Dynamic causal models for EEG, MEG and LFPs

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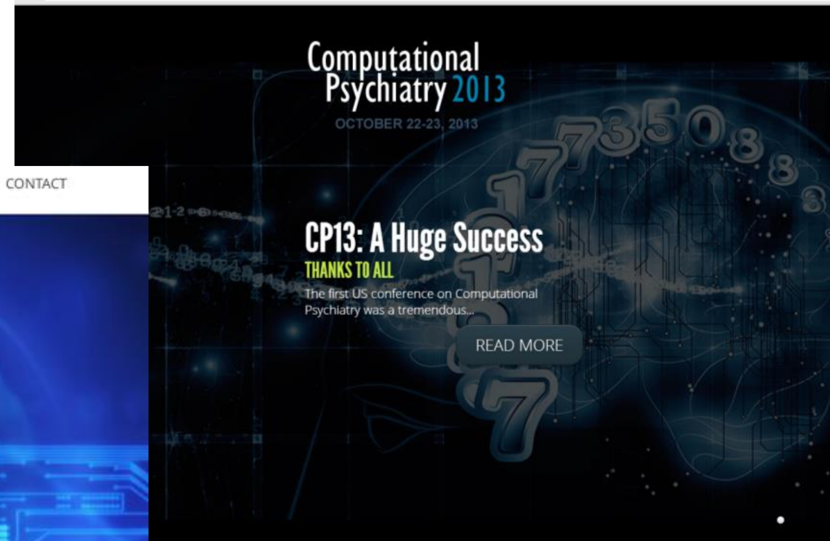
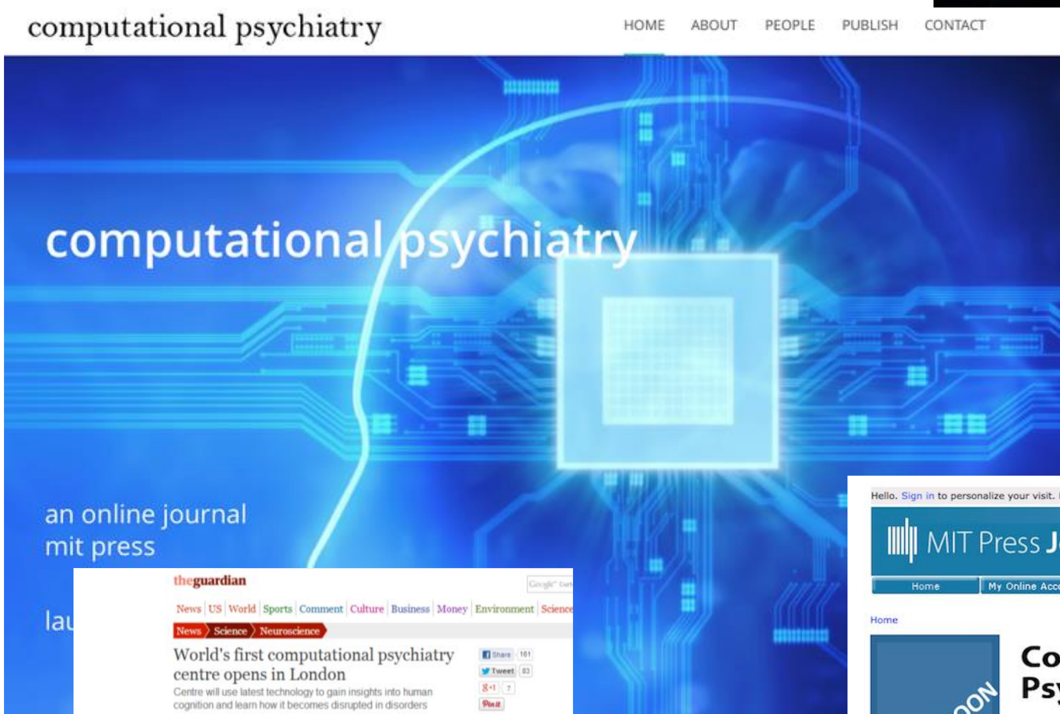
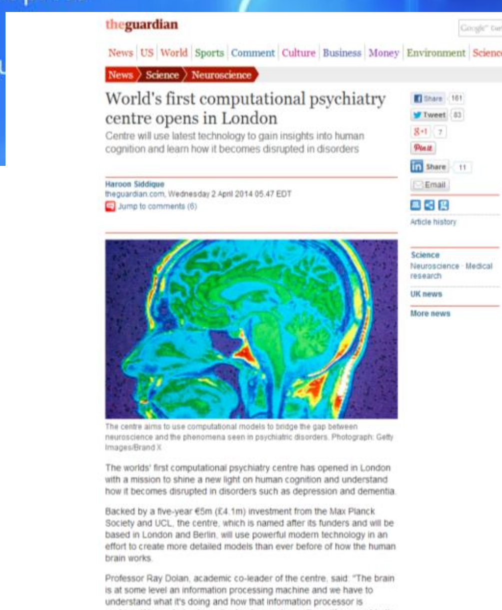
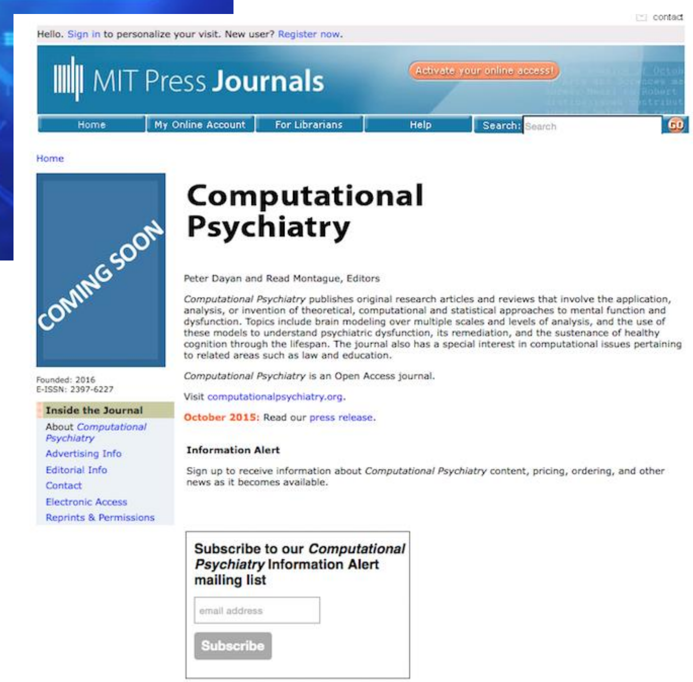
Computational Psychiatry









Computational Psychiatry

Clinical Neuroscience 3: 89–97 (1995)

Schizophrenia: A Disconnection Syndrome?

Karl J. Friston and Christopher D. Frith

Rationale

Aberrant Brain Connectivity

Clinical Neuroscience 3: 89–97 (1995)

Schizophrenia: A Disconnection Syndrome?

Karl J. Friston and Christopher D. Frith

Distinction between regionally specific pathology and a pathology of interaction

- First order pathology: Hypofrontality
- First order psychological abnormality: impoverished motor behaviour
- Second order pathology: Relationship between PFC and temporal regions
- Second order psychological abnormality: failure to integrate intrinsically cued behaviour and perception

Connectivity in PET time series

- Normal subjects exhibited negative prefrontal temporal correlation while Schizophrenia patients exhibited positive prefrontal temporal correlations
- Reversal can be regarded as a failure of prefrontal cortex to suppress activity in the temporal lobe

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Synaptic Plasticity and Dysconnection in Schizophrenia

Klaas E. Stephan, Torsten Baldeweg, and Karl J. Friston

Biological Psychiatry, 2006

- Anatomical changes in structural connectivity
- Dysconnectivity could result from abnormal modulation of N-methyl-D-aspartate (NMDA)-dependent plasticity by other neurotransmitter systems

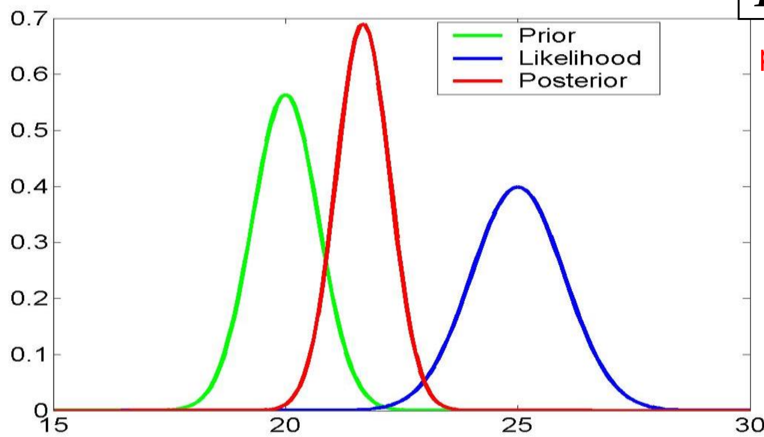
Bayes in the Brain

new data $p(y \mid \theta)$

prior knowledge $p(\theta)$

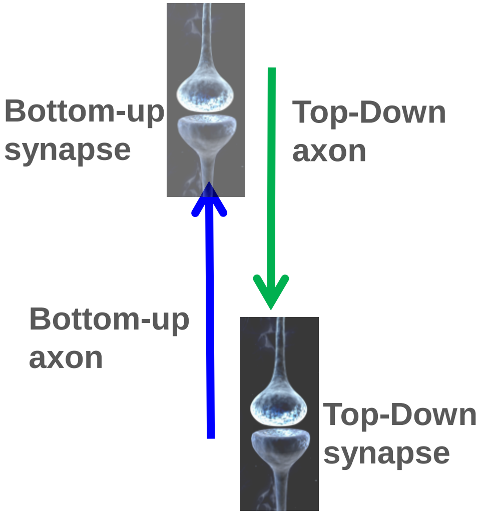
$$p(\theta \mid y) \propto p(y \mid \theta)\, p(\theta)$$

posterior $\propto$ likelihood • prior



"The general rule according to which visual representations determine themselves ... is that *we always find present* in the visual field such objects as would have to exist in order for them to produce the same impression on the neural apparatus under the *usual normal conditions* of the use of our eyes."

von Helmholtz ***Perception as Inference***



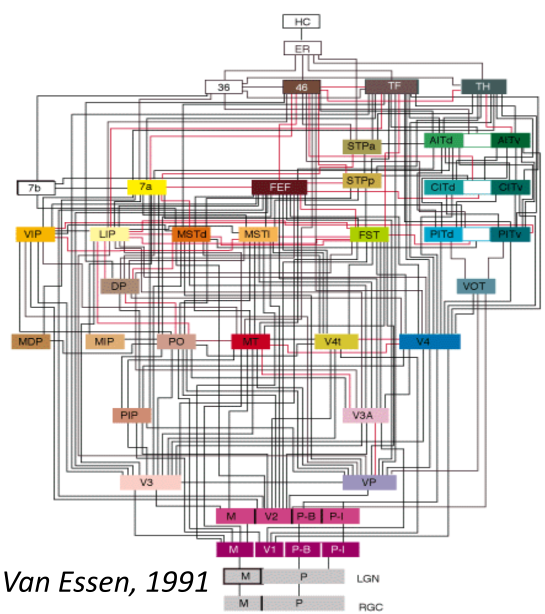
From disconnection to algorithmic break-down through Bayes

Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia

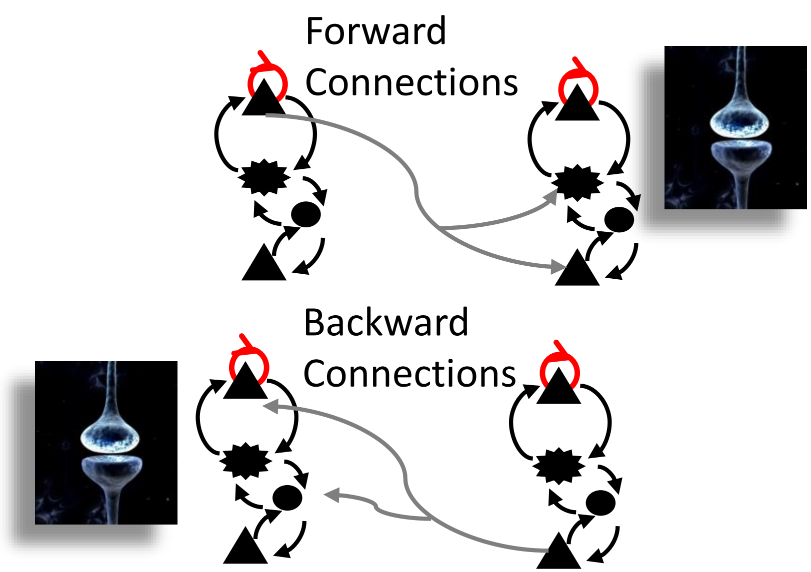
"Unusual perceptual experiences of patients and their sometimes bizarre beliefs (considered) as part of the same core abnormality — a disturbance in error-dependent updating of inferences and beliefs about the world. We suggest that it is possible to understand these symptoms in terms of a disturbed hierarchical Bayesian framework, without recourse to separate considerations of experience and belief."

Fletcher & Frith, Nature Reviews Neuroscience, 2009

How might a brain 'do' Bayesian Inference?

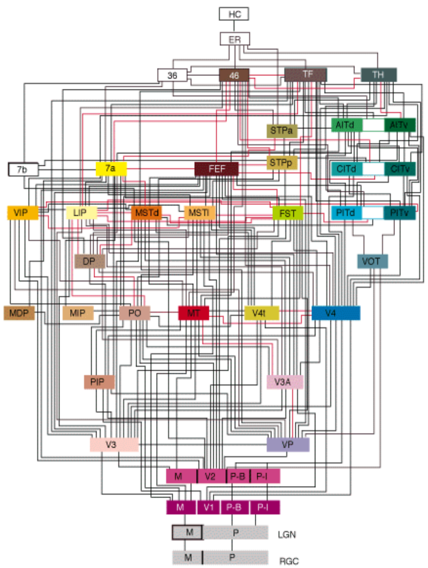


Felleman & Van Essen, 1991



A Refined Bayesian Predictive Coding Hypothesis

A Simple Message Passing Scheme to do Inference: The Free Energy Principle, Friston, 2006



Errors are modulated by DA, 5-HT, ACh, NA –
how sure is your prediction? Neuromodulators convey 'attention' to errors

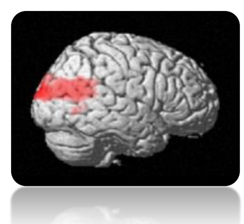
Errors Propagate up the cortical hierarchy

$$E = \Pi(x2 - x1)$$

Lower levels keep their representations

Prior Expectations Propagate down the cortical hierarchy, establishing an error when a mismatch occurs:

Forward prediction error



Backward predictions

Region x2 e.g. V5

Region x1 e.g. V1

From disconnection to algorithmic break-down through Bayes

frontiers in PSYCHIATRY

REVIEW ARTICLE
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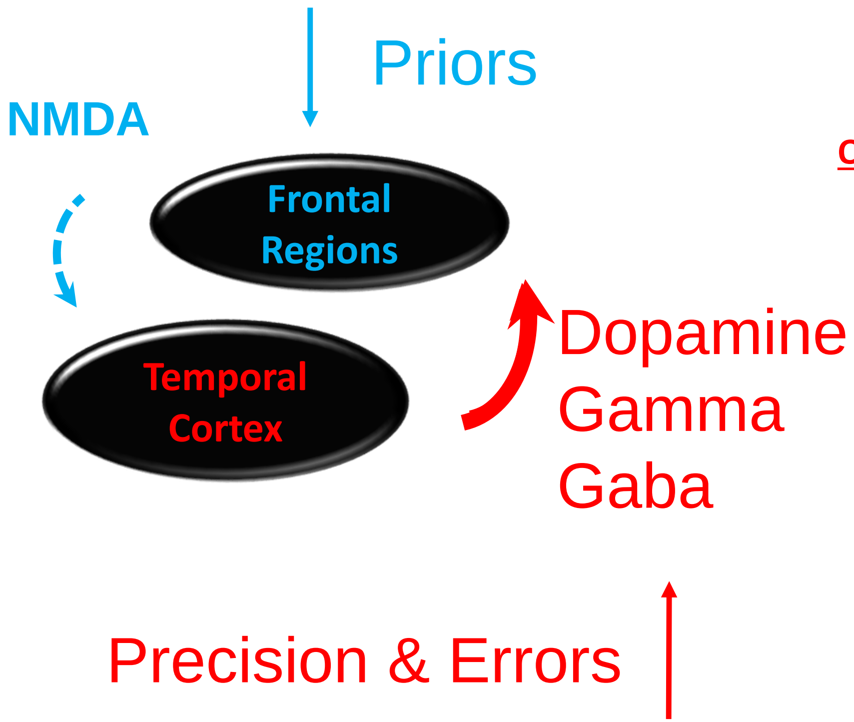
The computational anatomy of psychosis

Rick A. Adams[1]*, Klaas Enno Stephan[1,2,3], Harriet R. Brown[1], Christopher D. Frith[1] and Karl J. Friston[1]

[1] *Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, UK.*
[2] *Translational Neuromodeling Unit, Institute for Biomedical Engineering, University of Zurich, ETH Zurich, Zurich, Switzerland*
[3] *Laboratory for Social and Neural Systems Research, University of Zurich, Zurich, Switzerland*



Precision of Errors: DA

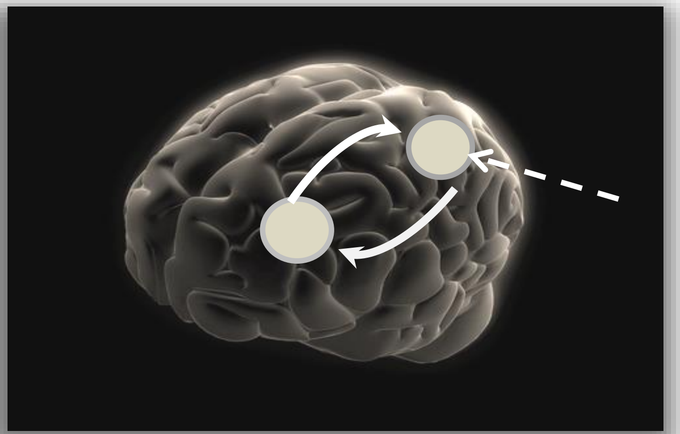
Overactive Errors

$$E = \Pi(x2 - x1)$$

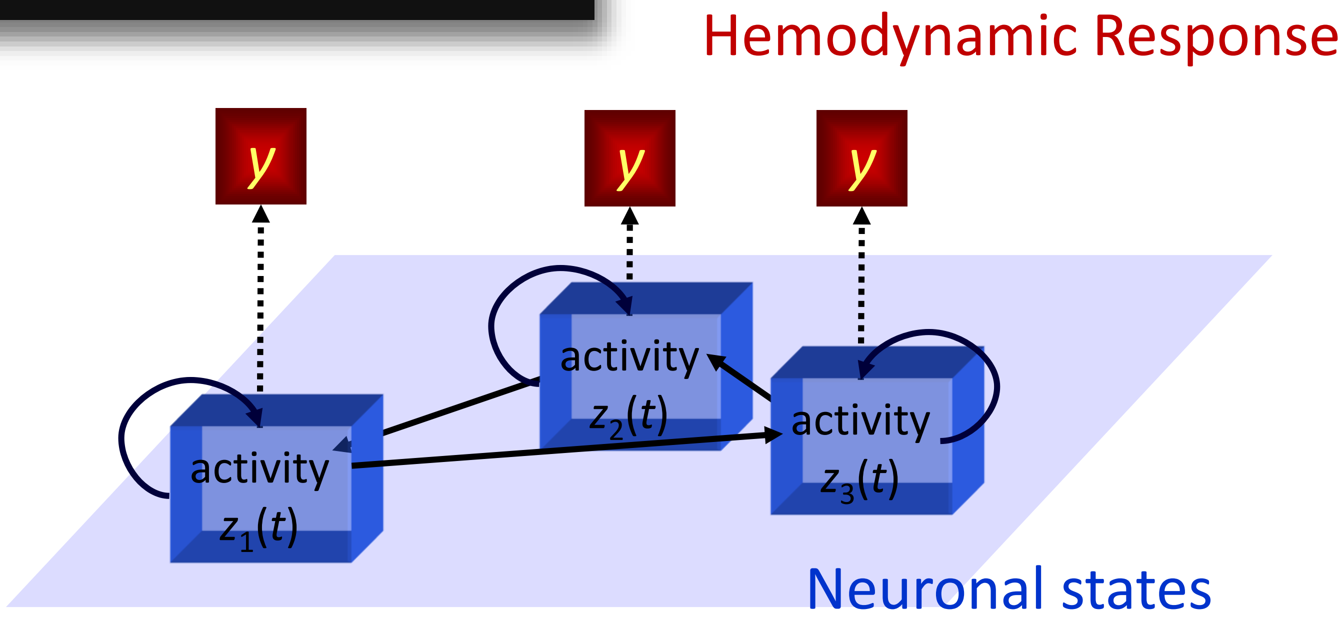
Mislearned/Misappropriated Priors

How would we test this in patients?

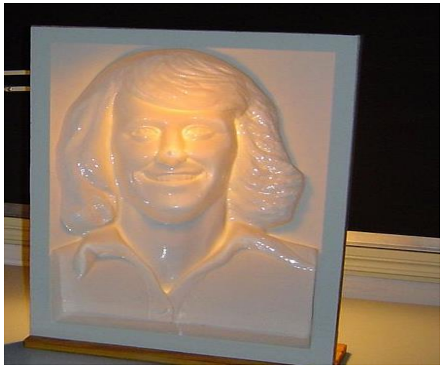
Connectivity from Human Neuroimaging Data: Dynamic Causal Models



For fMRI??



