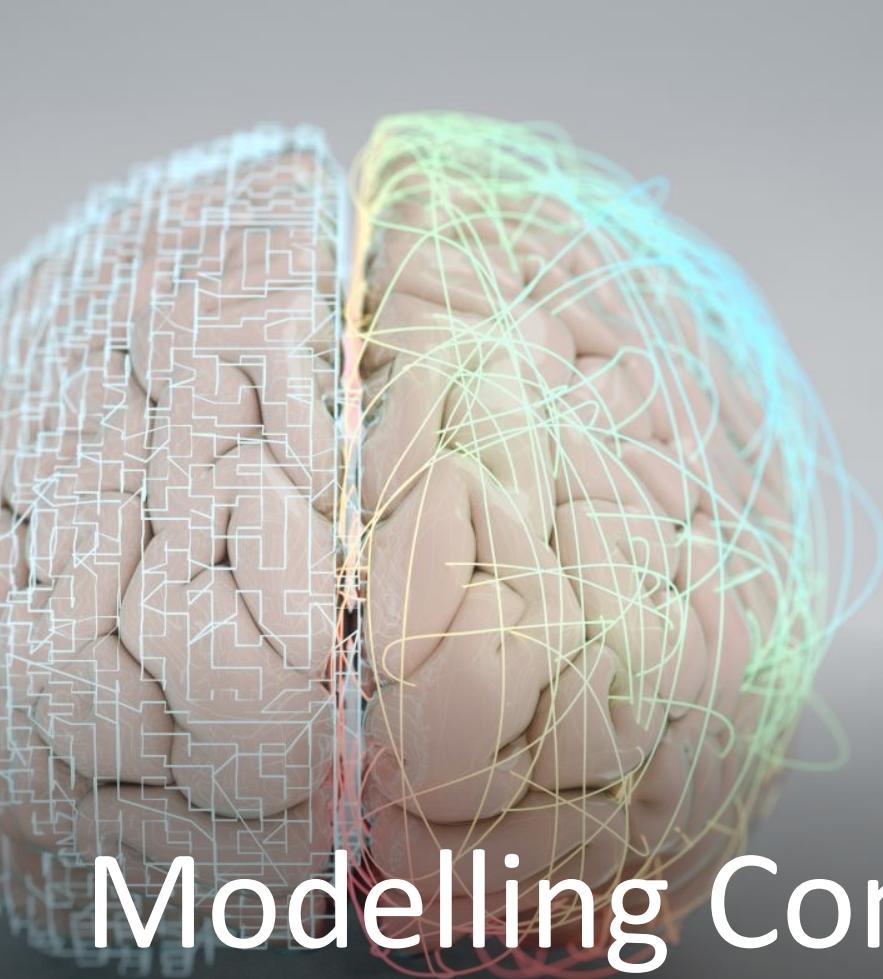




MODELING CONNECTIVITY: DCM for EEG

Professor Rosalyn Moran
Department of Neuroimaging,
IOPPN,
King's Institute for Artificial Intelligence
King's College London

15/09/2022, ETH Zurich
Computational Psychiatry Course 2022

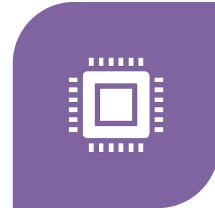
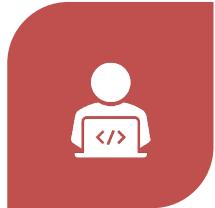


Modelling Connectivity in the Brain

“Normative models describe how an optimal system would work given the goals. They describe ‘what’ the brain is trying to do.”

“Process models are about the mechanisms, thus describing ‘how’ it is done.”

Normative to Process Models



DAYAN, HINTON, NEAL &
ZUMEL (1995) THE
HELMHOLTZ MACHINE

MONTAGUE, DAYAN,
SEJNOWSKI (1996)
DOPAMINE SYSTEMS
SIGNAL REWARD
PREDICTION ERRORS

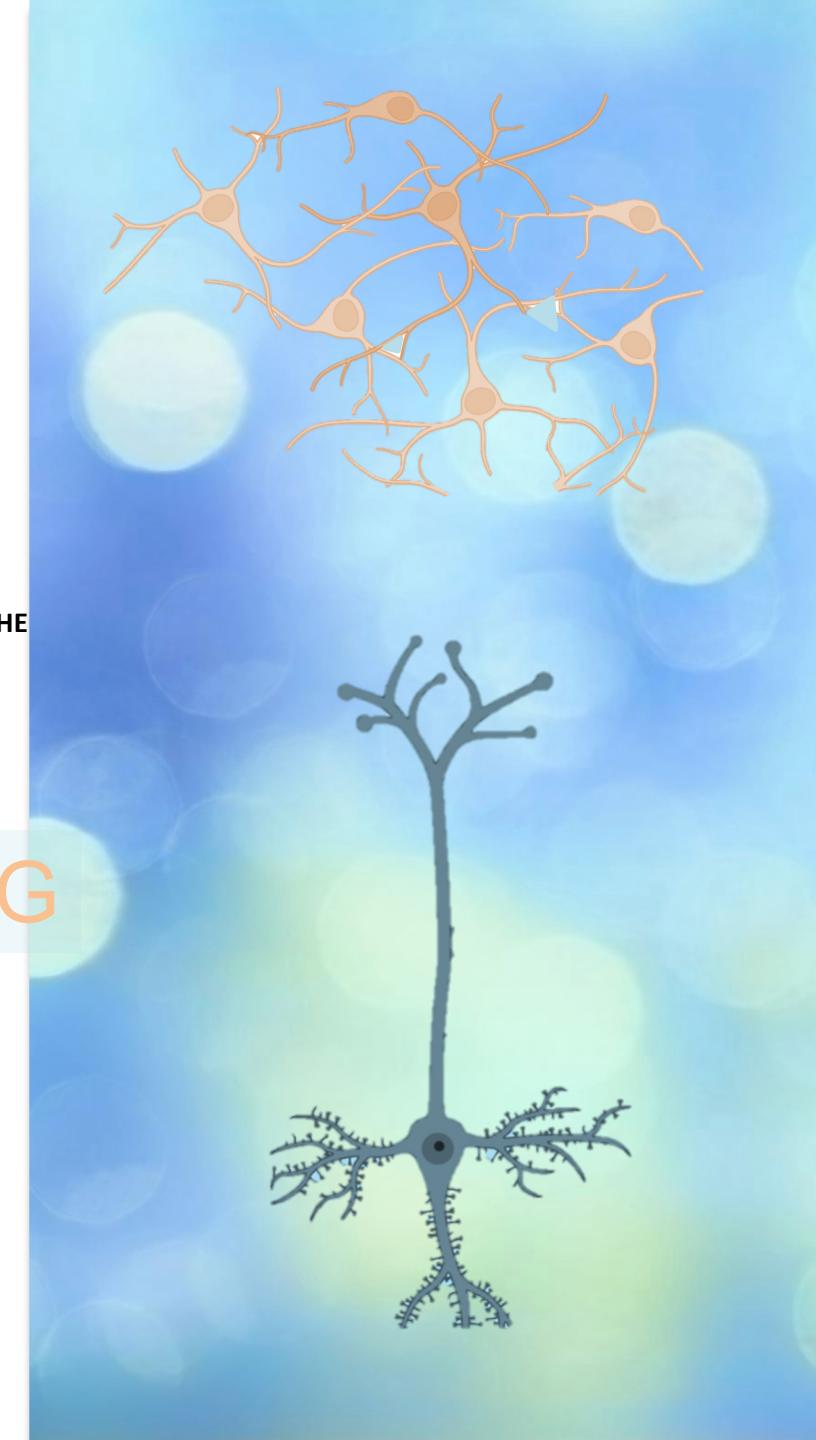
RAO & BALLARD (1999)
PREDICTIVE CODING IN THE
VISUAL CORTEX

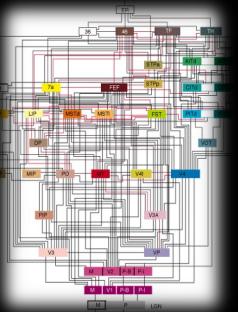


FRISTON (2010) **THE FREE-**
ENERGY PRINCIPLE: A
UNIFIED BRAIN THEORY?



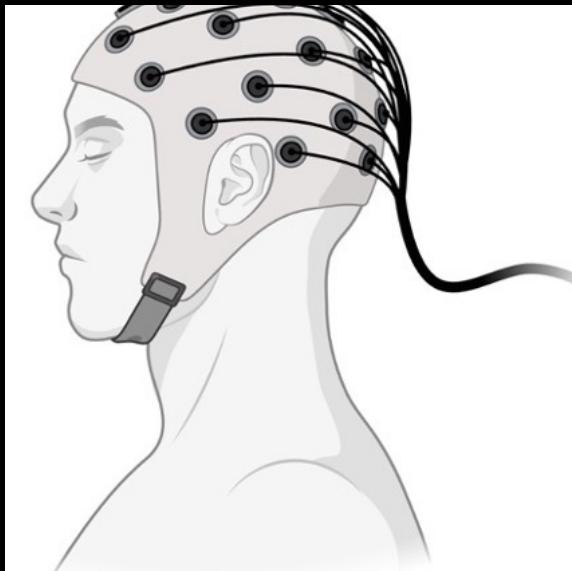
MORAN ET AL. (2012)
NEUROMODULATORS IN
PREDICTIVE CODING





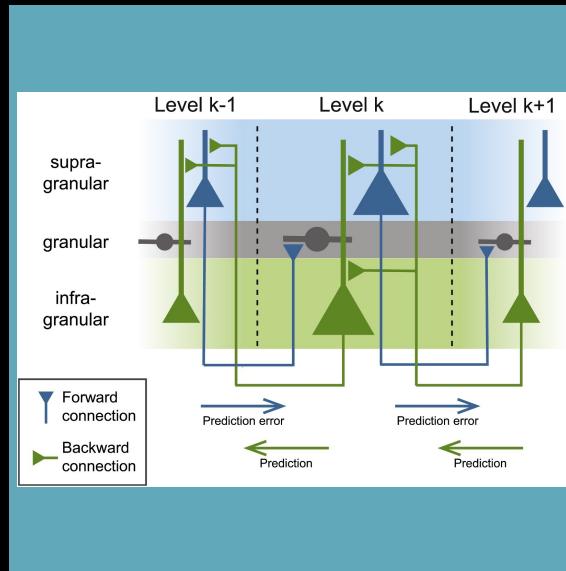
DCM for EEG

From Data to Cellular Connectivity, through Inference upon a Generative Model



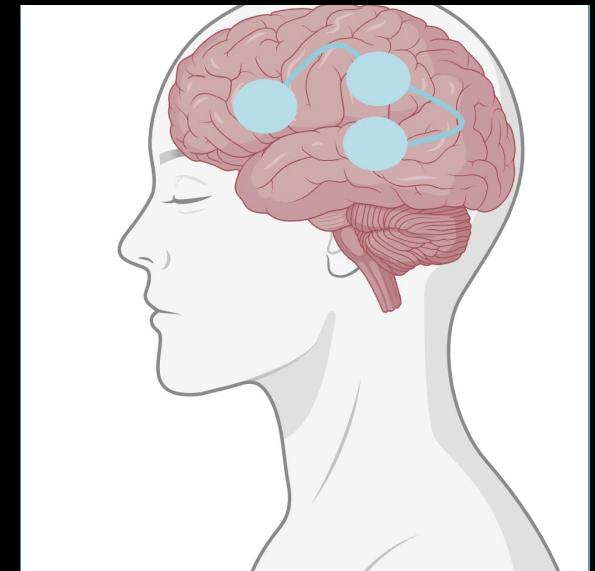
Scalp Data (EEG) or MEG or Local Field Potentials

Typically Analysed in Sensor Space



Predictive Coding Hierarchy

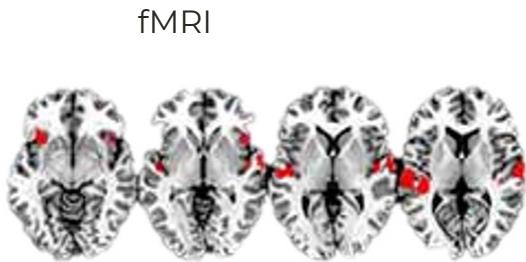
(Stephan et al. 2019, Bastos et al. 2011)



Network Analysis

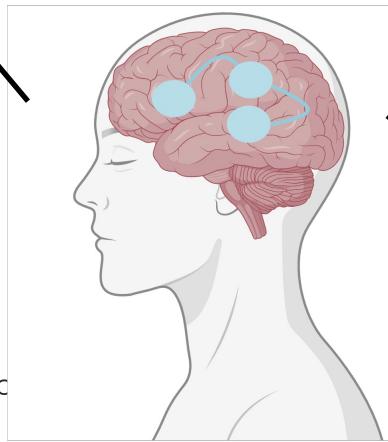
In Support of Theoretical Models (Or Not!)

