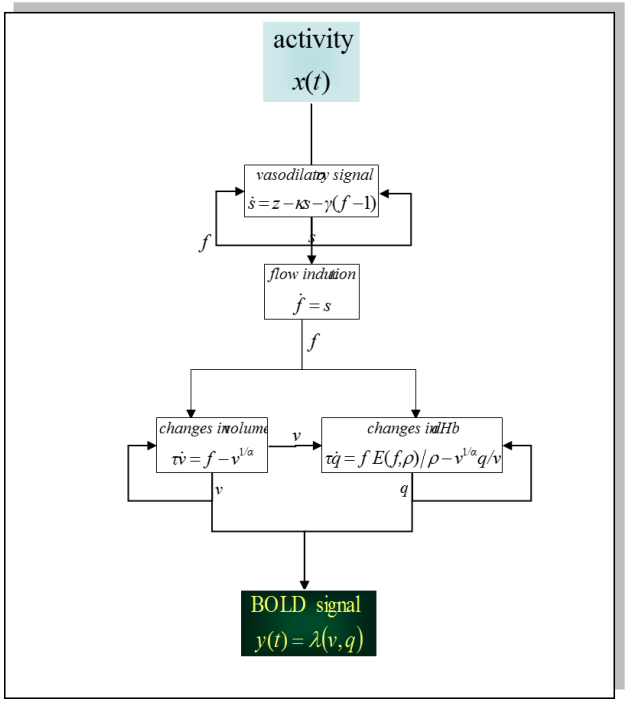
Neural

≠



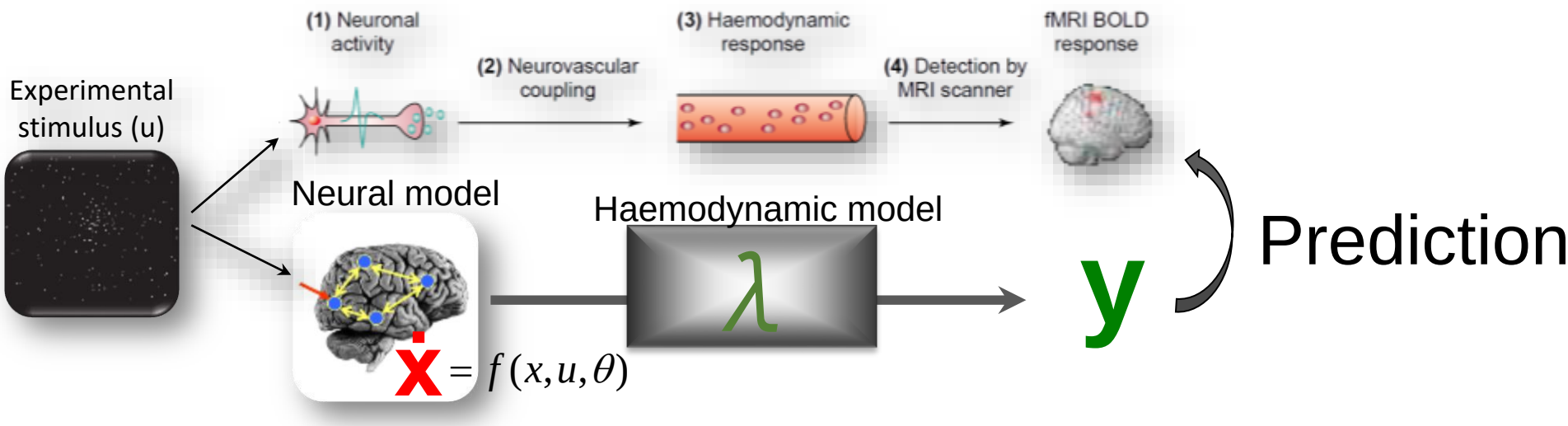
Haemodynamic





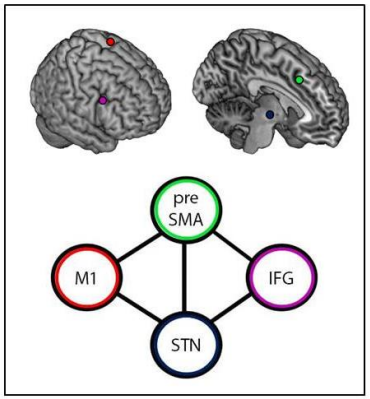
The aim of DCM is to estimate <u>parameters at the neuronal and vascular levels</u> such that the modelled and measured BOLD signals are optimally similar (maximising model evidence, F)

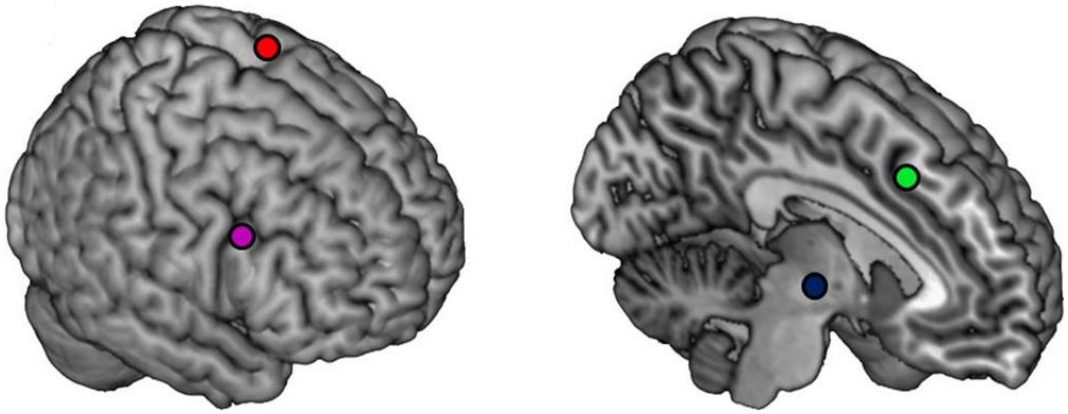
DCM for fMRI

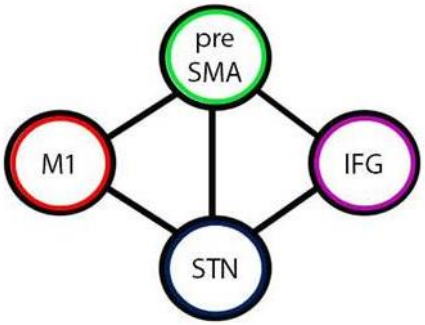


- The modelled neuronal dynamics ($\dot{x}$) are transformed into region-specific BOLD signals (**y**) by a hemodynamic model (**λ**)

System is modelled at its neuronal level (not directly accessible to fMRI).


pre
SMA
M1
IFG
STN

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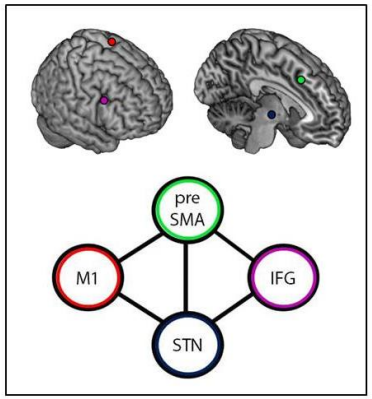


How to stop: a DCM study of the stop-signal response task

(Rae et al J Neurosci 2015)

LINEAR MODELS

NONLINEAR MODELS

Location of modulatory input (represented by ↖)

IFG-STN

preSMA-STN

IFG-preSMA

preSMA-IFG

IFG

preSMA

Model families

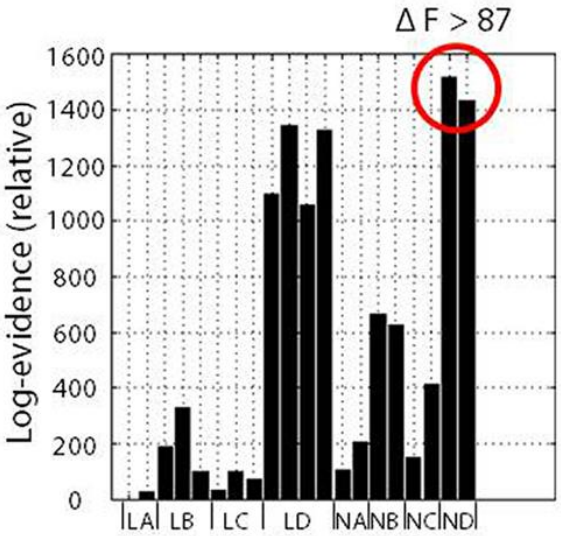
A

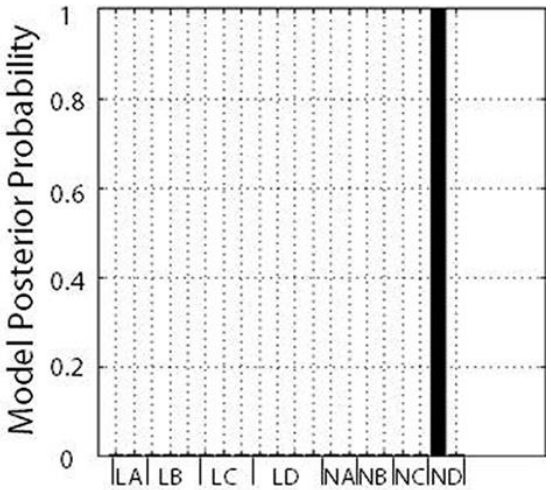
B

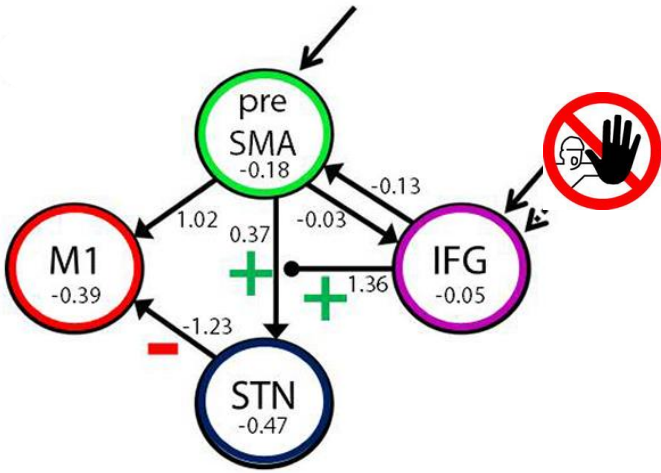
C

D

Bayesian model selection:
alternate hypotheses embedded in generative models

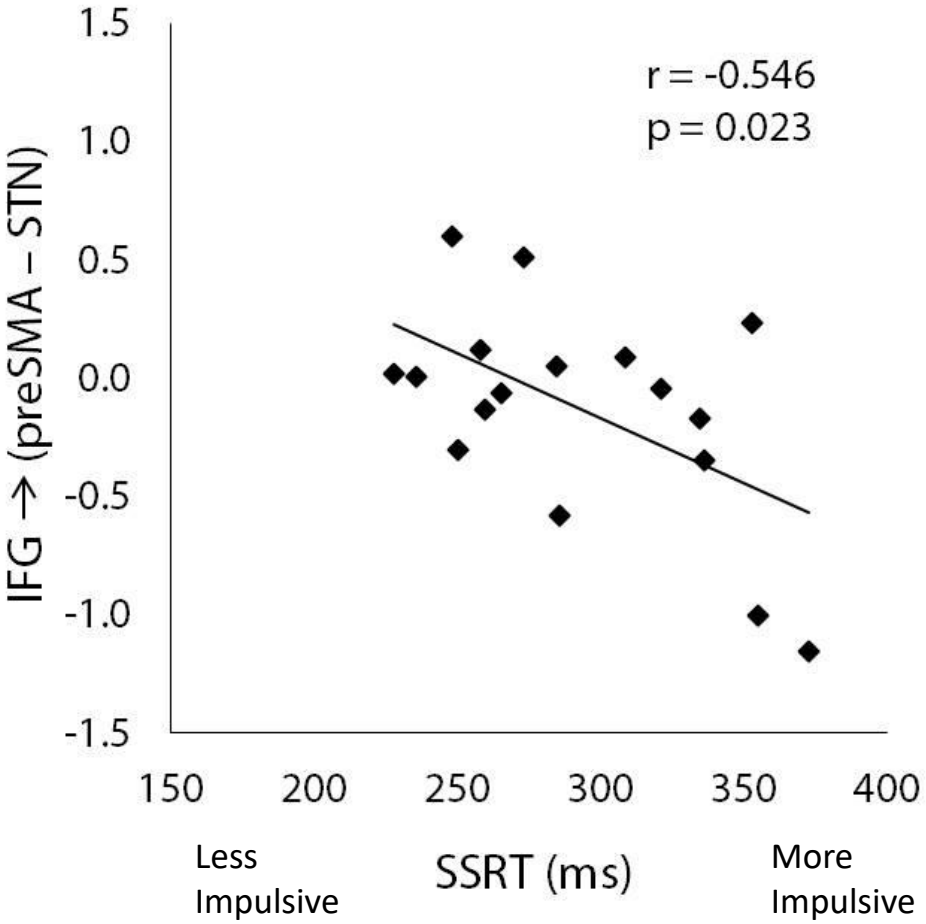


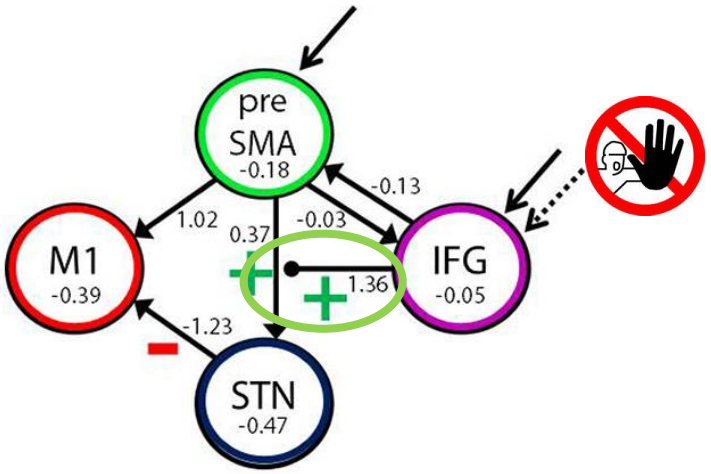




Rae et al., J Neurosci 2015

Stronger effective connectivity (DCM) means more efficient stopping (SSRT)



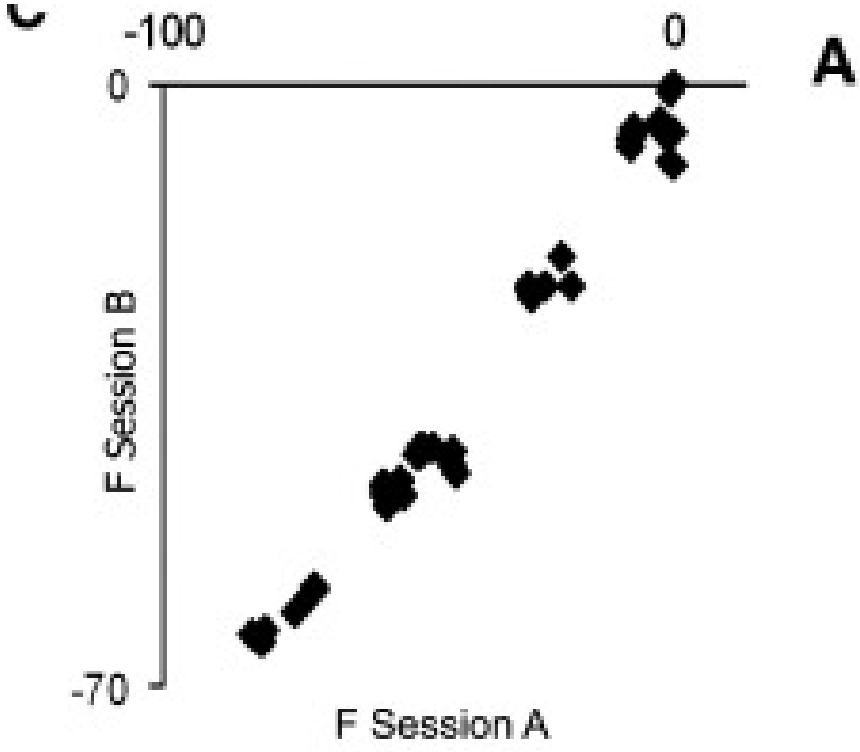


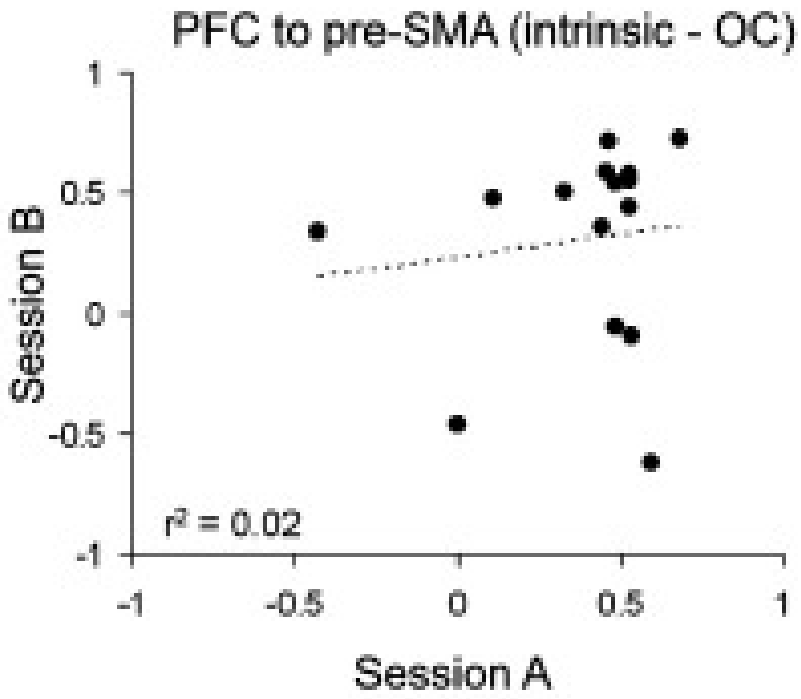
Increased connectivity from preSMA to STN; and modulation by inferior frontal gyrus modulation predict shorter SSRTs (better response inhibition)

Rae et al., J Neurosci 2015

Reliability ?