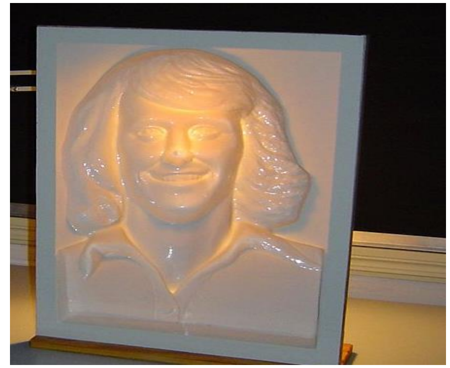
Dysconnection & DCM for fMRI



Dima, et al. 2009

Understanding why patients with schizophrenia do not perceive the hollow-mask illusion

Dysconnection & DCM for fMRI



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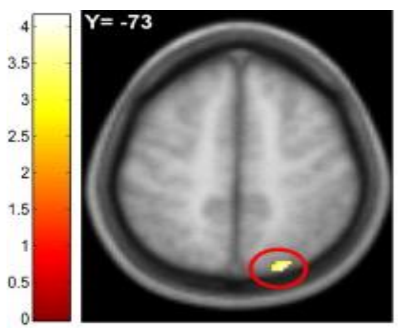
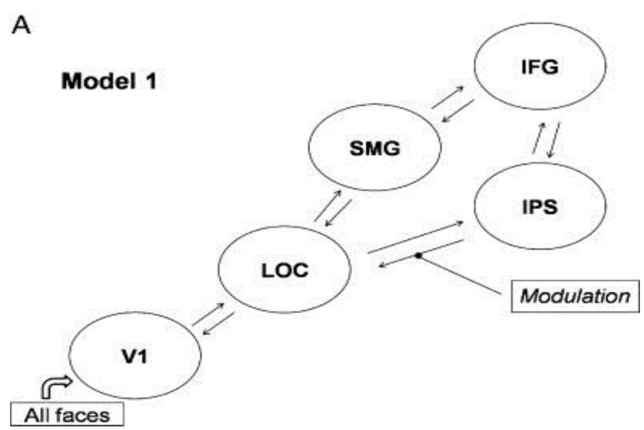
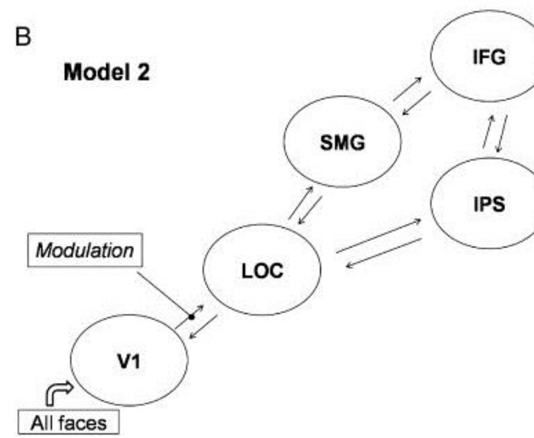
Understanding why patients with schizophrenia do not perceive the hollow-mask illusion





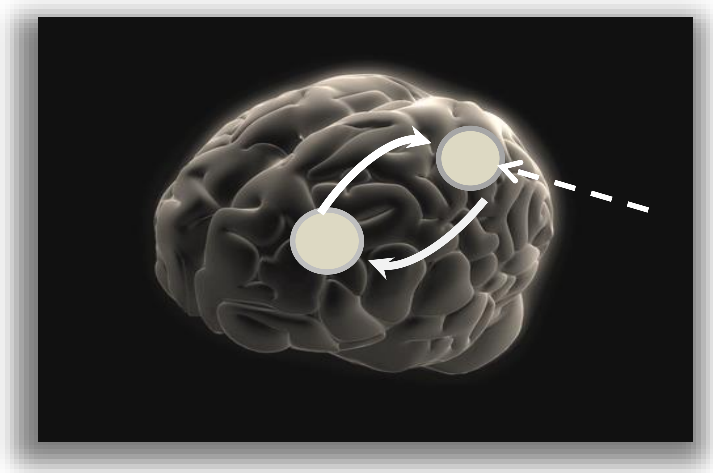


Control data better explained by model 1

Schizophrenic patient data better explained by model 2

ie. They exhibited **enhanced bottom-up** & **weaker top-down** processes to 'hollow' faces relative to controls, and correctly perceived the faces as hollow

Connectivity from Human Neuroimaging Data: Dynamic Causal Models

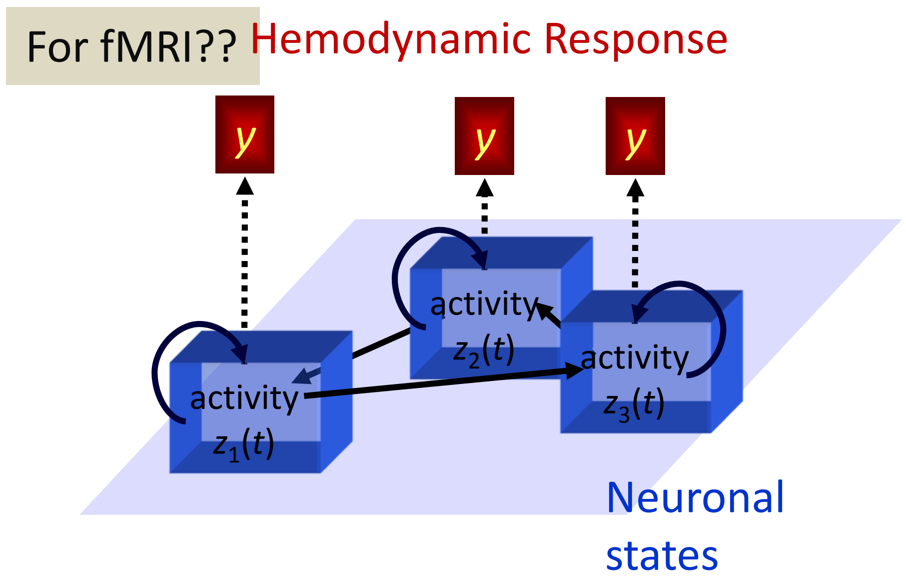


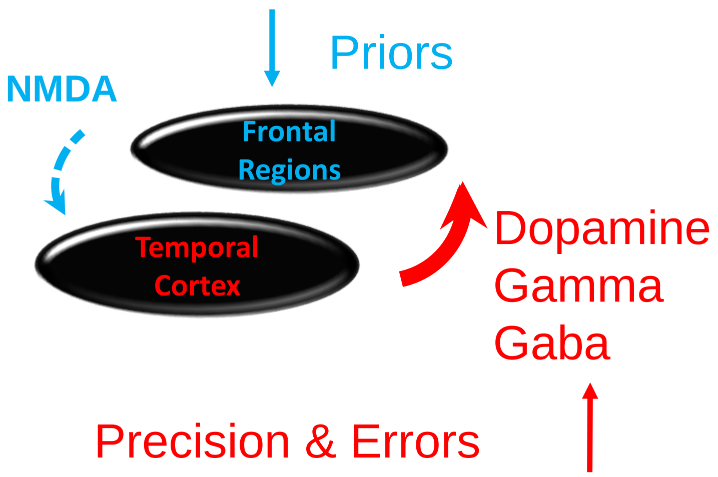
What are we missing?

The receptor profile of connectivity

Clues for molecular pathogenic pathways

A pharmacological target

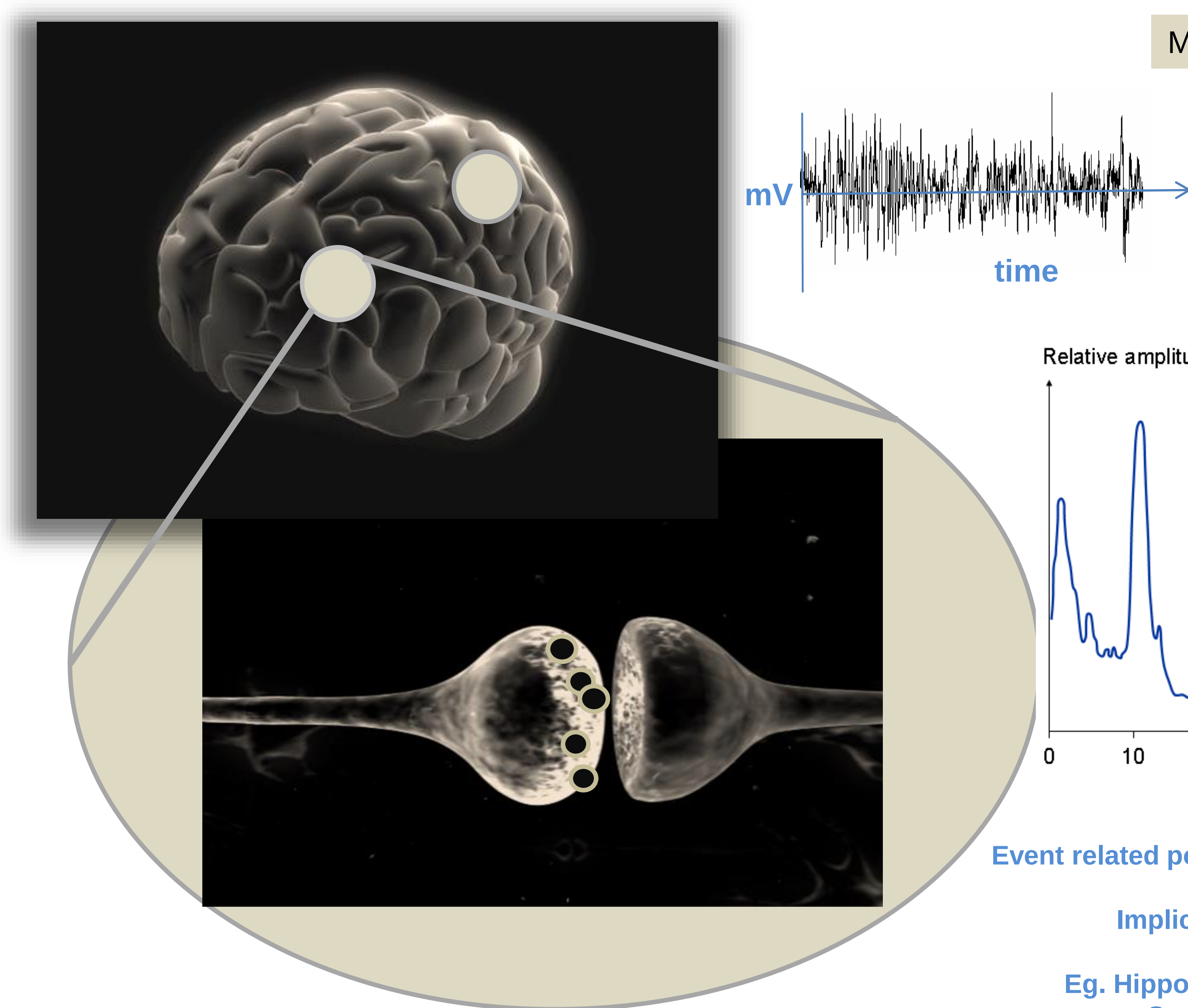


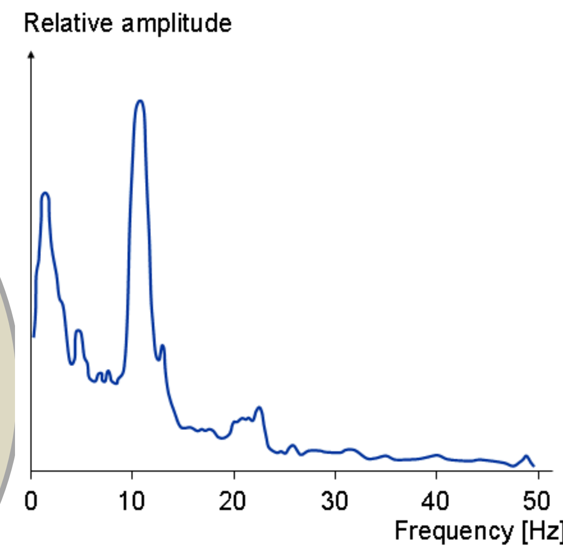


Dynamic Causal Models for Electrophysiology

Connectivity from EEG/LFP Data: Dynamic Causal Models

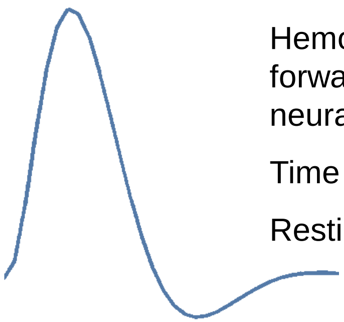
Milliseconds: M/EEG





Event related potentials & Oscillations of different frequencies
Implicated in specific cognitive tasks/regions
Eg. Hippocampal Theta (4 – 8 Hz) & Sensory Gamma (30 – 60 Hz)

Dynamic Causal Modeling: Generic Framework



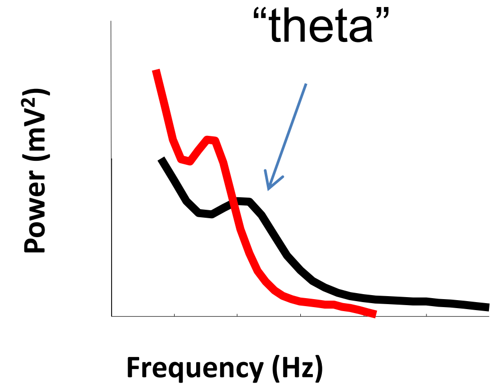
Hemodynamic
forward model:
neural activity BOLD

Time Domain Data

Resting State Data

Electromagnetic
forward model:
neural activity EEG
MEG
LFP

Time Domain ERP Data
Phase Domain Data
Time Frequency Data
Spectral Data



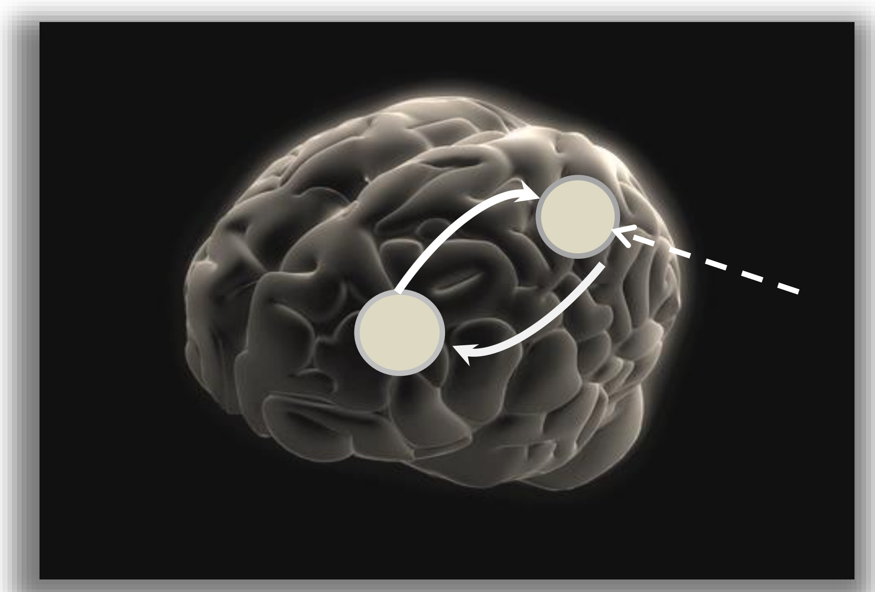
Neural state equation:

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

fMRI

simple neuronal model

(slow time scale)



EEG/MEG

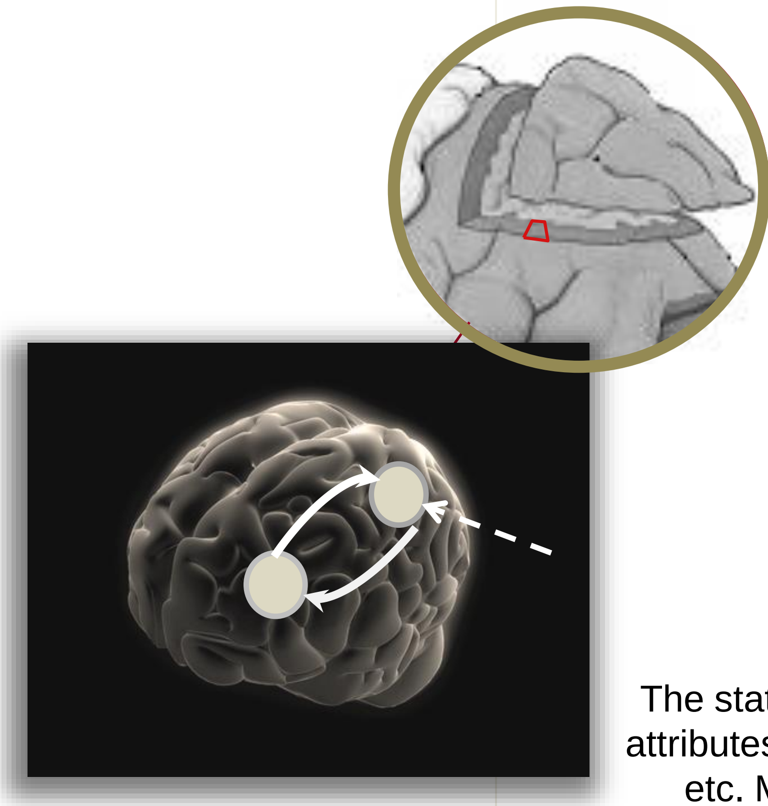
detailed neuronal model

(synaptic time scales)

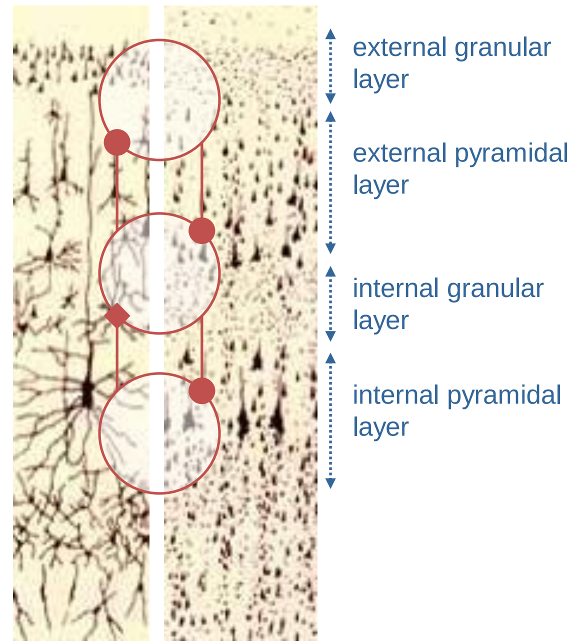
A Neural Mass Model

Macro and meso-scales: The Neural Mass Model

macro-scale

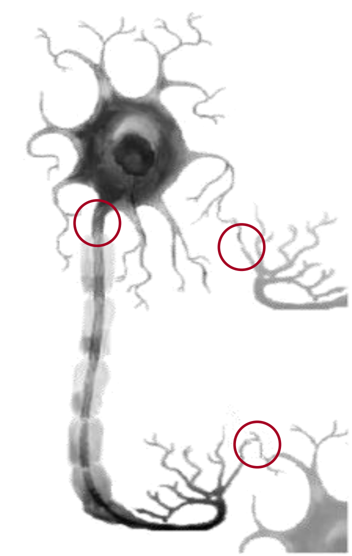


meso-scale

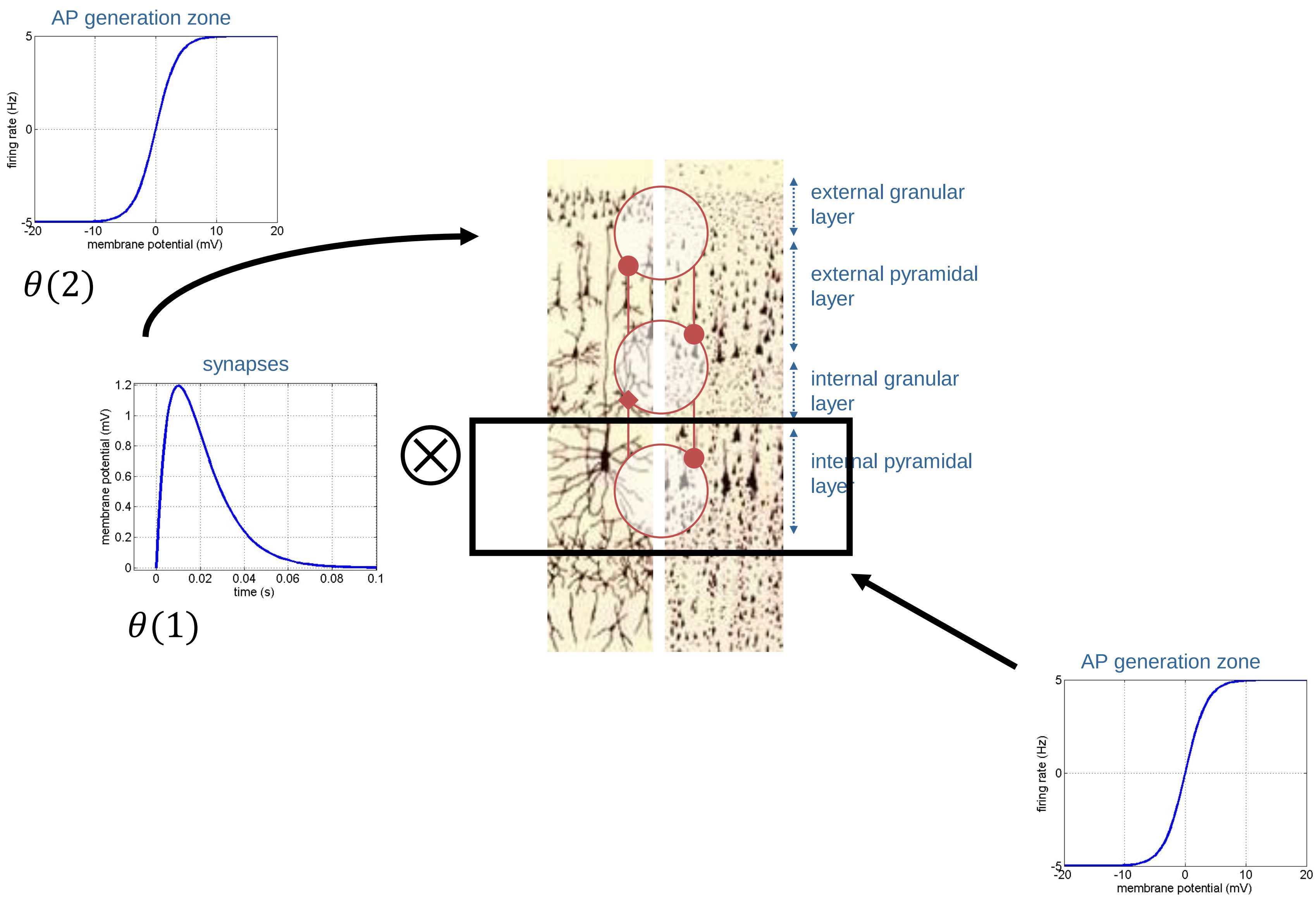


The state of a neuron comprises a number of attributes, membrane potentials, conductances etc. Modelling these states can become intractable. **Mean field approximations** summarise the states in terms of their ensemble density. **Neural mass models** consider only point densities and describe the interaction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

micro-scale



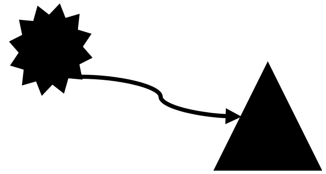
Meso-scale dynamics



Convolution Based Neural Mass Models

Convolution-Based Neural Mass Models in DCM

Spiny stellate cells

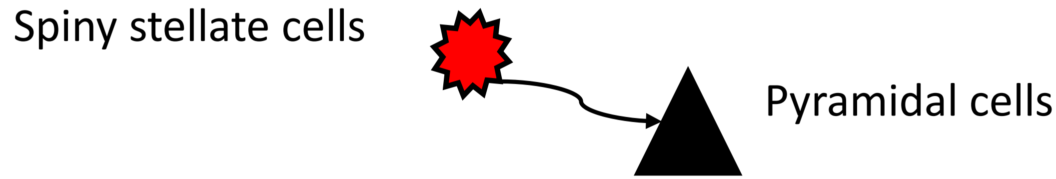


Pyramidal cells

$$v_{post} = \sigma(v_{pre}) \otimes h$$

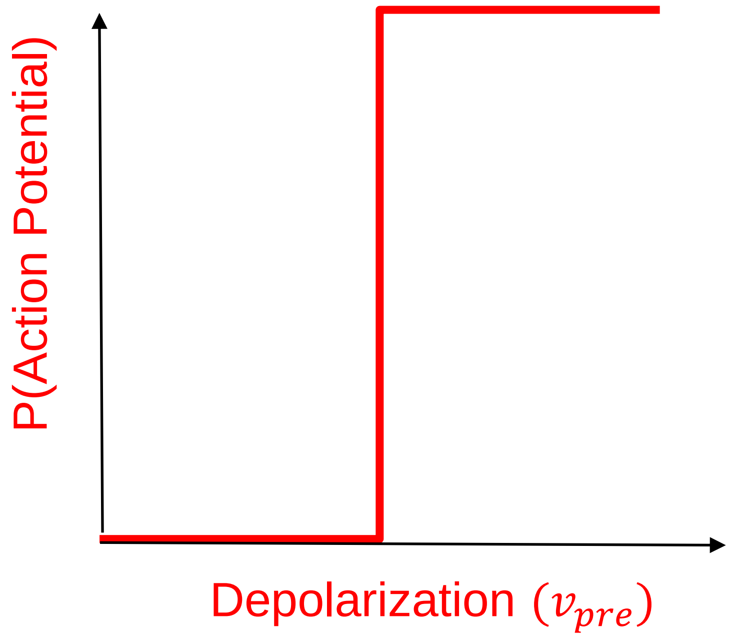
Take one spiny stellate cell.....