DCM for EEG



Forward Model (Hemodynamic Model)
Regions of Interest

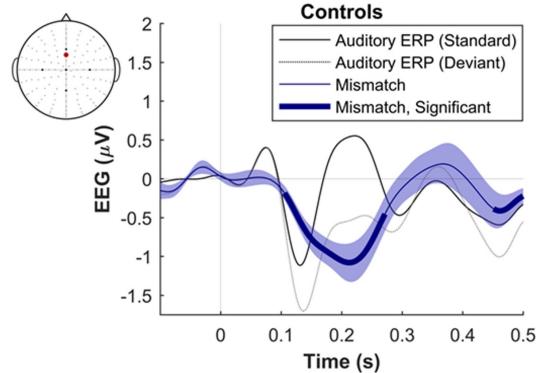
An all-purpose Tailor Expansion, 'x'
that can be extended with E-I components



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

Neural State Equations

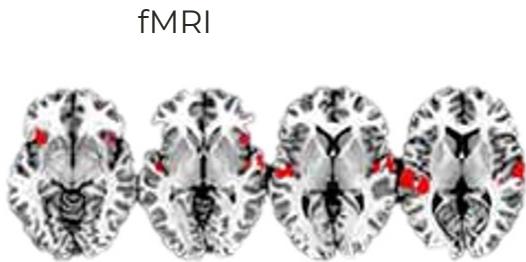
EEG/MEG EPRs/ERFs



Forward Model (Boundary Element Model) from Assumed MNI Coordinates

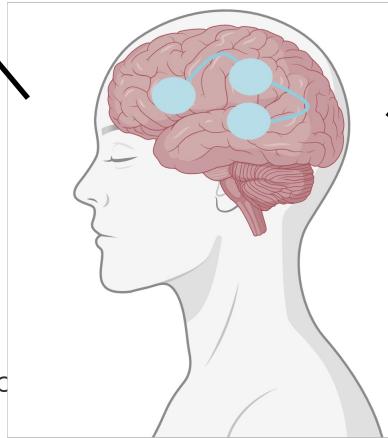
Detailed Neuronal Model, 'x' including Distinct Cell Types with Distinct Forward and Backward Afferents

DCM for EEG



Forward Model (Hemodynamic Model)
Regions of Interest

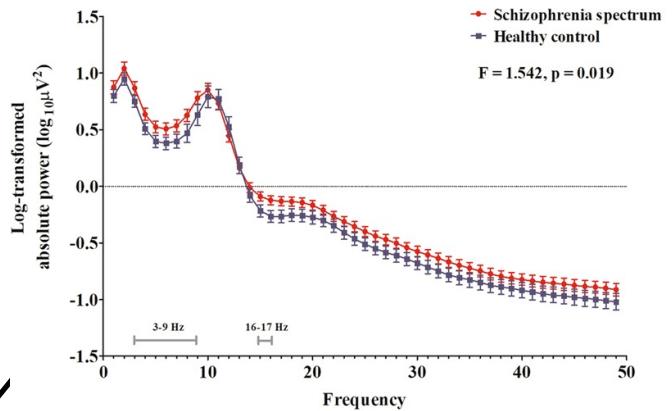
An all-purpose Tailor Expansion, 'x'
that can be extended with E-I components



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

Neural State Equations

EEG/MEG: Spectra



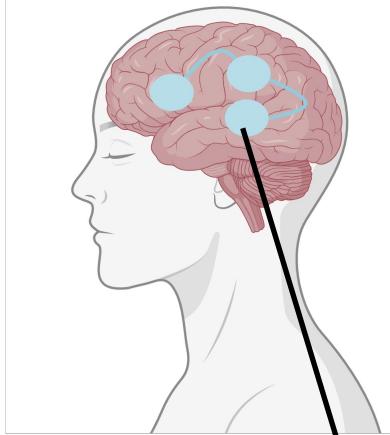
Kim et al, 2021, Thalamocortical dysrhythmia in patients with schizophrenia spectrum disorder and individuals at clinical high risk for psychosis

Forward Model (Boundary Element Model) from Assumed MNI Coordinates

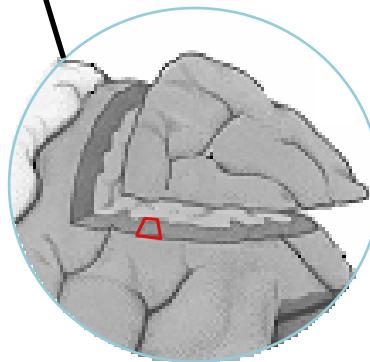
Detailed Neuronal Model, 'x' including Distinct Cell Types with Distinct Forward and Backward Afferents

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

Neural State Equations



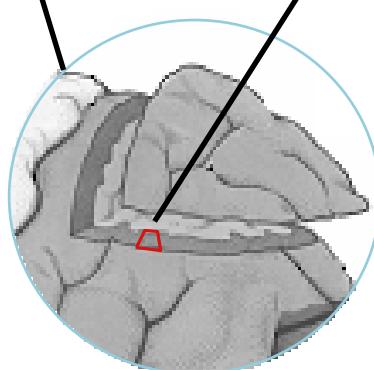
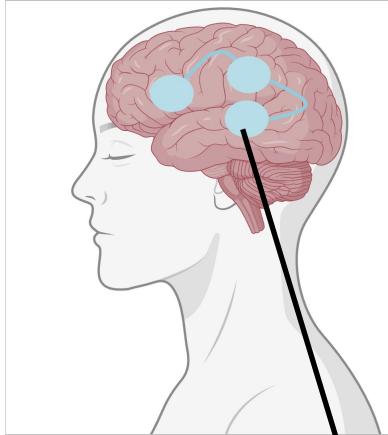
Meso Scale Modelling



Macroscopic Measurement

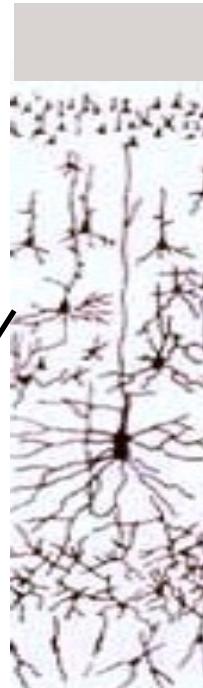
$$\frac{dx}{dt} = F(x, u, \theta)$$

Neural State Equations

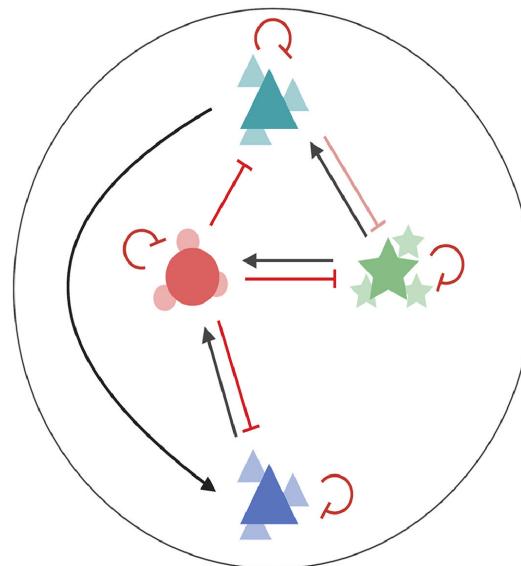


Macroscopic Measurement

Meso Scale Modelling



Laminar Architecture

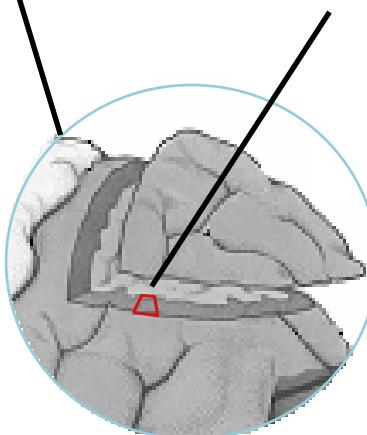
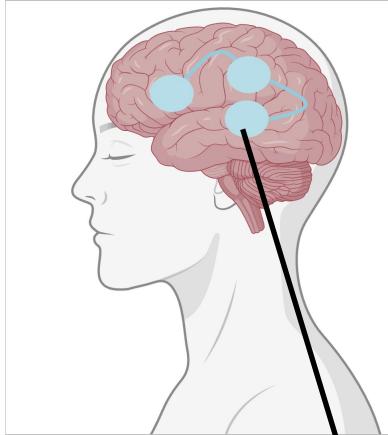


Mesoscopic Model (aggregated)

- AMPA and NMDAR
- GABA
- inhibitory interneuron
- ★ spiny stellate cell
- ▲ superficial pyramidal cell
- ▲ deep pyramidal cell

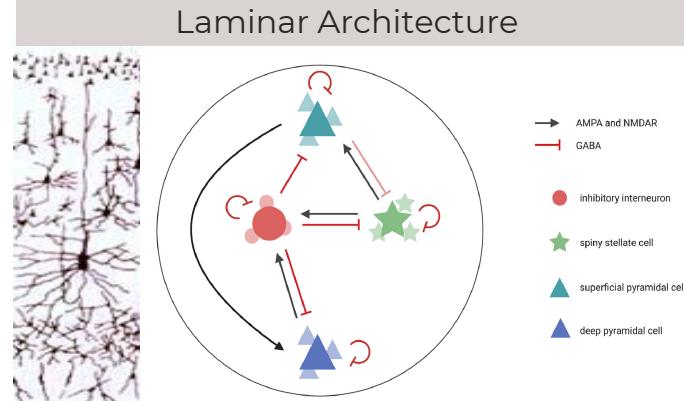
$$\frac{dx}{dt} = F(x, u, \theta)$$

Neural State Equations



Macroscopic Measurement

Meso Scale Modelling

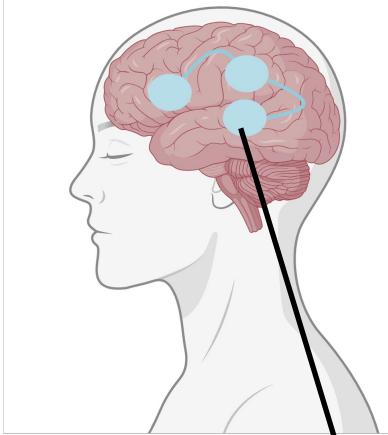


Mesoscopic Model (aggregated)

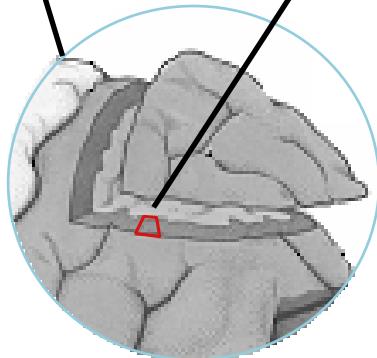
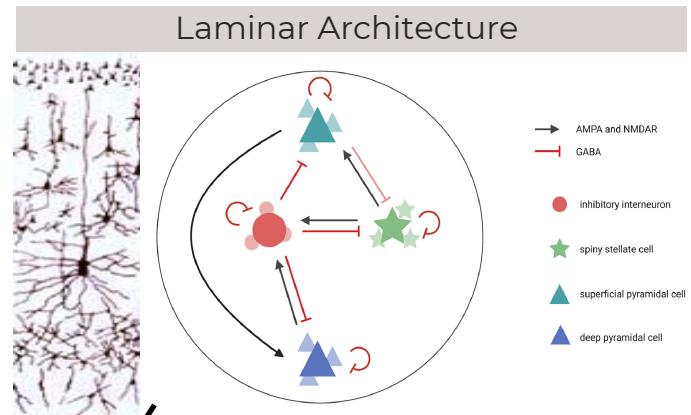
The state of a neuron comprises a number of attributes, membrane potentials, etc. Modelling these states can become intractable. *Mean field approximations* summarise the states in terms of their ensemble density. **Neural mass models** consider only point densities and describe the interaction of **the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

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

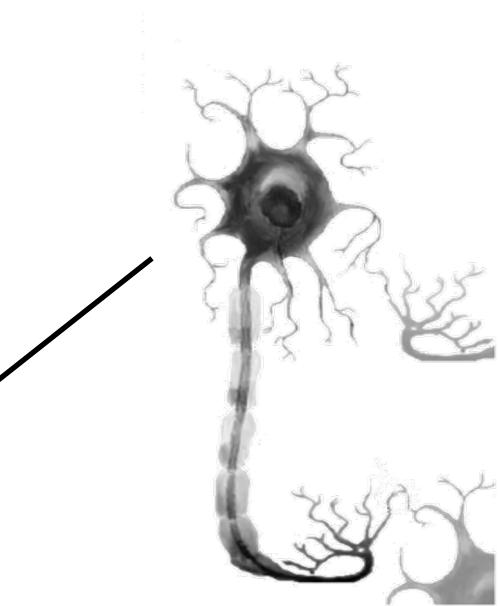
Neural State Equations



Meso Scale Modelling



Macroscopic Measurement

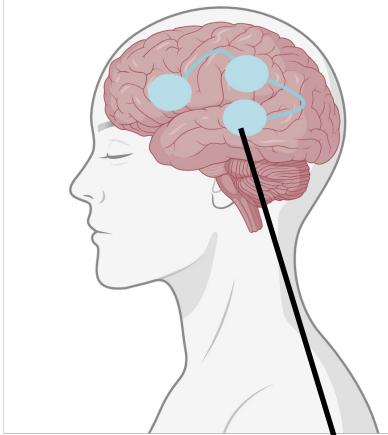


Microscopic
Dynamics (distributed)

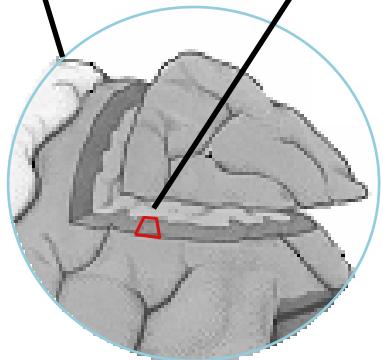
Mesoscopic Model (aggregated)