Test same subjects same task 2 weeks apart





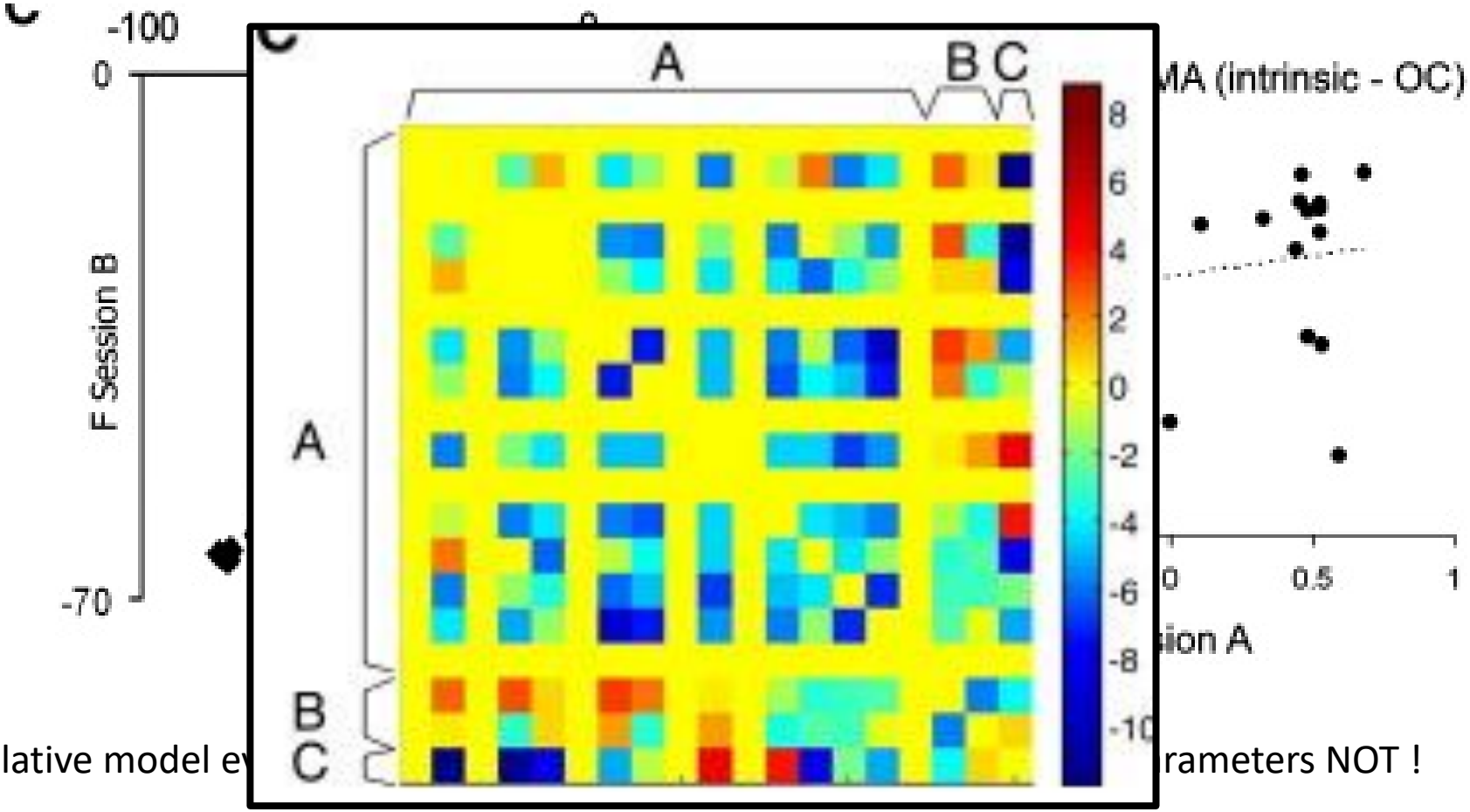
Relative model evidences very reliable

but individual parameters NOT !

Rowe et al Neuroimage 2010

Reliability ?

Test same subjects same task 2 weeks apart



Relative model ev rameters NOT !

Rowe et al Neuroimage 2010

M/EEG

MEG for dementia?

To open the bottleneck in drug development for dementia

To de-risk and accelerate early phase clinical trials

→With a new range of *in vivo* assays,

1. Sensitive to presence of disease
2. Sensitive to progression of disease
3. Elucidate disease mechanisms
4. Trial-ready eg. reliable, scalable

Test disease group: bv-FTD and PSP

Convergent phenotypes (Murley Brain 2020)

personality, impulsivity, apathy, social cognition

akinetic-rigidity, mixed movement disorder

poor survival (3-4 years from diagnosis)

AND convergent neurophysiology

(Sami Brain 2018; Hughes JOCN 2015; Cope J Neurosci 2022)

A brief history of MEG in dementia

- Sensitive and very well tolerated by patients
  (Hughes et al Brain 2011; JoCN 2013, Neuroimage 2013)

A brief history of MEG in FTD/PSP

- Sensitive and very well tolerated by patients
- Convergent physiology, TF and functional connectivity

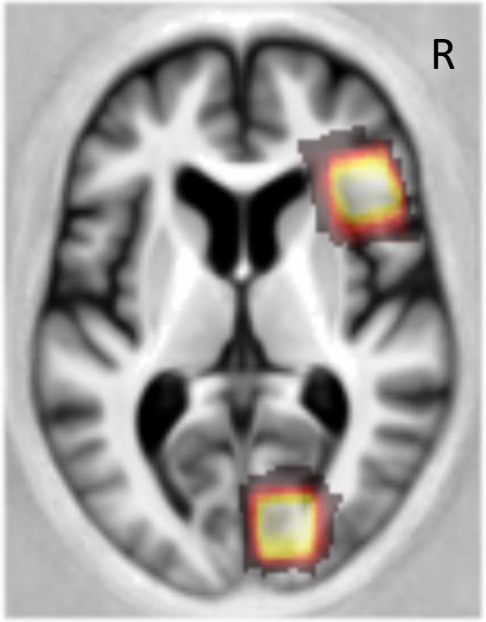
  Sami et al Brain 2018 – Hughes et al Brain 2018

A brief history of MEG in FTD/PSP

- Sensitive and very well tolerated by patients
- Convergent physiology, TF and connectivity
- Validation of GABA-ergic deficits

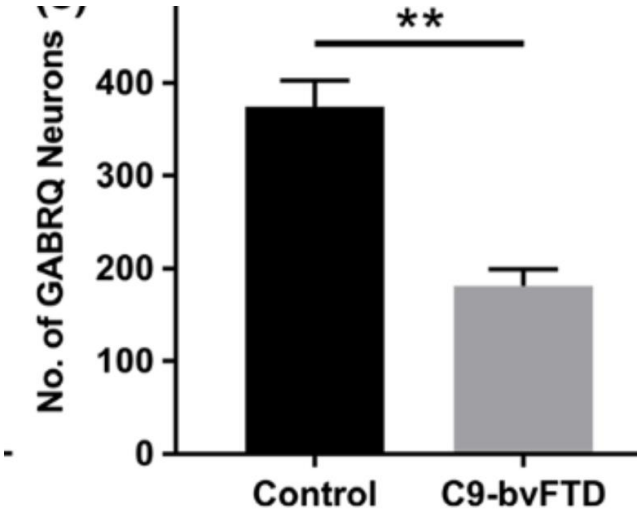
Restoring GABA-ergic function

GABA: the principal inhibitory neurotransmitter reduced by frontotemporal dementia and progressive supranuclear palsy

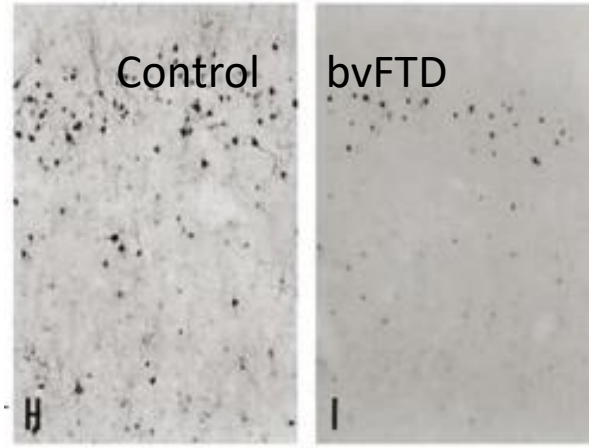


in vivo spectroscopy by 7T

Loss of GABA RQ neurons in PFC



Calbindin



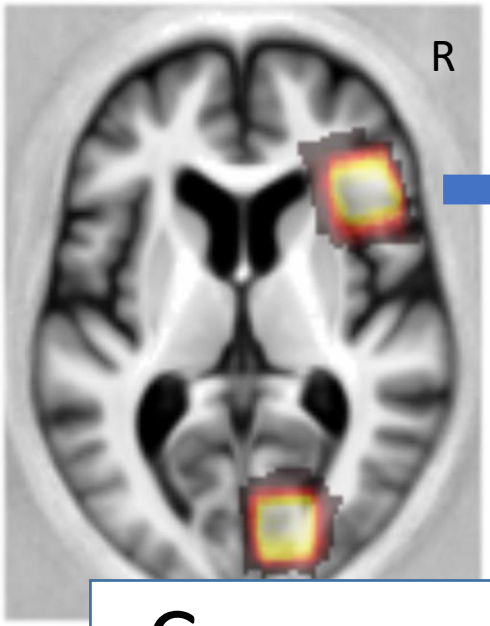
Murley et al, Brain 2020b

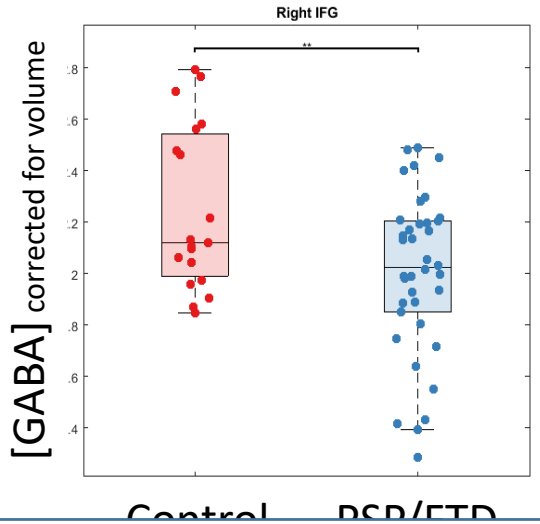
Murley and Rowe, Brain 2018

Gami-Patel et al, Neuropath Appl Neurop 2019

Restoring GABA-ergic function

GABA: in vivo quantification by sLaser MR Spectroscopy at 7T, with LC modelling





People with PSP or FTD type dementias are (***sometimes***) deficient in prefrontal cortical GABA

This **loss of inhibitory neurotransmission correlates with impulsivity**

in viv

Can we restore function by enhancing GABA in Frontotemporal dementia?

Murley et al, Brain 2020b

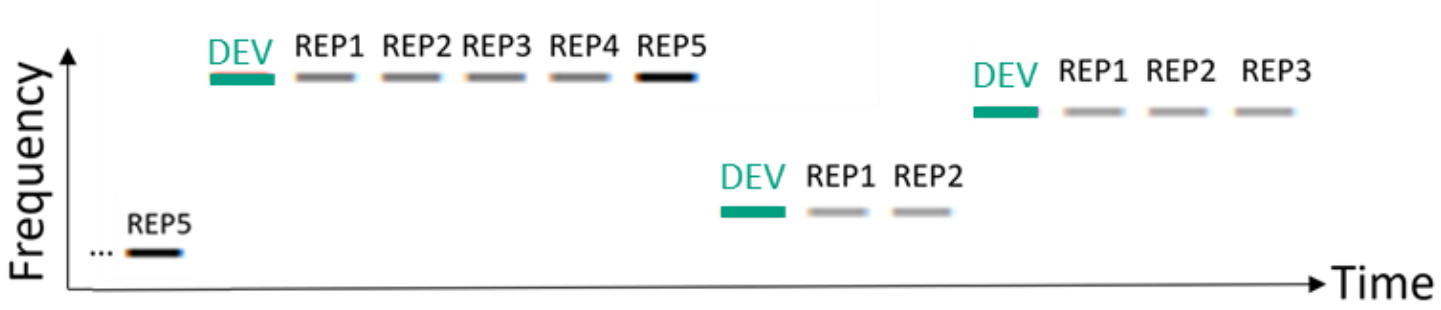
Murley and Rowe, Brain 2018

Double-blind placebo controlled ph-MEG

Placebo vs Tiagabine 10mg (GABA reuptake inhibitor)

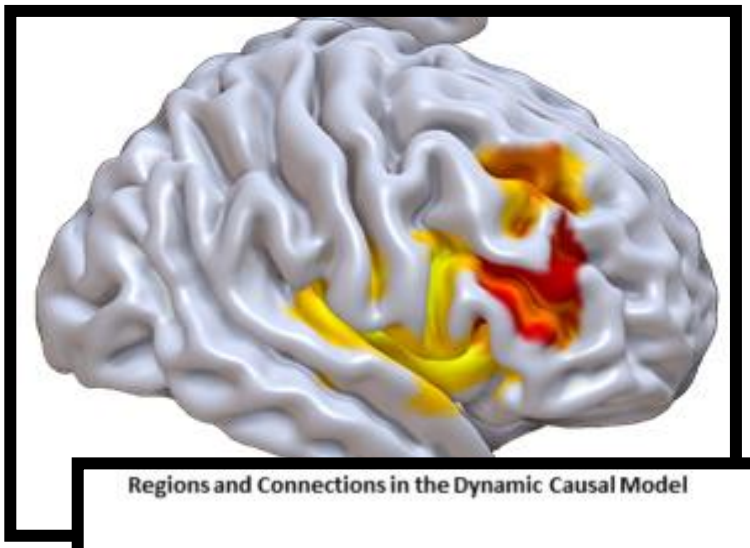
32 patients vs 20 matched controls
(note expected large effect sizes, d>1: power + range)

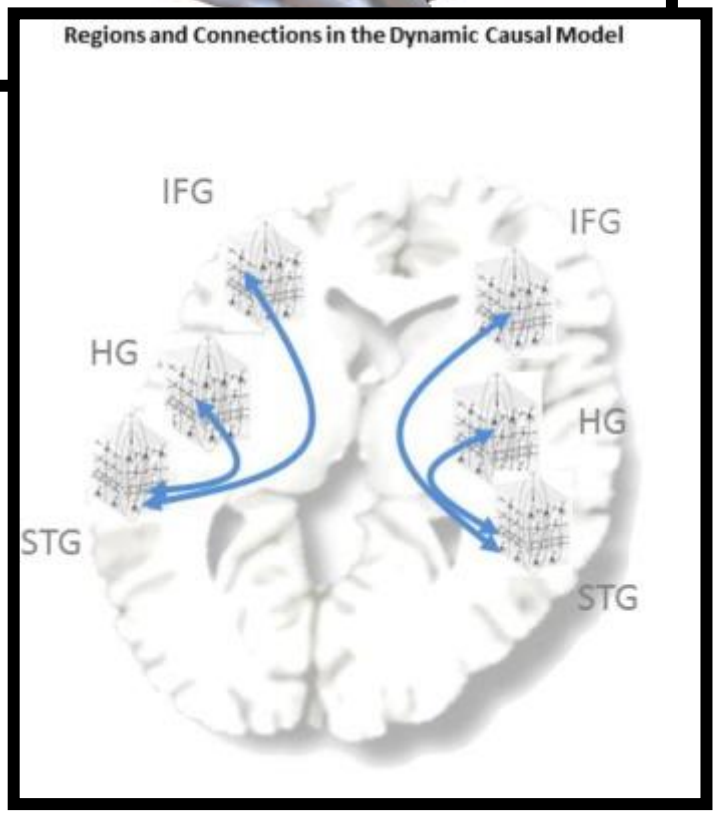
Elekta Vectorview 306 MEG



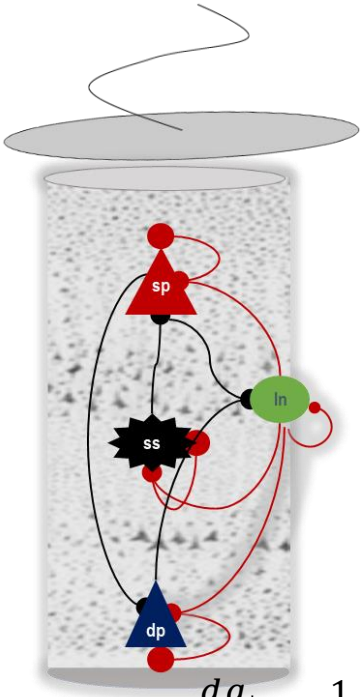
Adams et al Brain 2021

Dynamic Causal Models of human cognitive physiology





$$LFP = L(sp + J_1 * ss + J2 * dp)$$



$$\frac{dV}{dt} = \frac{1}{C}[g_L(V_L - V) + g_{AMPA}(V_{AMPA} - V) + g_{GABA}(V_{GABA} - V) + g_{NMDA}\, m(V)(V_{NMDA} - V)]$$

$$\frac{dg_*}{dt} = \frac{1}{\tau_*}\left(\sum_{k=sp,inh,dp,ss} H_k\, \sigma_k - g_*\right) + u,$$