Convolution-Based Neural Mass Models in DCM



$$v_{post} = \sigma(v_{pre}) \otimes h$$

$H(v_{pre})$ Heaviside function

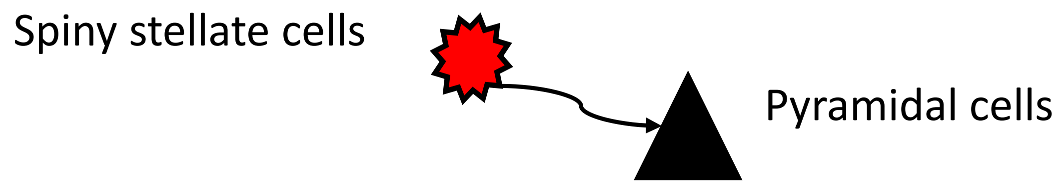


Take a population of spiny stellate cells & assume either:

1. Unimodal distribution over firing thresholds
2. Unimodal distribution over population

Membrane depolarizations

Convolution-Based Neural Mass Models in DCM



$$v_{post} = \sigma(v_{pre}) \otimes h$$

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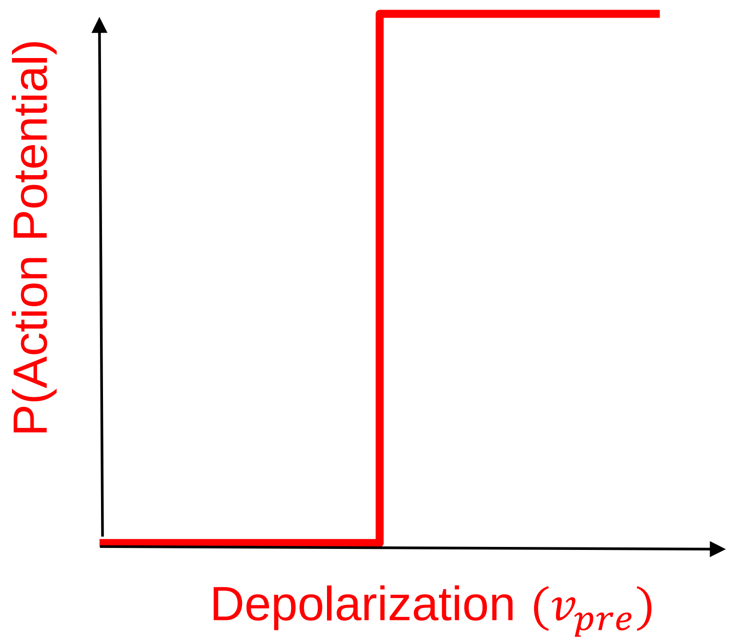
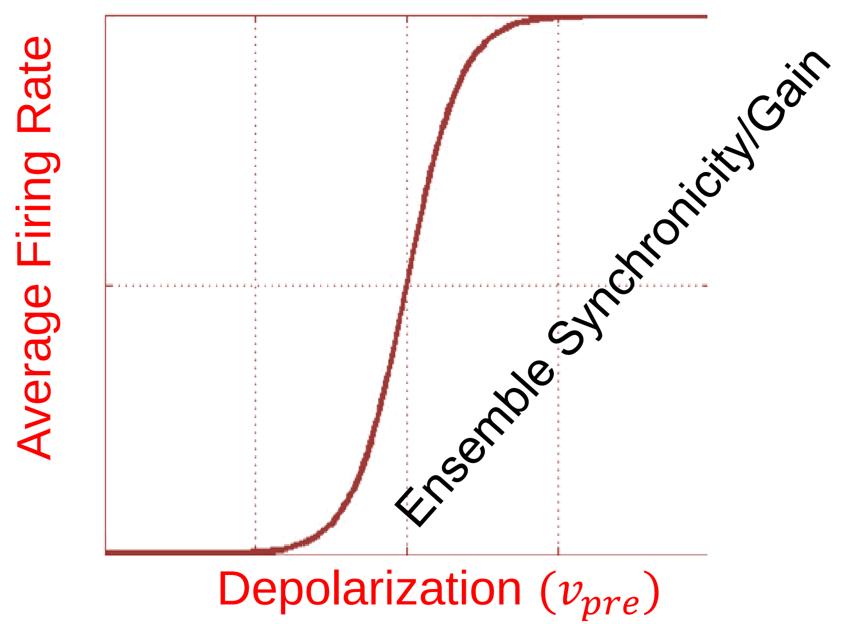
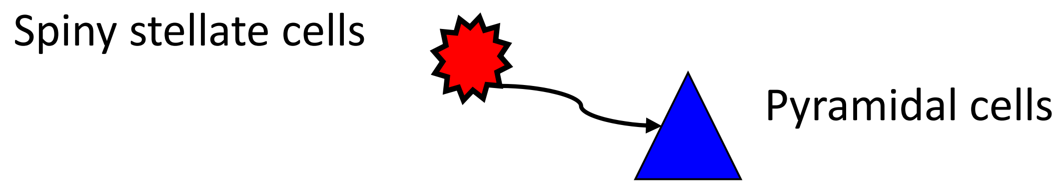


$\sigma(v_{pre})$ Sigmoidal Presynaptic Firing Function



Convolution-Based Neural Mass Models in DCM



$$v_{post} = \sigma(v_{pre}) \otimes h$$

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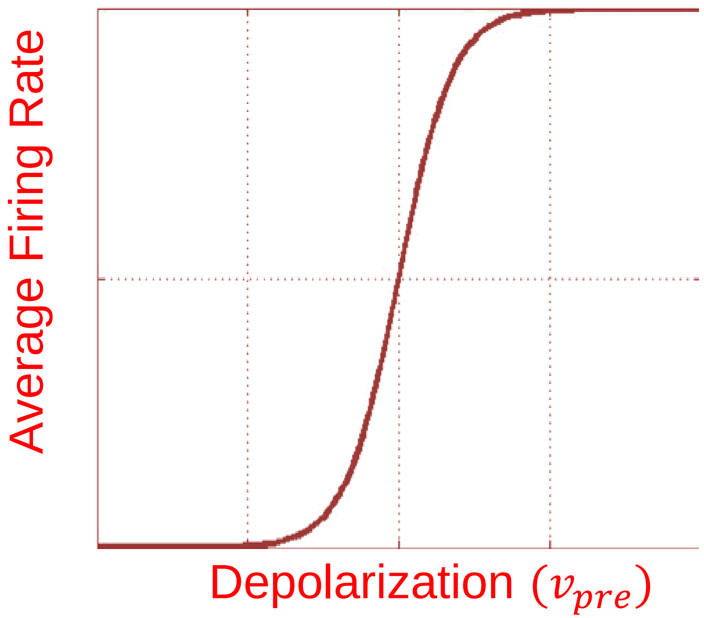
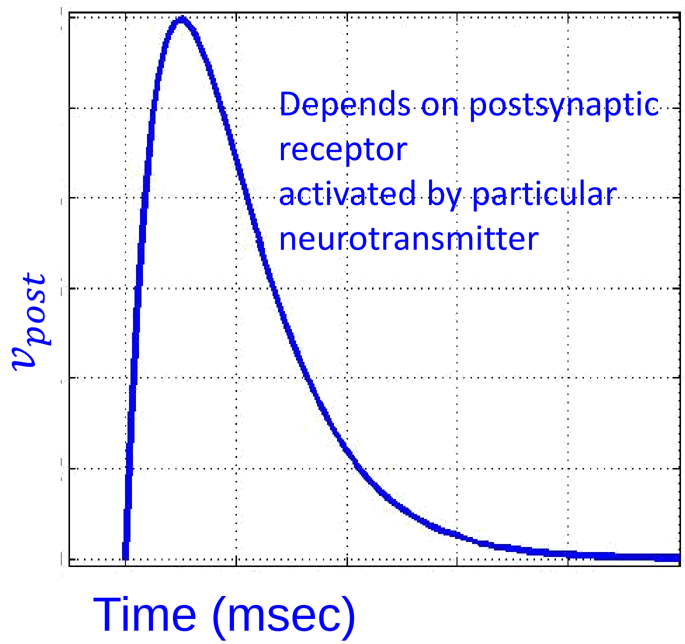
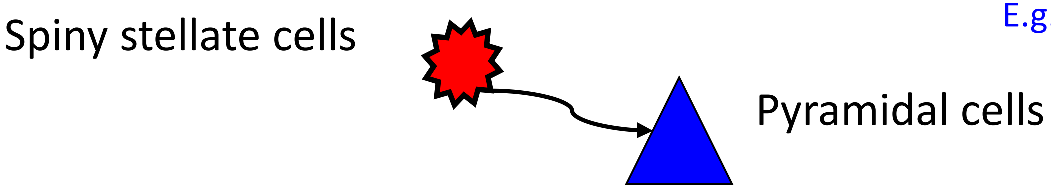


h Postsynaptic Kernel



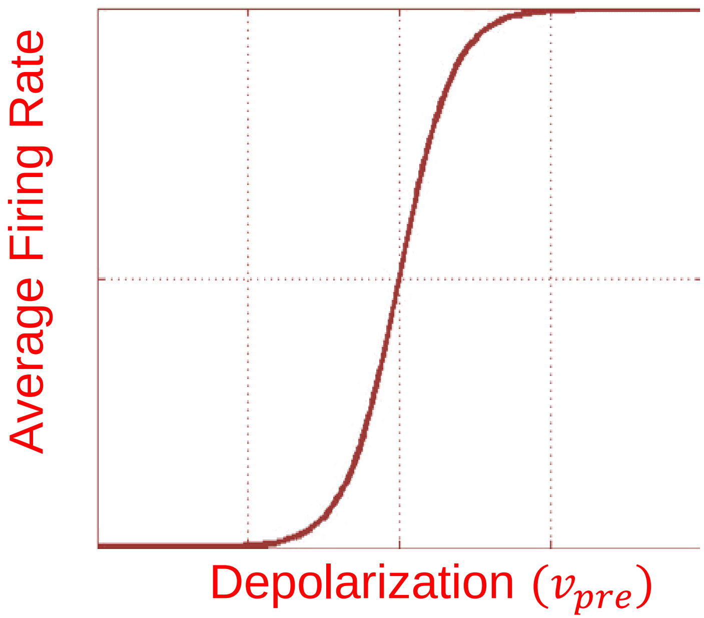
Convolution-Based Neural Mass Models in DCM



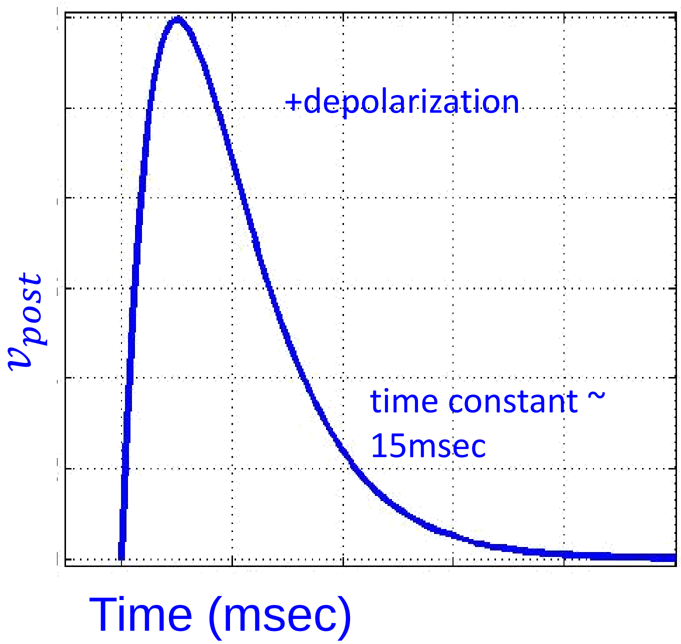
E.g. Glutamate from SS to AMPA receptor

$$v_{post} = \sigma(v_{pre}) \otimes h$$

$\sigma(v_{pre})$ Sigmoidal Presynaptic Firing Function

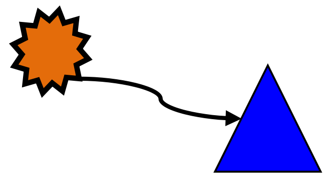


h Postsynaptic Kernel



Convolution-Based Neural Mass Models in DCM

Inhibitory interneuron

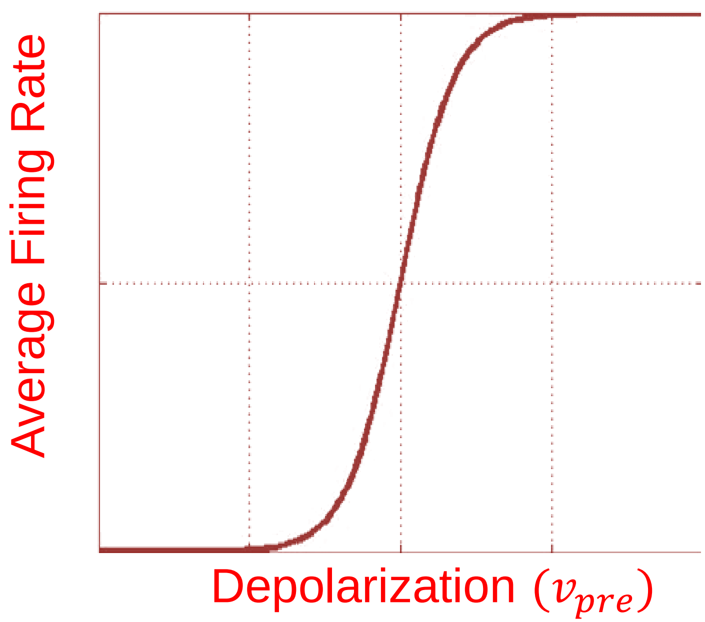


Pyramidal cells

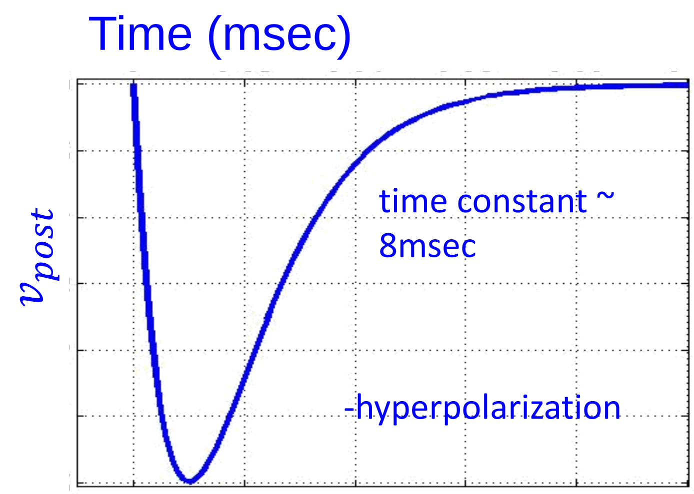
E.g. GABA from inhibitory interneuron to GABAa receptor

$$v_{post} = \sigma(v_{pre}) \otimes h$$

$\sigma(v_{pre})$ Sigmoidal Presynaptic Firing Function

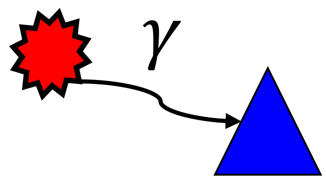


h Postsynaptic Kernel



Convolution-Based Neural Mass Models in DCM

Spiny stellate cells



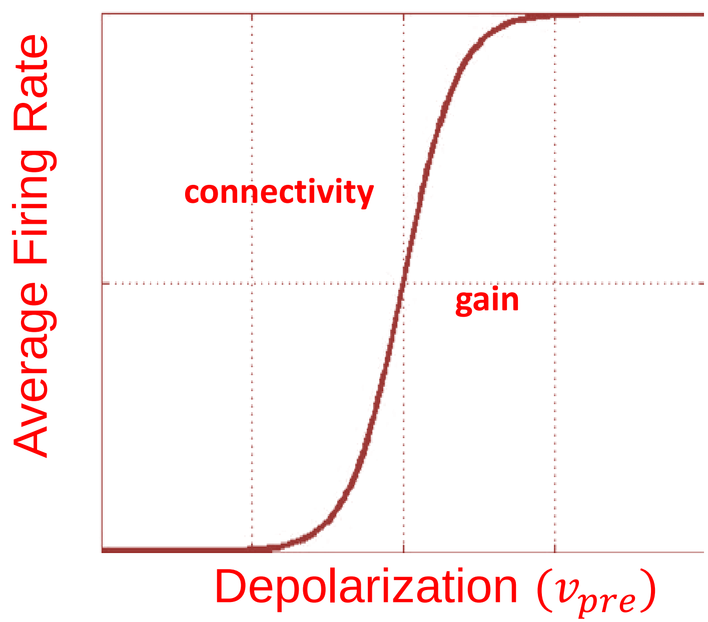
Pyramidal cells

Connectivity?

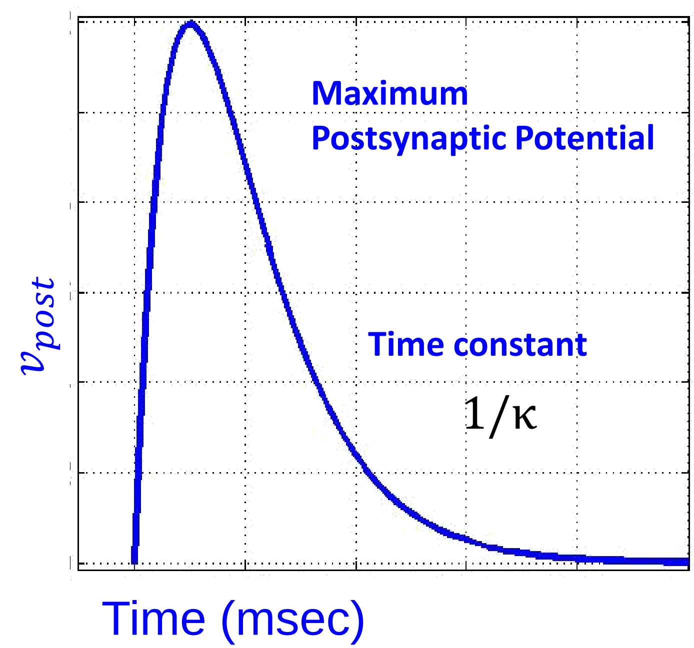
$$v_{post} = \gamma\sigma(v_{pre}) \otimes h$$

$$\theta = \{\gamma, gain, H, \tau\}$$

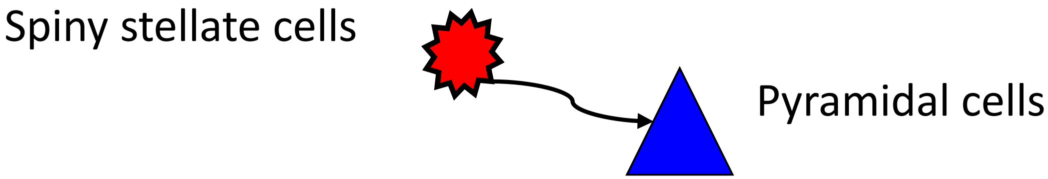
$\gamma\sigma(v_{pre})$ Sigmoidal Presynaptic Firing Function



h Postsynaptic Kernel



Convolution to ODEs



$$v_{post} = \gamma\sigma(v_{pre}) \otimes h$$

$$v_{post} = \int_0^t h(t-\tau)\,\gamma\sigma(v_{pre})\,d\tau$$

Convolution Equation

By parts twice

$$\ddot{v}_{post} = H\kappa\gamma\sigma\left(v_{pre}\right) - 2\kappa\dot{v}_{post} - \kappa v_{post}$$

Second Order Differential Equation

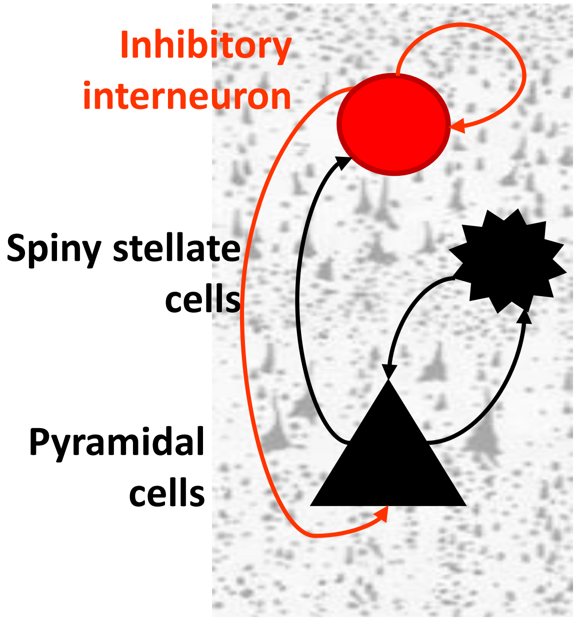
$$\dot{v}_{post} = i$$

$$\dot{i} = H\kappa\gamma\sigma\left(v_{pre}\right) - 2\kappa i - \kappa v_{post}$$

2 Coupled First Order Differential

For each transmitter receptor pair

Multilaminar NMMS



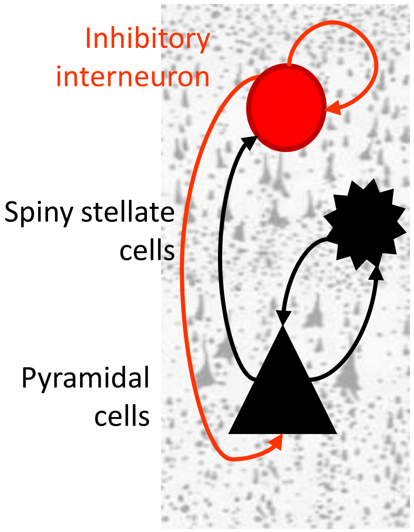
Assume GABA from inhibitory interneurons activate GABAa receptors

Assume glutamate from pyramidal cells & spiny stellate cells activate AMPA receptors

Then construct interlaminar connectivity

5 connections giving 5x2 coupled first order differential equations

One region: 12 equations 10 + 2 difference



Inhibitory cells in extragranular layers

$$\dot{v}_4 = i_4$$
$$\dot{i}_4 = \kappa_e H_e \gamma_3 \sigma(v_6) - 2\kappa_e i_4 - \kappa_e^2 v_4$$
$$\dot{v}_5 = i_5$$
$$\dot{i}_5 = \kappa_i H_i \gamma_5 \sigma(v_7) - 2\kappa_i i_5 - \kappa_i^2 v_5$$
$$\dot{v}_7 = i_4 - i_5$$

γ_5

γ_4

γ_3

Excitatory spiny cells being granular layers

$$\dot{v}_1 = i_1$$
$$\dot{i}_1 = \kappa_e H_e \gamma_1 (\sigma(v_6) + I) - 2\kappa_e i_1 - \kappa_e^2 v_1$$

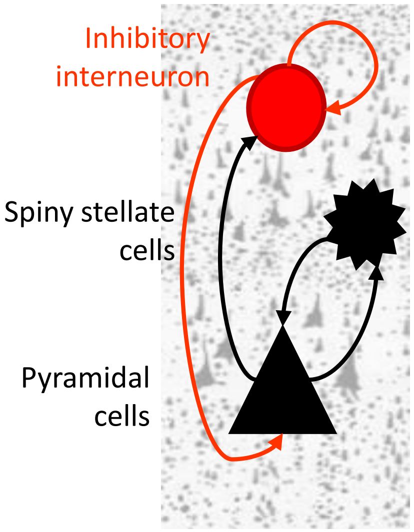
γ_1

γ_2

$$\dot{v}_2 = i_2$$
$$\dot{i}_2 = \kappa_e H_e \gamma_2 \sigma(v_1) - 2\kappa_e i_2 - \kappa_e^2 v_2$$
$$\dot{v}_3 = i_3$$
$$\dot{i}_3 = \kappa_i H_i \gamma_4 \sigma(v_7) - 2\kappa_i i_3 - \kappa_i^2 v_3$$
$$\dot{v}_6 = i_2 - i_3$$