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

Neural State Equations

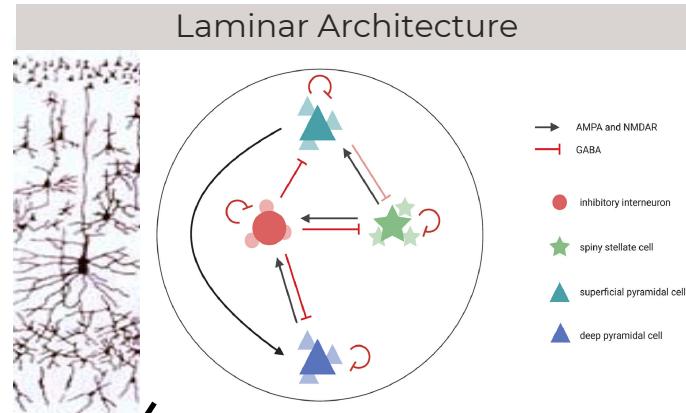


Meso Scale Modelling

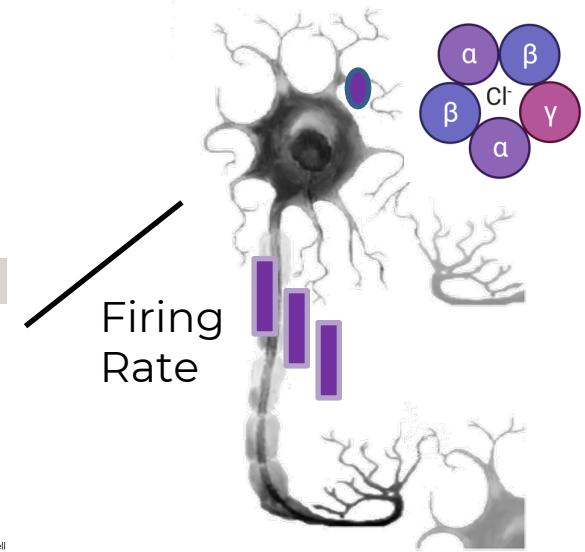


Mesoscopic Model (aggregated)

Macroscopic Measurement



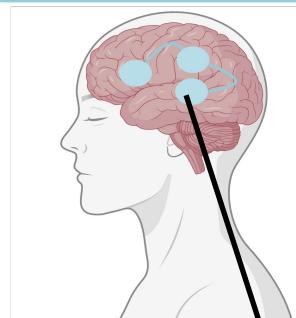
Receptor Responses



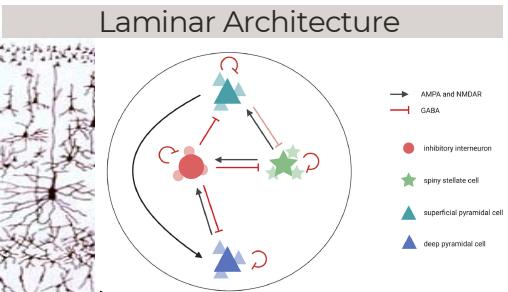
Microscopic
Dynamics (distributed)

Meso Scale Modelling

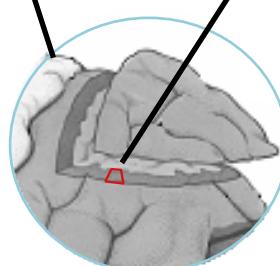
Neural State
Equations



$$\frac{dV_{sp_ii}}{dt} = F(V, g, u, \theta)$$
$$\frac{dV_{sp_pyr}}{dt} = F(V, g, u, \theta)$$
$$\frac{dV_{ss_layerIV}}{dt} = F(V, g, u, \theta)$$
$$\frac{dV_{dp_pyr}}{dt} = F(V, g, u, \theta)$$

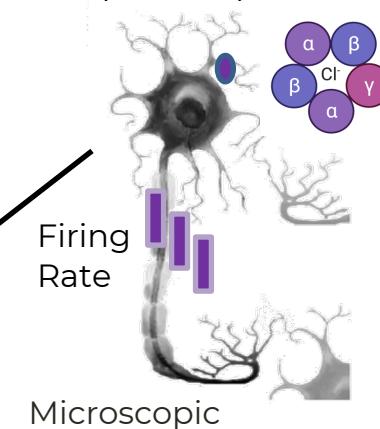


Macroscopic Measurement



Mesoscopic Model (aggregated)

Receptor Responses



Firing
Rate

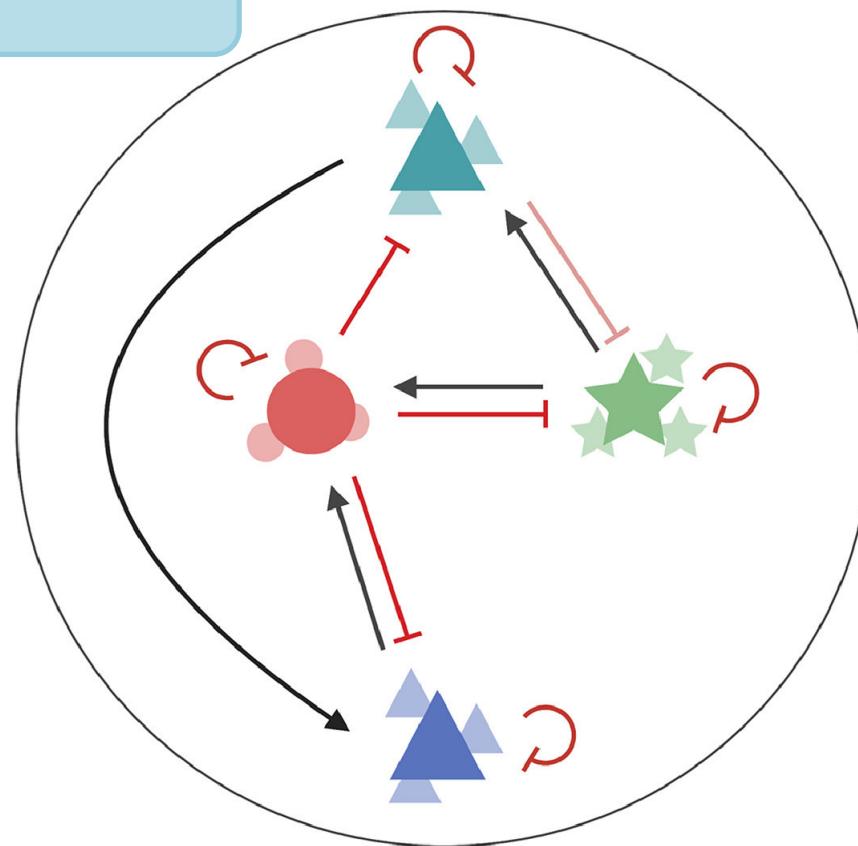
Microscopic

Dynamics (distributed)

Conductance Based Models

$$\frac{dV_{sp_pyr}}{dt} = F(V, g, u, \theta)$$

Neural State Equations



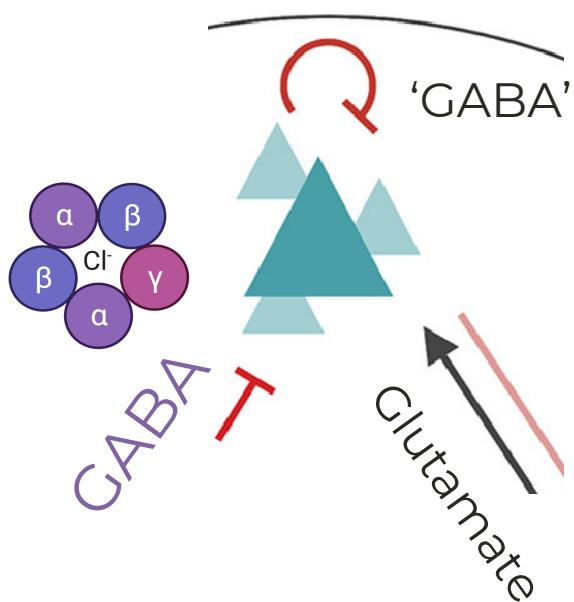
- AMPA and NMDAR
- GABA
- inhibitory interneuron
- ★ spiny stellate cell
- ▲ superficial pyramidal cell
- ▲ deep pyramidal cell

Conductance Based Models

$$\frac{dV_{sp_pyr}}{dt} = F(V, g, u, \theta)$$

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

Neural State Equations



Ohm's Law $V = IR$

Ohm's Law for A Capacitor
Capacitance x Rate of Change of Voltage = Current

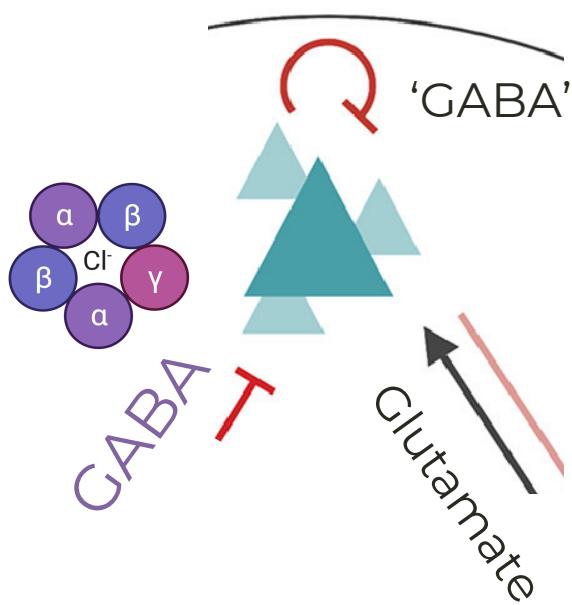
$$C\dot{V} = I$$

Conductance Based Models

$$\frac{dV_{sp_pyr}}{dt} = F(V, g, u, \theta)$$

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

Neural State Equations



$$V = IR$$

Ohm's Law

Conductance (Siemen's) = 1/Resistance (Ohms)

$$\frac{1}{R}V = I \quad gV = I$$

Ohm's Law for A Capacitor
Capacitance x Rate of Change of Voltage = Current

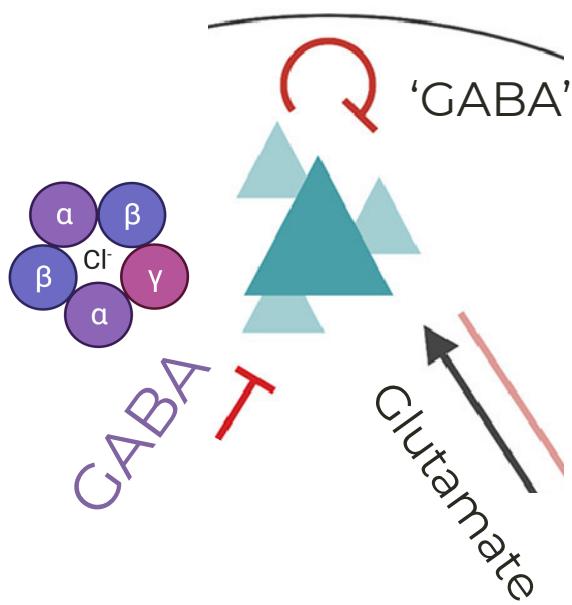
$$CV' = I$$

Conductance Based Models

$$\frac{dV_{sp_pyr}}{dt} = F(V, g, u, \theta)$$

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

Neural State Equations



$$V = IR$$

Ohm's Law

Conductance (Siemen's) = 1/Resistance (Ohms)

$$\frac{1}{R}V = I \quad gV = I$$

Capacitance x Rate of Change of Voltage =
= Conductance x Voltage across the membrane

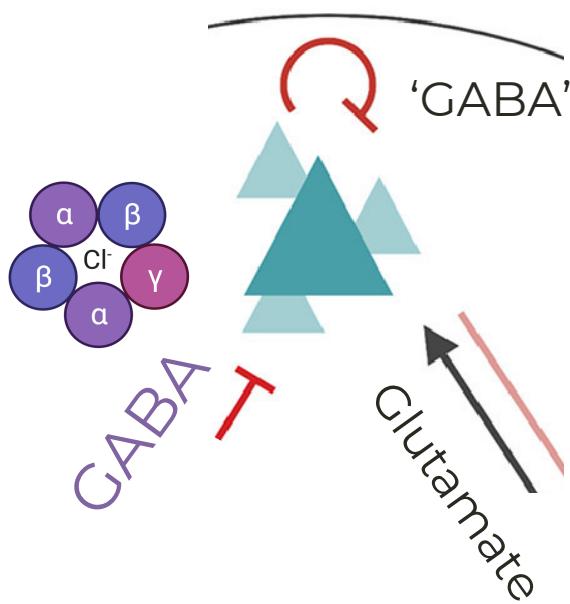
$$C\dot{V} = gV$$

Reversal Potentials

$$C \frac{dV_{-sp-pyr}}{dt}$$

$$C\dot{V} = gV$$

Neural State Equations

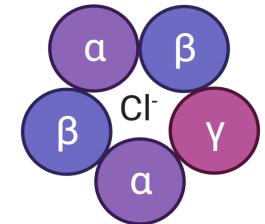


However, the Neuron is not Electrically Neutral, but repels ions with a reversal potential
Correct for this:

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

$$V_{rev_cl} = -65mV$$

*Model Parameter (low variance)

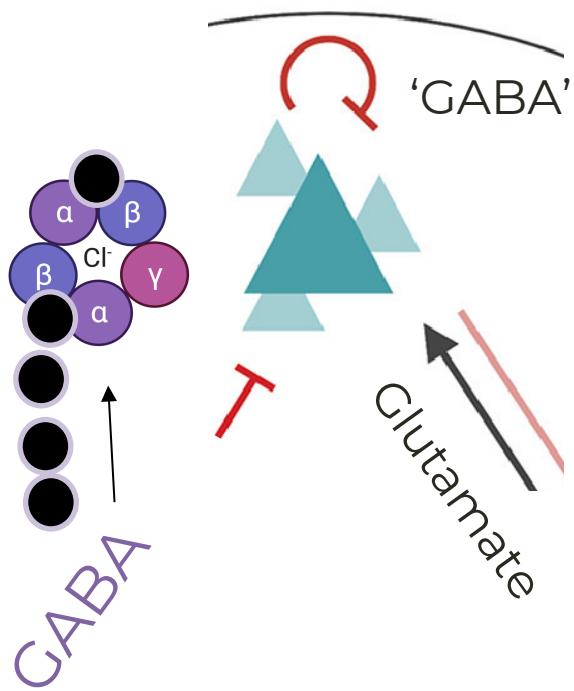


Dynamic Conductance I

$$C \frac{dV_{sp-pyr}}{dt}$$

$$C\dot{V} = gV$$

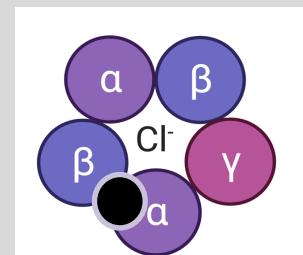
Neural State Equations



Once bound to GABA, the receptor changes conformation within the membrane, opening the pore in order to allow chloride anions to enter:

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

$$\dot{g} = \frac{1}{\tau_{GABAa}}(\gamma - g)$$



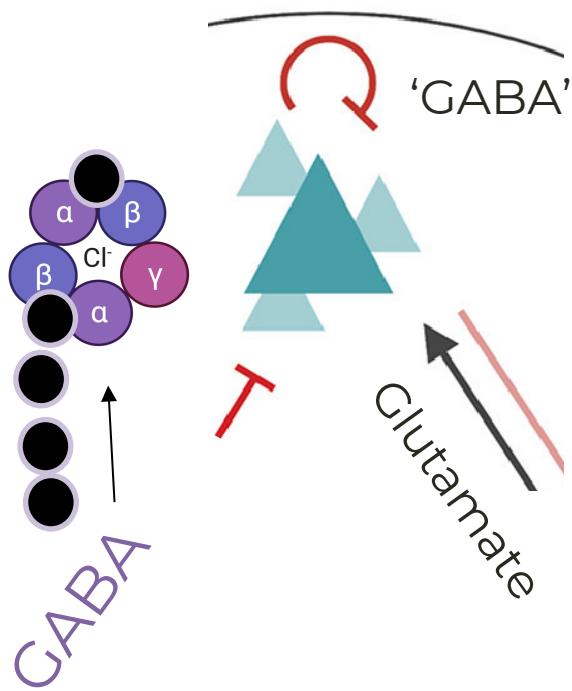
However, they open with a certain time constant (or rate $\frac{1}{\tau}$, and are limited by the number of channels available (they autocorrect) g

Dynamic Conductance II

$$C \frac{dV_{sp-pyr}}{dt}$$

$$C\dot{V} = gV$$

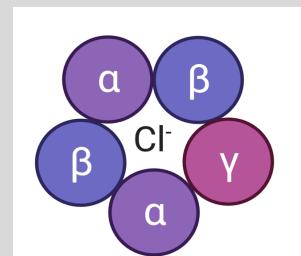
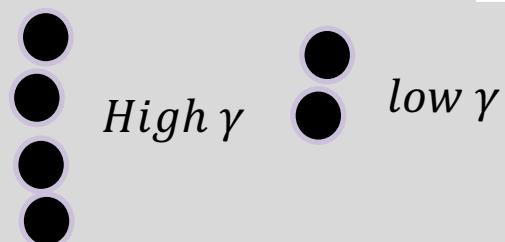
Neural State Equations



An effective synapse will have lots of GABA and high connectivity. An ineffective synapse will have less GABA and lower connectivity. γ represent connectivity

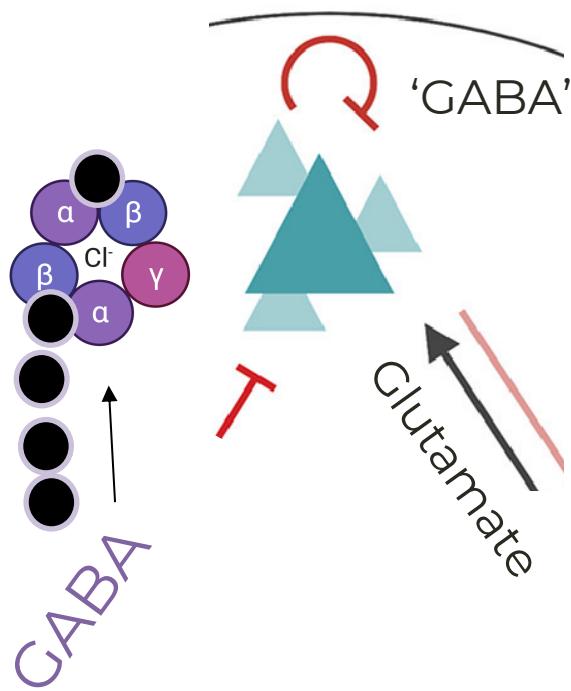
$$C\dot{V} = g(V - V_{rev})$$

$$\dot{g} = \frac{1}{\tau_{GABAa}}(\gamma - g)$$



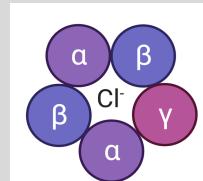
And a few other synapses

Neural State Equations



$$C\dot{V} = g_{Cl}(V - V_{rev_{Cl}}) + g_{NA}(V - V_{rev_{NA}}) + g_{CA}f_{mg}(V - V_{rev_{CA}})$$

$$\dot{g_{Cl}} = \frac{1}{\tau_{GABAa}} (\gamma_1 - g_{Cl})$$



$$\dot{g_{NA}} = \frac{1}{\tau_{AMPA}} (\gamma_2 - g_{NA})$$

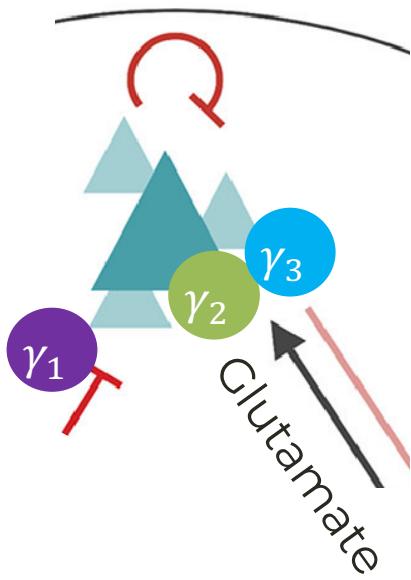


$$\dot{g_{CA}} = \frac{1}{\tau_{NMDA}} (\gamma_3 - g_{CA})$$



Parameters with Well Studied Prior Values

Neural State Equations

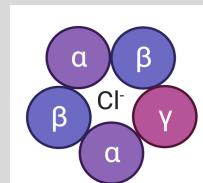


$$C\dot{V} = g_{Cl}(V - V_{rev_Cl}) + g_{NA}(V - V_{rev_{NA}}) + g_{CA}f_{mg}(V - V_{rev_{CA}})$$

$$\dot{g_{Cl}} = \frac{1}{\tau_{GABAa}} (\gamma_1 - g_{Cl})$$

$$\dot{g_{NA}} = \frac{1}{\tau_{AMPA}} (\gamma_2 - g_{NA})$$

$$\dot{g_{CA}} = \frac{1}{\tau_{NMDA}} (\gamma_3 - g_{CA})$$



Voltage from the Macroscopic Measurement

Neural State Equations

And build into layers ... and then add Extrinsic Connections !

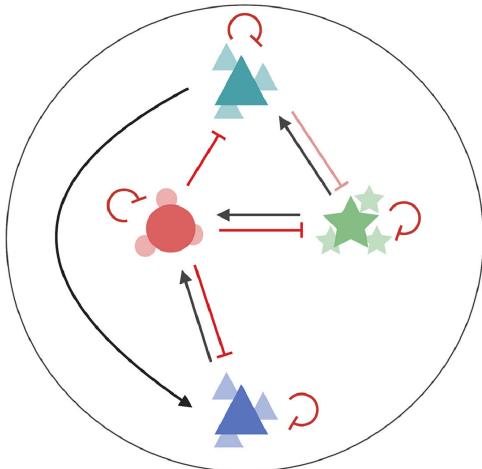
Output is $V_{dp} + V_{sp}$

$$C\dot{V}_{dp} = g_{Cl}(V_{dp} - V_{rev_{Cl}}) + g_{NA}(V_{dp} - V_{rev_{NA}}) + g_{CA}f_{mg}(V_{dp} - V_{rev_{CA}})$$

$$C\dot{V}_{sp} = g_{Cl}(V_{sp} - V_{rev_{Cl}}) + g_{NA}(V_{sp} - V_{rev_{NA}}) + g_{CA}f_{mg}(V_{sp} - V_{rev_{CA}})$$

$$C\dot{V}_{ss} = g_{Cl}(V_{ss} - V_{rev_{Cl}}) + g_{NA}(V_{ss} - V_{rev_{NA}}) + g_{CA}f_{mg}(V_{ss} - V_{rev_{CA}})$$

$$C\dot{V}_{ii} = g_{Cl}(V_{ii} - V_{rev_{Cl}}) + g_{NA}(V_{ii} - V_{rev_{NA}}) + g_{CA}f_{mg}(V_{ii} - V_{rev_{CA}})$$

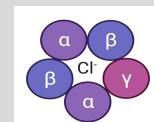


x4

$$\dot{g_{Cl}} = \frac{1}{\tau_{GABAa}} (\gamma_1 - g_{Cl})$$

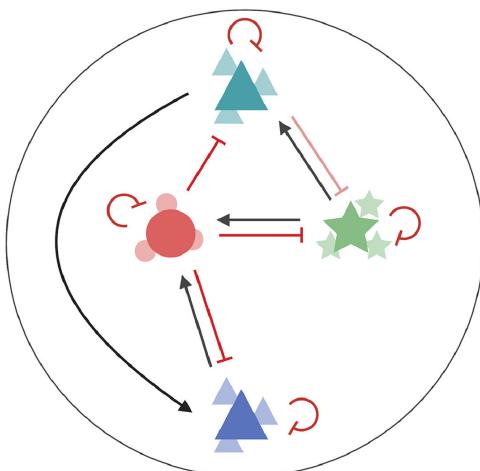
$$\dot{g_{NA}} = \frac{1}{\tau_{AMPA}} (\gamma_2 - g_{NA})$$

$$\dot{g_{CA}} = \frac{1}{\tau_{NMDA}} (\gamma_3 - g_{CA})$$

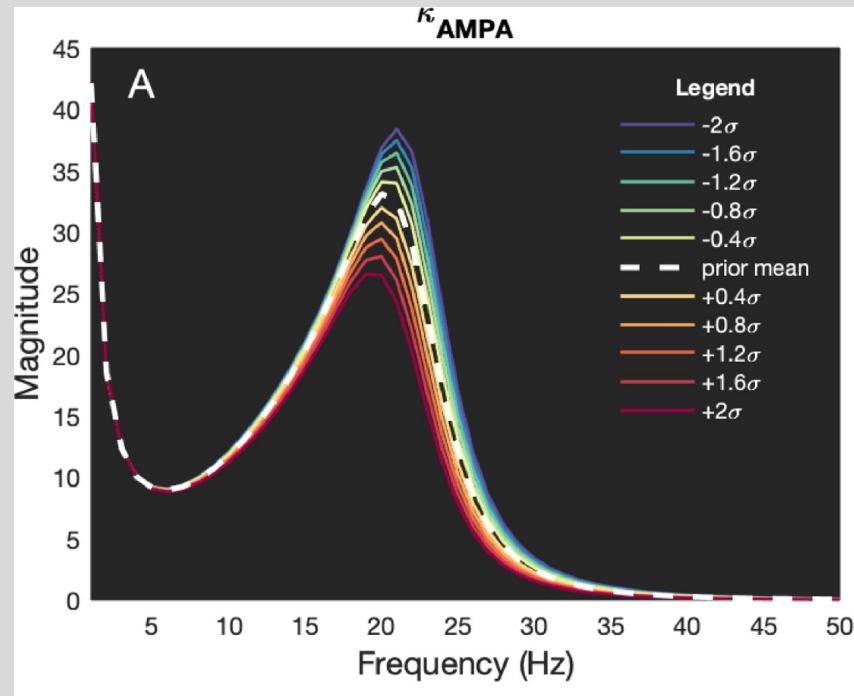


Voltage from the Macroscopic Measurement

Neural State Equations



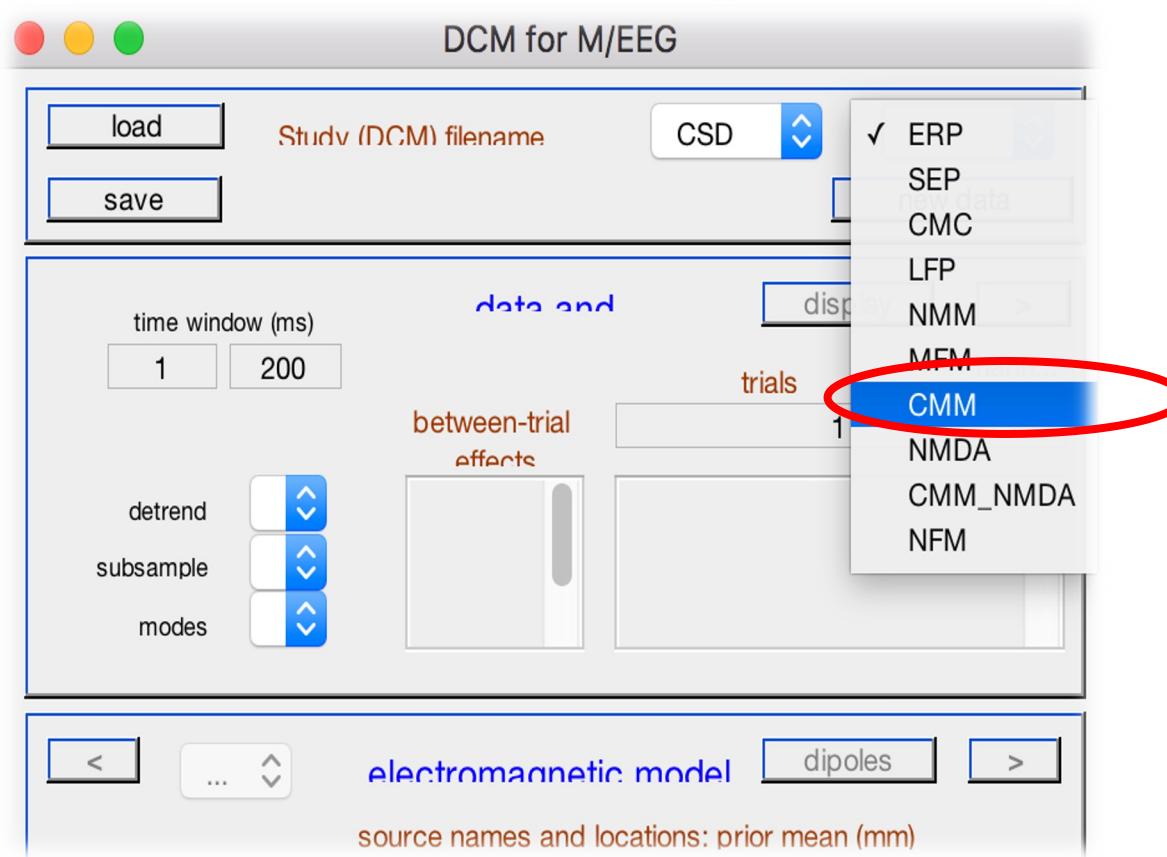
Effect of AMPA Time Constant (Pereira et al, 2021,
Conductance-based dynamic causal modeling: A
mathematical review of its application to cross-power spectral
densities)



$$\dot{g_{NA}} = \frac{1}{\tau_{AMPA}} (\gamma_2 - g_{NA})$$



Selecting Conductance Based Models



DCM for EEG, Examples

Connectivity changes underlying
spectral EEG changes during propofol-induced loss of
consciousness.