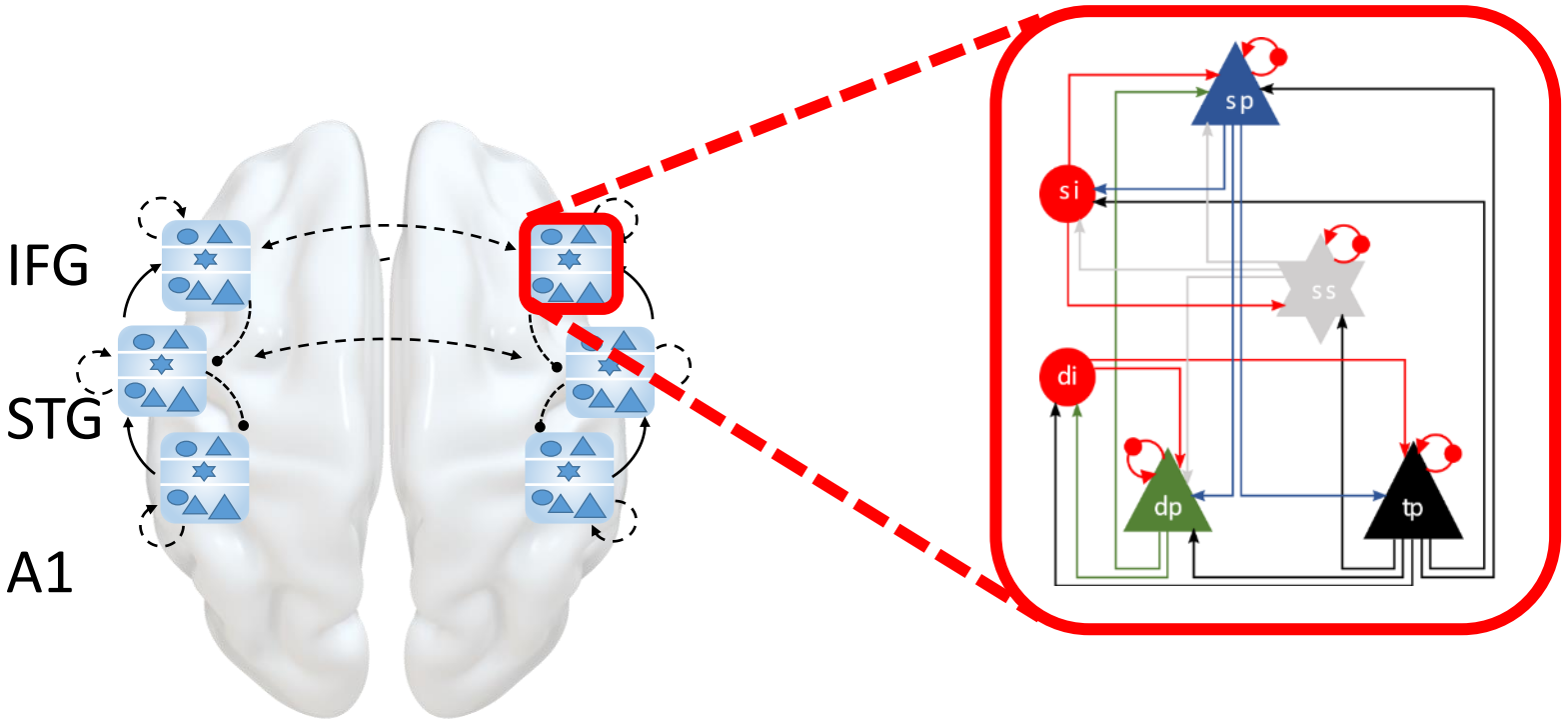
$$*= [L, AMPA, GABA, NMDA]$$

A tractable canonical microcircuit model of human cortex

Gilbert et al NI 2016, Symonds et al Brain 2018 (Ros Moran/Karl Friston)

Dynamic causal model

Extended 6-cell dynamic causal model of MMN network

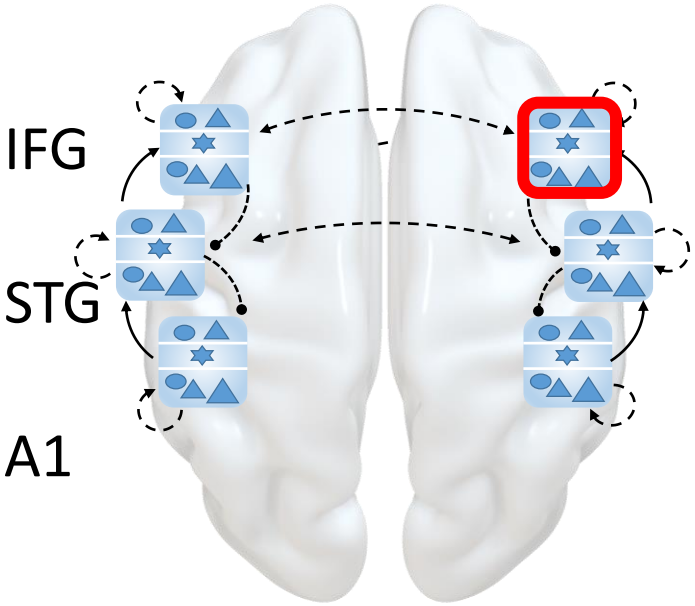


First level inversion MEG to DCM, then second level group analysis

Adams et al Brain 2021
Adams et al J Neurosci 2020

Dynamic causal model

Extended 6-cell 6-region dynamic causal model of MMN network



Unknowns within region
LFP signal $(L, J_{1,2})$
Intrinsic connections H
Time constants τ_*
Membrane capacitance C
Firing thresholds parameters (S)
Mean exogenous input (E)
Delay (D)

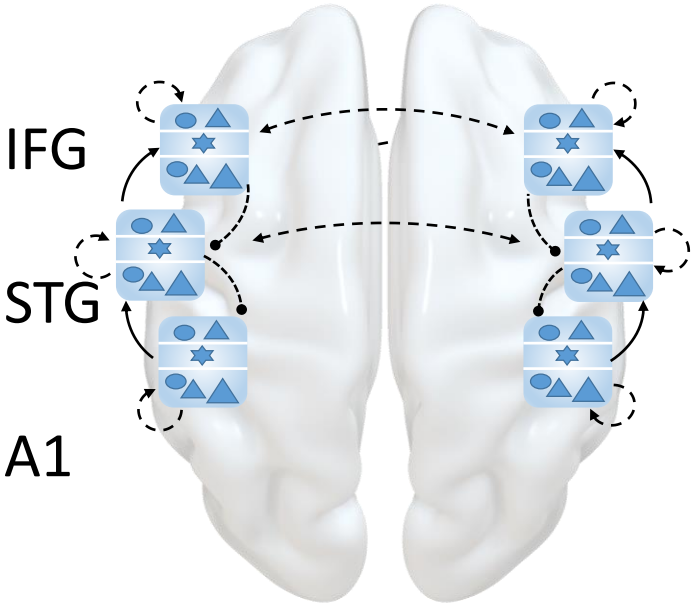
Unknowns between region
Forward and backward

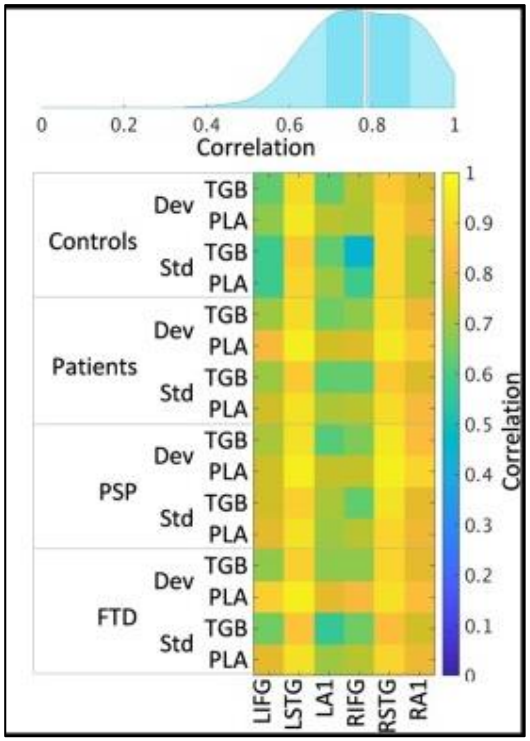
Neuronal noise terms
Channel noise terms (specific and common)

Adams et al Brain 2021
Adams et al J Neurosci 2020

Dynamic causal model

Extended 6-cell CMC dynamic causal model of MMN network; higher model evidences than 4-cell CMC standard model

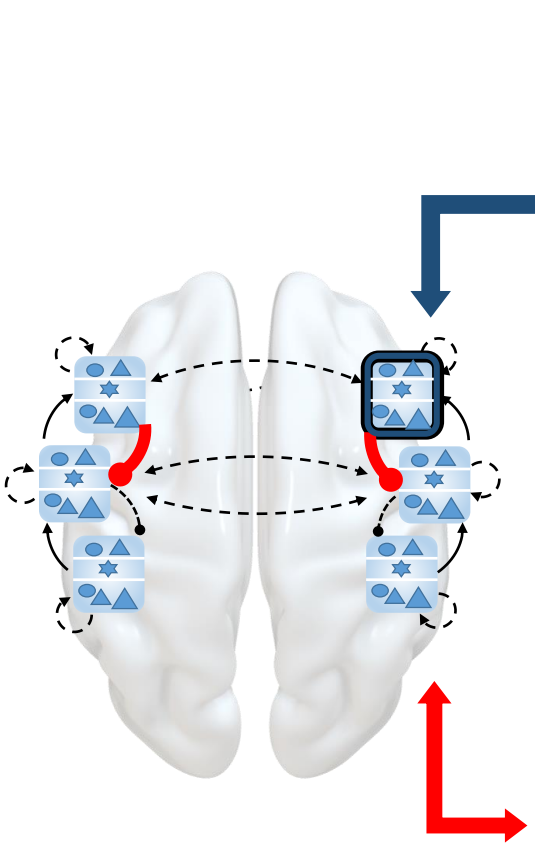


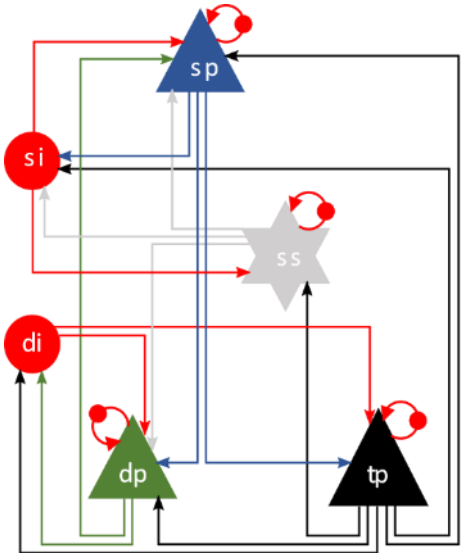


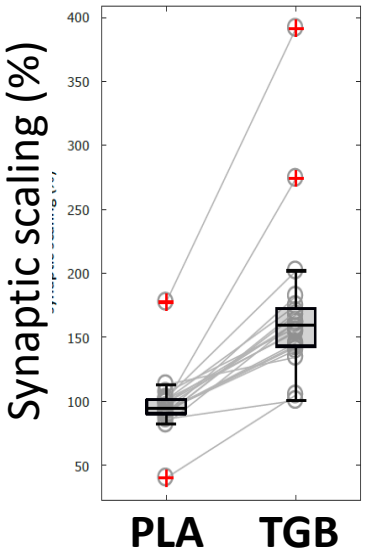
Accurate generative model (high correlation with observed time series)

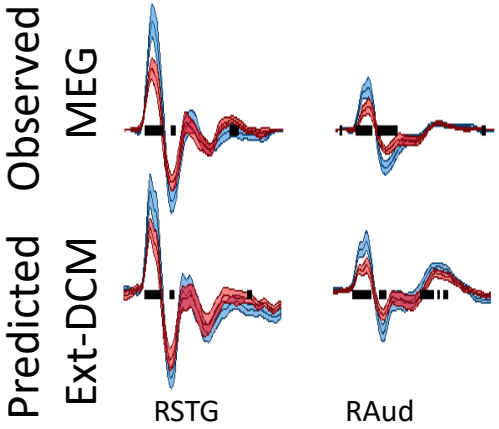
Adams et al Brain 2021
Adams et al J Neurosci 2020

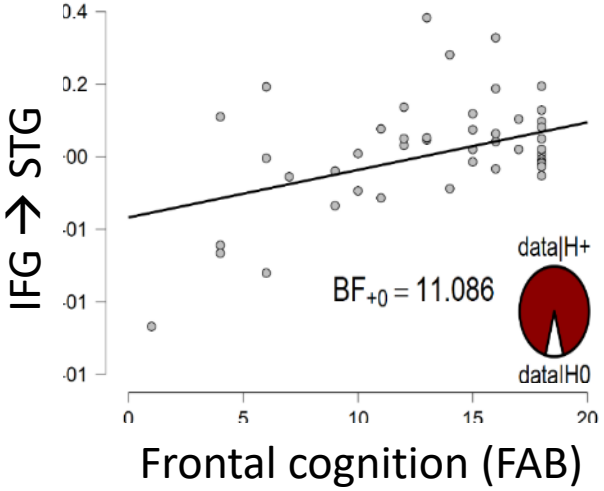
Veracity of dynamic causal models of dementia? x3





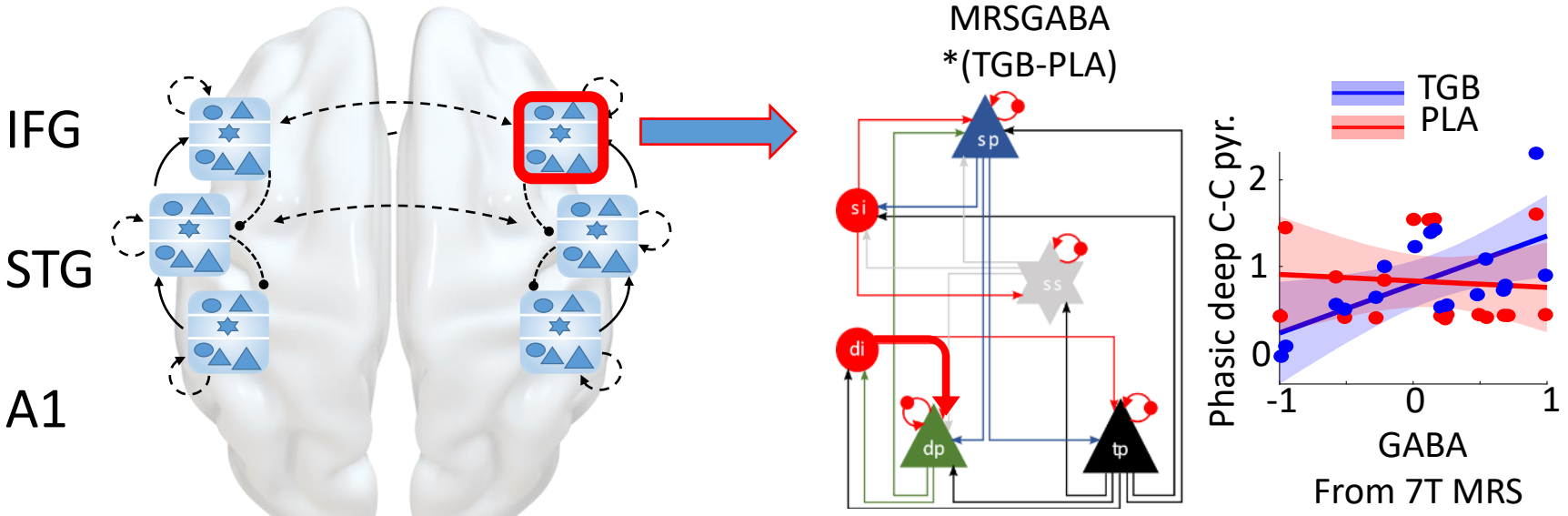






Shaw et al, Cortex 2019; Adams et al J Neurosci 2020; Adams et al Brain 2021

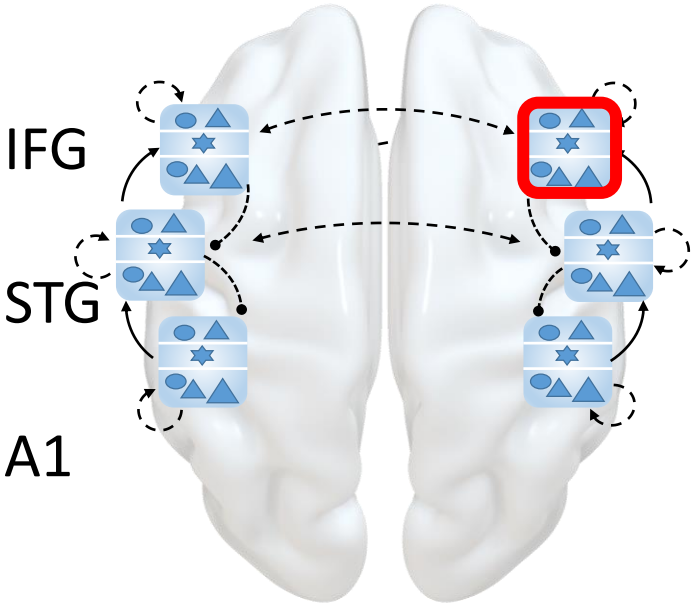
How does Tiagabine work, and for whom?
(individual response predicted by 7T MRS)