Excitatory pyramidal cells in extragranular layers

One region: 12 equations 10 + 2 difference



$I = u(\mathrm{t})$

Exogenous Input

Inhibitory cells in extragranular layers

$$
\begin{aligned}
\dot{v}_4 &= i_4 \\
\dot{i}_4 &= \kappa_e H_e \gamma_3 \sigma(v_6) - 2\kappa_e i_4 - \kappa_e^2 v_4 \\
\dot{v}_5 &= i_5 \\
\dot{i}_5 &= \kappa_i H_i \gamma_5 \sigma(v_7) - 2\kappa_i i_5 - \kappa_i^2 v_5 \\
\dot{v}_7 &= i_4 - i_5
\end{aligned}
$$

γ_5

γ_4 γ_3

Excitatory spiny cells being granular layers

$$
\begin{aligned}
\dot{v}_1 &= i_1 \\
\dot{i}_1 &= \kappa_e H_e \gamma_1 (\sigma(v_6) + I) - 2\kappa_e i_1 - \kappa_e^2 v_1
\end{aligned}
$$

γ_1 γ_2

$$
\begin{aligned}
\dot{v}_2 &= i_2 \\
\dot{i}_2 &= \kappa_e H_e \gamma_2 \sigma(v_1) - 2\kappa_e i_2 - \kappa_e^2 v_2 \\
\dot{v}_3 &= i_3 \\
\dot{i}_3 &= \kappa_i H_i \gamma_4 \sigma(v_7) - 2\kappa_i i_3 - \kappa_i^2 v_3 \\
\dot{v}_6 &= i_2 - i_3
\end{aligned}
$$

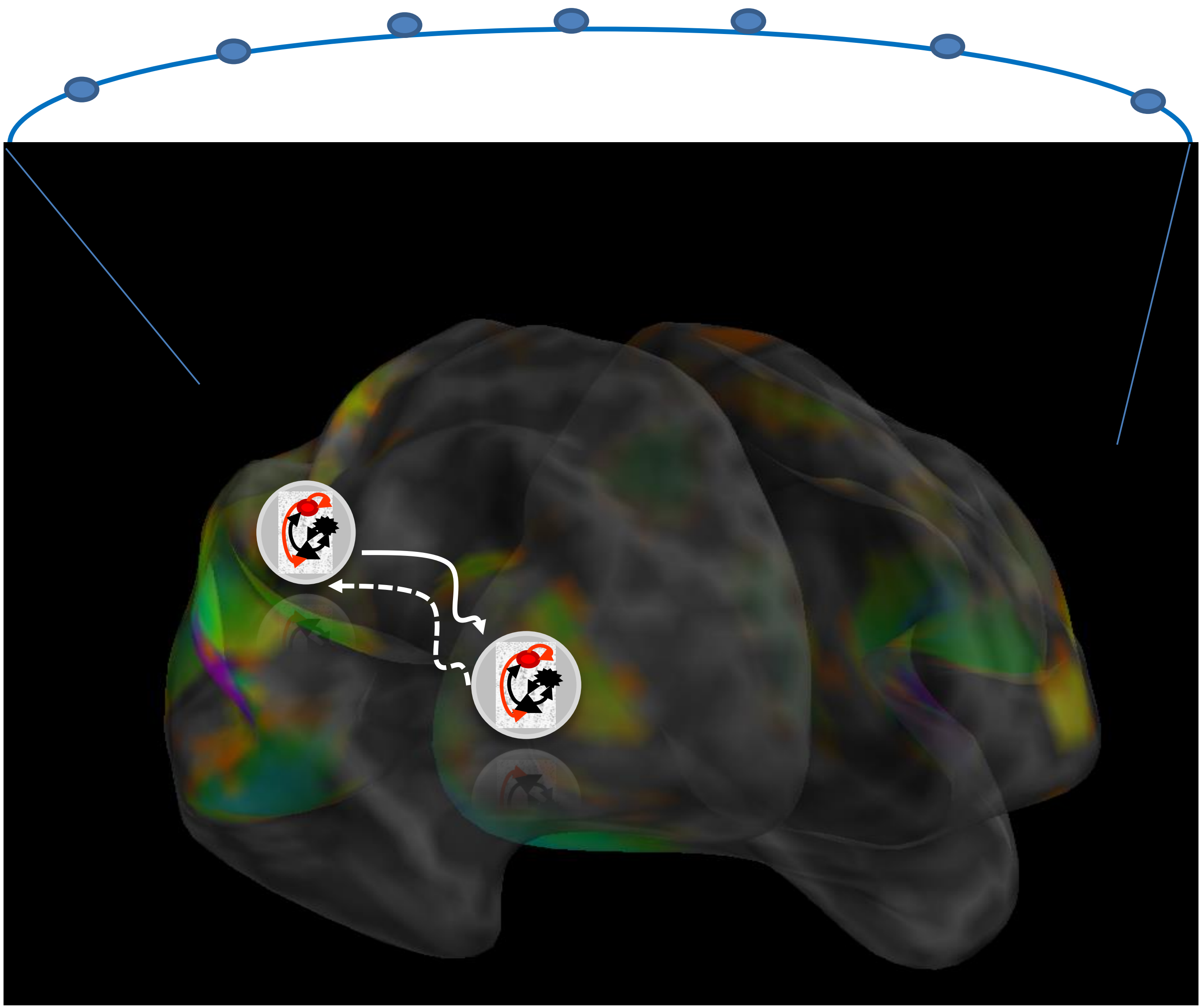
Excitatory pyramidal cells in extragranular layers

Dipole

Measured response: $g(v_6)$

Forward Model: Neural Mass Models in DCM

Empirical
Observations
(eg Sensor Level)



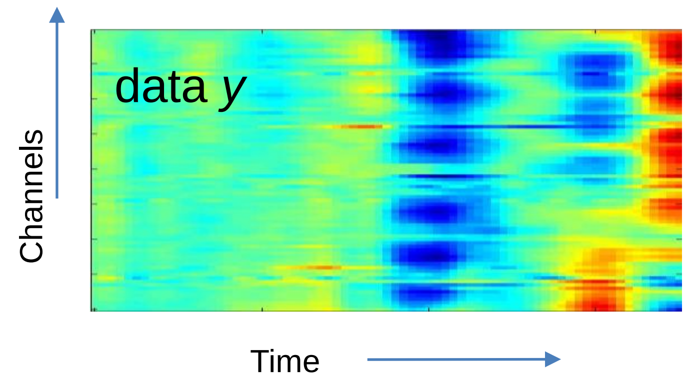
$$Y = g(\theta_g, v_6)$$

Lead Field

$$\dot{v} = f(\theta_f, u)$$

Interconnected
Neural mass
models

Neural Mass Models in DCM for ERPs

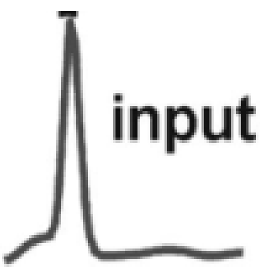


Event-Related Potentials

$$Y = g(\theta_g, v_6)$$

Lead Field

$$u = u(t)$$



$$\dot{v} = f(\theta_f, u)$$

Interconnected Neural mass models

State equations from time to spectral domain

Time Differential Equations

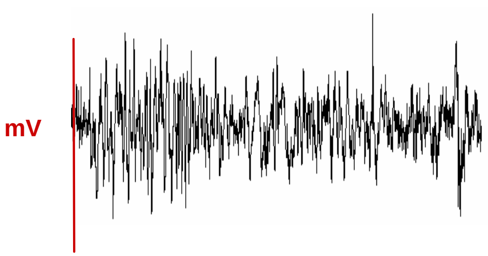
$$Y = g(\theta_g, v_6)$$
$$\dot{v} = f(\theta_f, u)$$

Linearise

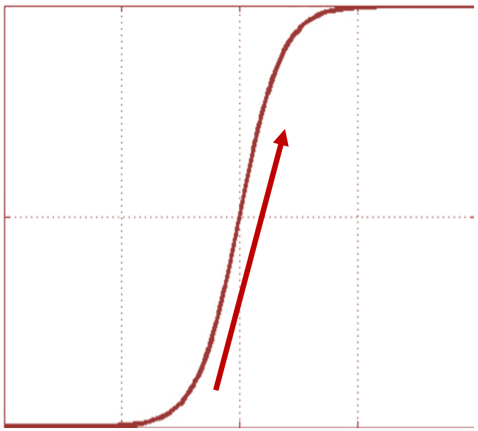
$$Y = g(\theta_g, v_6)$$
$$\dot{v} = A(\theta_f) + Bu$$

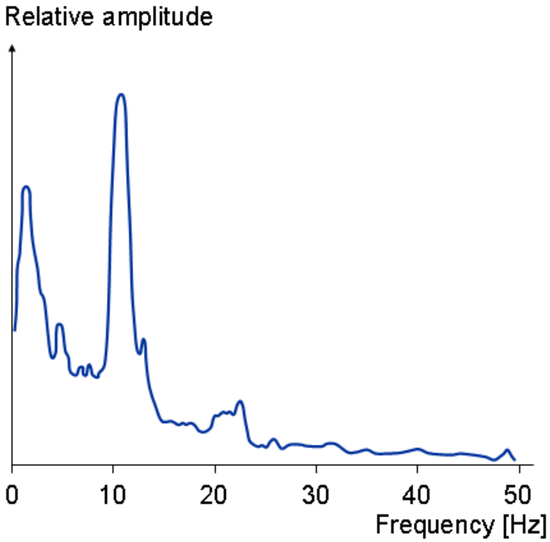
Analytic Transfer Function in the Frequency domain

$$H(s) = g(sI - A)B$$



White/Pink Noise





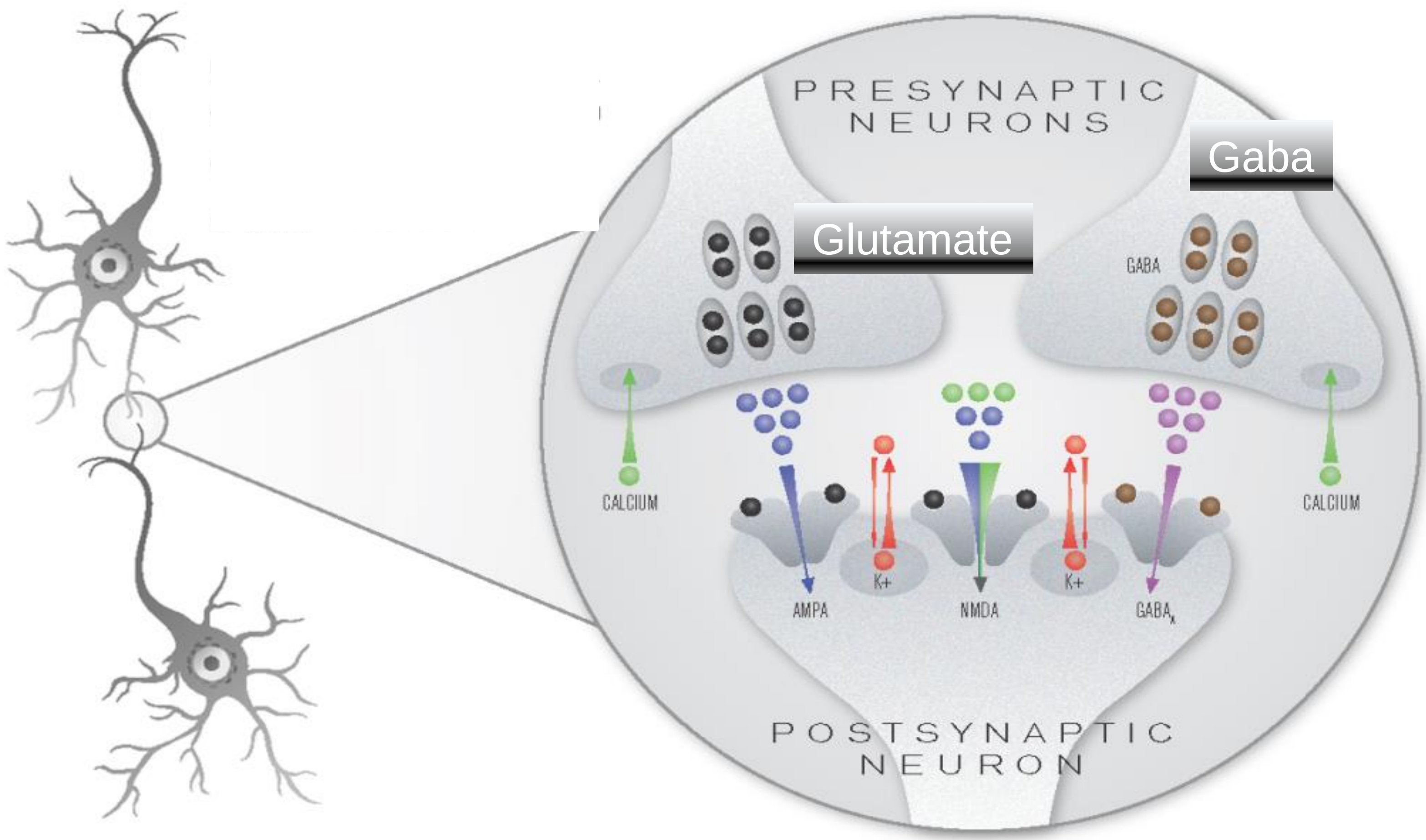
Conductance Based Neural Mass Models

Conductance-Based Neural Mass Models in DCM

Current in = Conductance X Potential Difference

$$C\dot{V} = g(V_{rev} - V)$$

Ohm's Law V = IR
Ohm's Law for a Capacitor I = C dv/dt



Conductance-Based Neural Mass Models in DCM

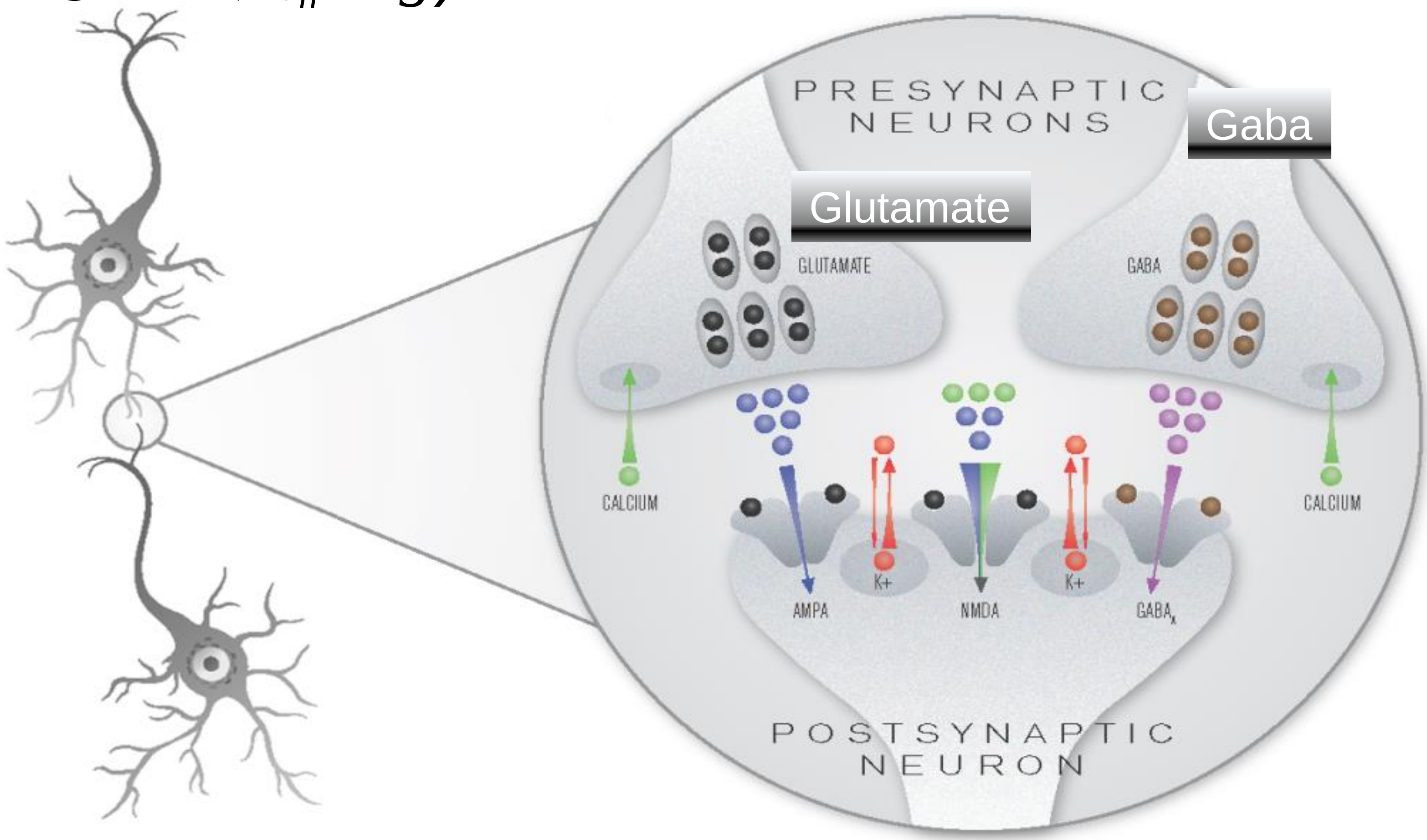
Current in = Conductance X Potential Difference

$$C\dot{V} = g(V_{rev} - V)$$

$$\dot{g} = \kappa(\gamma_{aff} - g)$$

Ohm's Law V = IR
Ohm's Law for a Capacitor I = C dv/dt

Dynamic Conductance



Conductance-Based Neural Mass Models in DCM

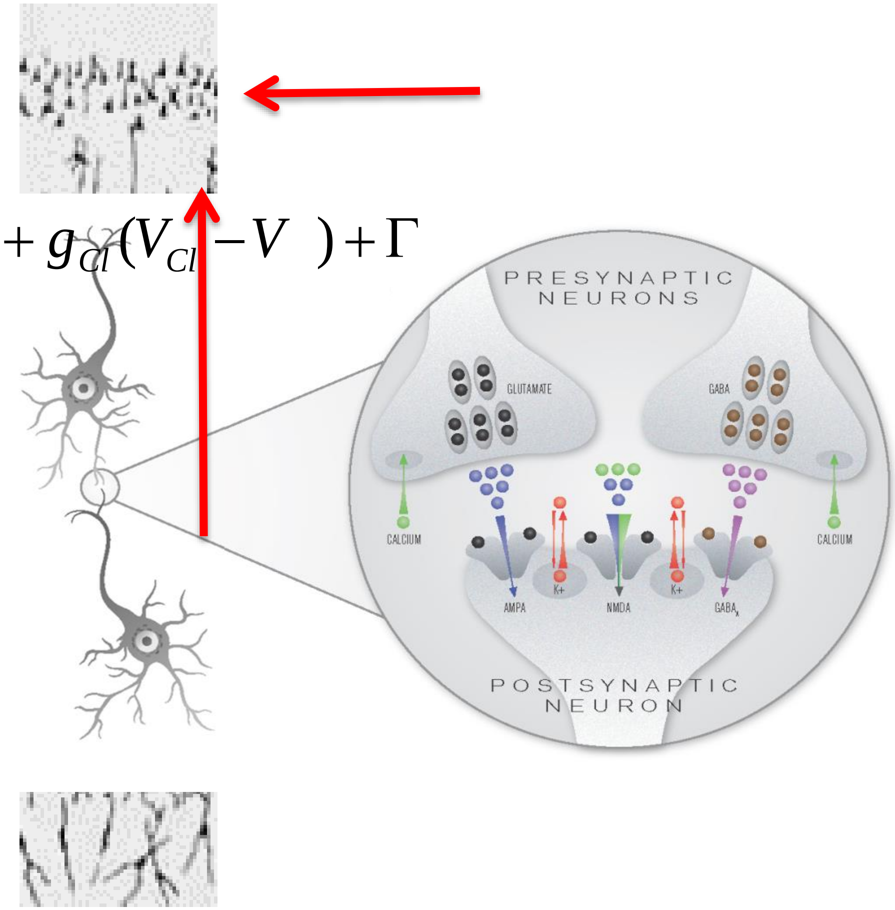
Connectivity driven by different neurotransmitters and receptors

$$C\dot{V} = g_{Na}(V_{Na} - V) + g_{Ca} f_{MG}(V_{Ca} - V) + g_{Cl}(V_{Cl} - V) + \Gamma$$

$$\dot{g}_{Na} = \kappa_{AMPA}(\gamma_{ec}\sigma - g_{Na}) + \Gamma$$

$$\dot{g}_{Cl} = \kappa_{GABA}(\gamma_{ii}\sigma - g_{Cl}) + \Gamma$$

$$\dot{g}_{Ca} = \kappa_{NMDA}(\gamma_{ec}\sigma - g_{Ca}) + \Gamma$$



State equations & parameters

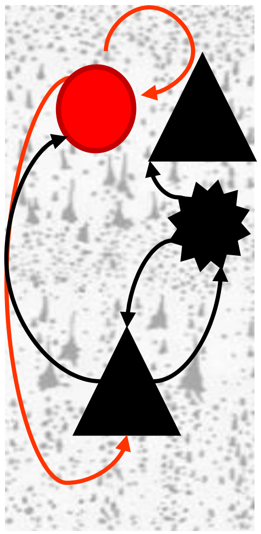
$$\dot{x} = F(x, u, \theta) \qquad \theta = \{\gamma, \kappa, V_{rev}, V_{thresh}, C\}$$

Conductance-Based Neural Mass Models in DCM

Inhibitory interneuron

Spiny stellate cells

Pyramidal cells



Inhibitory cells in extragranular layers

Exogenous input

$I(t)$

Excitatory spiny cells in granular layers

γ_{ii}

γ_{ec}

Measured response

Excitatory pyramidal cells in extragranular layers

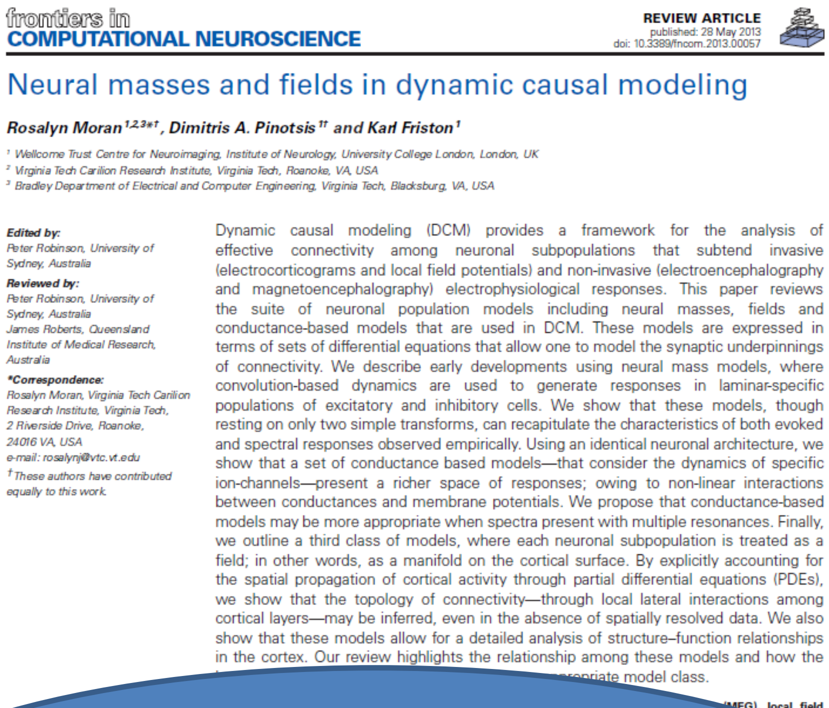
$$C\dot{V} = g_{Na}(V_{Na} - V) + g_{Ca} f_{MG}(V_{Ca} - V) + g_{Cl}(V_{Cl} - V) + \Gamma$$

$$\dot{g}_{Na} = \kappa_{AMPA}(\gamma_{ec}\sigma - g_{Na}) + \Gamma$$

$$\dot{g}_{Cl} = \kappa_{GABA}(\gamma_{ii}\sigma - g_{Cl}) + \Gamma$$

$$\dot{g}_{Ca} = \kappa_{NMDA}(\gamma_{ec}\sigma - g_{Ca}) + \Gamma$$

A selection of intrinsic architectures in SPM



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Neural masses and fields in dynamic causal modeling