M. Boly et al. Journal of Neuroscience, 2012

Connectivity changes underlying
spectral EEG changes during propofol-induced loss of
consciousness.

Wake

Mild Sedation: Responsive to
command

Deep Sedation: Loss of Consciousness



Connectivity changes underlying
spectral EEG changes during propofol-induced loss of
consciousness.

Wake

Mild Sedation: Responsive to
command

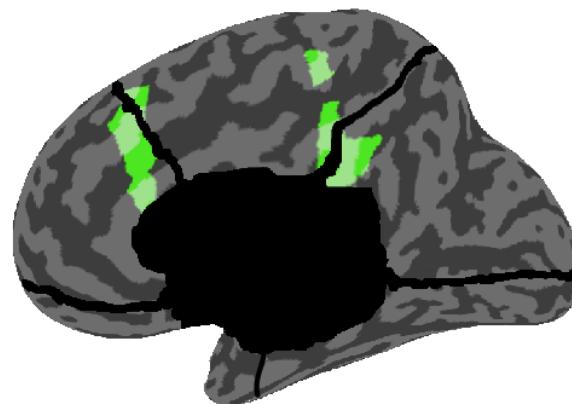
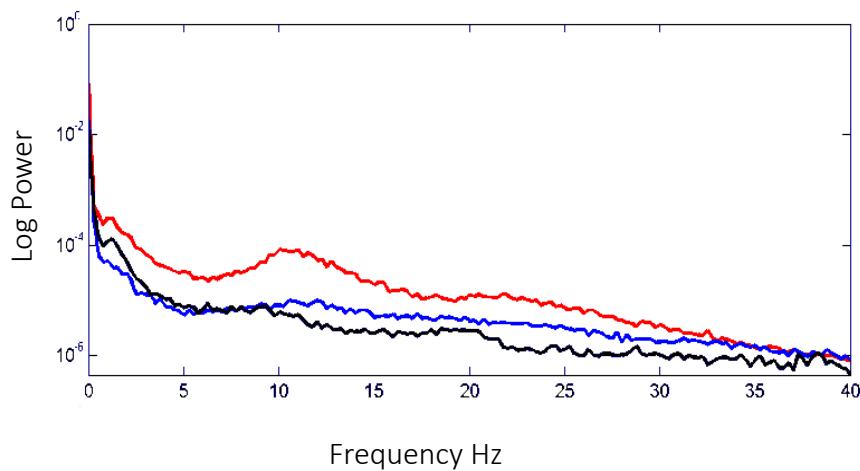
Deep Sedation: Loss of Consciousness



Differential Source Activity

Connectivity changes underlying
spectral EEG changes during propofol-induced loss of
consciousness.

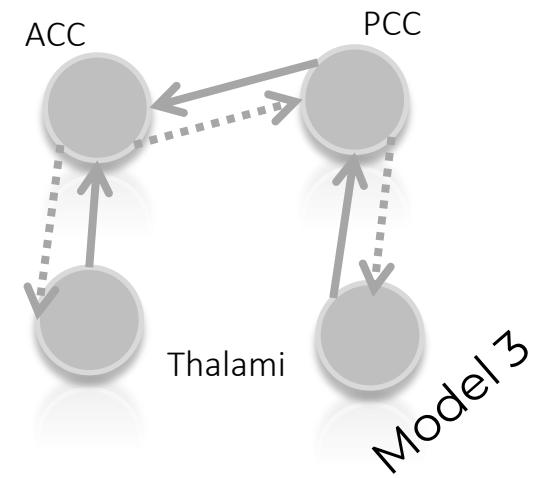
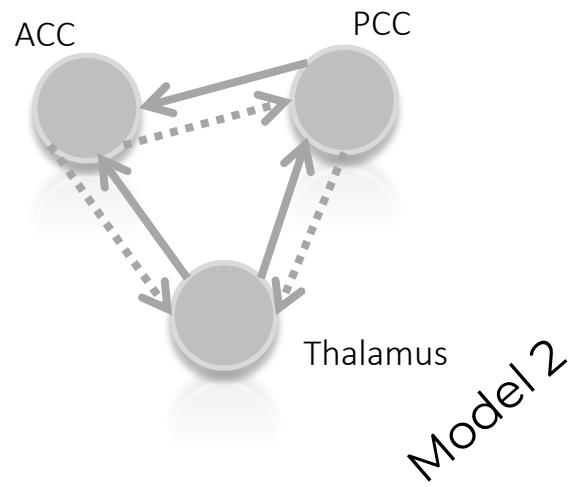
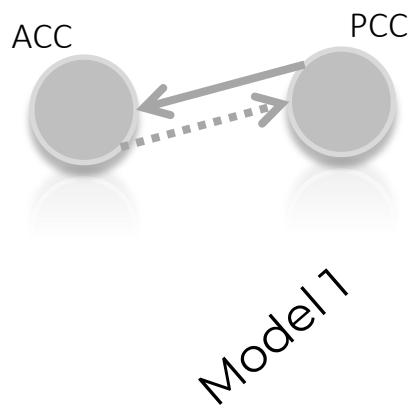
Wake
Mild Sedation: Responsive to
command
Deep Sedation: Loss of Consciousness



Differential Source Activity

Connectivity changes underlying
spectral EEG changes during propofol-induced loss of
consciousness.

Wake
Mild Sedation: Responsive to
command
Deep Sedation: Loss of Consciousness



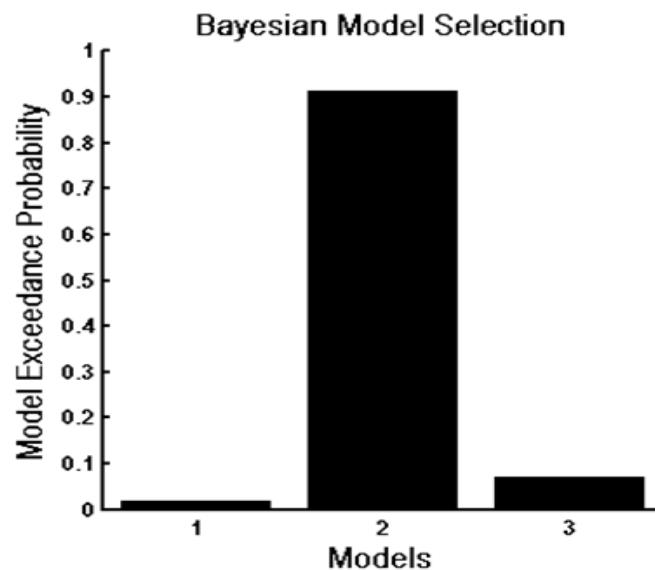
Bayesian Model Comparison

Connectivity changes underlying
spectral EEG changes during propofol-induced loss of
consciousness.

Wake

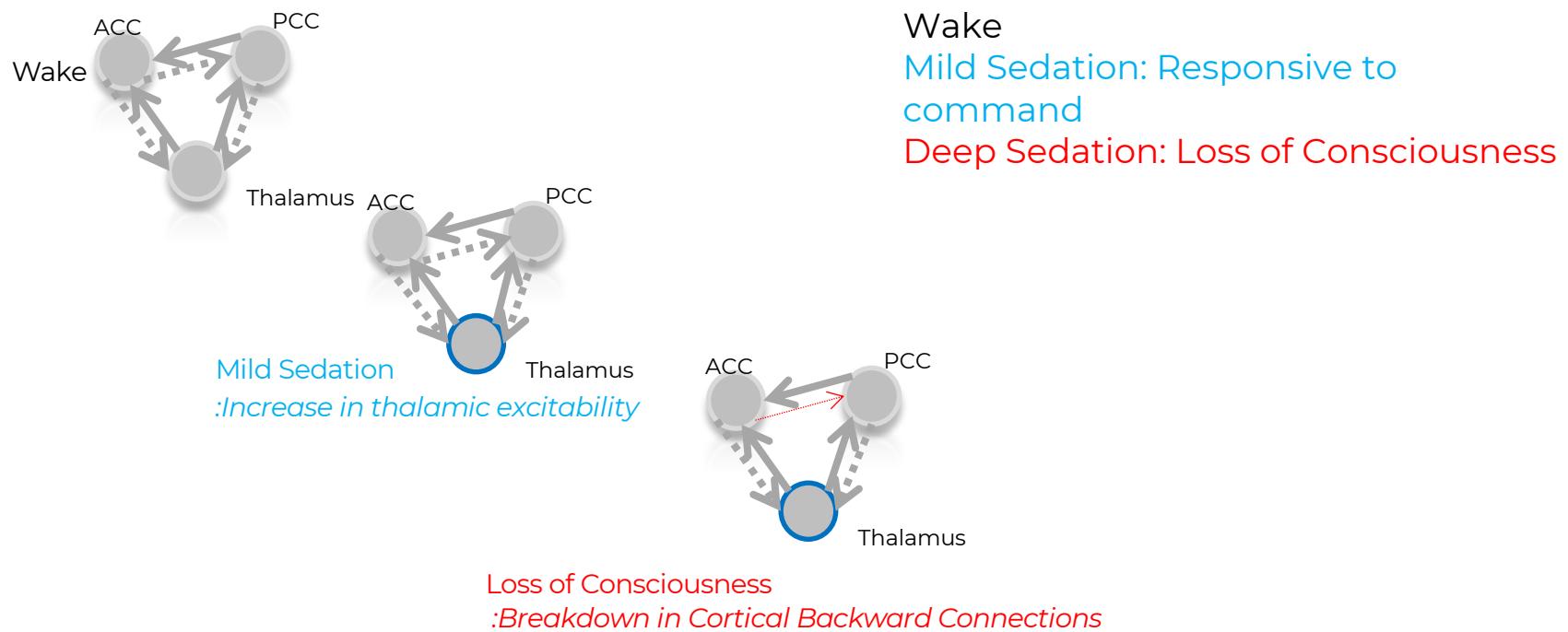
Mild Sedation: Responsive to
command

Deep Sedation: Loss of Consciousness



Bayesian Model Comparison

Connectivity changes underlying spectral EEG changes during propofol-induced loss of consciousness.



Model Parameters

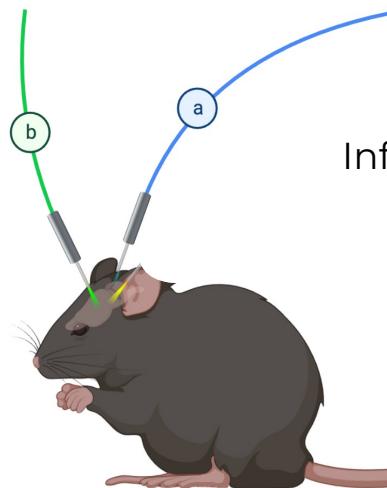
Ketamine and Local Field Potentials

More than just an NMDA Antagonist?

Moran et al, 2014, Neuropsychopharmacology,
Losing Control Under Ketamine: Suppressed Cortico-Hippocampal Drive Following
Acute Ketamine in Rats

Ketamine and Local Field Potentials

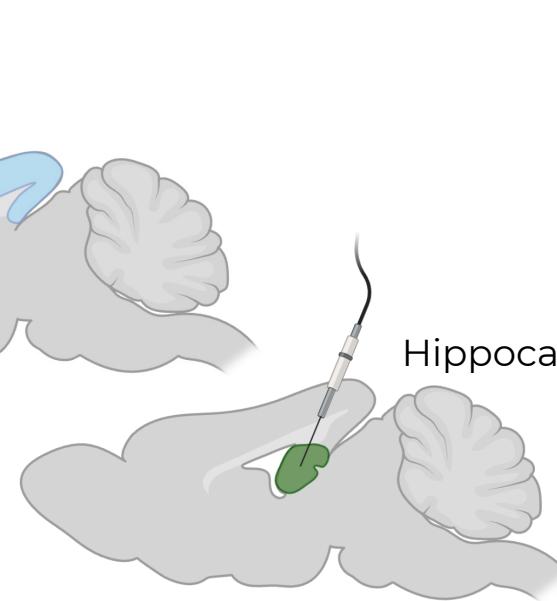
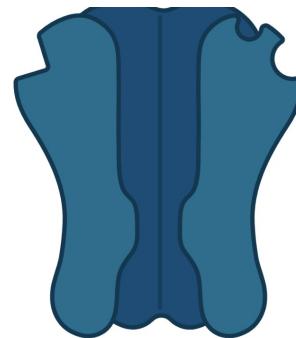
More than just an NMDA Antagonist?