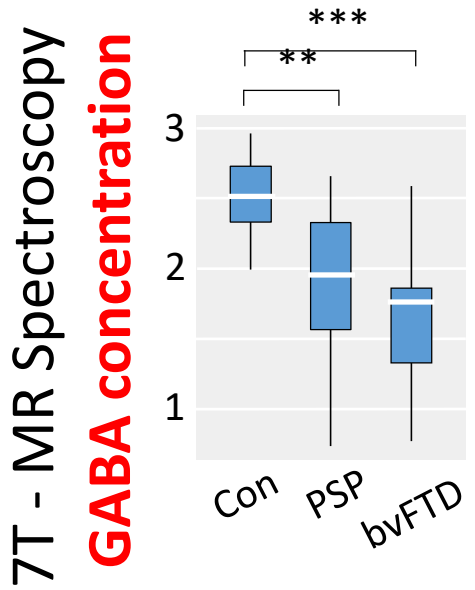


The effect of a GABA-ergic reuptake inhibitor (Tiagabine)
To restore frontal lobe cognitive physiology
Depends on deep GABA-ergic interneurons
As a function of individual GABA levels
→ Precision of pharmacology and phenotype

Adams et al, Brain 2021
or now use "pe-DCM"s Adams BIOMAG poster 40/351

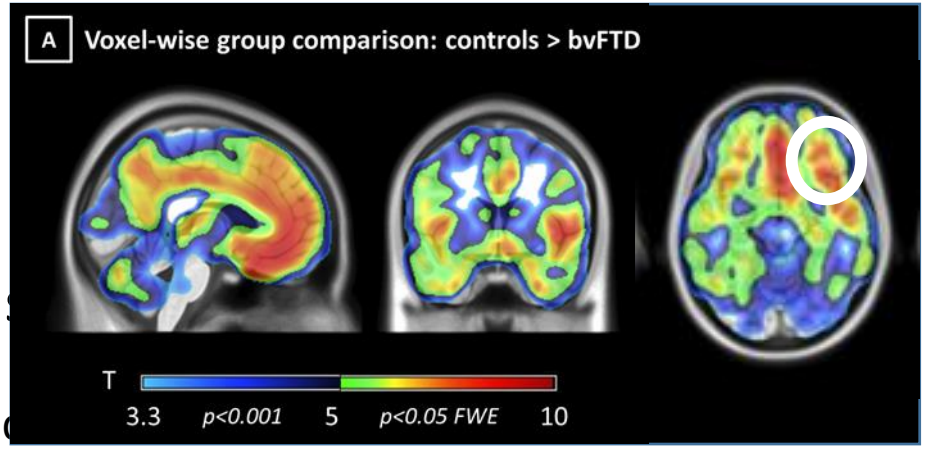
Dynamic causal models of disease?





Loss of synapses

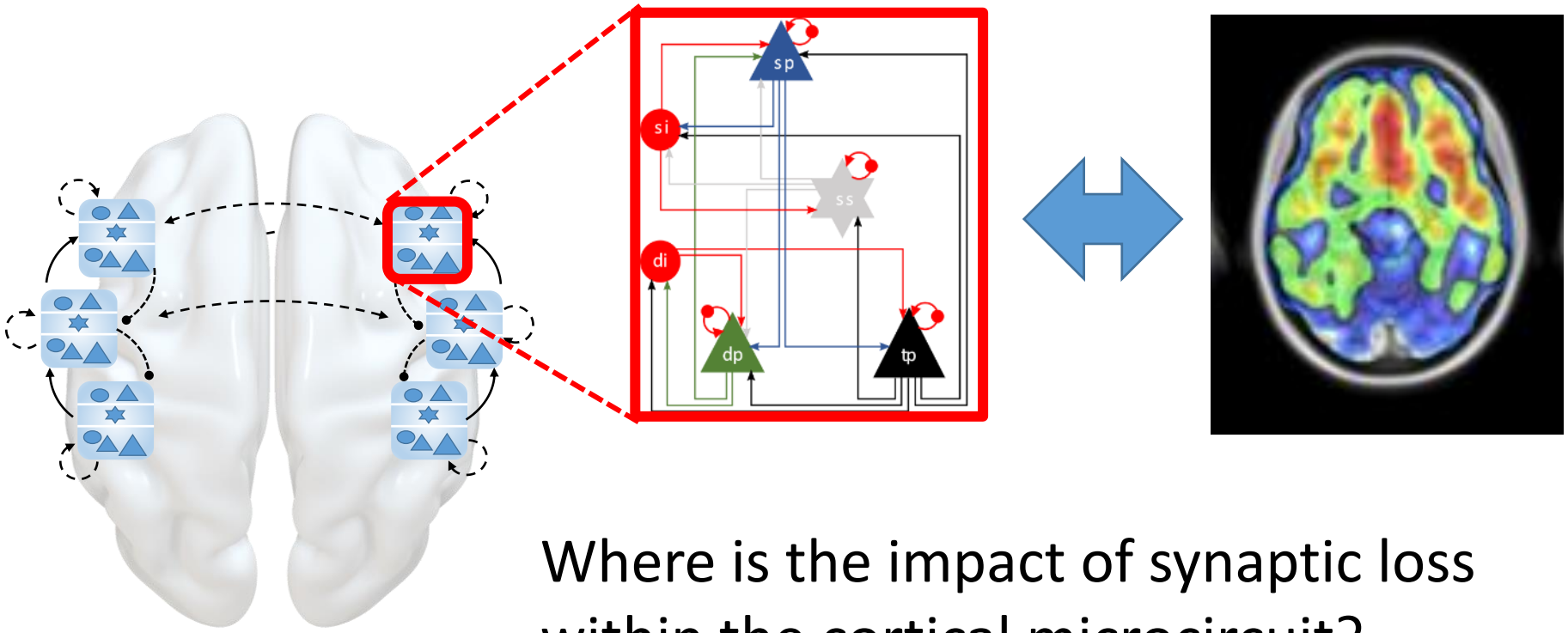
11C-UCBJ PET



Severe loss of GABA (sLaser) &

Murley et al Brain 2020; Malpetti et al un

Pathology enriched Dynamic causal models



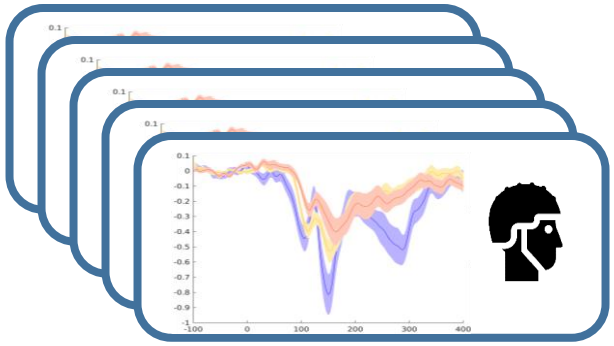
Where is the impact of synaptic loss within the cortical microcircuit?

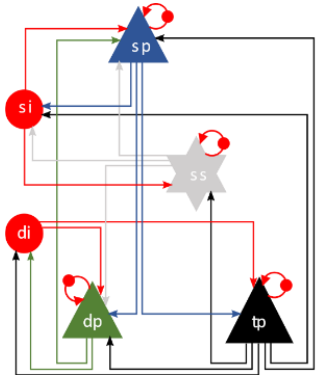
Can we integrate PET into the DCM?

Adams et al under review; Shaw et al Cereb Cortex 2021

Pathology enriched Dynamic causal models

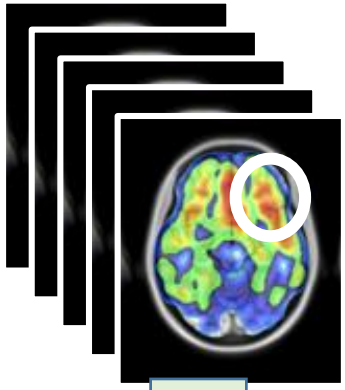
Can we integrate PET into the DCM?





First level DCM

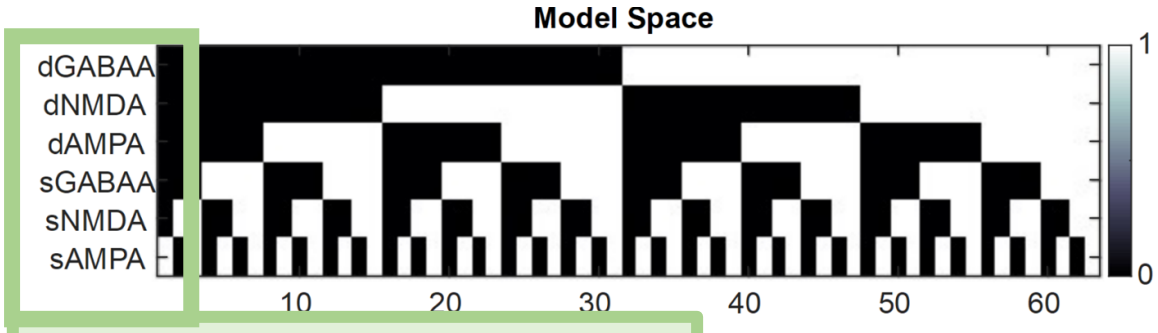
Posterior estimate of parameters and first level model evidences



PET

Second level group DCM (PEB)

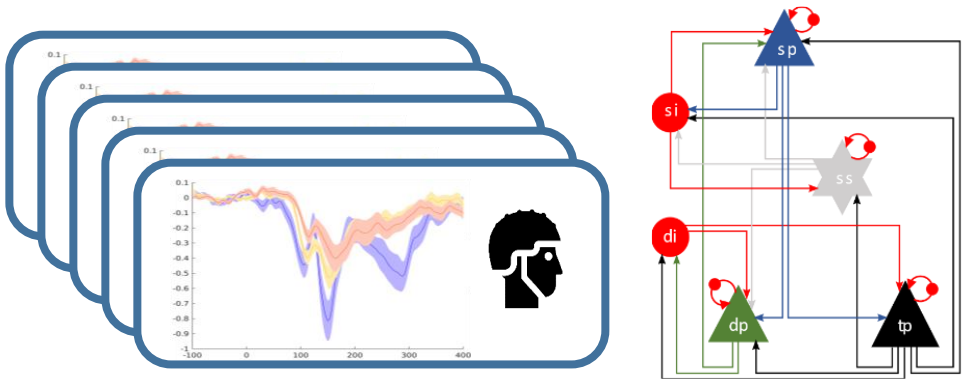
Group DCM inversion informed by PET as empirical prior



Model evidences re site of action
Posterior estimate of parameters
Model prediction vs observed

Adams et al under review; Shaw et al Cereb Cortex 2021

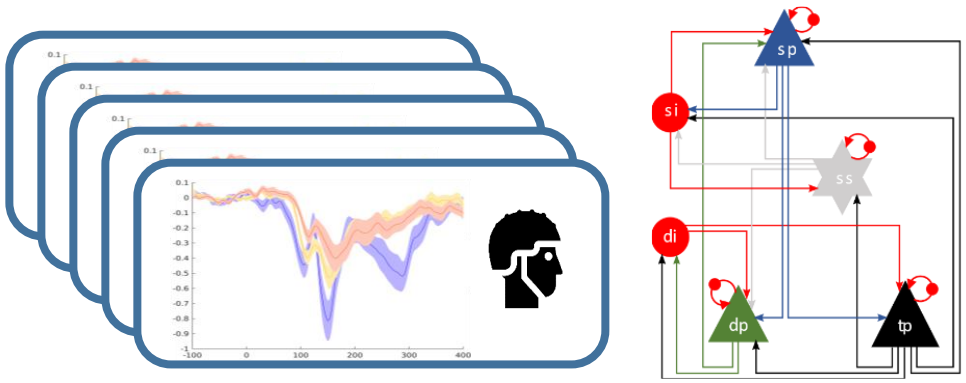
Pathology enriched Dynamic causal models



"where in the cortical microcircuit (which neuron class, which neuro-transmitter) does prior knowledge of an individual's synapse loss (PET) improve the model evidence (improve generative model to reproduce the observed data better)"

Adams et al under review; Shaw et al Cereb Cortex 2021

Pathology enriched Dynamic causal models



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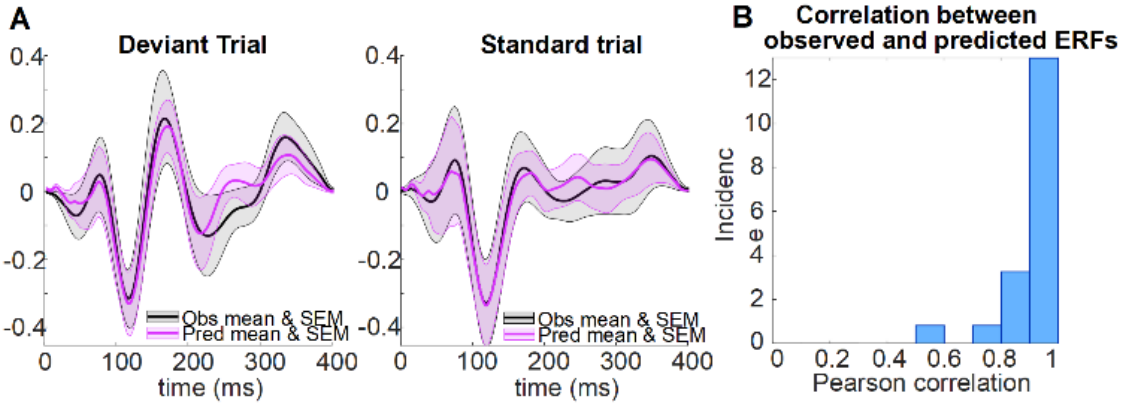
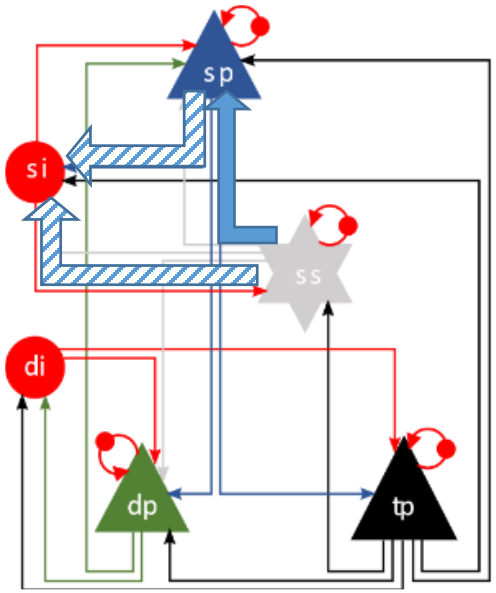