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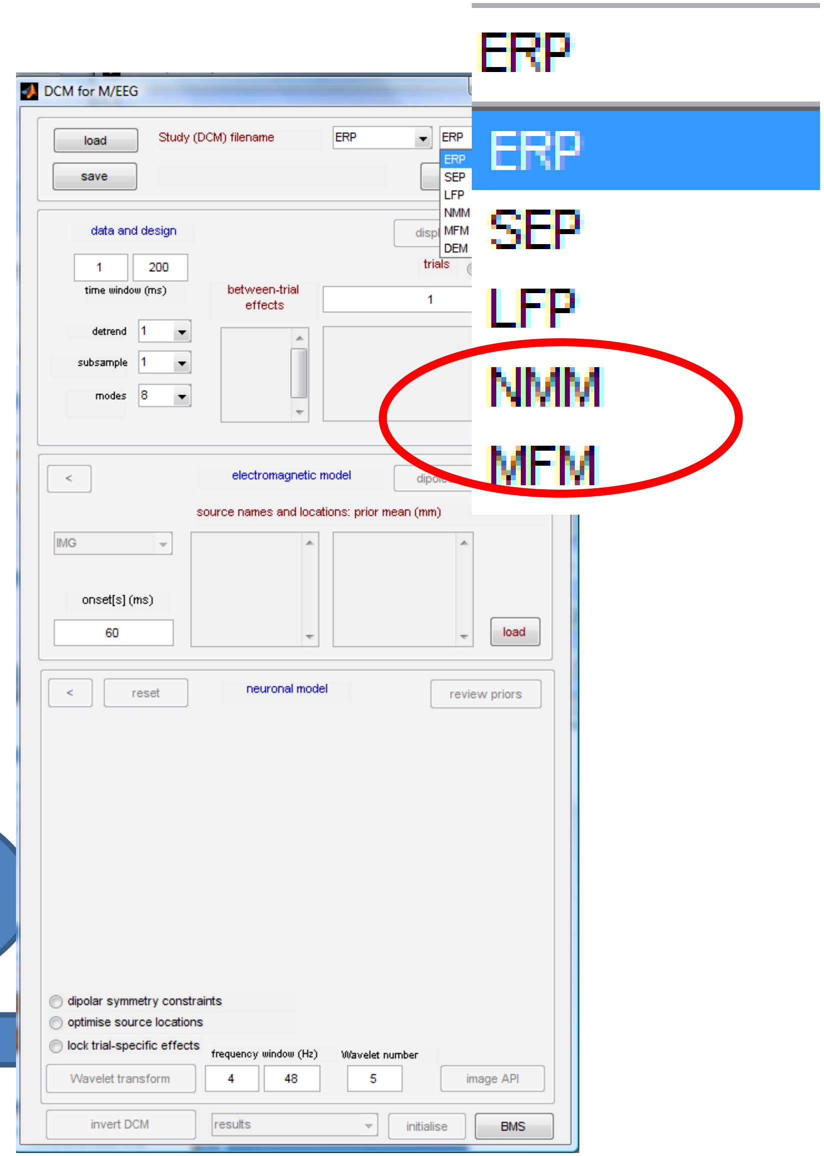
Dynamic causal modeling (DCM) provides a framework for the analysis of effective connectivity among neuronal subpopulations that subtend invasive (electrocorticograms and local field potentials) and non-invasive (electroencephalography and magnetoencephalography) electrophysiological responses. This paper reviews the suite of neuronal population models including neural masses, fields and conductance-based models that are used in DCM. These models are expressed in terms of sets of differential equations that allow one to model the synaptic underpinnings of connectivity. We describe early developments using neural mass models, where convolution-based dynamics are used to generate responses in laminar-specific populations of excitatory and inhibitory cells. We show that these models, though resting on only two simple transforms, can recapitulate the characteristics of both evoked and spectral responses observed empirically. Using an identical neuronal architecture, we show that a set of conductance based models—that consider the dynamics of specific ion-channels—present a richer space of responses; owing to non-linear interactions between conductances and membrane potentials. We propose that conductance-based models may be more appropriate when spectra present with multiple resonances. Finally, we outline a third class of models, where each neuronal subpopulation is treated as a field; in other words, as a manifold on the cortical surface. By explicitly accounting for the spatial propagation of cortical activity through partial differential equations (PDEs), we show that the topology of connectivity—through local lateral interactions among cortical layers—may be inferred, even in the absence of spatially resolved data. We also show that these models allow for a detailed analysis of structure–function relationships in the cortex. Our review highlights the relationship among these models and how the ... appropriate model class.

... (MEG), local field



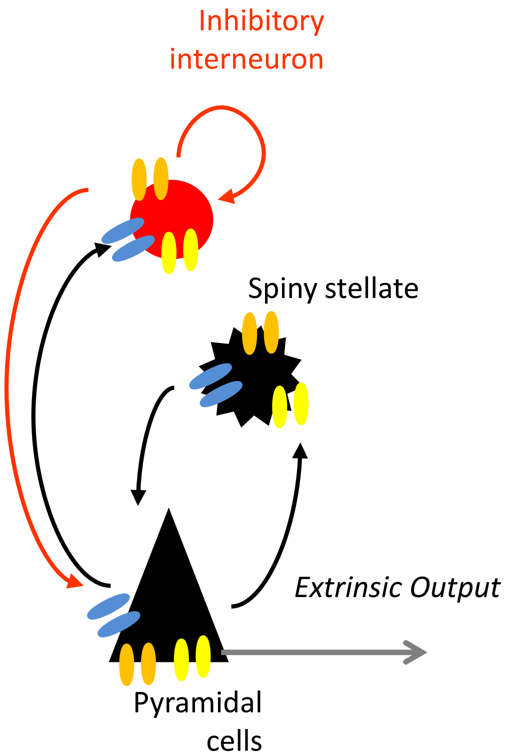
A suite of neuronal population models including neural masses, fields and conductance-based models…expressed in terms of sets of differential equations

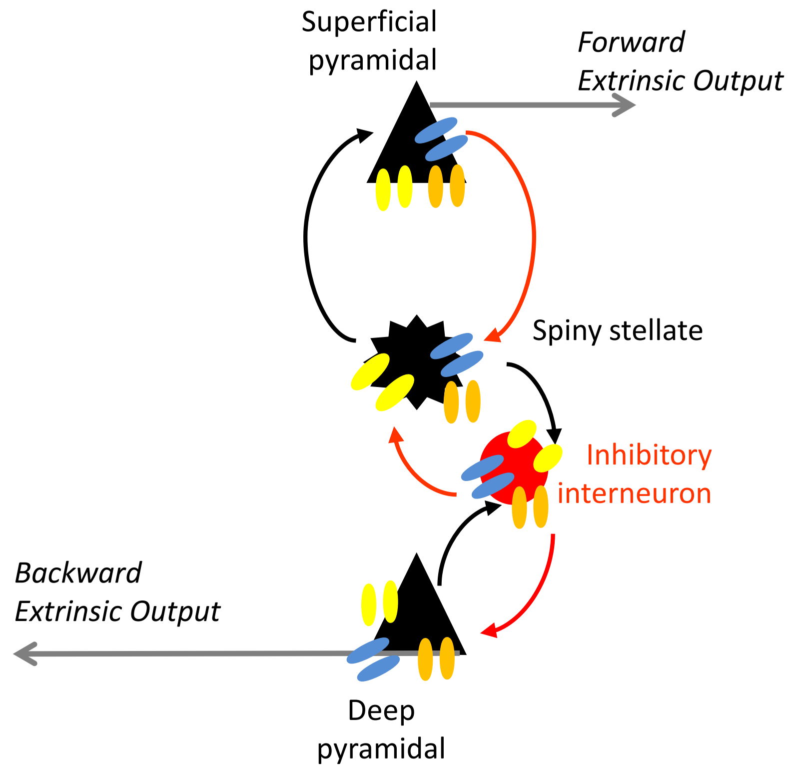
Predictive coding-based Neural Mass Models in DCM

Neuron
Perspective

Canonical Microcircuits for Predictive Coding

Andre M. Bastos,[1,2,6] W. Martin Usrey,[1,3,4] Rick A. Adams,[8] George R. Mangun,[2,3,5] Pascal Fries,[6,7] and Karl J. Friston[8,*]





GABA Receptors

AMPA Receptors

NMDA Receptors

$$C\dot{V} = g(V_{rev} - V) + \Gamma$$

$$\dot{g} = \kappa(\gamma_{aff}\sigma(\mu_{aff} - V_{threshold}, \Sigma_{aff}) - g) + \Gamma$$

Moran et al. 2011, Neuroimage

4-subpopulation
Canonical Microcircuit

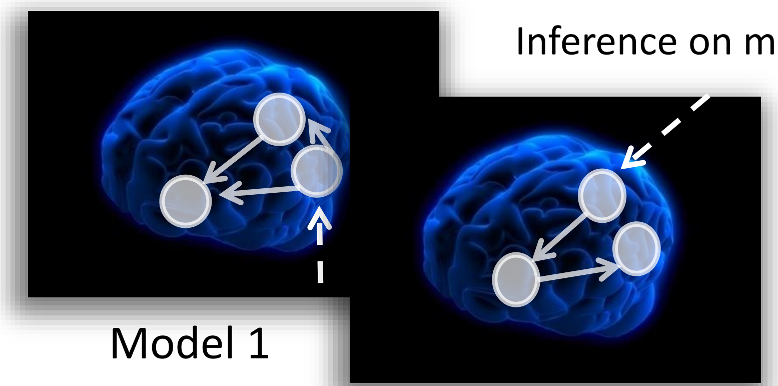
Model Inversion & Inference

Bayesian Inversion

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

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

Inference on models



Model 1

Model 2

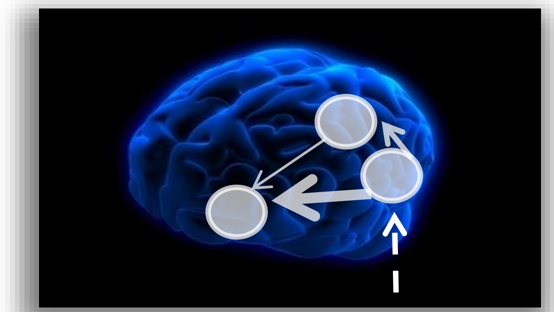
Model comparison via Bayes factor:

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

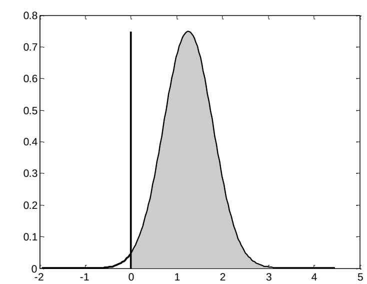
accounts for <u>both</u> accuracy and complexity of the model

allows for inference about structure (generalisability) of the model

Inference on parameters



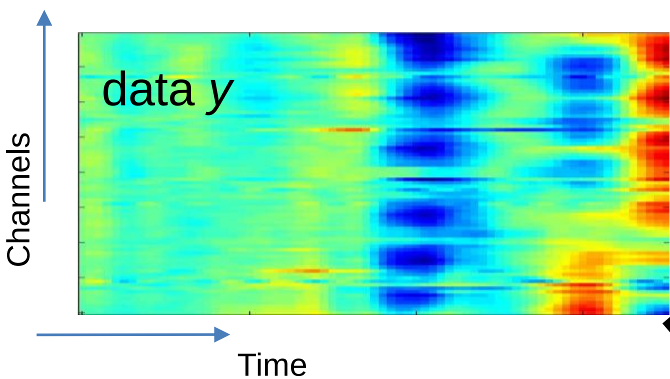
Model 1



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

Data & Hypotheses

Event-Related Potentials



Model *1* → $p(y \mid m_1)$

$p(\theta \mid y, m_1)$

Model *2* → $p(y \mid m_2)$

$p(\theta \mid y, m_2)$

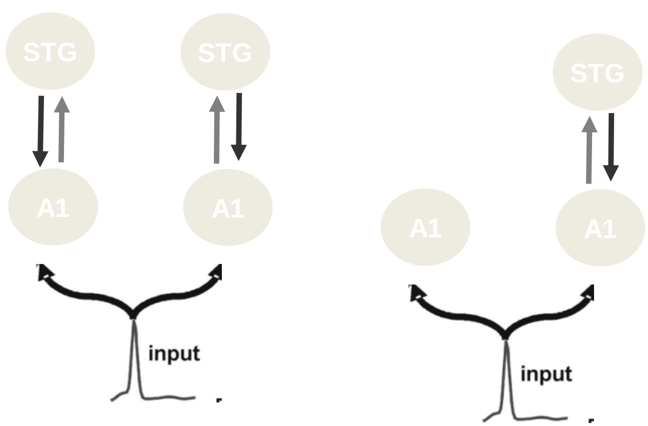
⋮

Model *n* → $p(y \mid m_n)$

$p(\theta \mid y, m_n)$

Model selection:

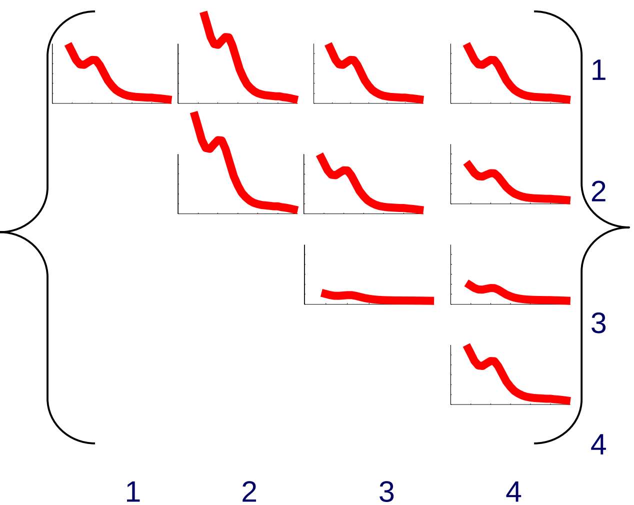
$p(y \mid m_i)$

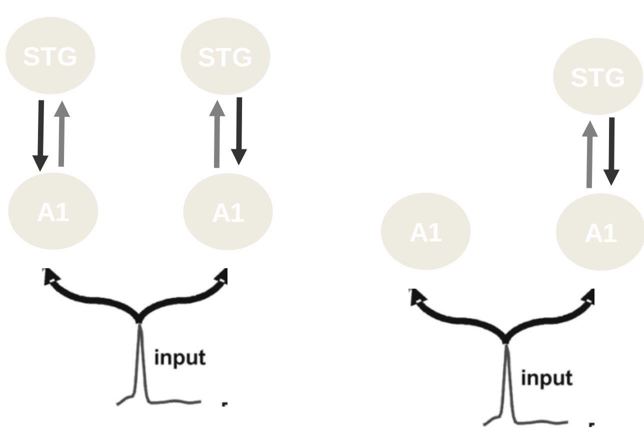


best?

Data & Hypotheses

Spectral Responses





best?

Model *1* → $p(y \mid m_1)$, $p(\theta \mid y, m_1)$

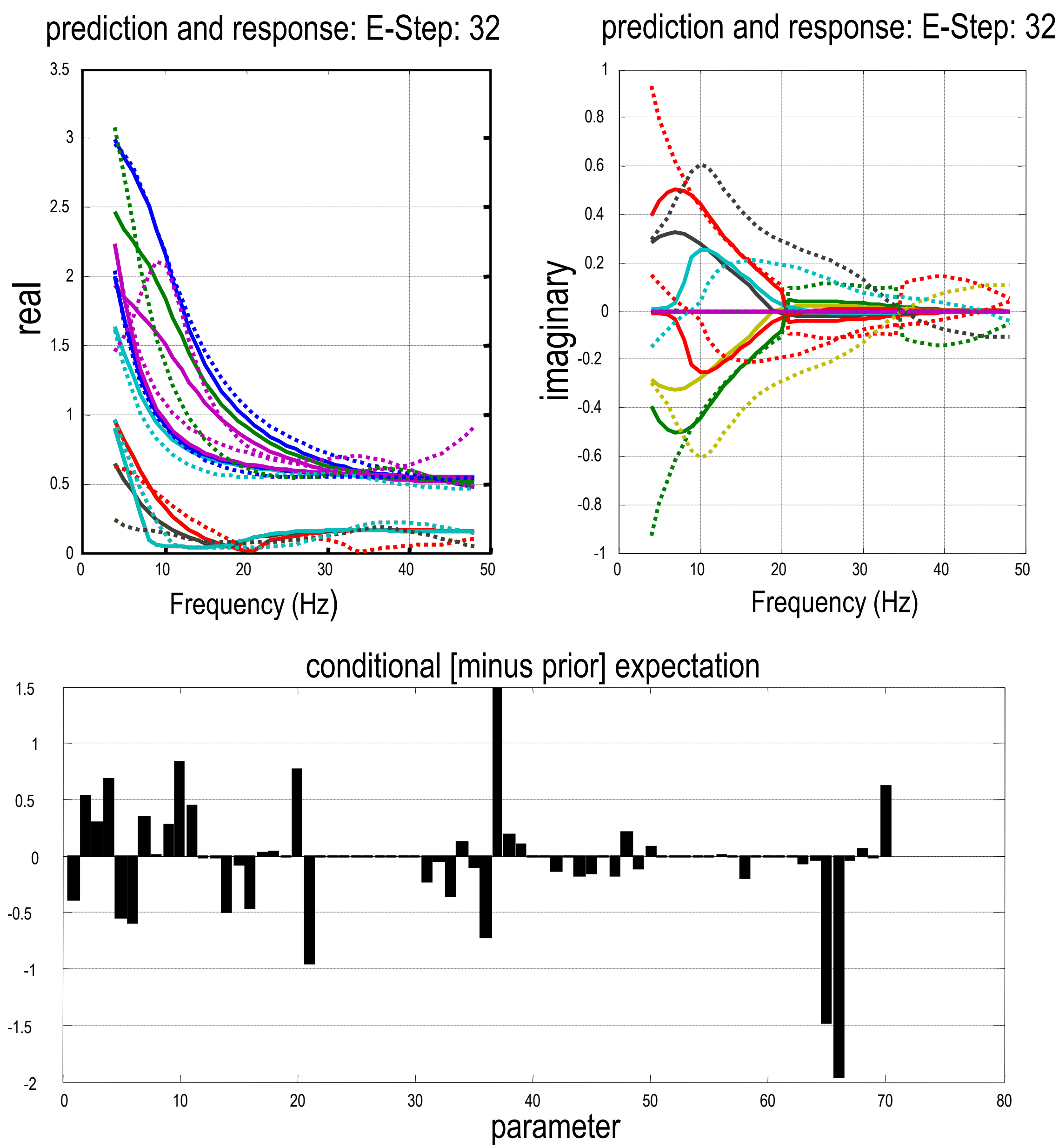
Model *2* → $p(y \mid m_2)$, $p(\theta \mid y, m_2)$

⋮

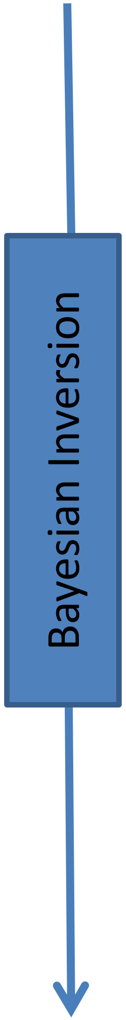
Model *n* → $p(y \mid m_n)$, $p(\theta \mid y, m_n)$

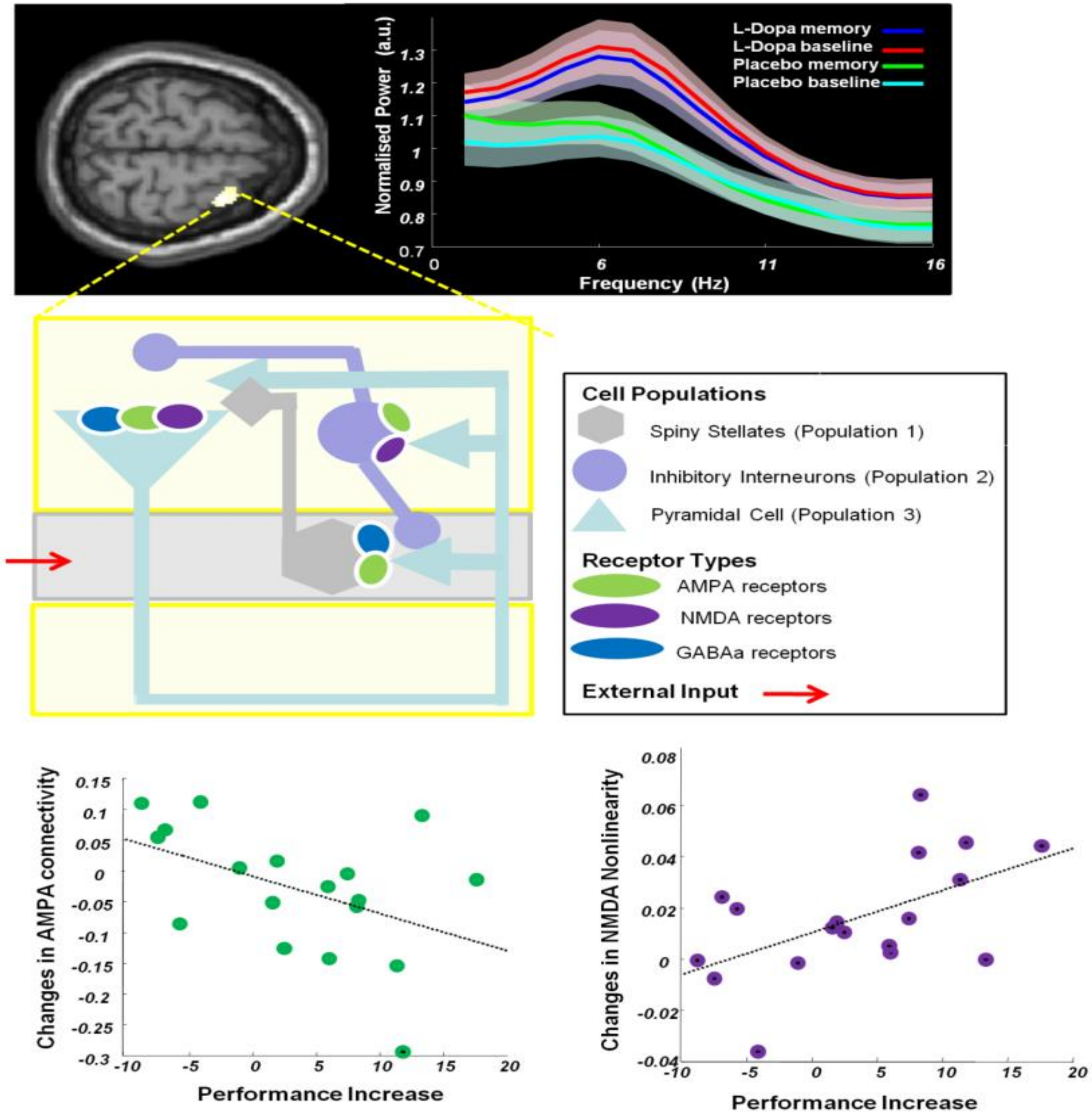
Model selection: $p(y \mid m_i)$

Inversion in the real & complex domain



Model Validation

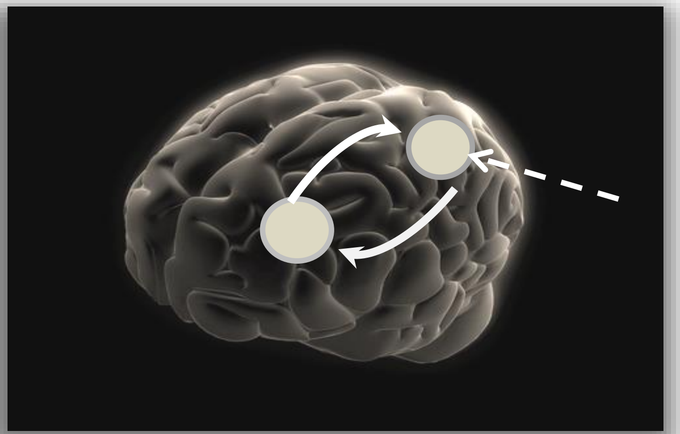




Moran, Symmonds et al 2011

Ketamine Example

Connectivity from Human Neuroimaging Data: Dynamic Causal Models



What have we gained?