5 Minutes of
'Steady State' Recordings
In freely moving animals

Infralimbic Cortex

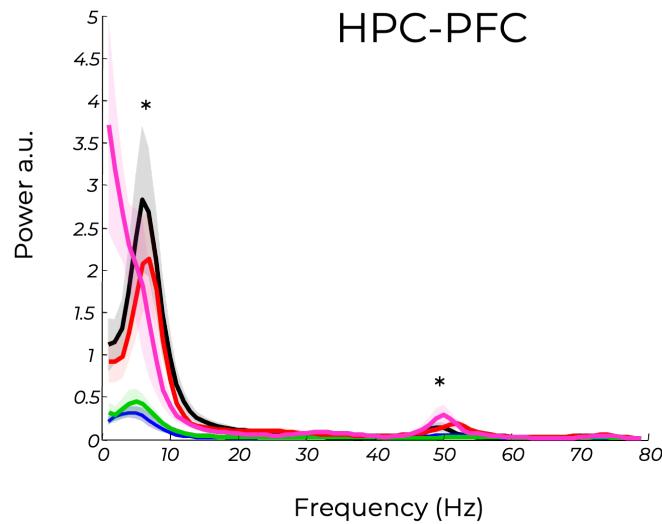
Hippocampus



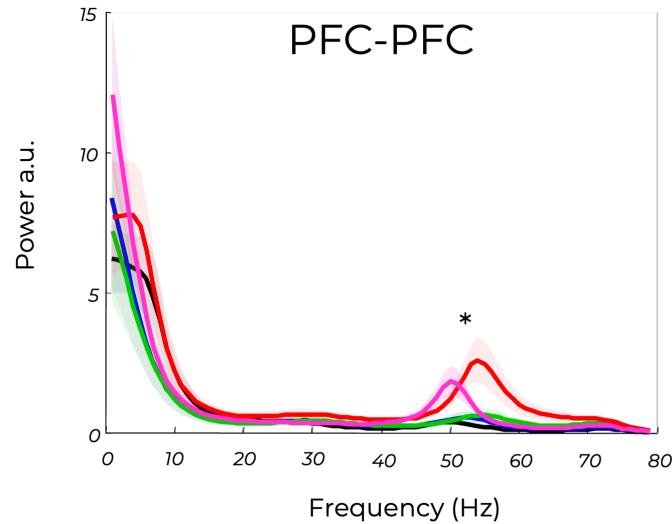
Doses of Ketamine 0 – 40 mg/kg

Ketamine and Local Field Potentials

More than just an NMDA Antagonist?



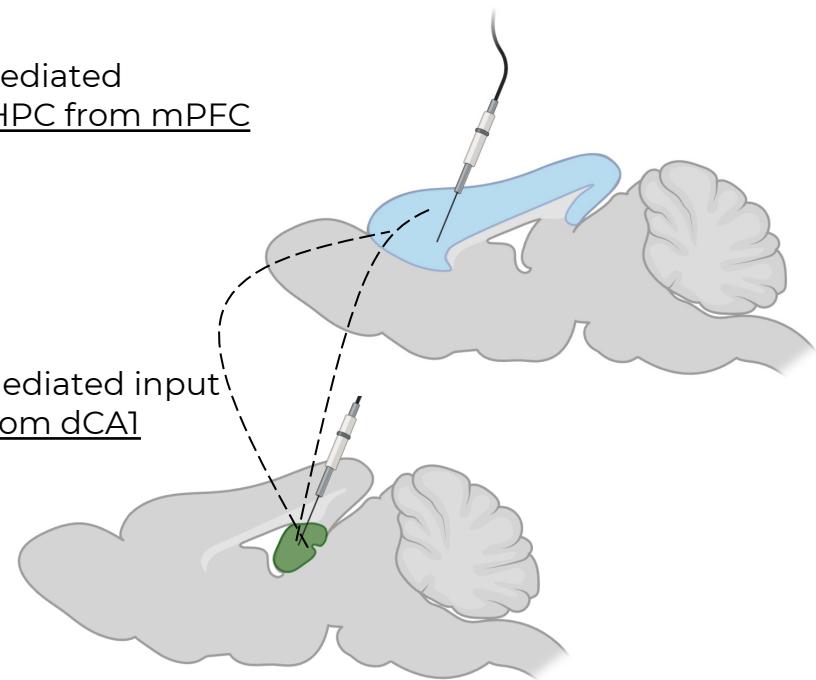
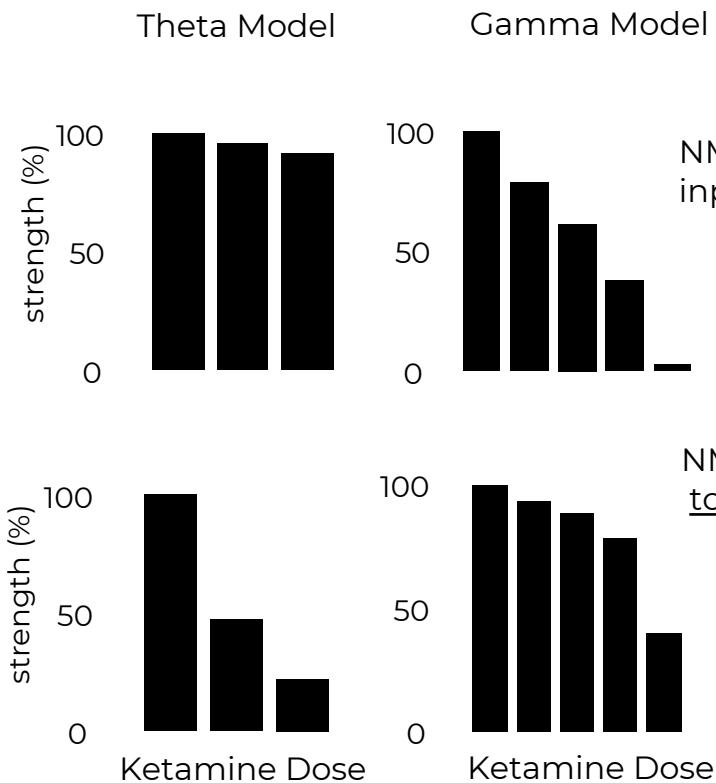
Effects on Theta and Gamma in
Hippocampus and in cross
frequency spectrum



Effect on Gamma in Prefrontal
Cortex

Ketamine and Local Field Potentials

More than just an NMDA Antagonist?

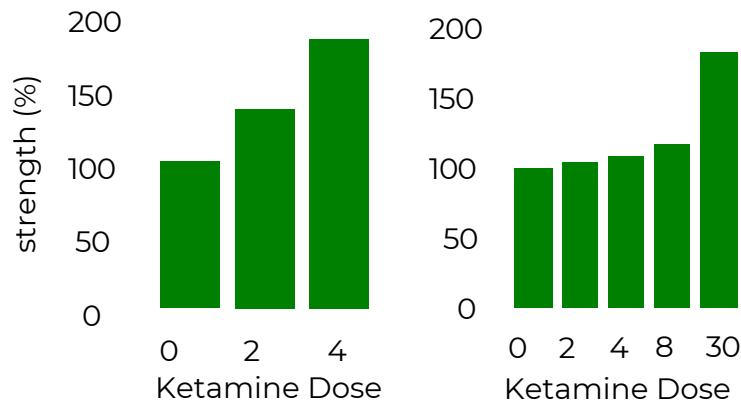


Circuit Changes in NMDA Mediated Connectivity - Decreased

Ketamine and Local Field Potentials

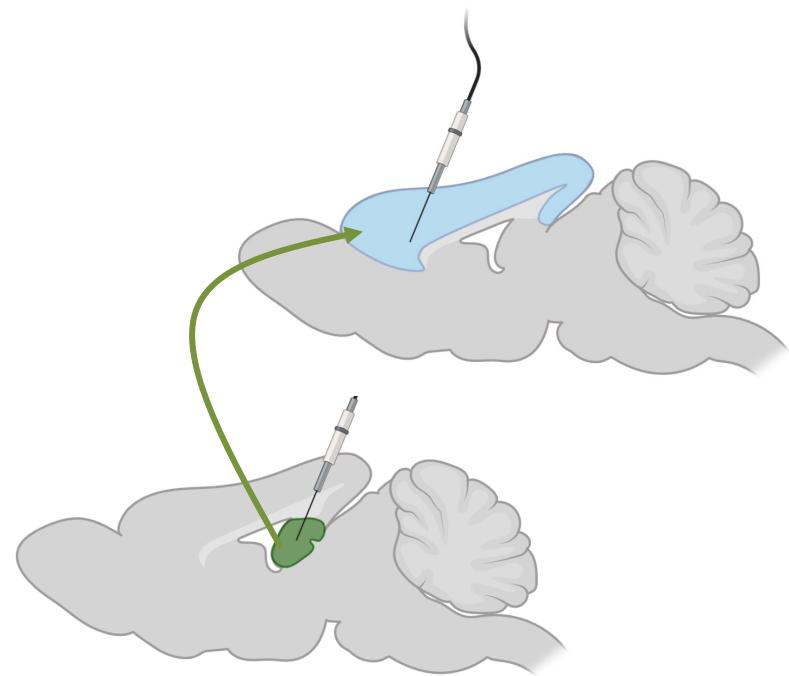
More than just an NMDA Antagonist?

AMPA-mediated input to PFC from dCA1



Increases in AMPA (Bottom-up)

Mediated Connectivity



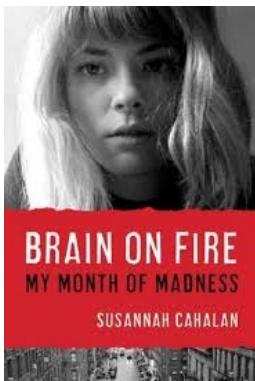
DCM of Human EEG Data in Psychosis-related Autoimmune Disease (NMDA Encephalitis)

Symmonds, et al, 2018, Brain

Ion channels in EEG: isolating channel dysfunction in NMDA
receptor antibody encephalitis

DCM of Human EEG Data in Psychosis-related Autoimmune Disease (NMDA Encephalitis)

“I was walking through Times Square, during which colors appeared aggressively bright. I remember thinking: “I’m seeing everything in a sinister light now. Everything is dripping in terrible meaning.”



“In the spring of 2009, I was the 217th person ever to be diagnosed with anti-NMDA-receptor autoimmune encephalitis. Just a year later, that figure had doubled. Now the number is in the thousands. Yet Dr. Bailey, considered one of the best neurologists in the country, had never heard of it.”

DCM of Human EEG Data in Psychosis-related Autoimmune Disease (NMDA Encephalitis)

- “A severe, multistage, treatable disorder presenting with psychosis” (Wandinger, Dalmua, 2011)
- Autoimmune disorder – including a paraneoplastic syndrome from teratoma or other tumors. Autoantibodies attenuate NMDAR function through the internalization of NMDAR

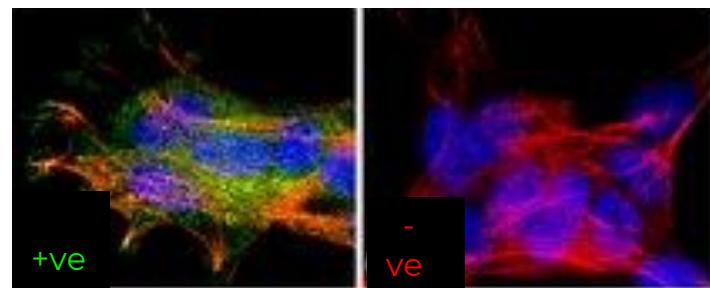
Symptoms



Diagnosis: A positive antibody titer

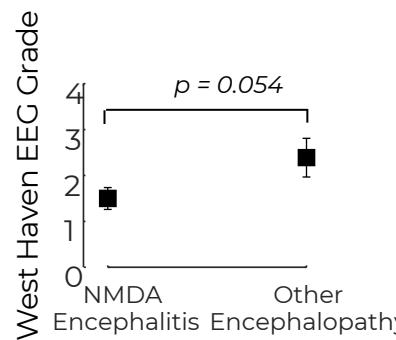
Treatment: intravenous corticosteroids
and intravenous immunoglobulins

Prognosis: 75% Recovery, 6 – 25% mortality



DCM of Human EEG Data NMDA Encephalitis

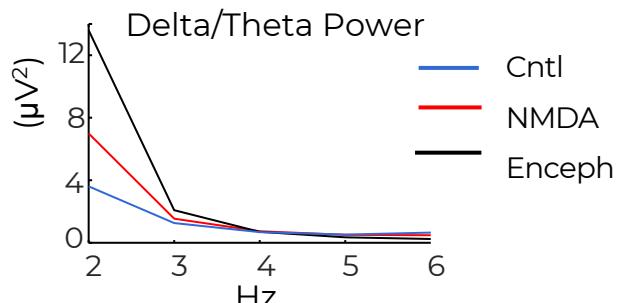
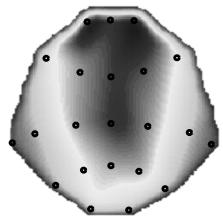
Anti-NMDA Receptor Encephalitis	Encephalopathy (Brain slowing)	Neurological Patient Controls
+ve Serum titer		
N = 31, Age 28 yrs +/- 16, (22 Female)	N = 18, Age 28 +/- 5, (11 Female)	N = 18, Age 31 +/- 6, (10 Female)
12 minutes Resting State 32-channel EEG	12 minutes Resting State 32-channel EEG	12 minutes Resting State 32-channel EEG
Acute, Subacute Recovering or Chronic	Etiology: Metabolic, Infectious & Hypoxic Cause	EEGs indistinguishable on clinical inspection
Treatment: steroids, plasma exchange, IVG		