Adams et al under review; Shaw et al Cereb Cortex 2021

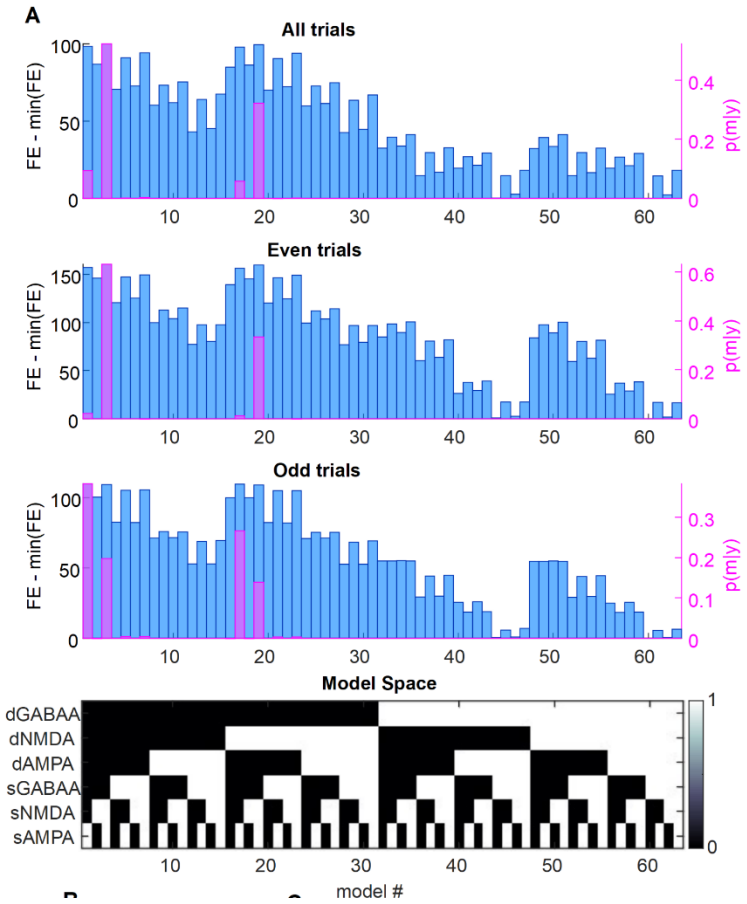
Pathology enriched Dynamic causal models

The model comparison suggests loss of synapses (UCBJ PET) affects the MEG generators (DCM) at the level of superficial pyramidal cells

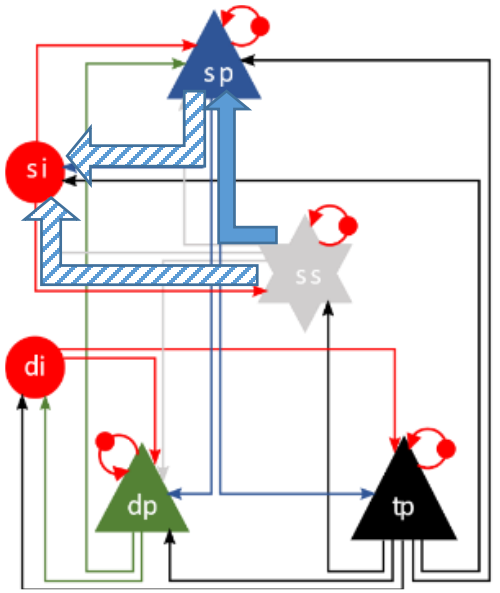


See Amirhossein Jafarian BIOMAG 2022 02-351
Adams et al under review; Shaw et al Cereb Cortex 2021

Pathology enriched Dynamic causal models

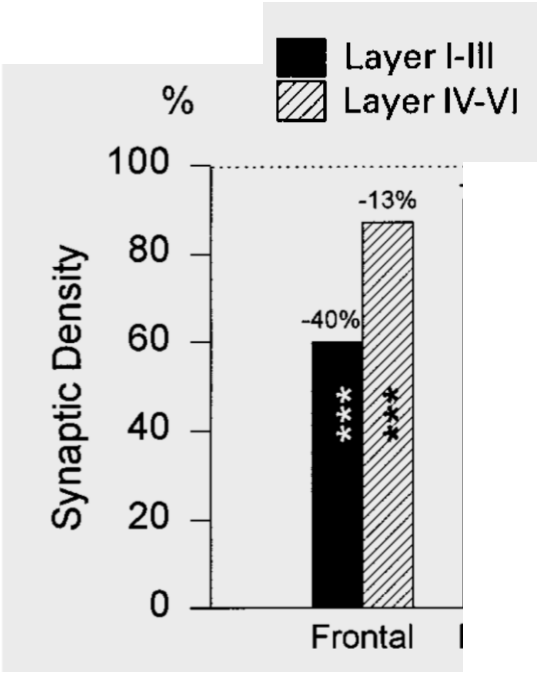


e model comparison
ggests loss of synapses
CBJ PET) affects the MEG
nerators (DCM) at the level
superficial pyramidal cells



See Amirhossein Jafarian BIOMAG 2022 02-351
Adams et al Brain 2022; Shaw et al Cereb Cortex 2021

Pathology enriched Dynamic causal models



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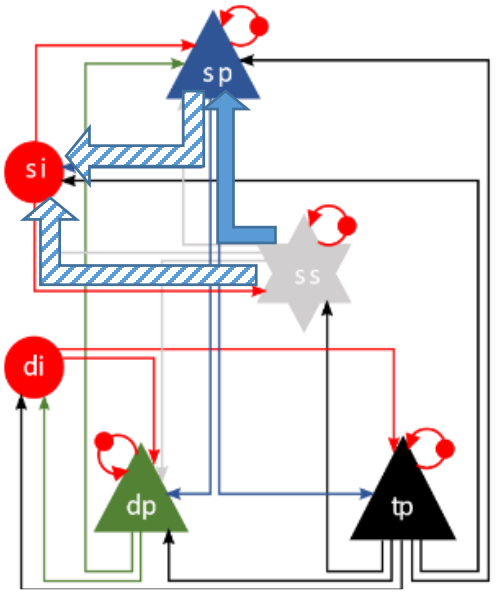


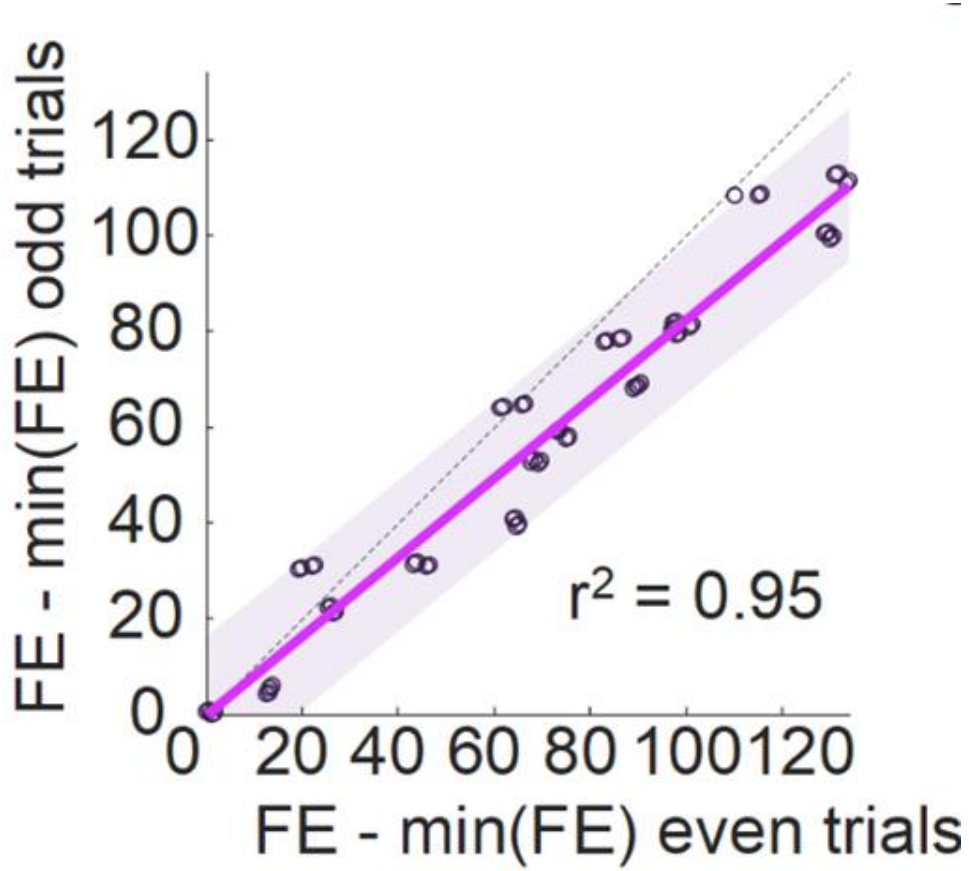
Synaptophysin reduced
in superficial layers
frontal cortex in FTD
At post mortem

Brun et al Neurodegeneration, 1995
Liu et al Dement Geriatr Cogn Disord 1999
Adams et al under review; Shaw et al Cereb Cortex 2021

Pathology enriched Dynamic causal models

Highly reliable in split sample analysis r2 ~0.95 for

Free energy (for hypothesis testing by model selection)



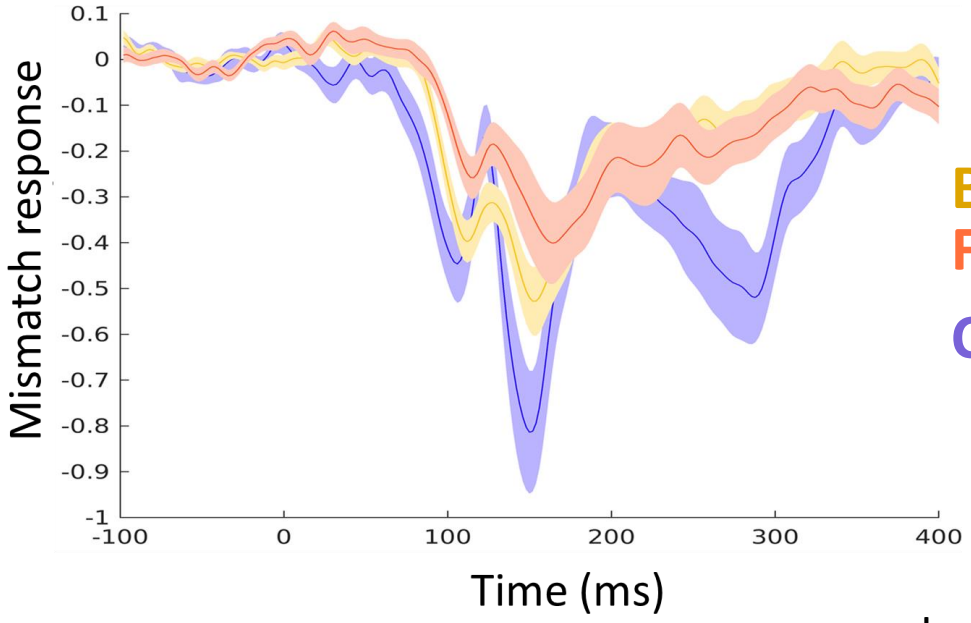
Adams et al Brain 2022; Shaw et al Cereb Cortex 2021

MEG bridge to disease models

New Therapeutics in Alzheimer's disease

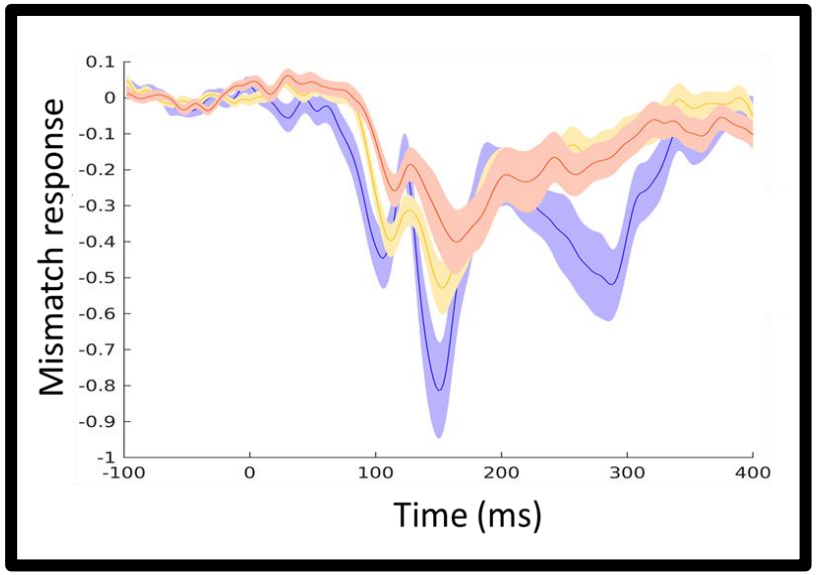
50*AD/MCI (amyloid positive) vs 15 controls

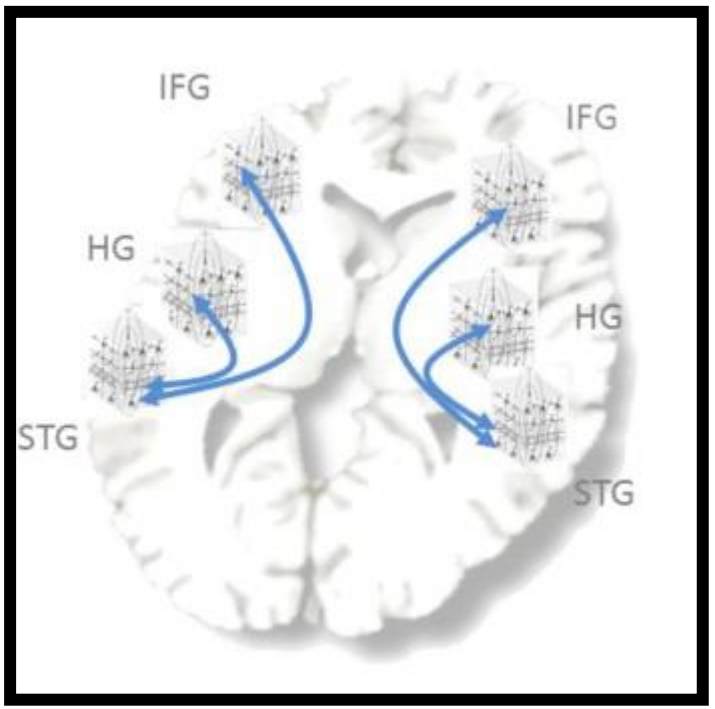
Roving auditory mismatch

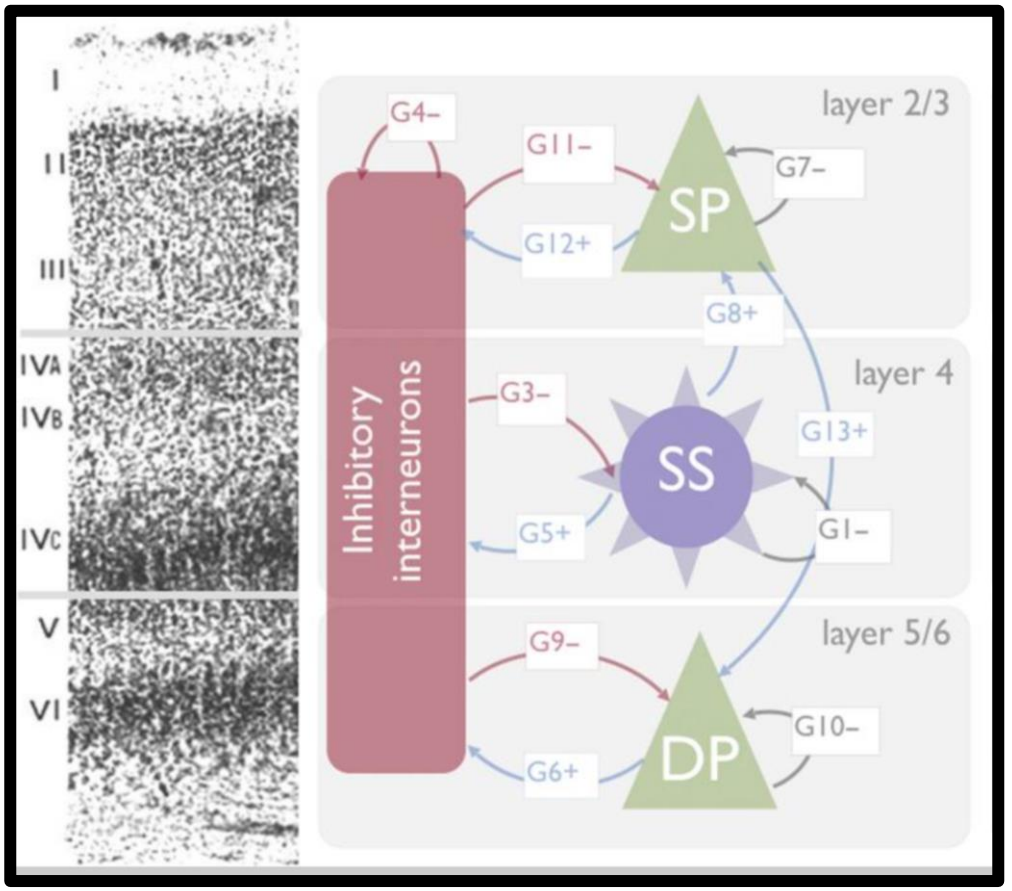


Lanskey et al BIOMAG Tuesday 12:30 09-541

Dynamic Causal Models of human cognitive physiology







convolution-based, mean-field neural mass model

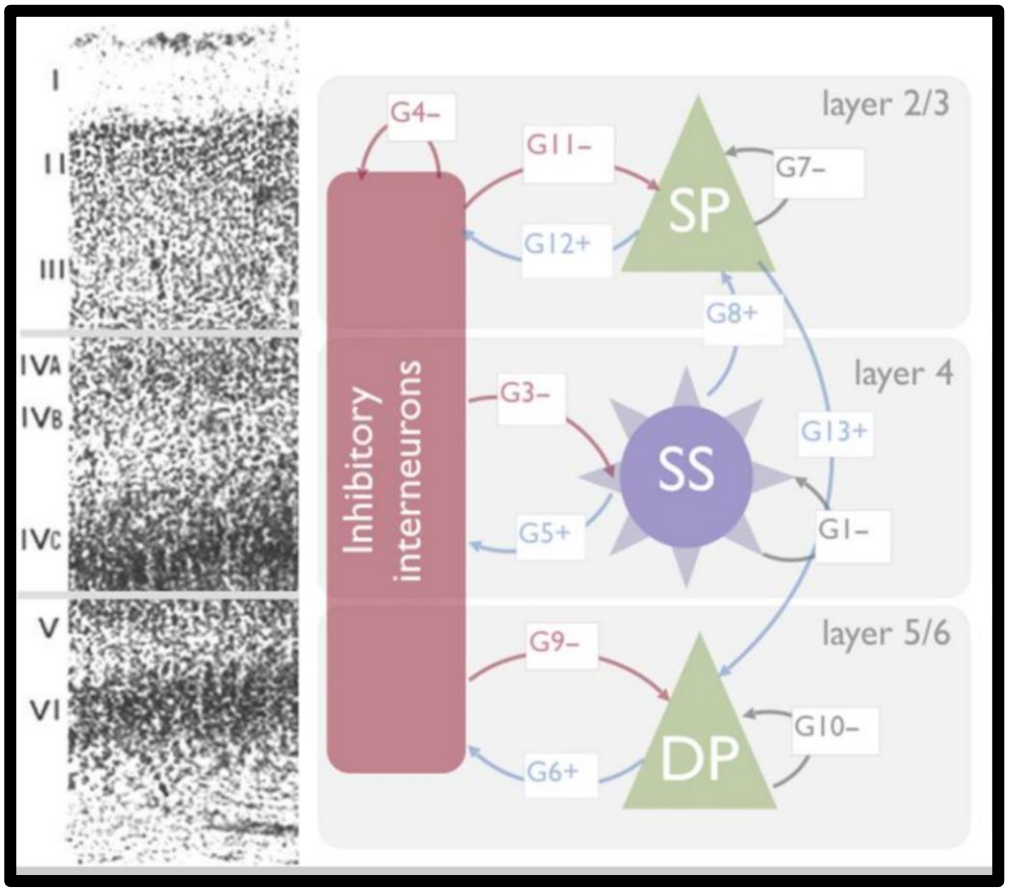
Shaw et al Cereb Cortex 2021; (after Ros Moran/Karl Friston)