The receptor profile of connectivity

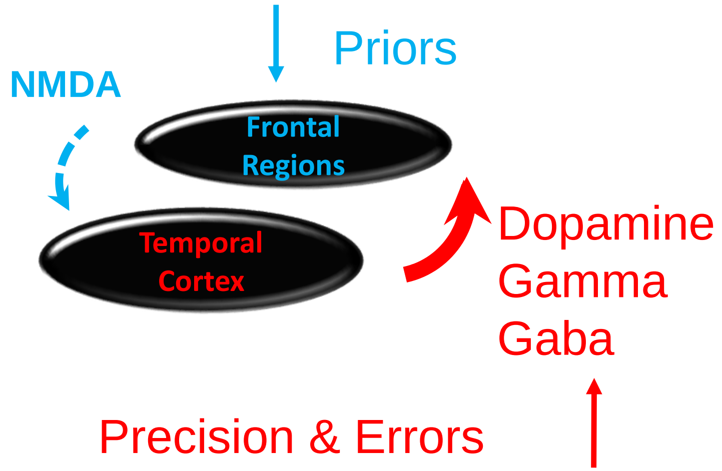
Clues for molecular pathogenic pathways

A pharmacological target

For EEG

Dysconnection

- *Reversal can be regarded as a failure of prefrontal cortex to suppress activity in the temporal lobe*
- *Dysconnectivity could result from abnormal modulation of N-methyl-D-aspartate (NMDA)-dependent plasticity by other neurotransmitter systems*



The Ketamine Model of Psychosis & Schizophrenia

Noncompetitive NMDA-r antagonist

Dissociative anaesthetic:

- "... a peculiar anaesthetic state in which marked sensory loss and analgesia as well as amnesia is not accompanied by actual loss of consciousness.” (Bonta, 2004)

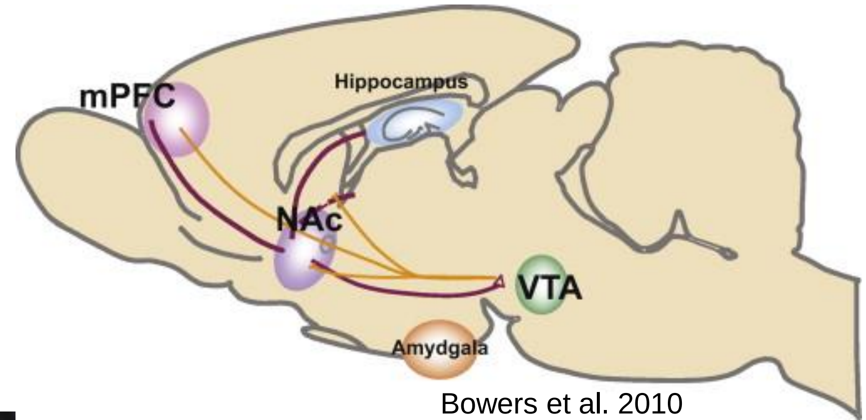
Subanaesthetic Doses:

- Model of psychosis in animals, producing hyperlocomotion and disruption of PPI

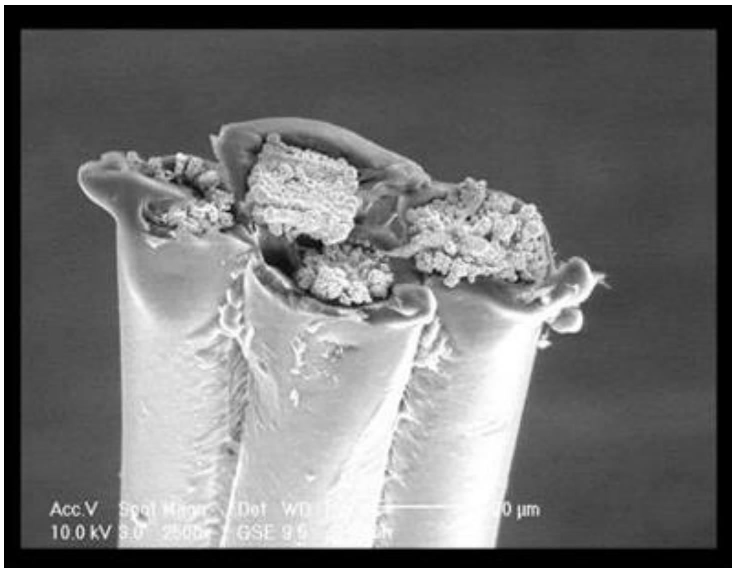
- Reproduces in humans both positive and negative symptoms of schizophrenia along with associated cognitive deficits.

The Ketamine Model of Psychosis & Schizophrenia

With Matthew Jones, University of Bristol



Bowers et al. 2010



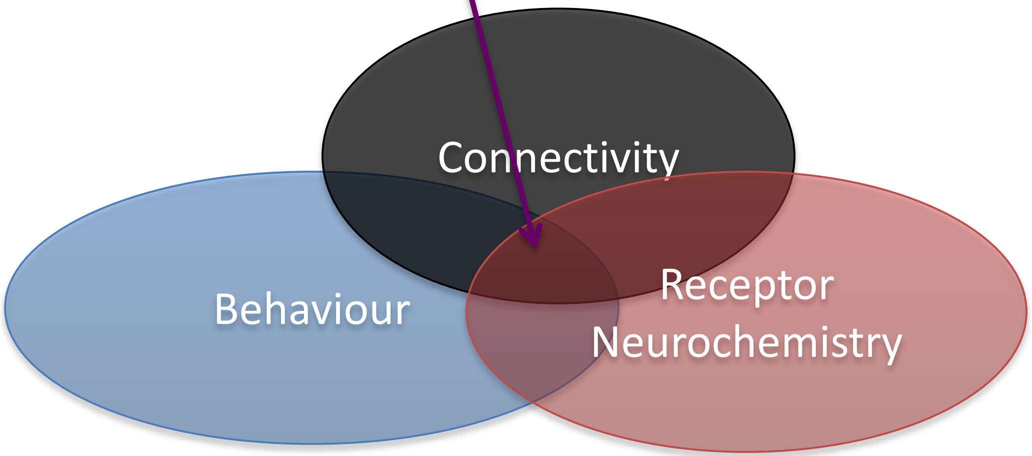
Hippocampal & Prefrontal Recordings

5 mins of recordings from freely moving rat: tetrodes in dCA1 & mPFC

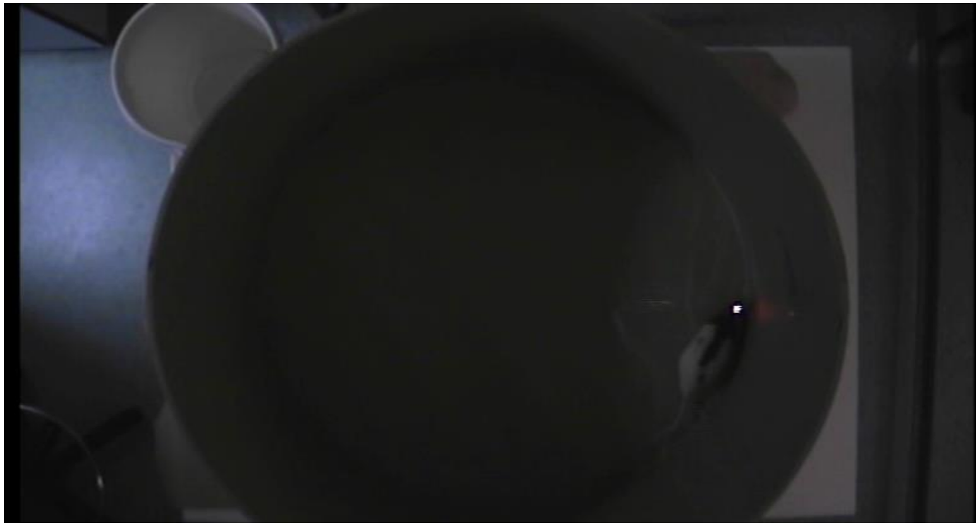
The Ketamine Model of Psychosis & Schizophrenia

Effects on Oscillations:

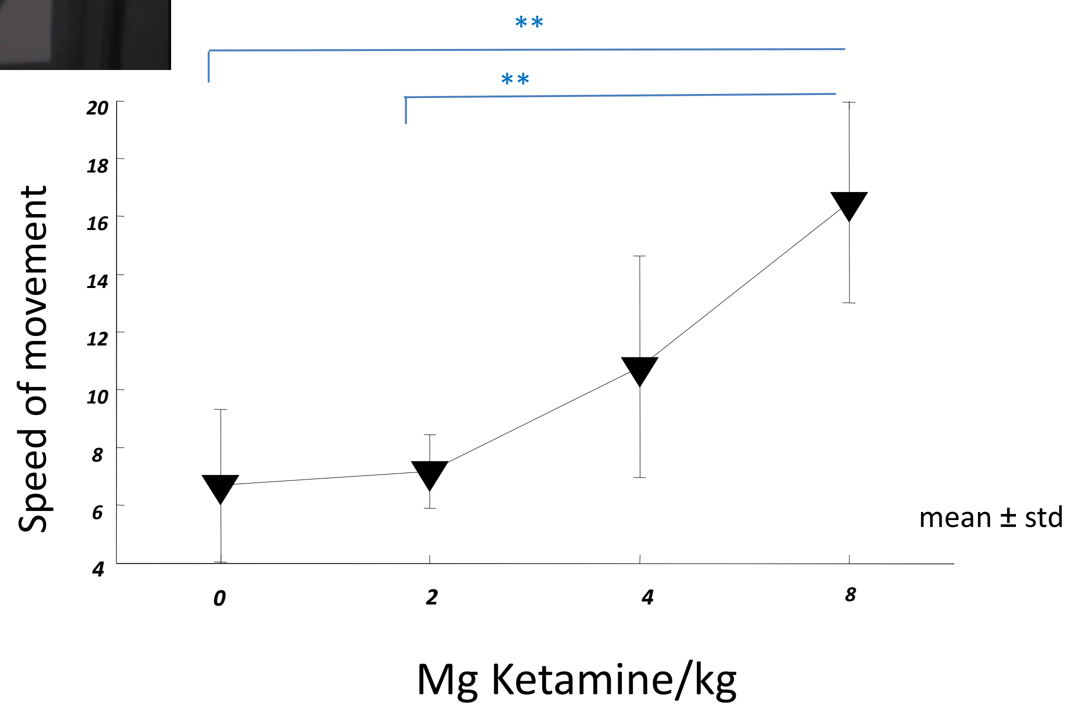
- Theta reduction in the hippocampus and Gamma enhancement in hippocampus and neocortex.
- Antipsychotic drugs (D2 antagonists) acutely reduce cortical gamma oscillations in rats (Jones et al. 2011).
- Aberrant beta and gamma synchrony observed in patient populations (Uhlhaas et al. 2008).
- Reduced or enhanced gamma depending on state late/prodromal (Sun et al. 2011).



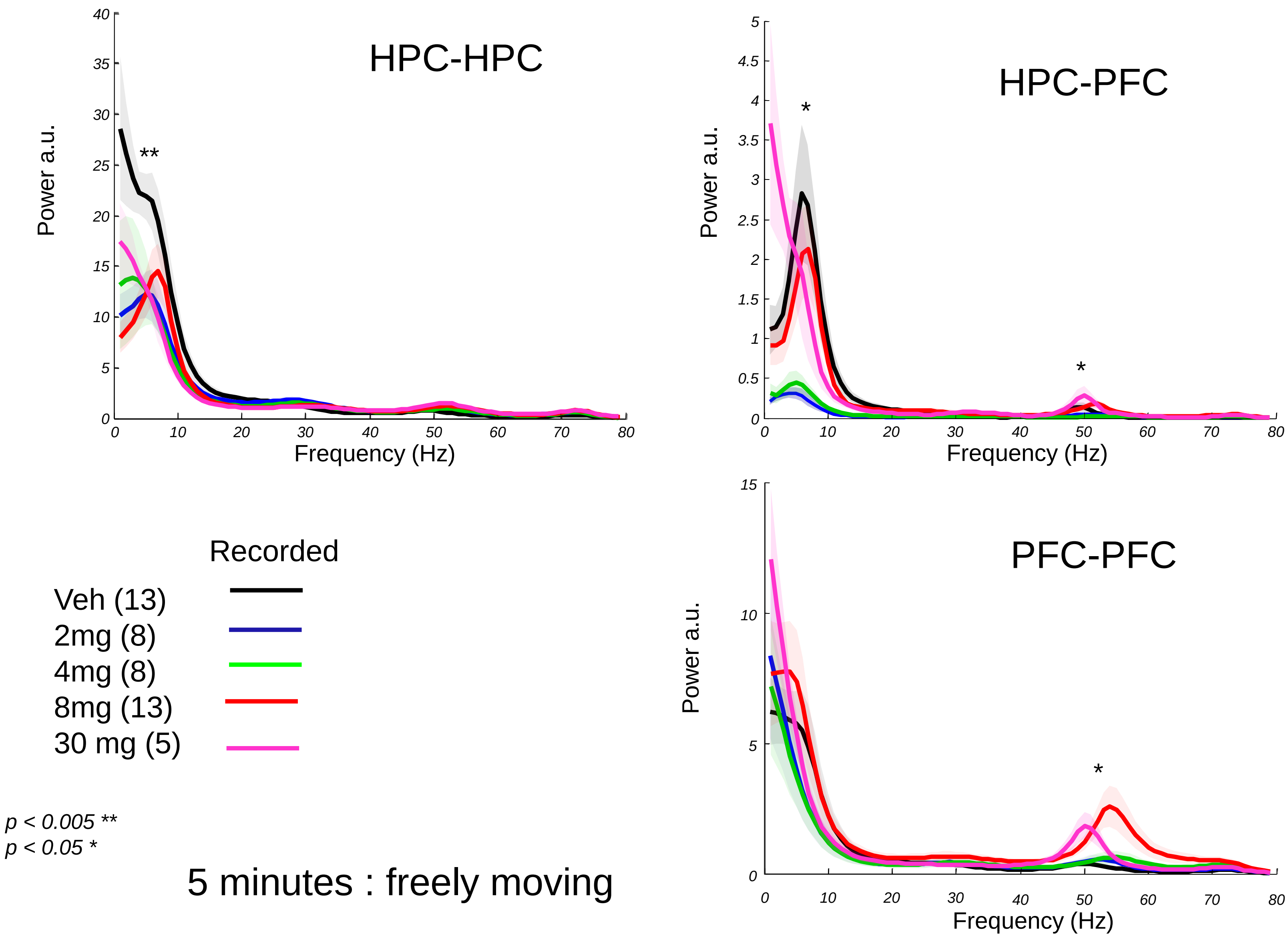
Behavioural Phenotype



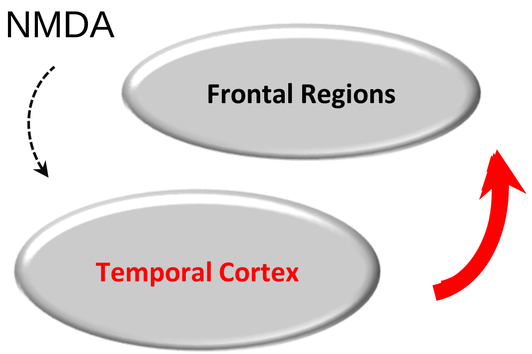
Hyper-locomotion



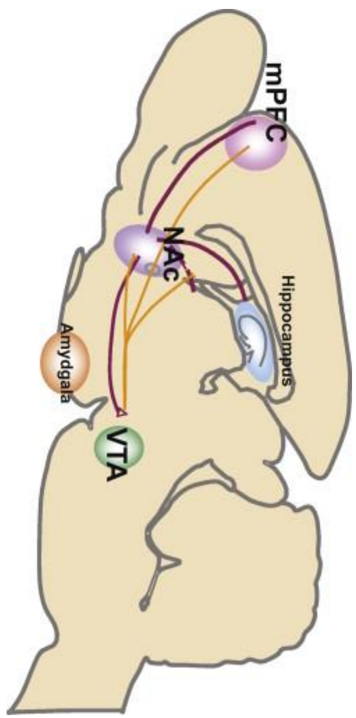
Oscillatory Characteristics

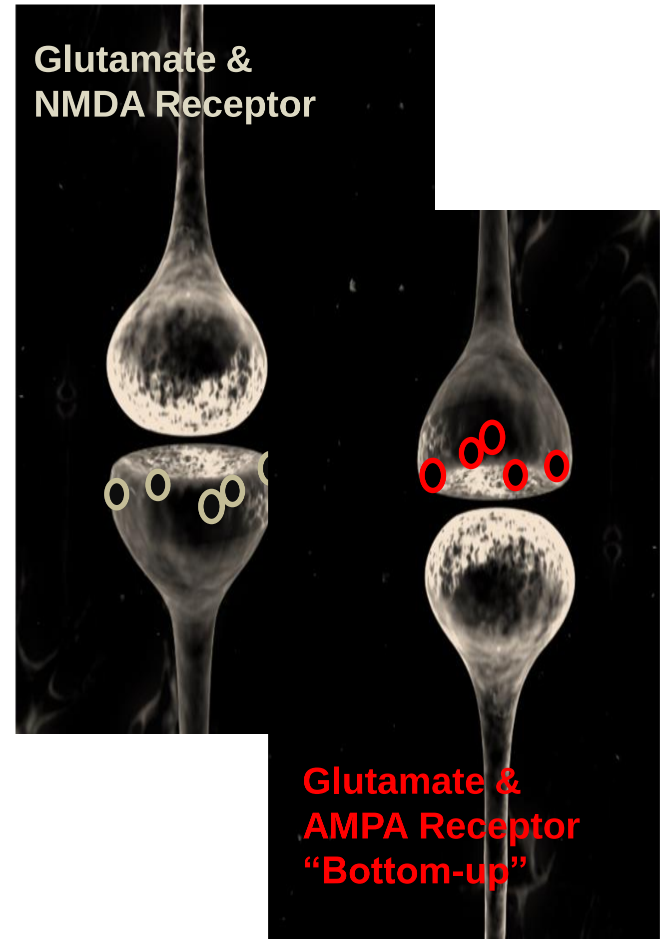


Hypothesis, Data & Model-based analysis:



Dopamine
Gamma
Gaba



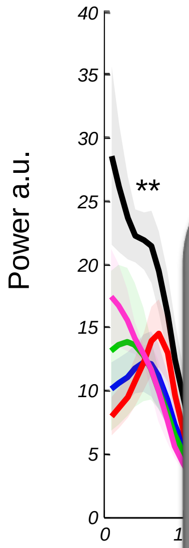


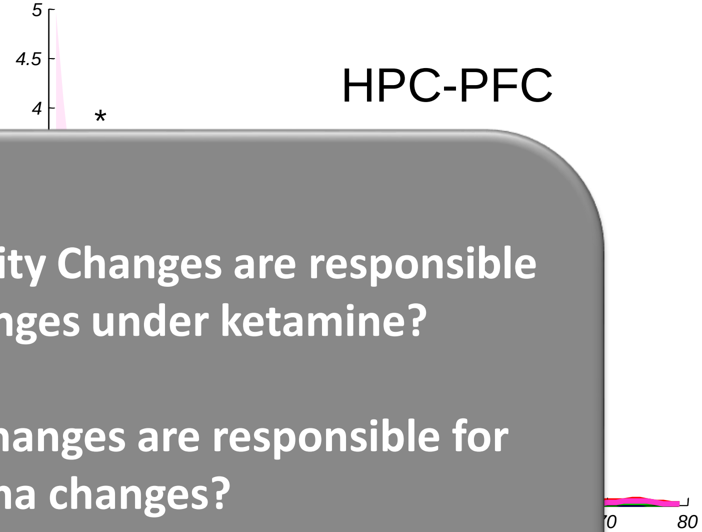
Hippocampal & Prefrontal Recordings

5 mins of recordings from freely moving rat: tetrodes in dCA1 & mPFC

Ketamine Dose: 0, 2, 4, 8, 30 mgkg-1

Hypothesis, Data & Model-based analysis:



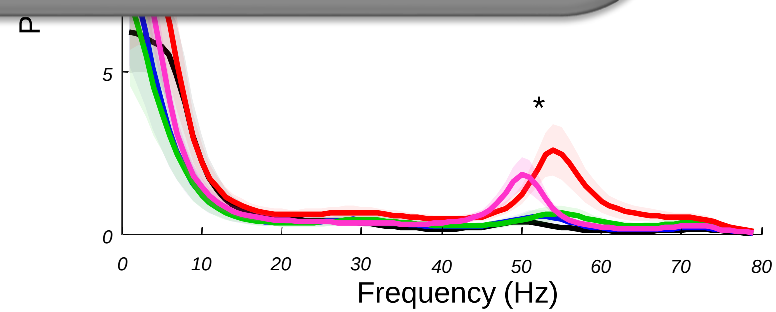


What Cortico-Limbic Connectivity Changes are responsible for theta and gamma changes under ketamine?

What Intrinsic Connectivity Changes are responsible for theta and gamma changes?

What Receptors are involved at these extrinsic & intrinsic synapses?