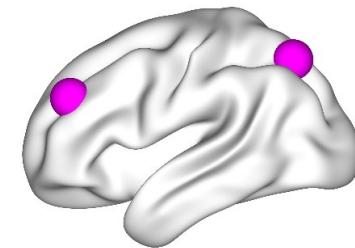
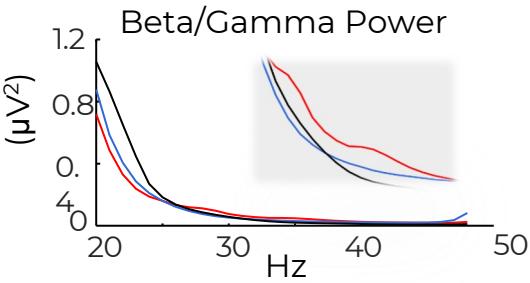
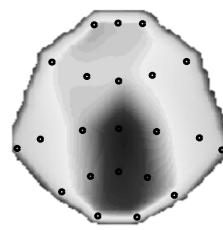
DCM of Human EEG Data NMDA Encephalitis

Empirical Spectra

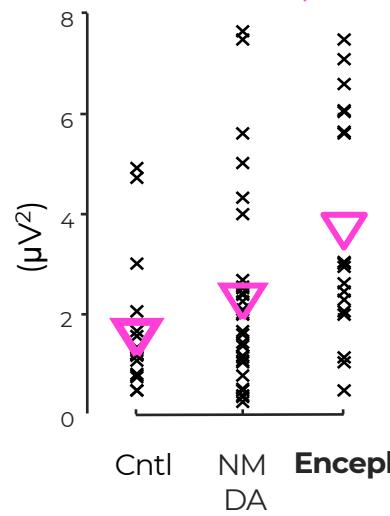
Power (2-6 Hz)



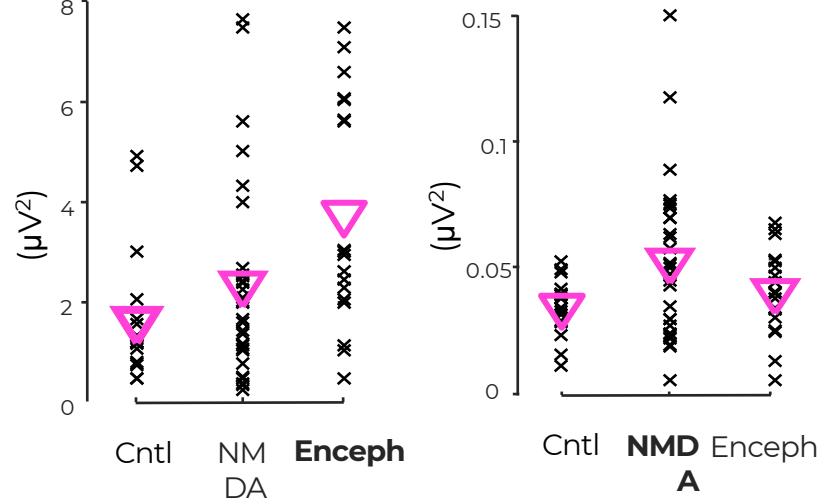
Power (20-48 Hz)



Delta Power



Gamma Power

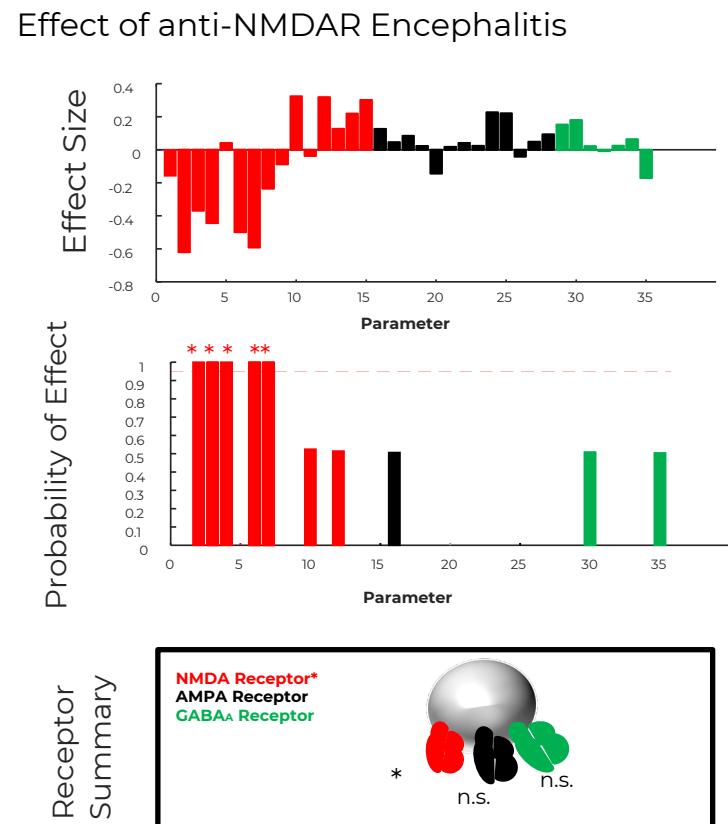
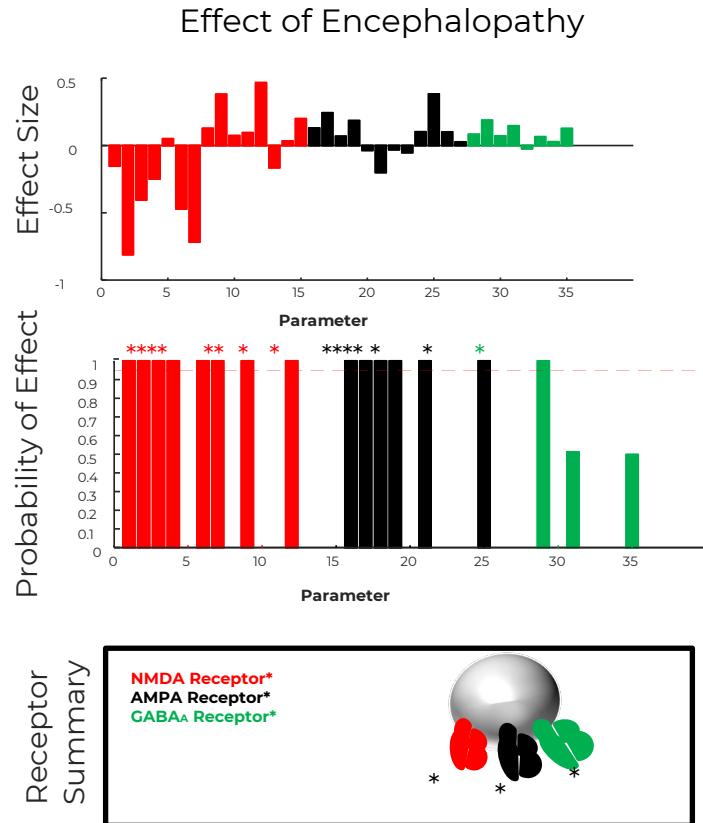


Enceph

NMD **A**

DCM of Human EEG Data NMDA Encephalitis

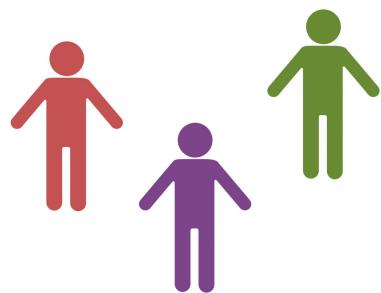
Parameter Effects



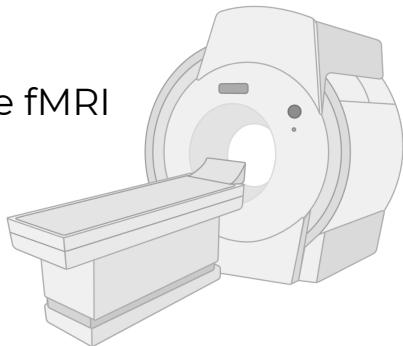
DCM for EEG in patients with Schizophrenia

Adams, et al, 2022, Biological Psychiatry
*Computational Modeling of Electroencephalography and Functional
Magnetic Resonance Imaging Paradigms Indicates a Consistent Loss of
Pyramidal Cell Synaptic Gain in Schizophrenia*

Four Paradigms in a Large Sample



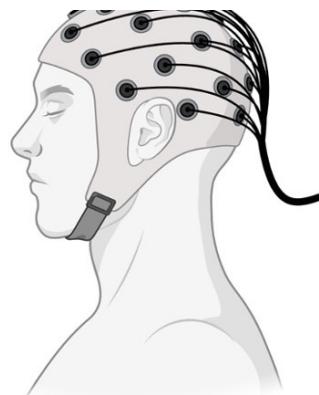
Resting State fMRI



108 PSCz

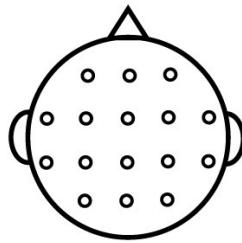
57 Relatives

108 Healthy Controls

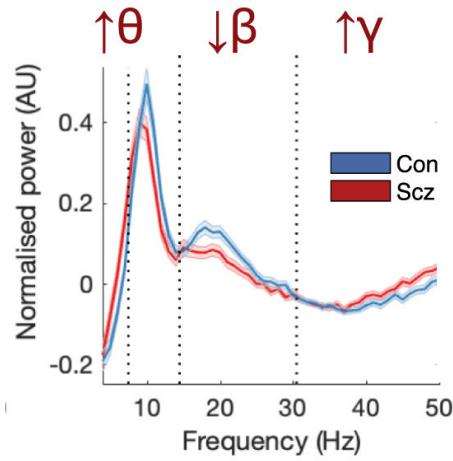


EEG
Resting State,
MMN ERPs and
ASSR (Auditory Steady State) Gamma Band Responses

Constructing the DCM for Resting State



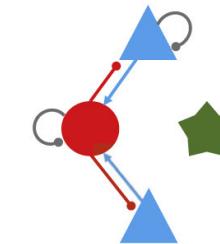
64 Channels



Spectral Differences

Eyes open,

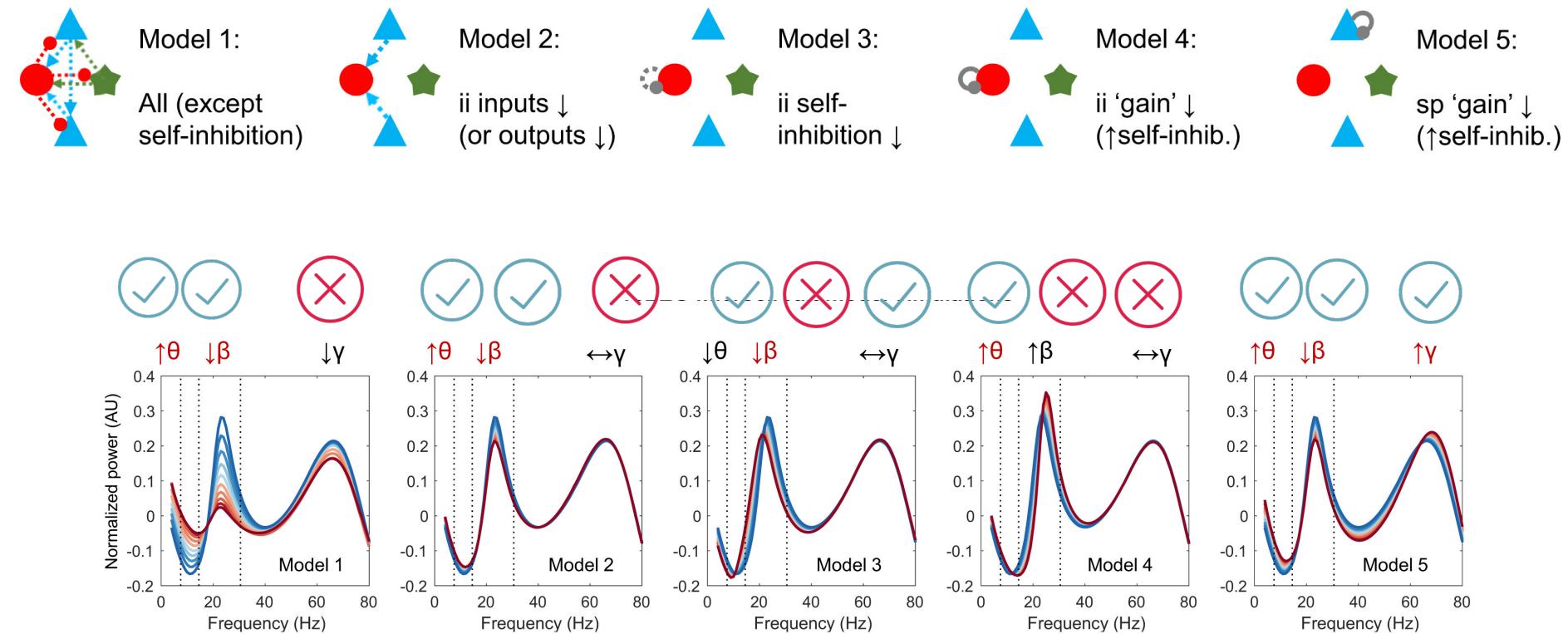
Similar results seen
in eyes closed state



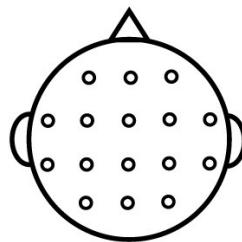
One-Region DCM

Parameters from the DCM for Resting State

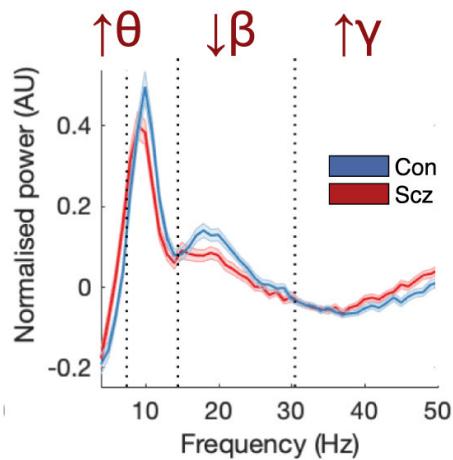
One-Region DCM, what groups of parameters best explain the spectral differences



Results from the DCM for Resting State



64 Channels



Spectral Differences



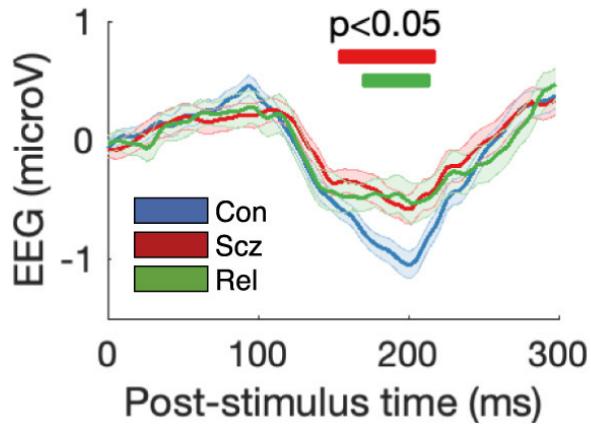
Model 5:
sp 'gain' ↓
(↑self-inhib.)