Dynamic Causal Models of human cognitive physiology

$$\acute{x}_v = x_i$$

$$\acute{x}_i = KU - 2Kx_i - K^2x_v$$

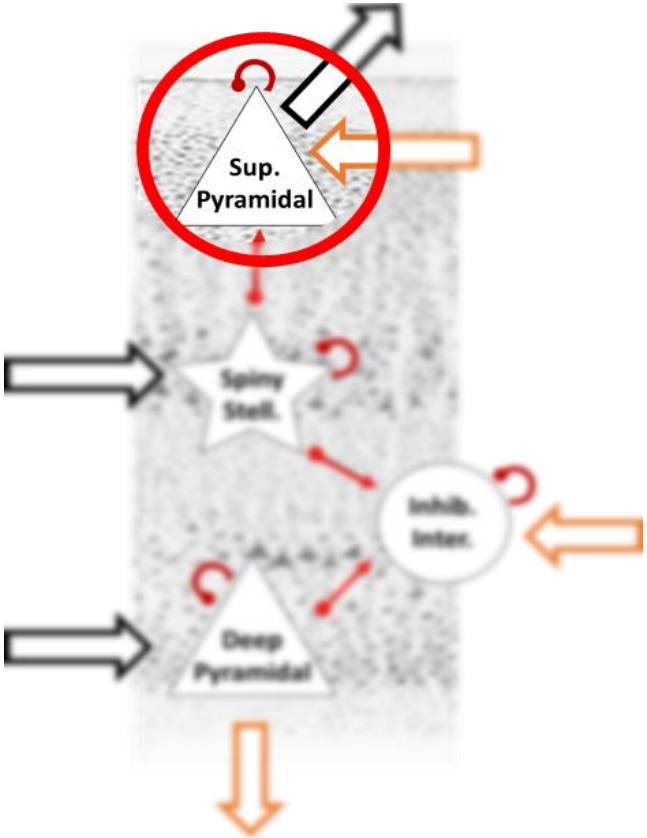
$$U = Sd + H + E$$

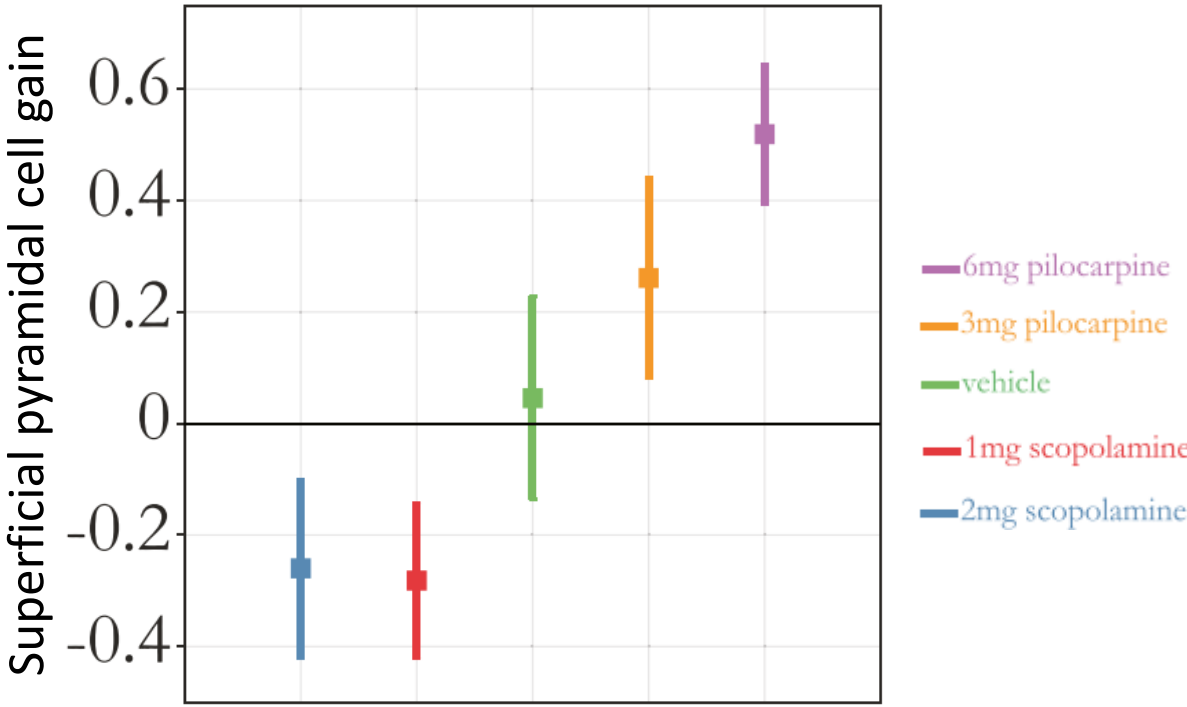


convolution-based, mean-field neural mass model; with voltage (x_v) and current (x_i), *K* rate-constant; *S* extrinsic projections(s) to the layer; *d* is the presynaptic firing (sigmoid activation function); *H* sum of postsynaptic-currents

Shaw et al Cereb Cortex 2021; (after Ros Moran/Karl Friston)

Can MEG build bridges to disease models?



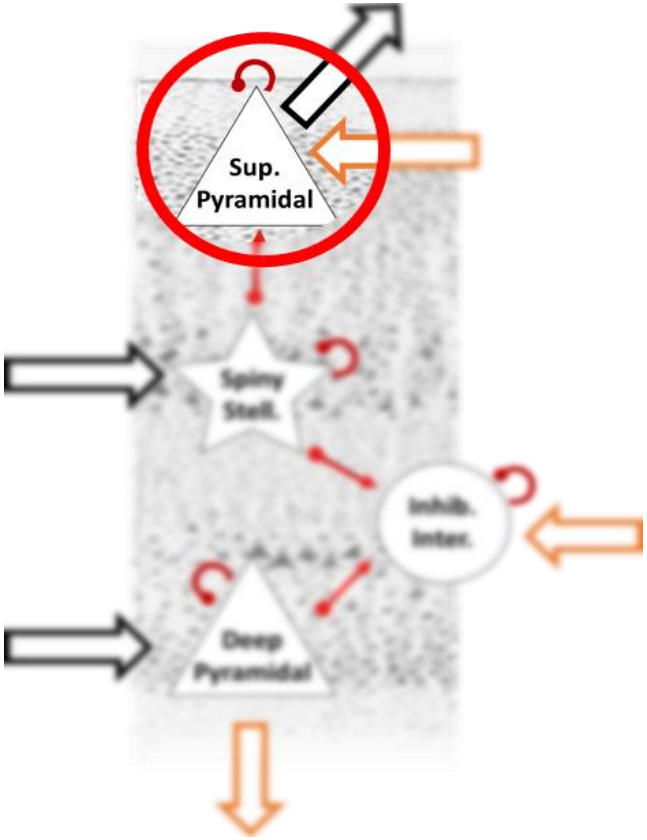


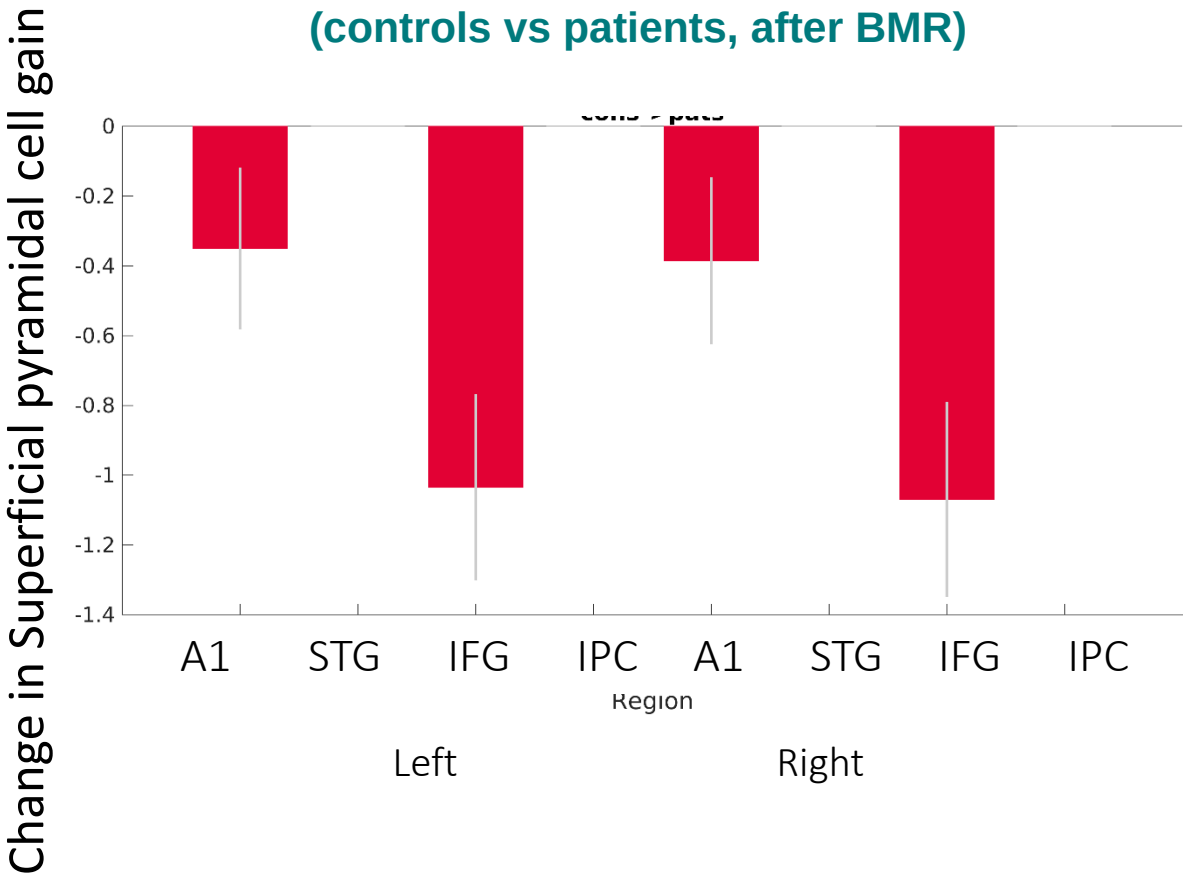
4-cell convolution model
of cortical microcircuits

Lanskey et al BIOMAG Tuesday 12:30 09-541

Schöbi et al. Neuroimage 2021; 237

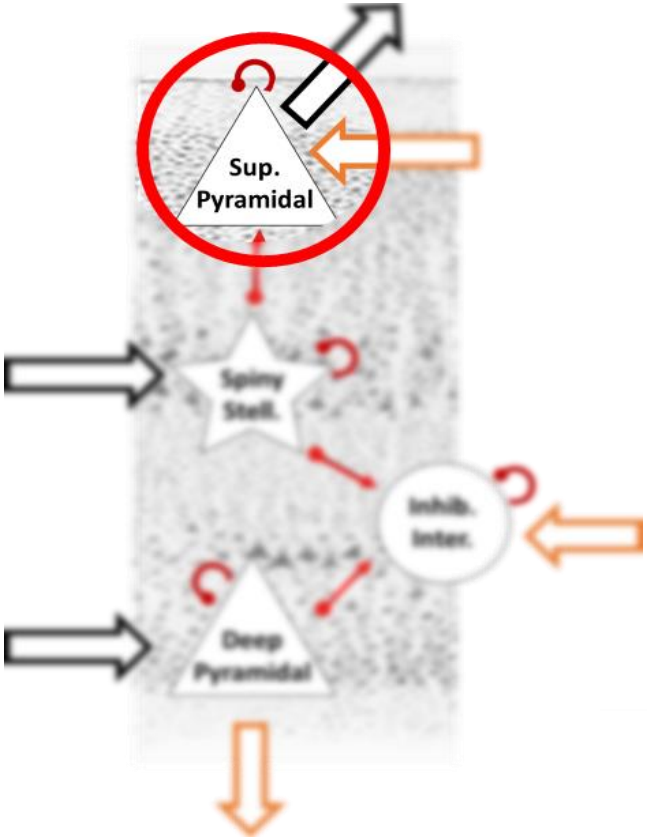
Can MEG build bridges to disease models?

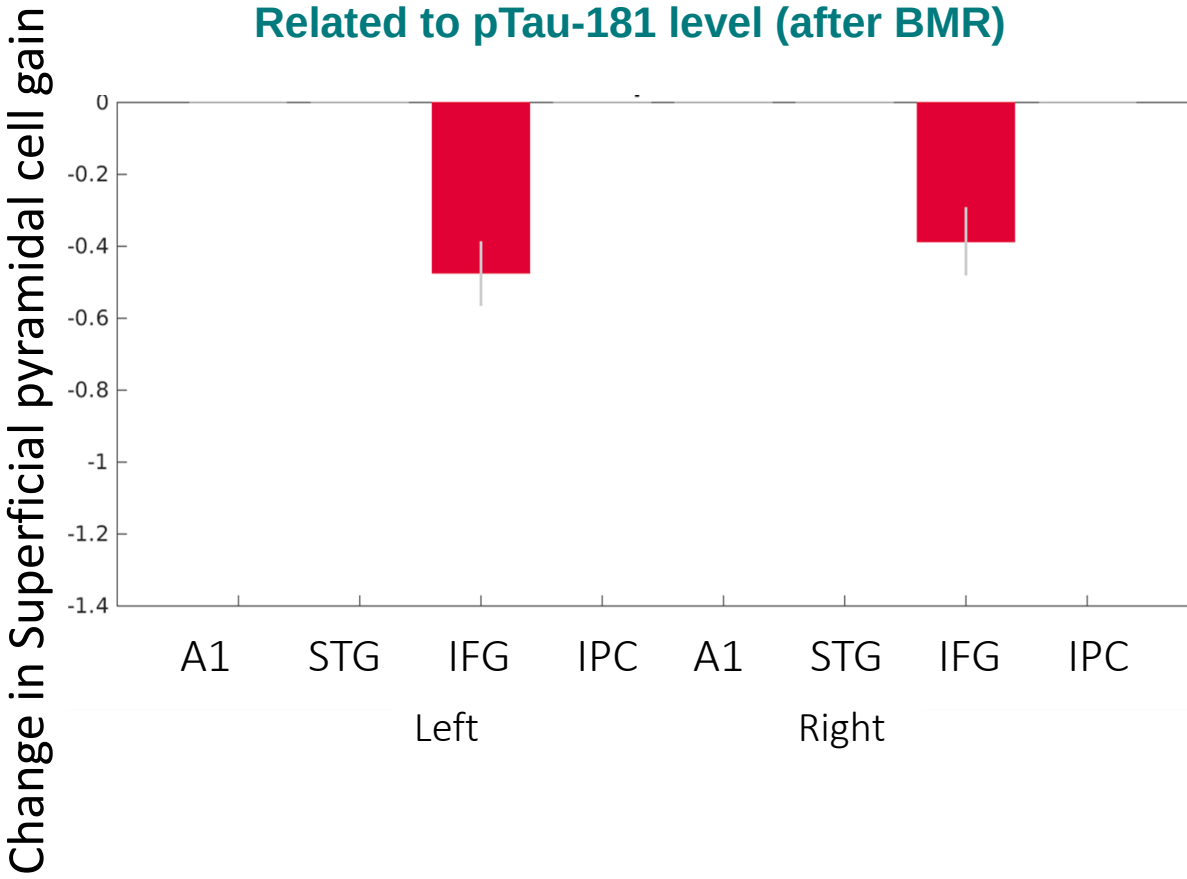




4-cell convolution model
of cortical microcircuits
With PEB of DCM

Can MEG build bridges to disease models?