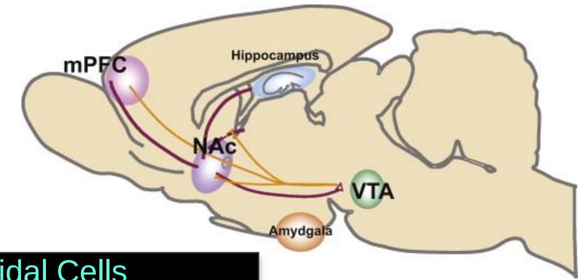
Veh (13)
2mg (8)
4mg (8)
8mg (13)
30 mg (5)

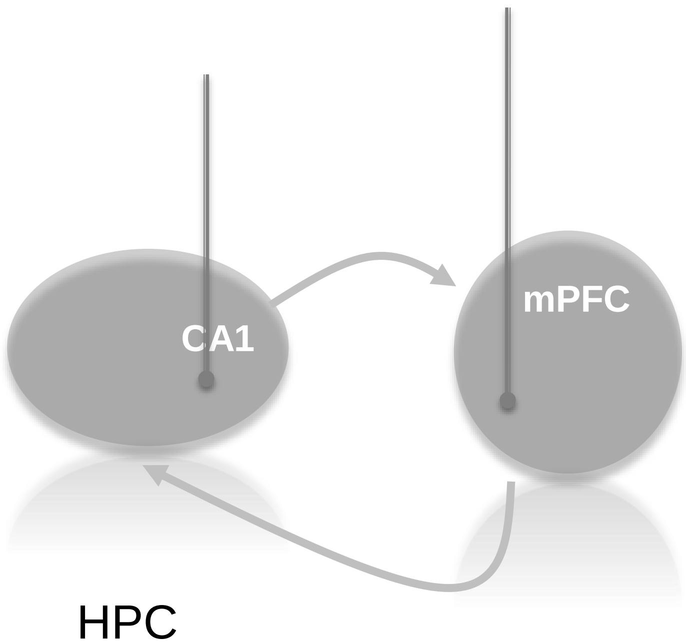


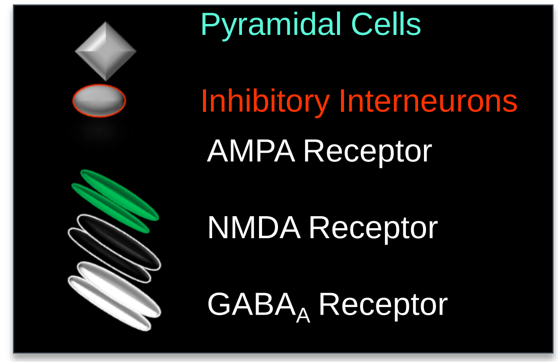
*$p < 0.005$ ***
*$p < 0.05$ **

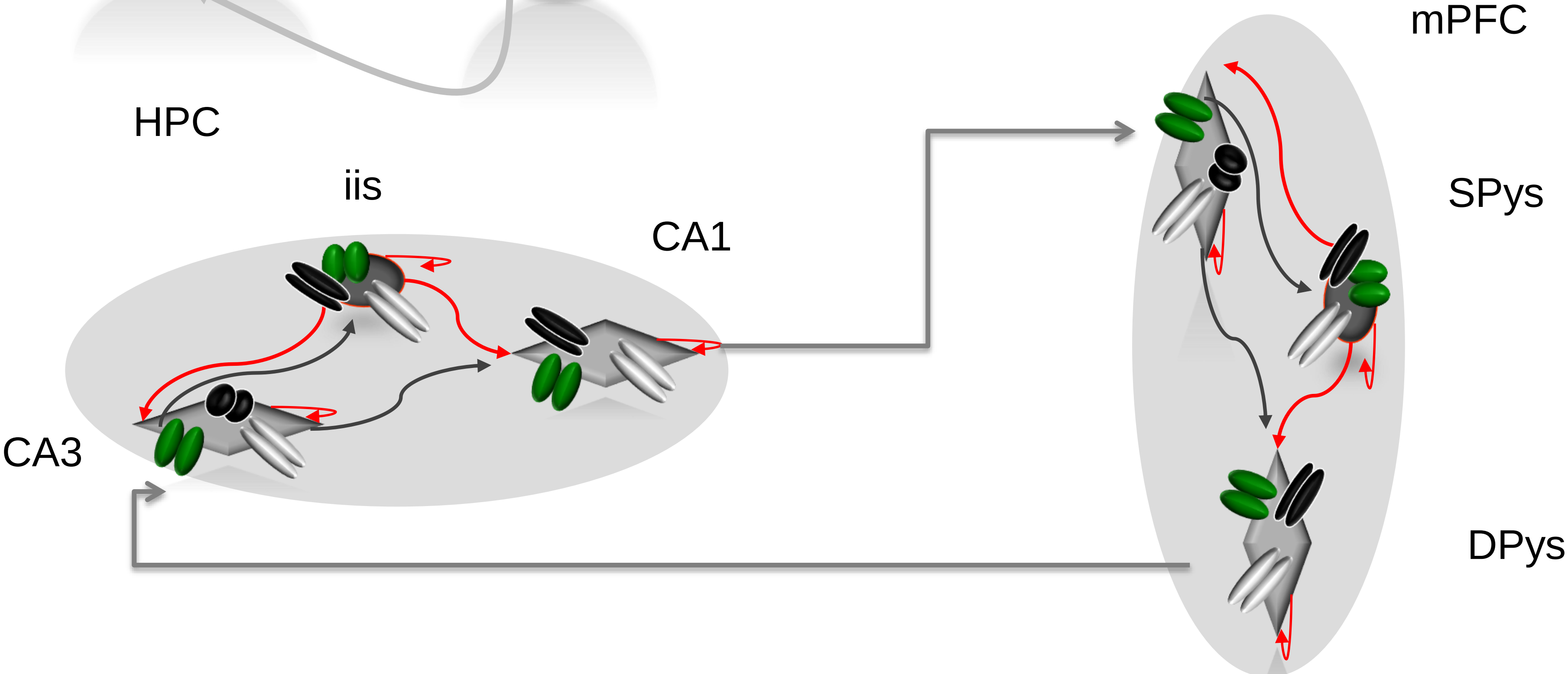
5 minutes : freely moving

Proposed Architecture







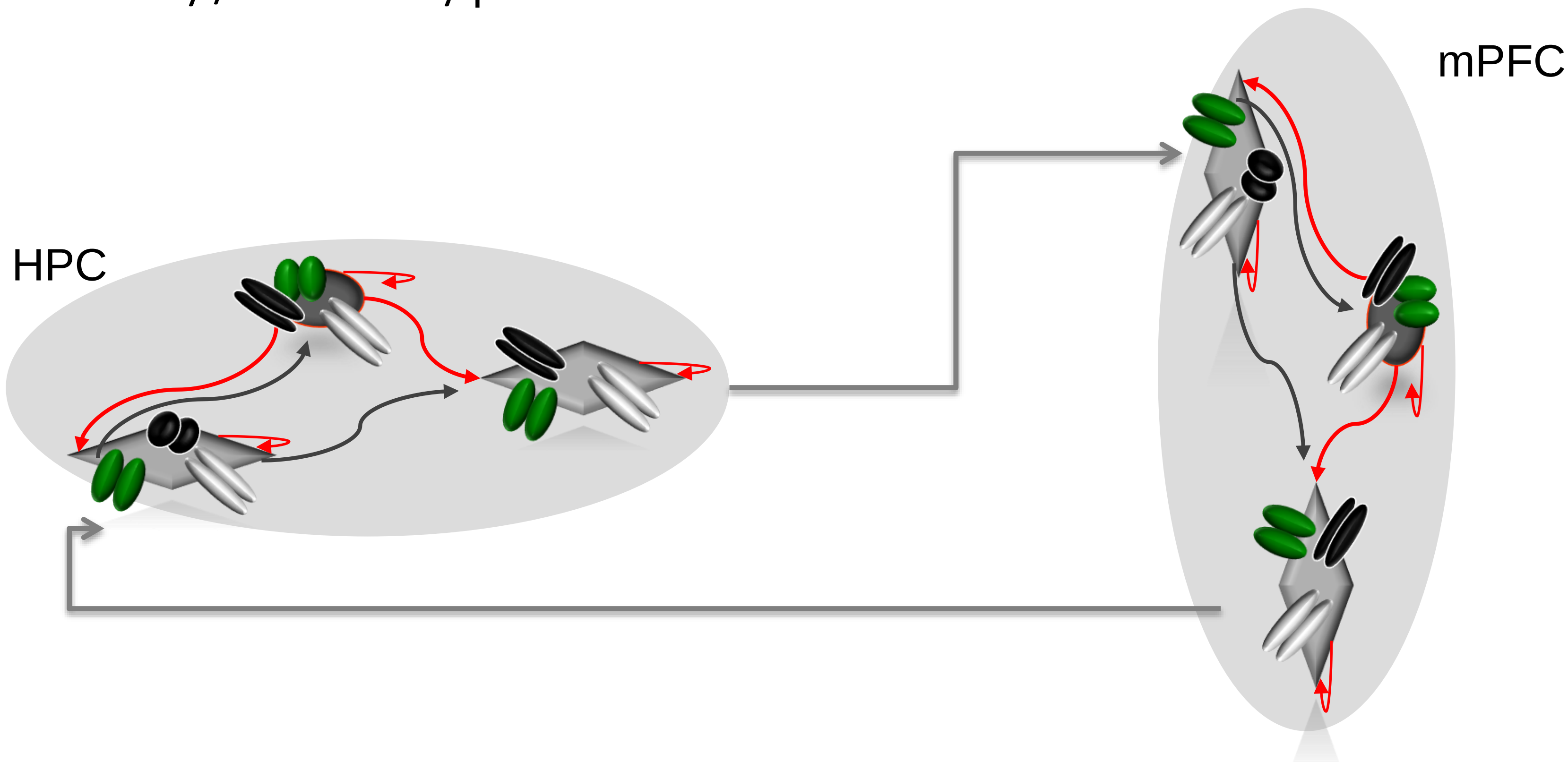


Model Comparison

Ketamine doses parametrically modulate:

1. All extrinsic connections,
2. Intrinsic NMDA and
3. Inhibitory / Modulatory processes

$$\gamma = \gamma + B_{ket}\gamma$$



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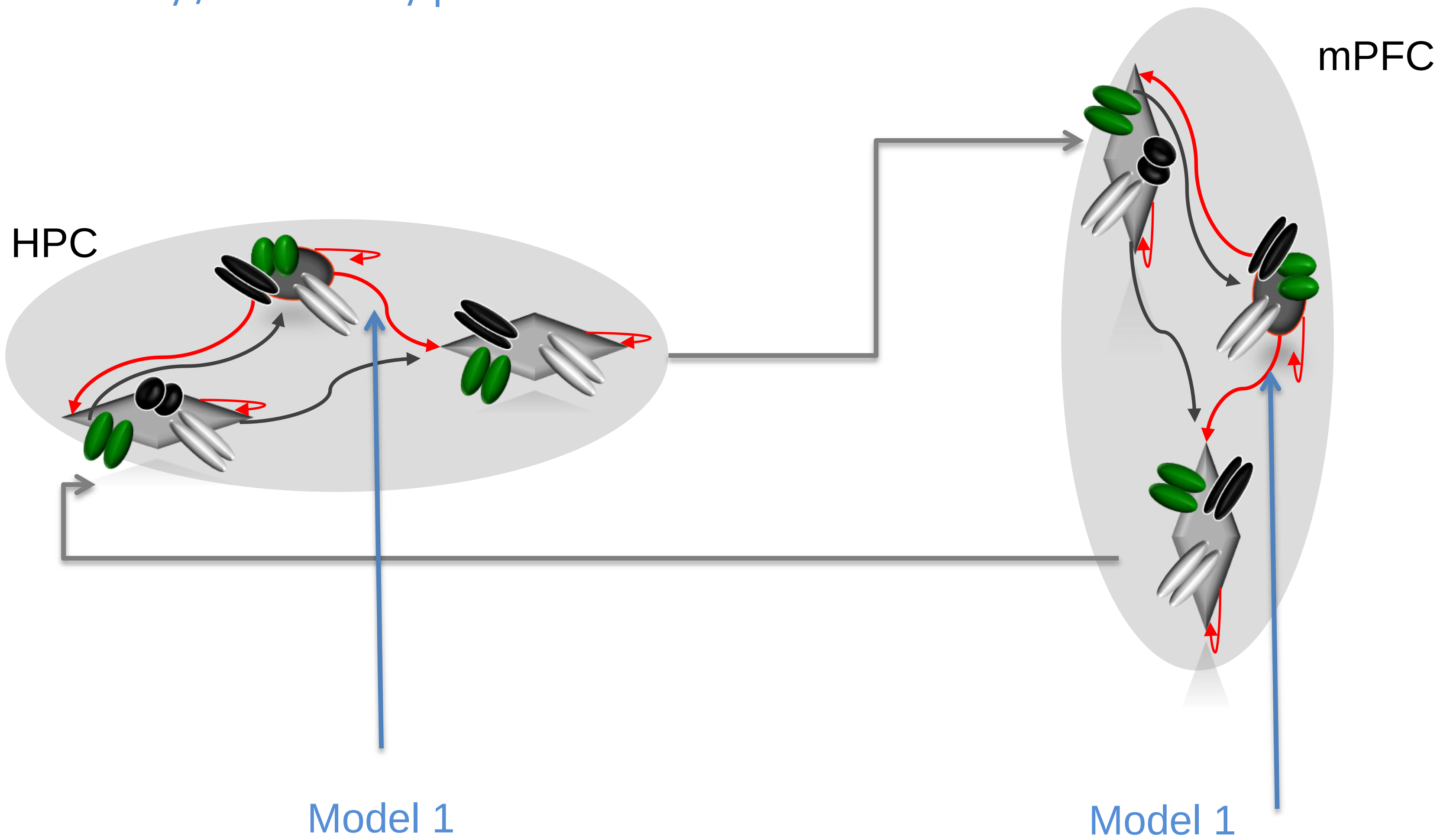

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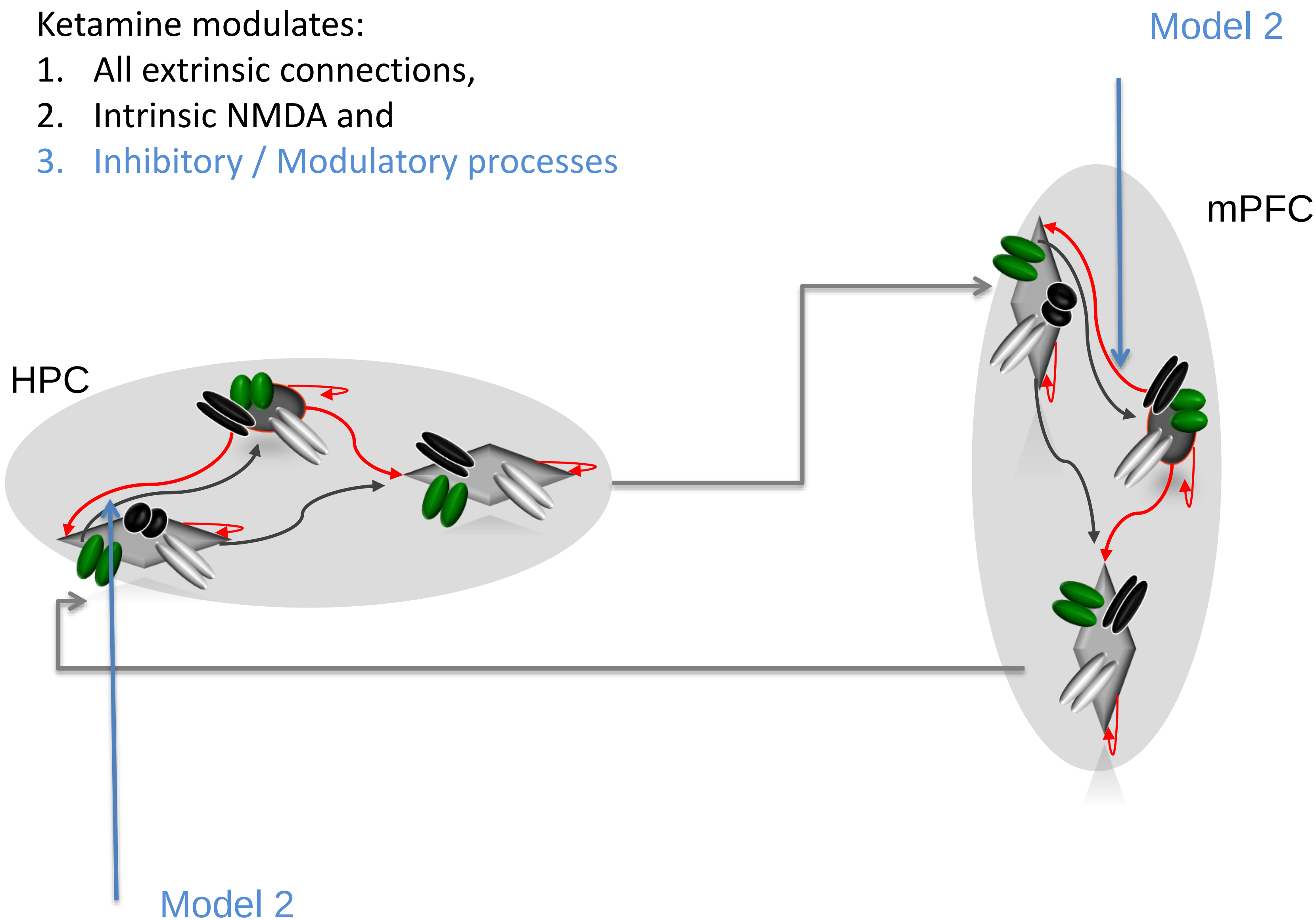
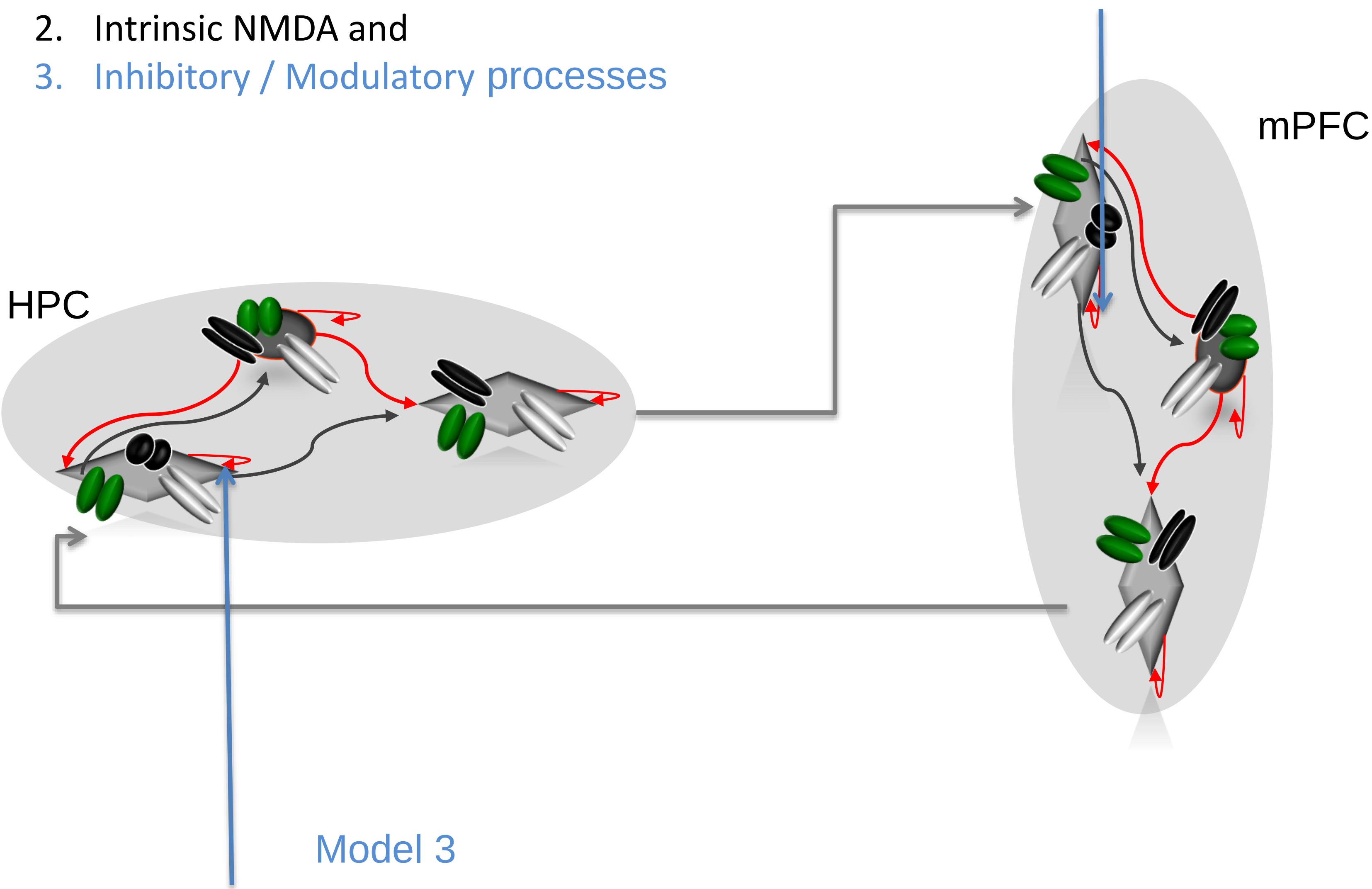


Model Comparison

Ketamine modulates:

1. All extrinsic connections,
2. Intrinsic NMDA and
3. Inhibitory / Modulatory processes



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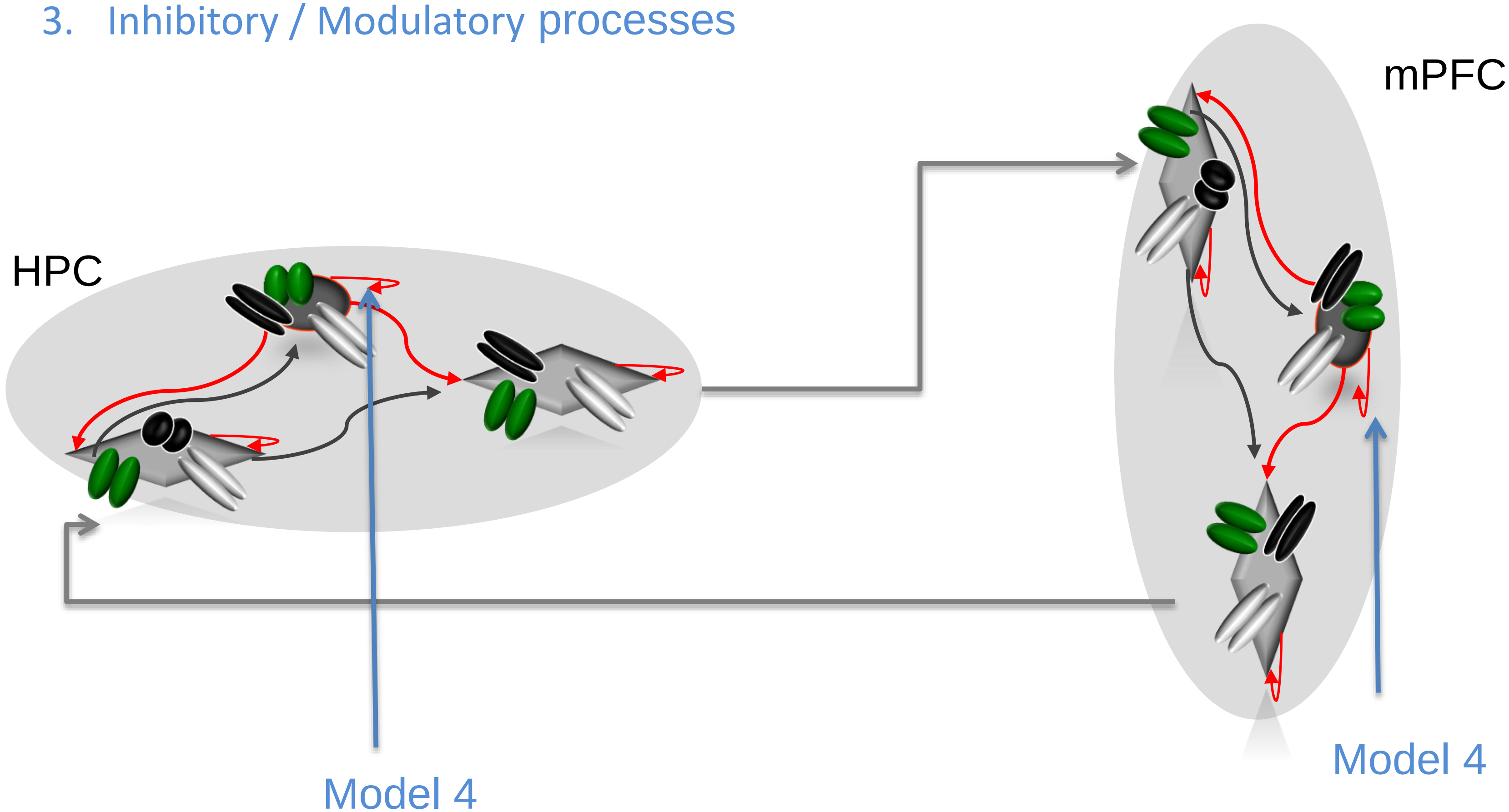