Reduction in Superficial
Pyramidal Cell Gain in
patients explains
spectral differences

Constructing the DCM for ERP : Mismatch Negativity

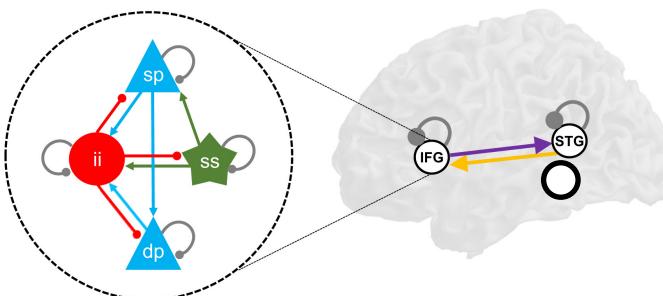


Auditory Mismatch



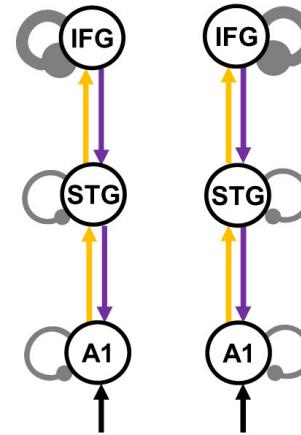
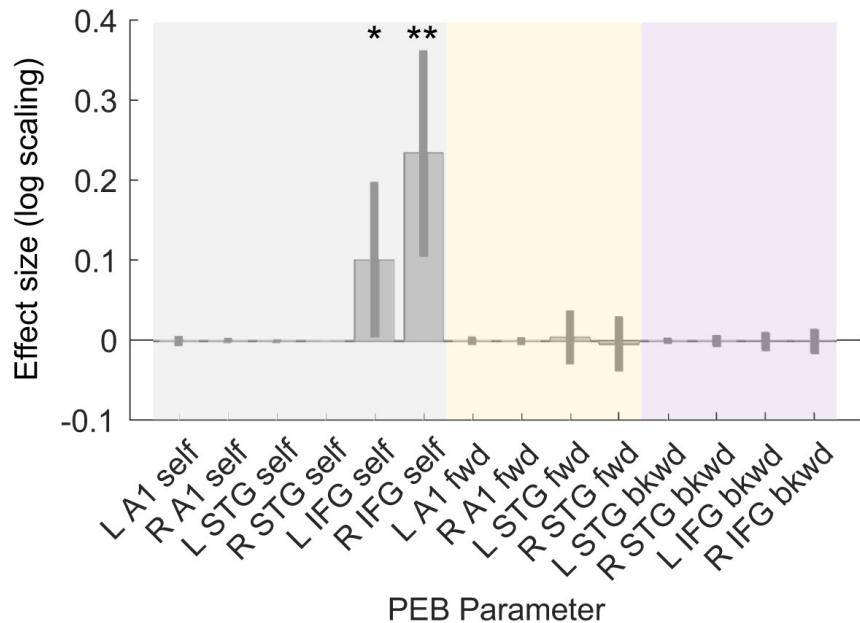
MMN Differences in ERPs
Around 150 – 200 msec

Six-Region DCM



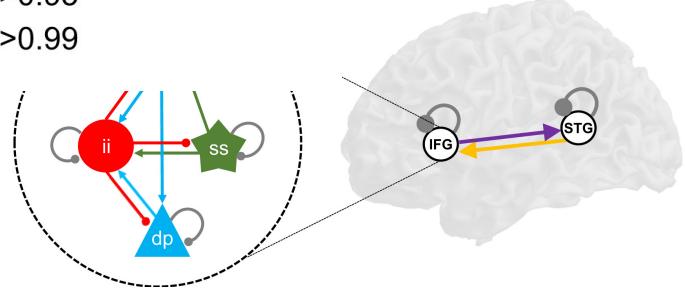
Results of the DCM for ERP : Mismatch Negativity

Connectivity parameters, deviants–standards: Scz > Con



Reduction in Superficial Pyramidal Cell Gain in patients explains MMN Differences

* p>0.95
** p>0.99

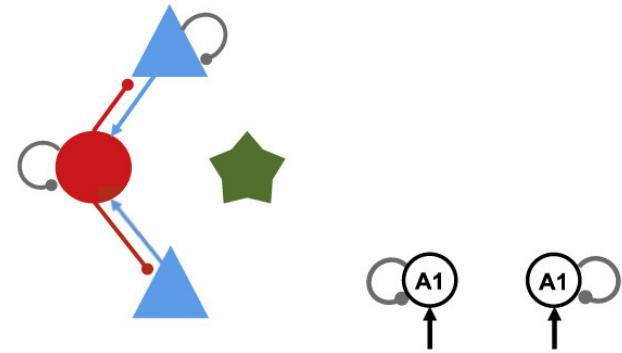
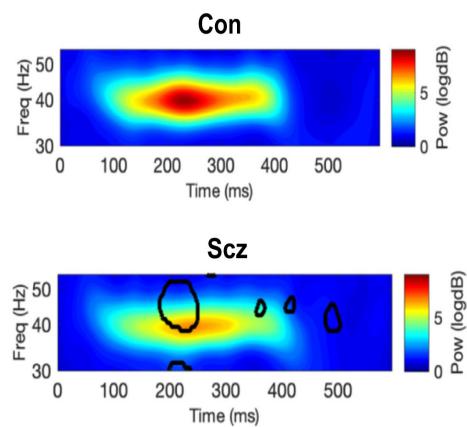


Constructing the DCM for ASSR



40 Hz

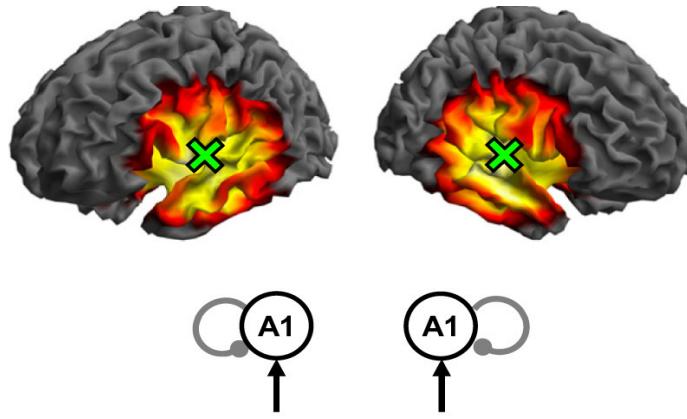
Auditory 'Clicks'



Two-Region DCM

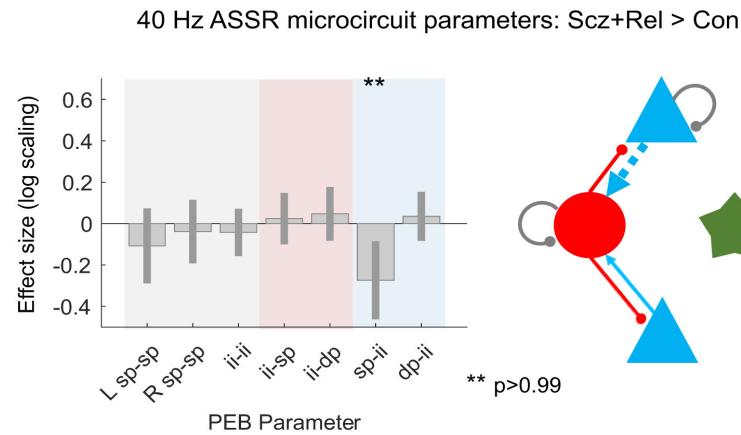
Reductions in Steady State
Gamma is PScz

Results of DCM for ASSR

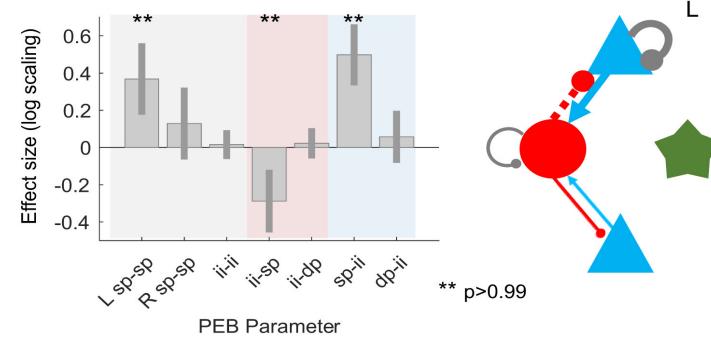


Disinhibition associated with Perceptual
(positive) traits

Reduced Inhibitory Drive in PScz & Rel

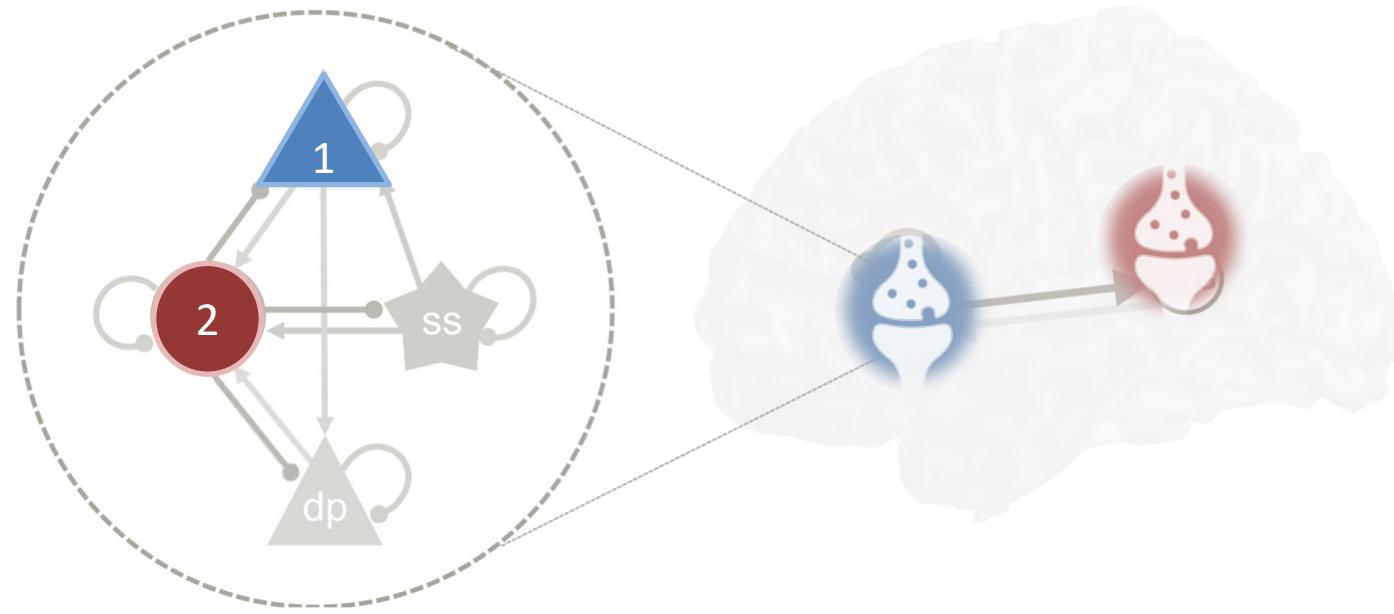


40 Hz ASSR parameters vs Auditory Perceptual Trait: Scz only



Conclusions of the Study

A Cascade of Synaptic Changes



These findings are more commensurate with the hypothesis that in PScz,

- (1) a primary loss of synaptic gain on pyramidal cells is then compensated by
- (2) interneuron downregulation (rather than the converse).

They further suggest that psychotic symptoms relate to this secondary downregulation.

Why these models?

DCM for EEG

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 connectivity and their belief
mappings.

Potential to scale to clinical setting

DCM for EEG

Why these models can be mildly irritating :

Local Minima (not the model's fault)



Thank You!!

And the TNU & The FIL Methods Group