4-cell convolution model
of cortical microcircuits
With PEB of DCM

Is DCM with MEG reliable?

“if I did the same experiment again would I get the same answer?”

Frequentist correlations, ICC etc

- problematic in multivariate complex models

Model Selection

PEB contrast

Is DCM with MEG reliable?

A hierarchy of expectation:

Same site, same subjects, same session, different trials

Same site, same subjects, different sessions

Same site, different subjects

Different site

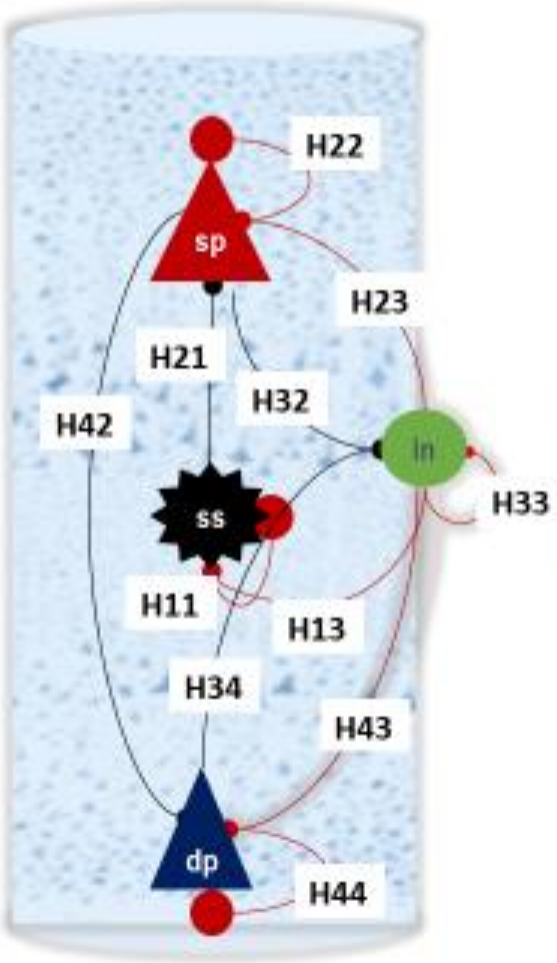
Is DCM with MEG reliable?

DCM for CSD (MEG) at rest in Alzheimer's disease

Amir Jafarian et al Subm

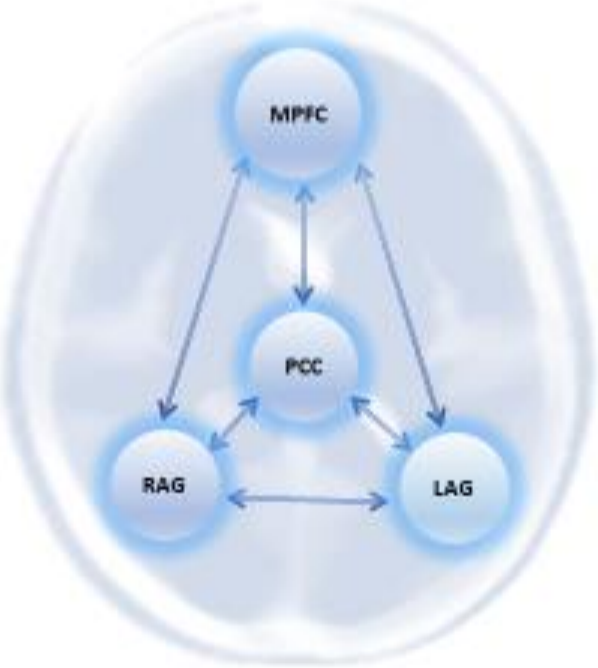
(a) Cortical Column

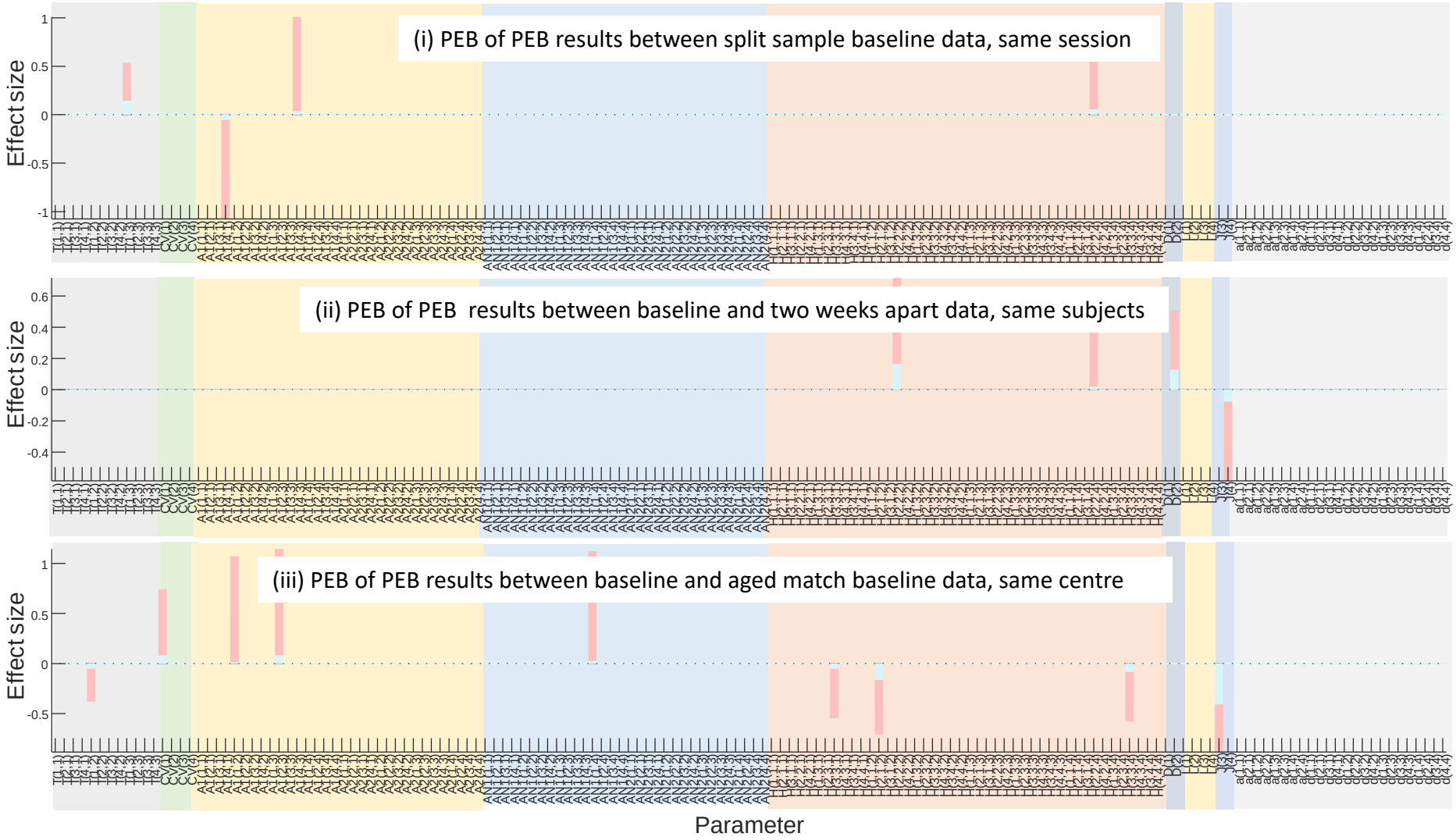
(b) Mesoscale model



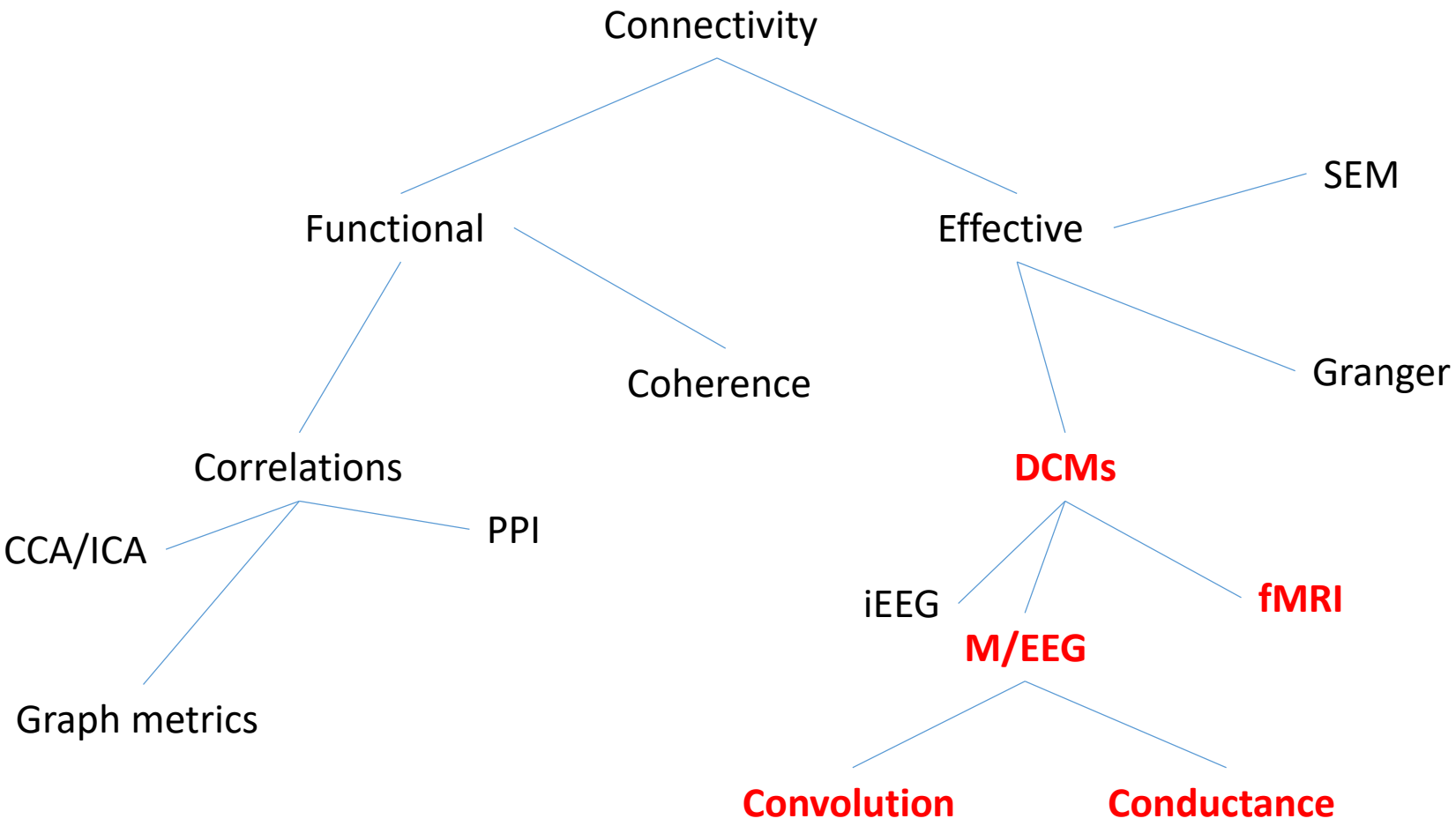
ss: Spiny stellate cells
sp: Superficial pyramidal cells
in: Inhibitory interneurons
dp: Deep pyramidal cells

(b) Default mode network




(i) PEB of PEB results between split sample baseline data, same session
(ii) PEB of PEB results between baseline and two weeks apart data, same subjects
(iii) PEB of PEB results between baseline and aged match baseline data, same centre
Effect size
Parameter

Summary:
DCM in the family of brain connectivity methods



Summary

To de-risk and accelerate early phase clinical trials with new MEG assays ….

1. Sensitive to presence of disease

Summary

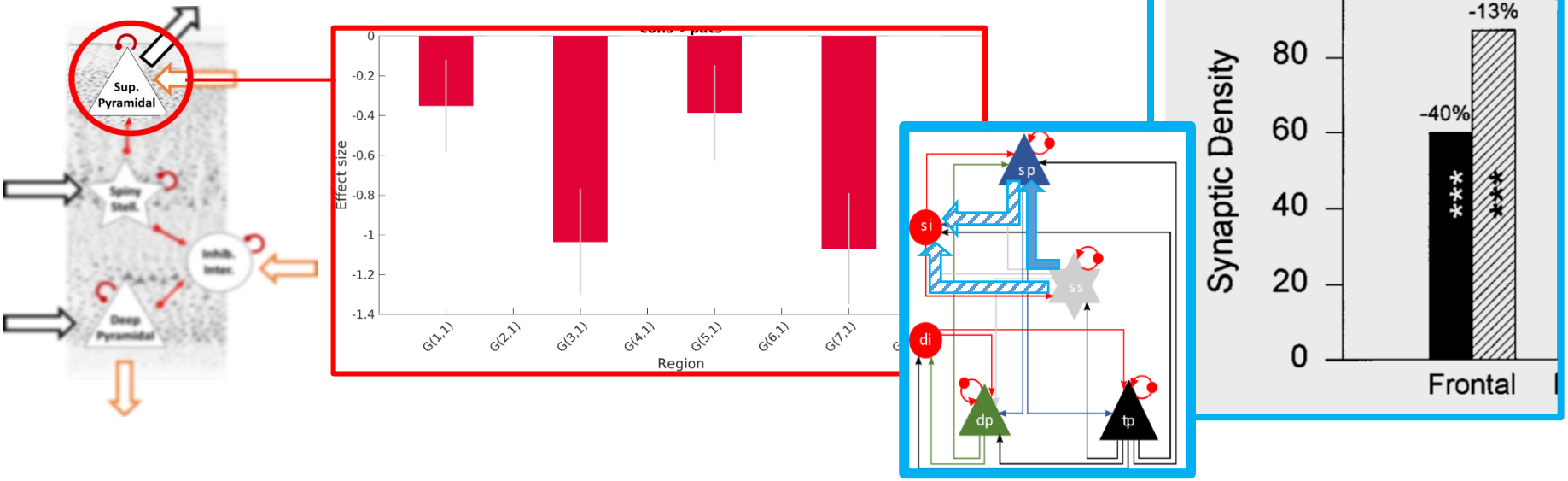
To de-risk and accelerate early phase clinical trials with new MEG assays ….

1. Sensitive to presence of disease (AD, PSP, FTD, PD)
2. Sensitive to progression of disease (AD)

Summary

To de-risk and accelerate early phase clinical trials with new MEG assays ….

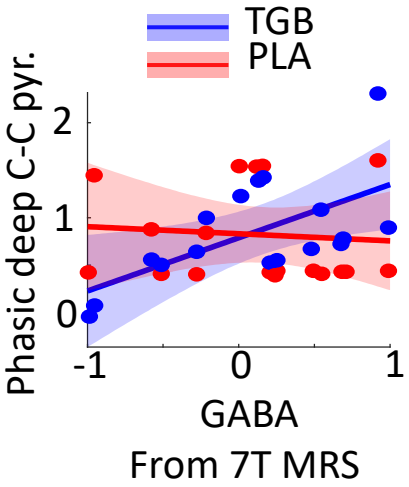
1. Sensitive to presence of disease
2. Sensitive to progression of disease
3. Elucidate disease mechanisms (DCM)

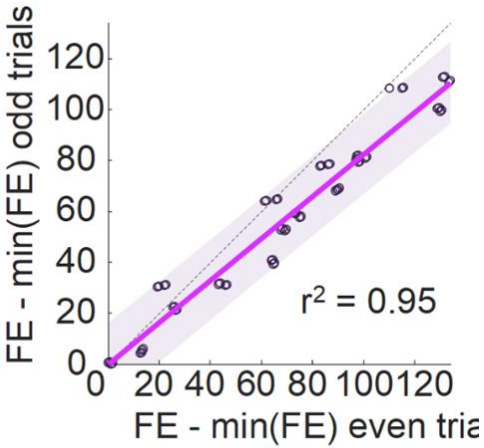


Summary

To de-risk and accelerate early phase clinical trials with new MEG assays ….

1. Sensitive to presence of disease
2. Sensitive to progression of disease
3. Elucidate disease mechanisms
4. Trial-ready eg. ***reliable***, scalable, ***sensitive to drug***





Why choose Dynamic causal modelling ?

1. models interactions at the neuronal (not haemodynamic or sensor/lfp level).