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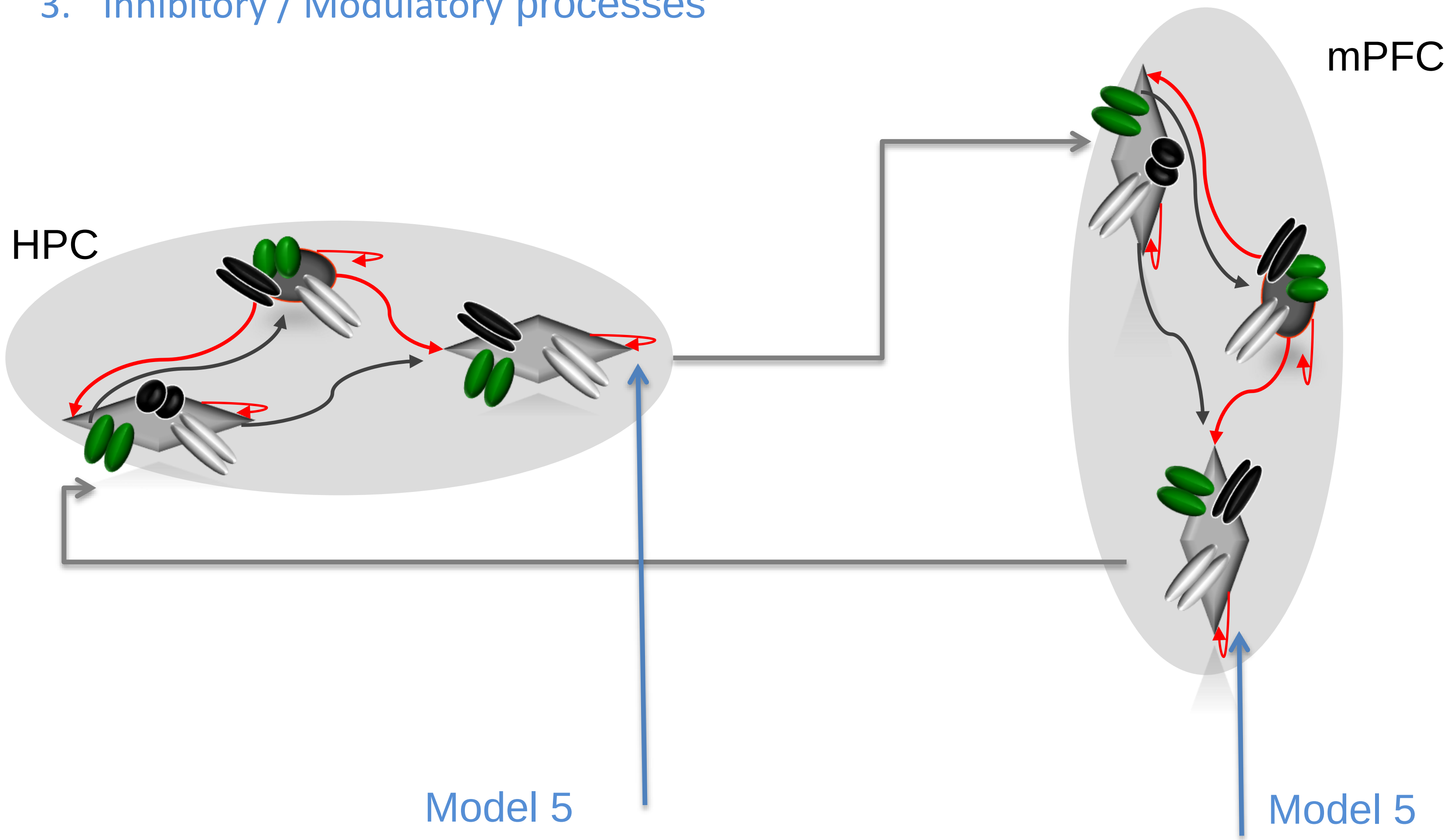

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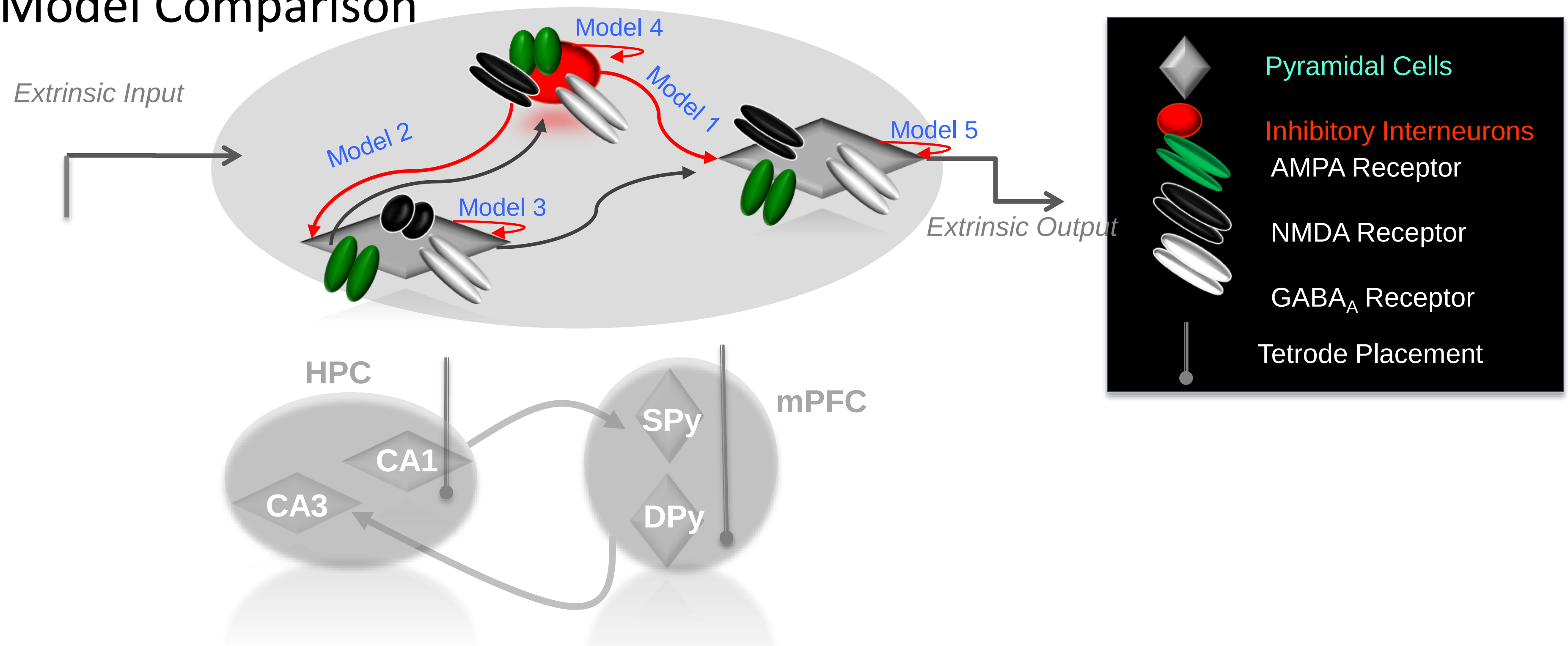
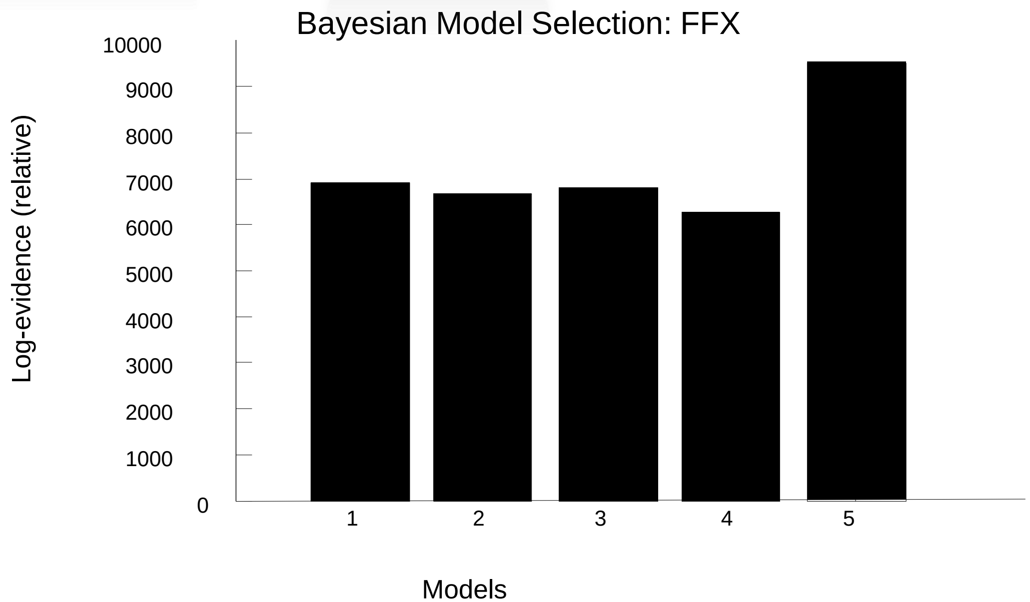
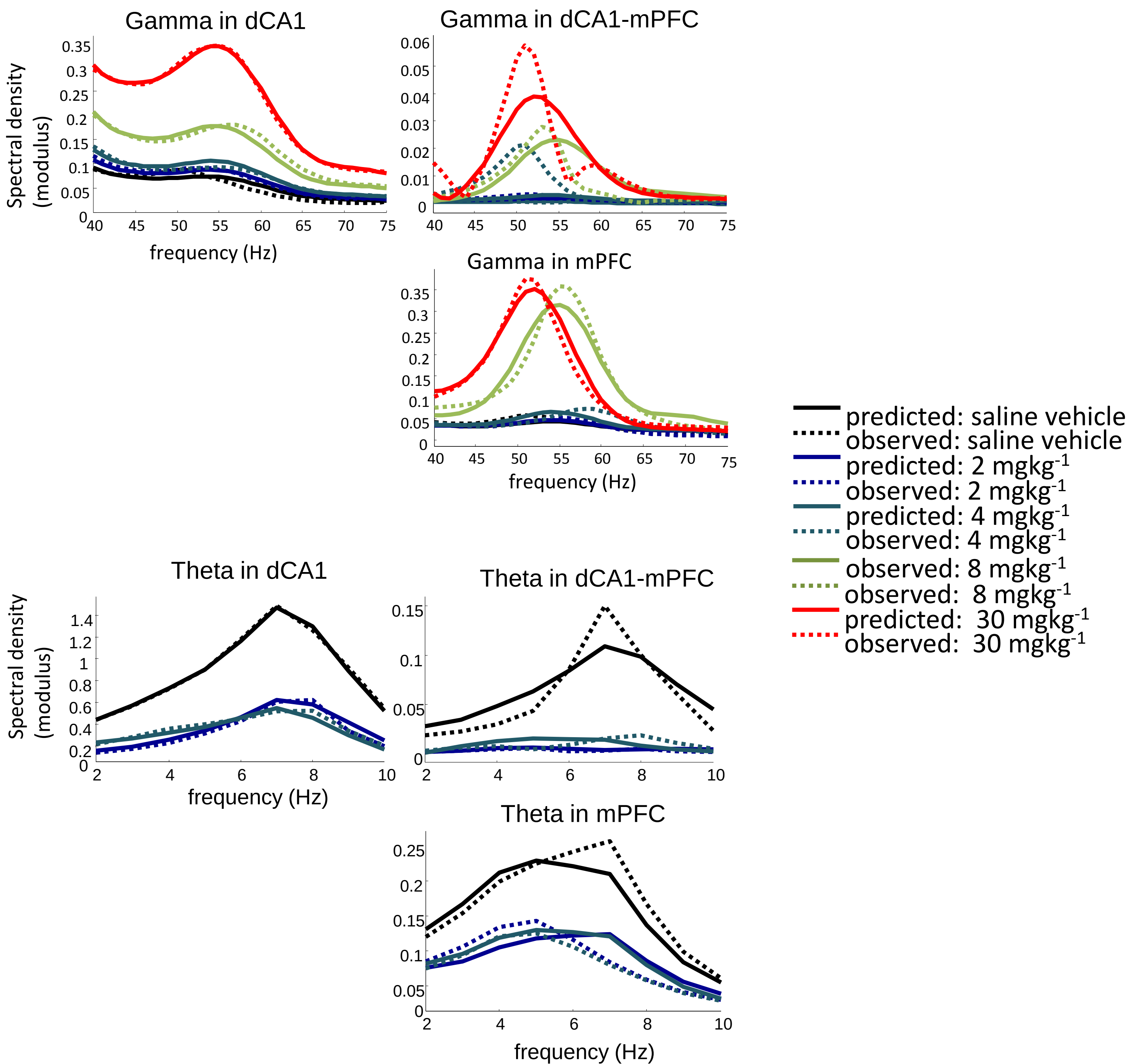
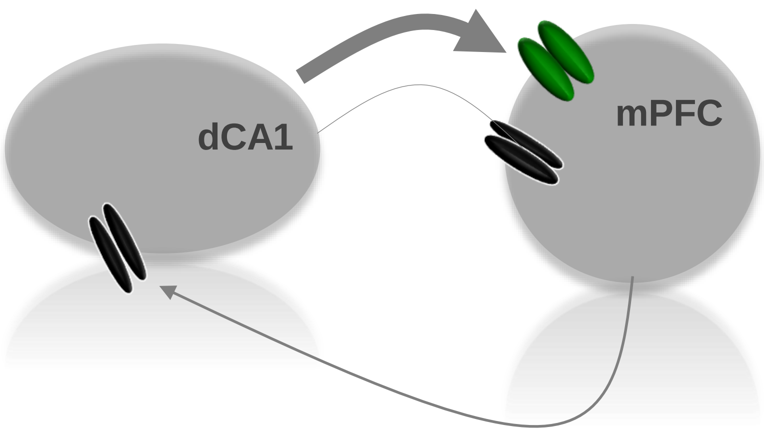


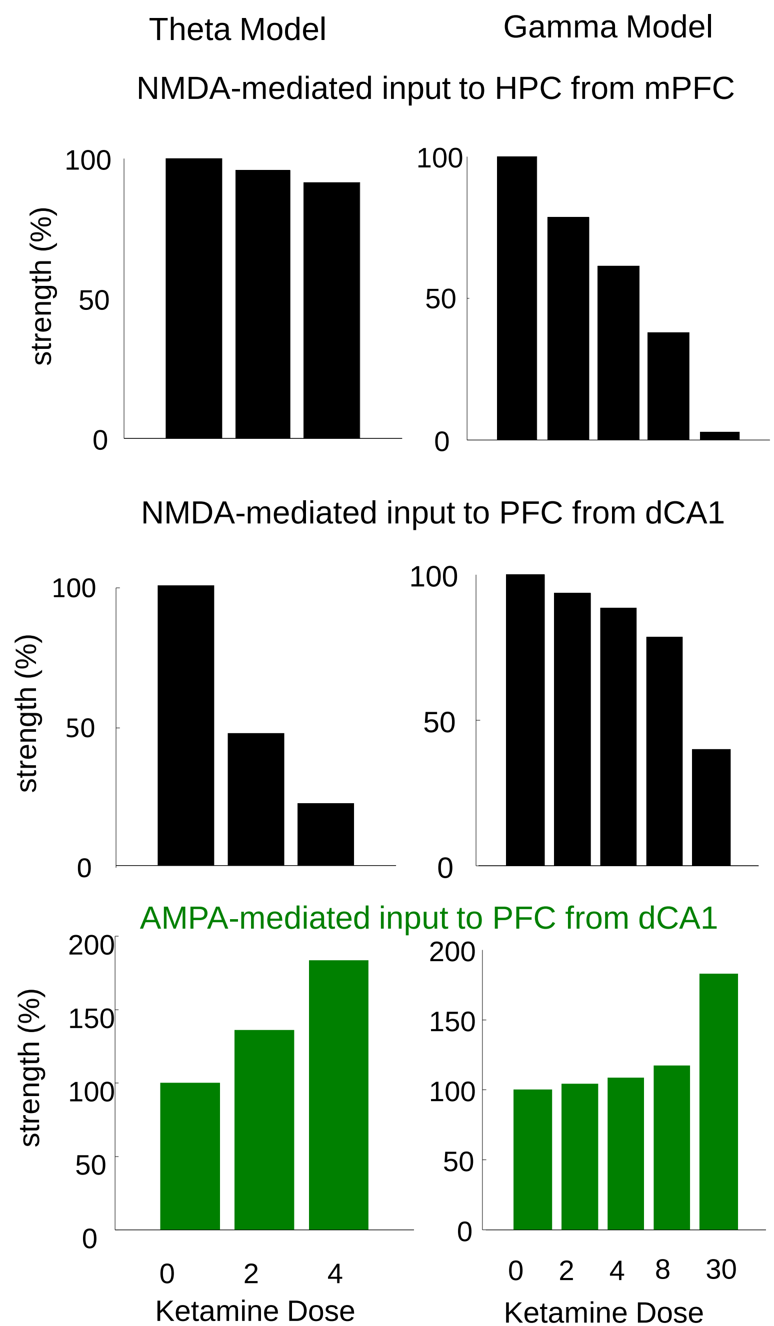


Model Fits


Gamma in dCA1
Gamma in dCA1-mPFC
Gamma in mPFC
Theta in dCA1
Theta in dCA1-mPFC
Theta in mPFC
Spectral density (modulus)
frequency (Hz)
predicted: saline vehicle
observed: saline vehicle
predicted: 2 mgkg^{-1}
observed: 2 mgkg^{-1}
predicted: 4 mgkg^{-1}
observed: 4 mgkg^{-1}
observed: 8 mgkg^{-1}
observed: 8 mgkg^{-1}
predicted: 30 mgkg^{-1}
observed: 30 mgkg^{-1}

Extrinsic Connectivity Changes under Ketamine



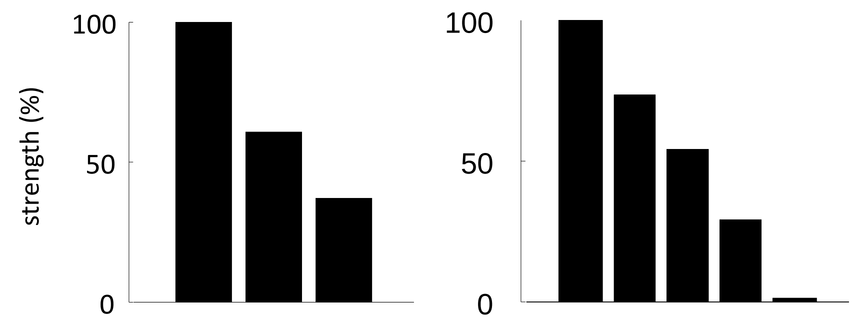


Intrinsic Connectivity Changes under Ketamine

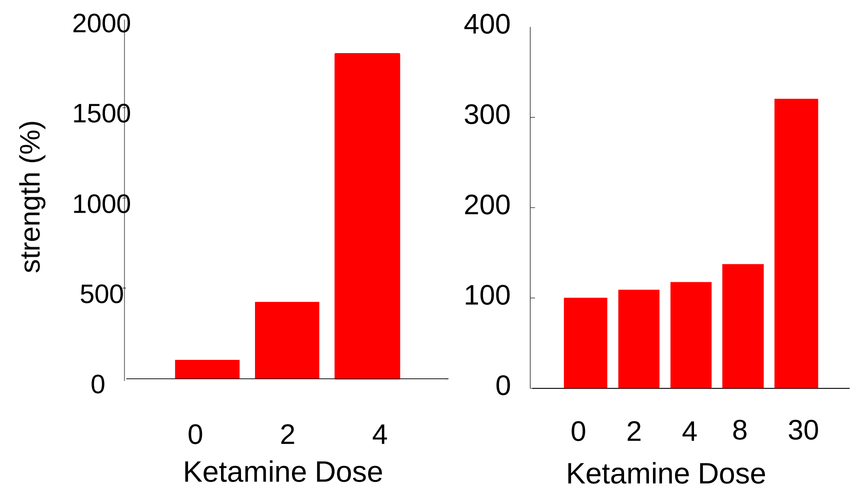
Confirmed by MUA in CA1:
High but uncorrelated unit activity

Theta Model   Gamma Model

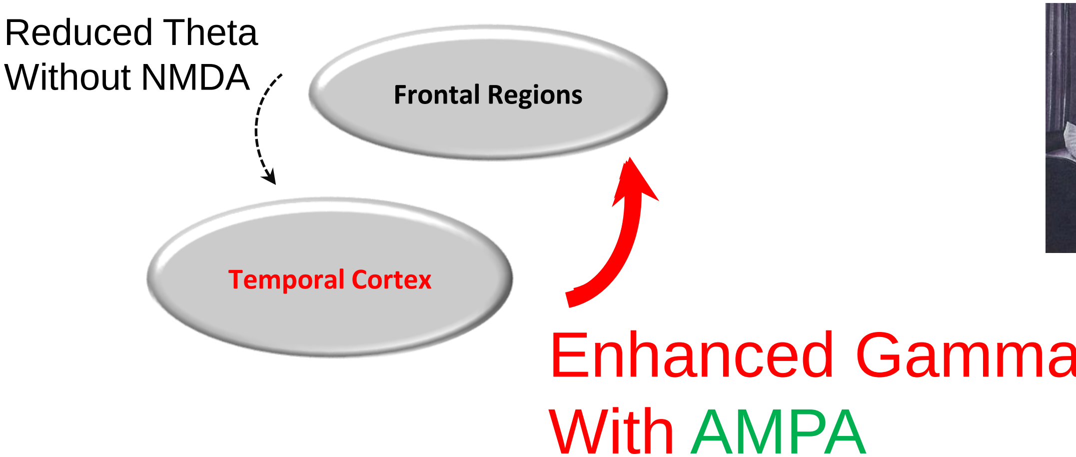
NMDA-mediated excitation of hippocampal Interneurons



1/Signal to Noise Ratio in the Hippocampus



Losing Control Under Ketamine



- Reduced Cortico-Limbic Control mediated by NMDA
- Enhanced Limbic-Cortico Drive via AMPA:
- Runaway bottom-up sensory-driven processing : disorganised cognition & environmental interactions
- Large difference in intrinsic processing: early dopaminergic D2 problem in schizophrenia?

Why these models?

Computational Psychiatry & DCMs for Electrophysiology

Why I think these models are useful:

Models of Synaptic Activity using invasive and non-invasive electrophysiological time series from large neuronal populations.

Useful models of pharmacological effects – where are the drug's effects most prominent, are other receptors affected?

Useful link to predictive coding: top-down vs. bottom up and their belief mappings.

Potential to scale to clinical settings: could patients be stratified based on endogenous connectivity profiles?

Computational Psychiatry & DCMs for Electrophysiology

Why these models can be more than mildly irritating :

Local Minima (not the model’s fault)

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Thank You

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