2. can include complex networks, reciprocal connections and loops, biologically plausible systems with feedforward and feedback connectivity….
   THEORETICAL AND ANATOMICAL MOTIVATION

3. can compare models/networks (Bayesian model selection)
   nested and non-nested models, families of models,
   use Free energy estimate of model evidence (adjusted for complexity)
   DESIGN YOUR STUDY AND FRAME HYPOTHESES WITH BMS IN MIND

4. applies to single subjects, heterogenous groups, & interventions

5. is easy to use and simple to understand…

Thank you

and thanks my great team at the

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And many others

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ccpp.cam.ac.uk

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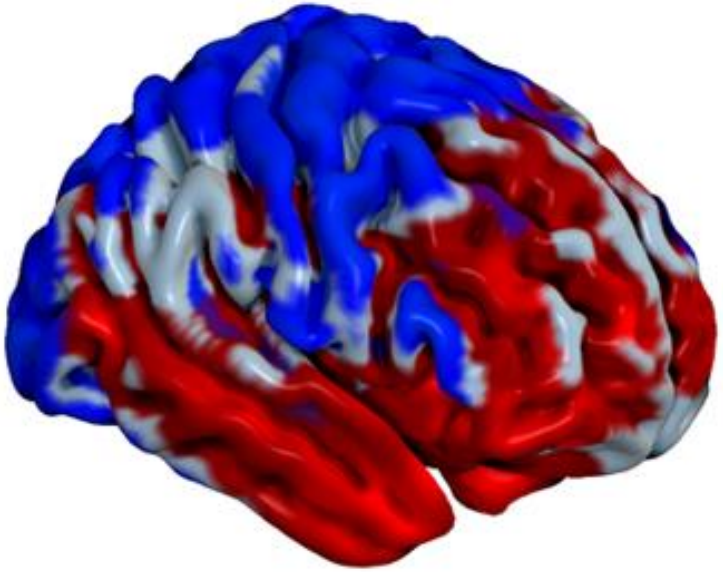
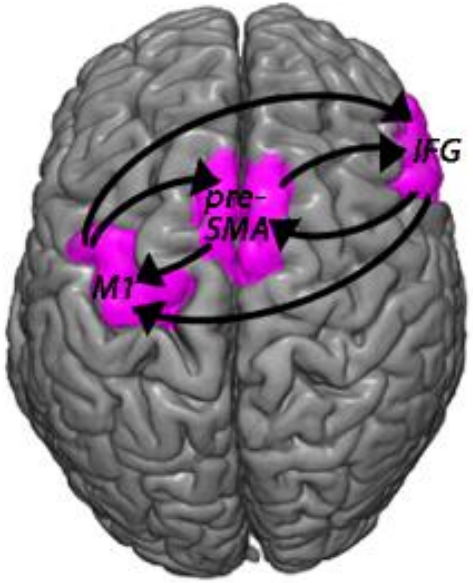
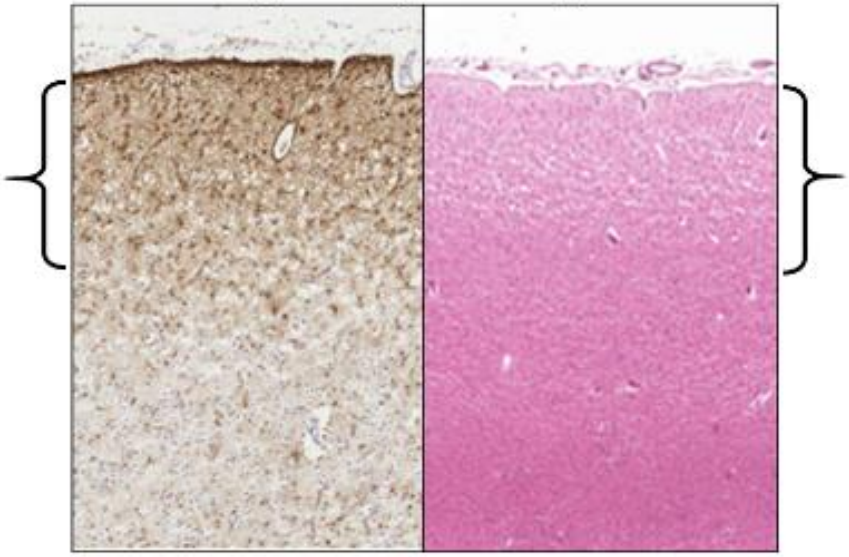
a) Grey and white matter atrophy in bvFTD



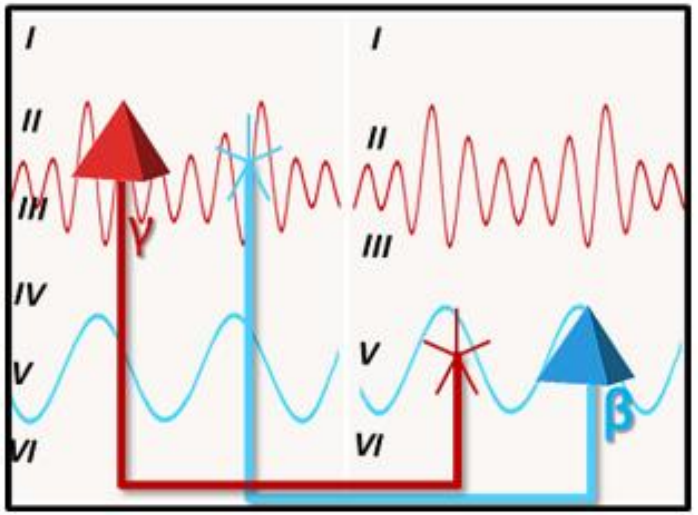
c) Model of task related frontal cortical interactions



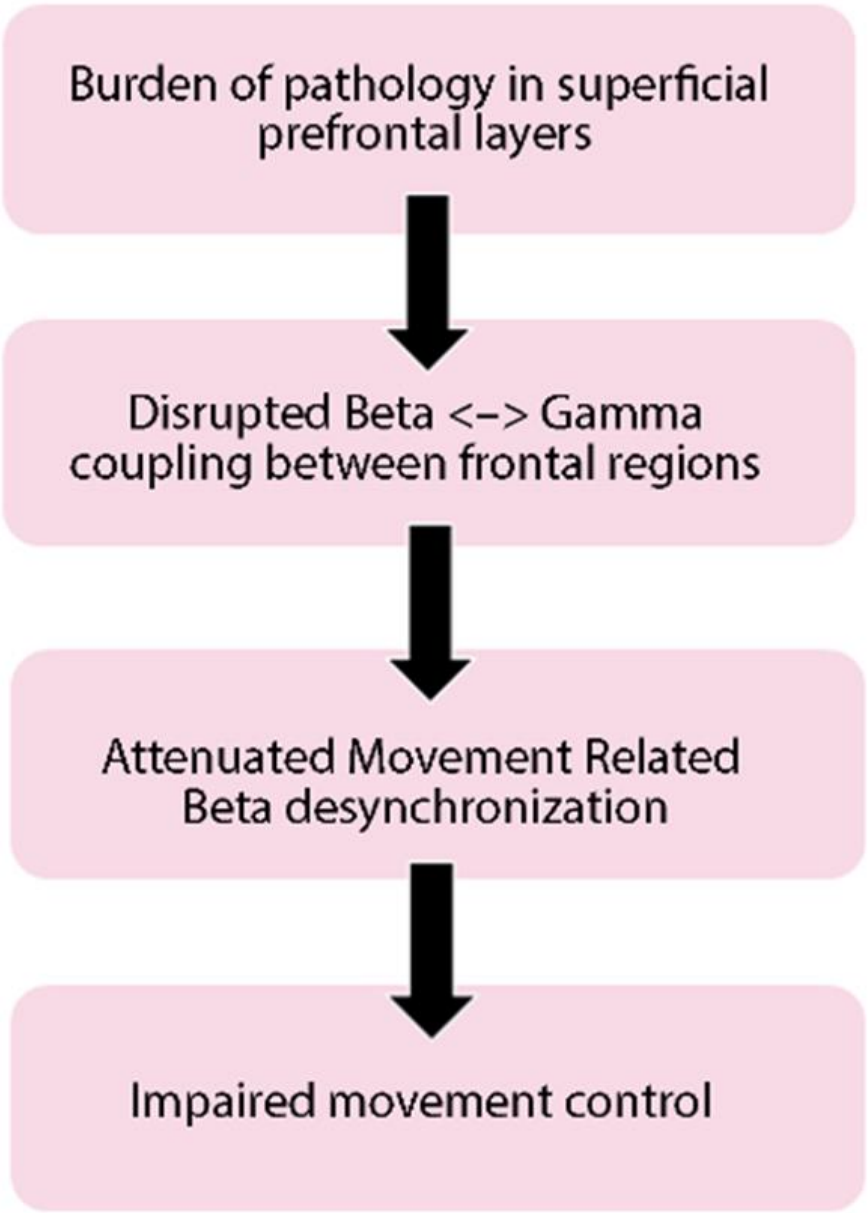
b) Laminar specific pathology in bvFTD

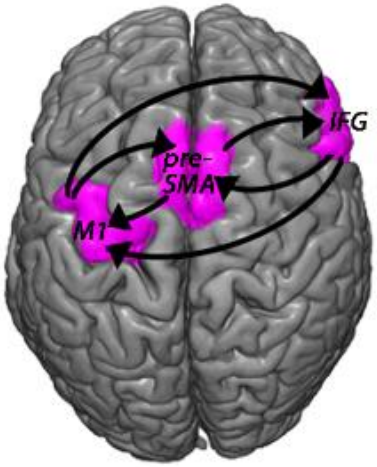


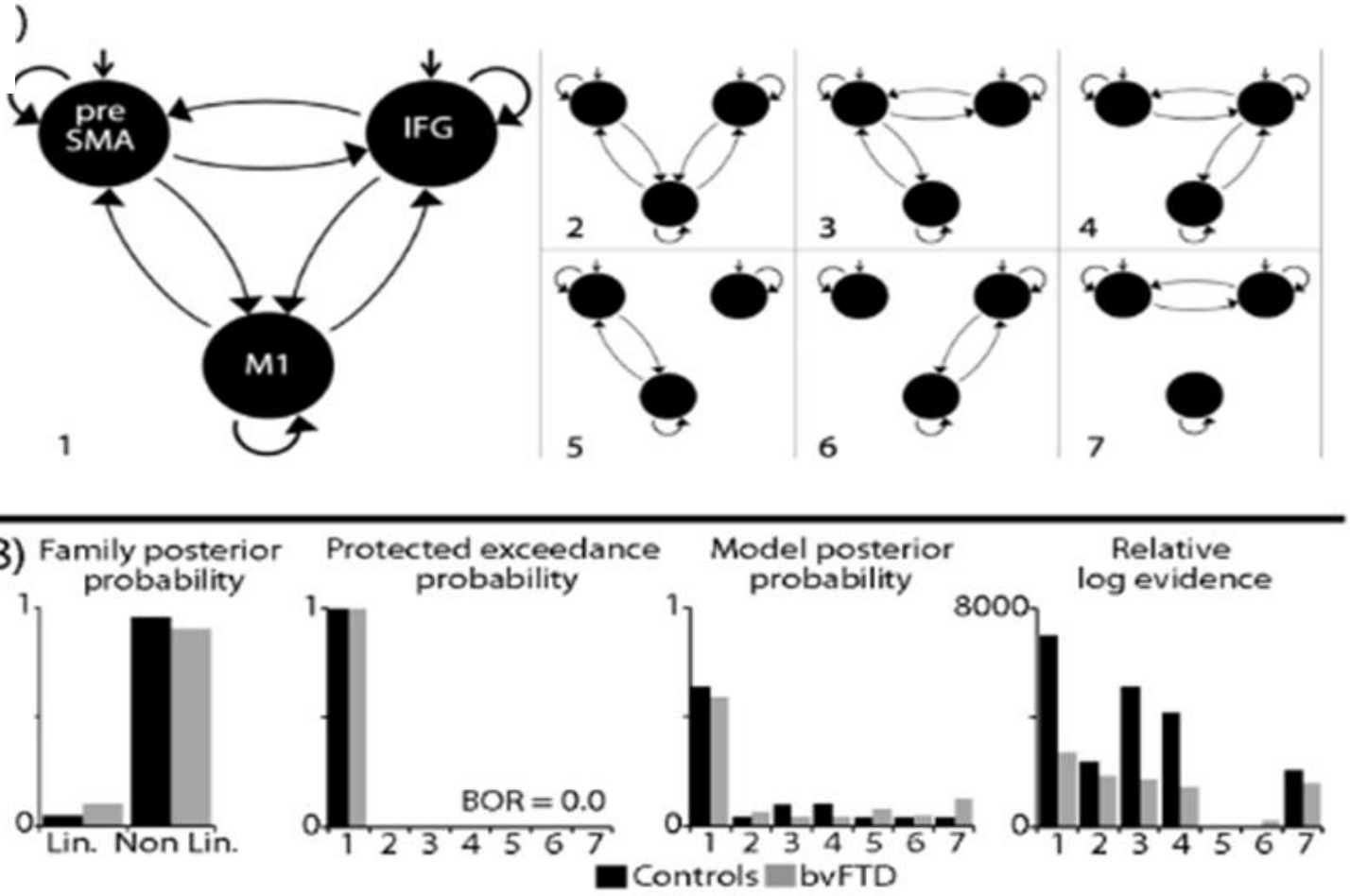
d) Schematic framework for laminar oscillatory connectivity



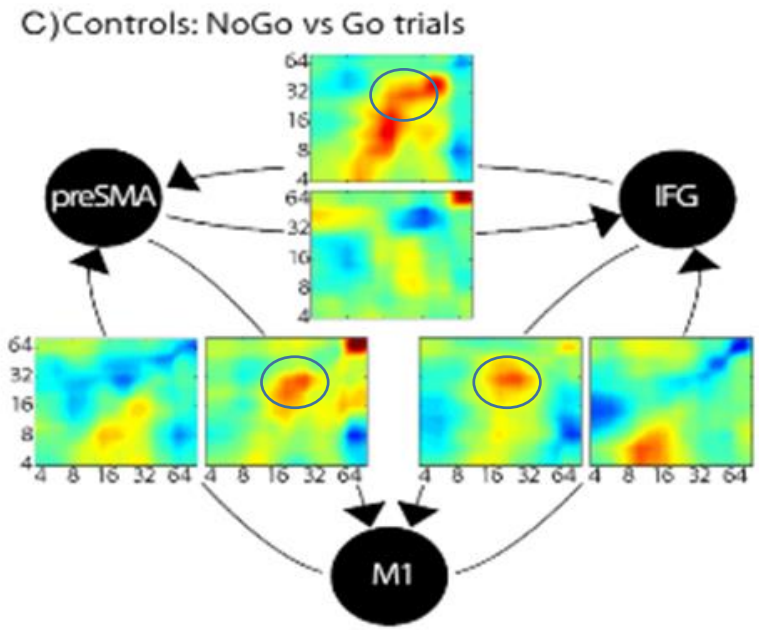
e) Hypothesis

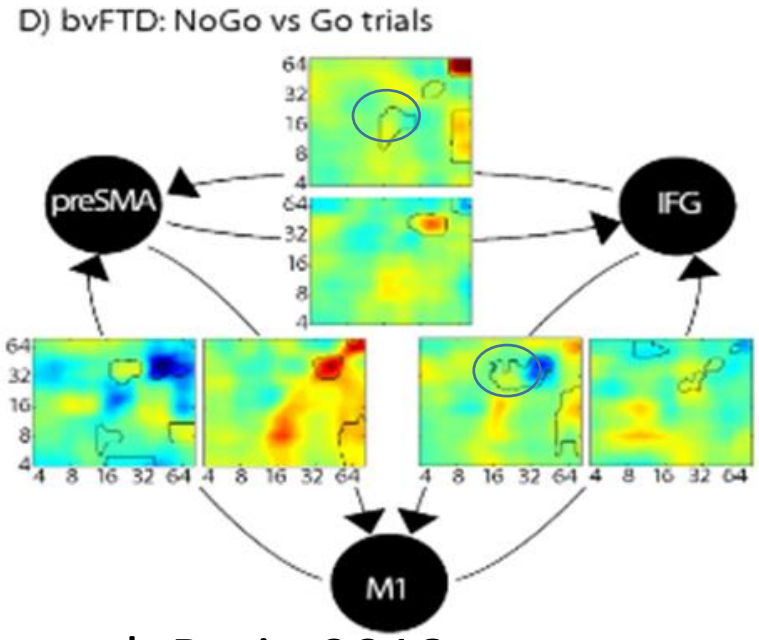






Hughes et al, Brain 2018





All trials - FTD loss of connectivity of the inferior frontal gyrus, particularly for gamma band interactions and theta to alpha coupling. Gamma connectivity between preSMA and motor cortex was enhanced.

NoGo vs Go: In controls, M1 greater beta/gamma coupling from IFG and preSMA, and from IFG to preSMA (top).

In FTD (bottom), a distinct loss of this coupling from IFG to preSMA and M1. Reciprocal frequency couplings are reduced.
FTD Note increase in positive and negative gamma to gamma coupling between preSMA and M1, and

The self-connections (not shown) also reveal a beta desynchronization by theta and alpha to beta couplings, which are diminished in patients.

Hughes et al, Brain 2018