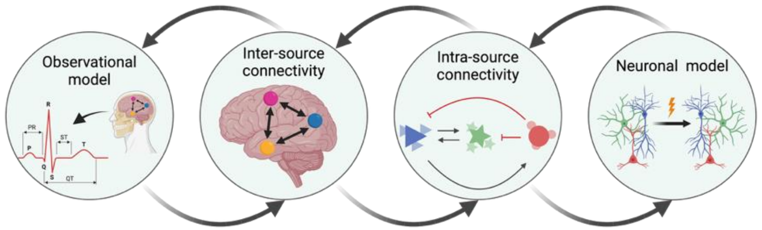

Dynamic Causal Modeling for MEG/EEG Data

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ETH
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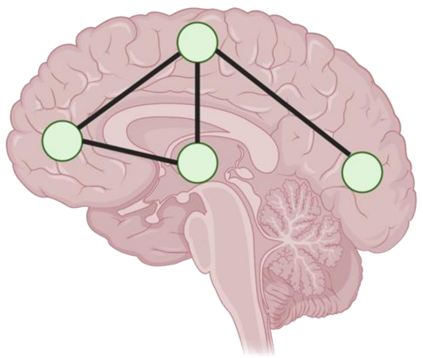
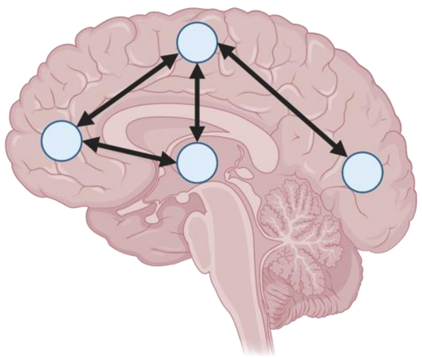
Brain connectivity

Brain connectivity



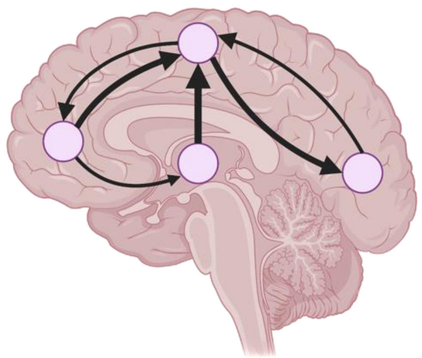
structural connectivity

- Presence of anatomical (physical) connections
- Diffusion weighted imaging (DWI), tractography, tracer studies



functional connectivity

- Statistical dependencies between regional time series
- Correlations, Independent Component Analysis (ICA), …



effective connectivity

- Directed influences between neuronal populations
- Granger causality, **Dynamic Causal Modeling**

Brain connectivity

Functional connectivity

- “Regions X, Y and Z form a network.”
- “Regions are more connected under condition A compared to B.”
- “This condition is associated with activation of X pathways.”

Effective connectivity

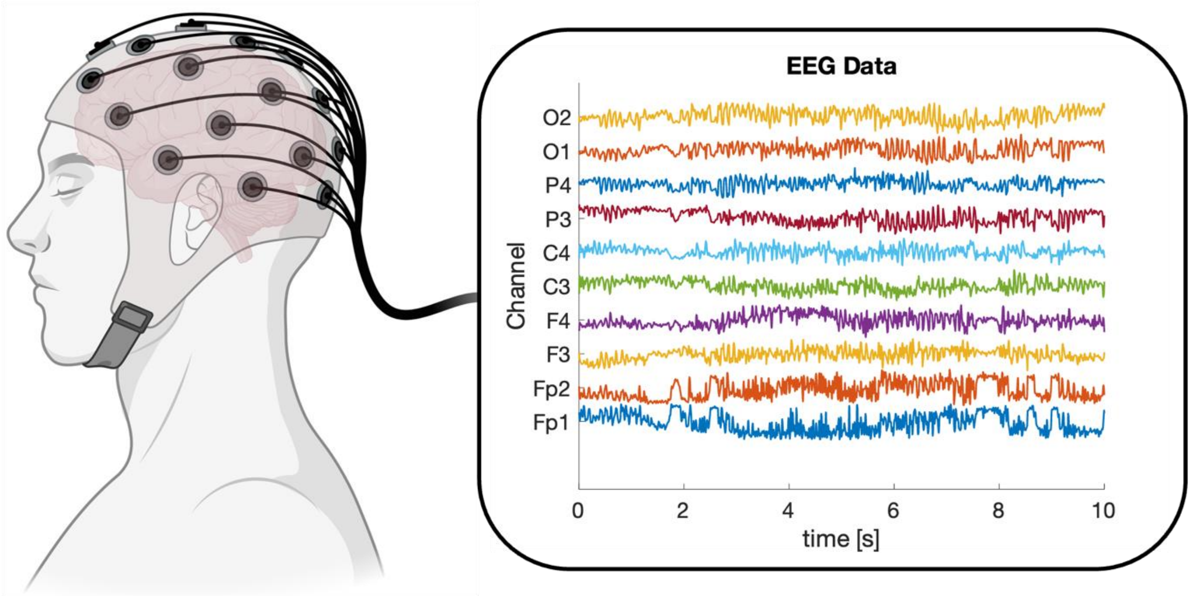
- “Region X gives rise to activity in region Y”
- ”Region Y inhibits region X.”

Magneto- / Electroencephalography

Magneto- / Electroencephalography

Properties

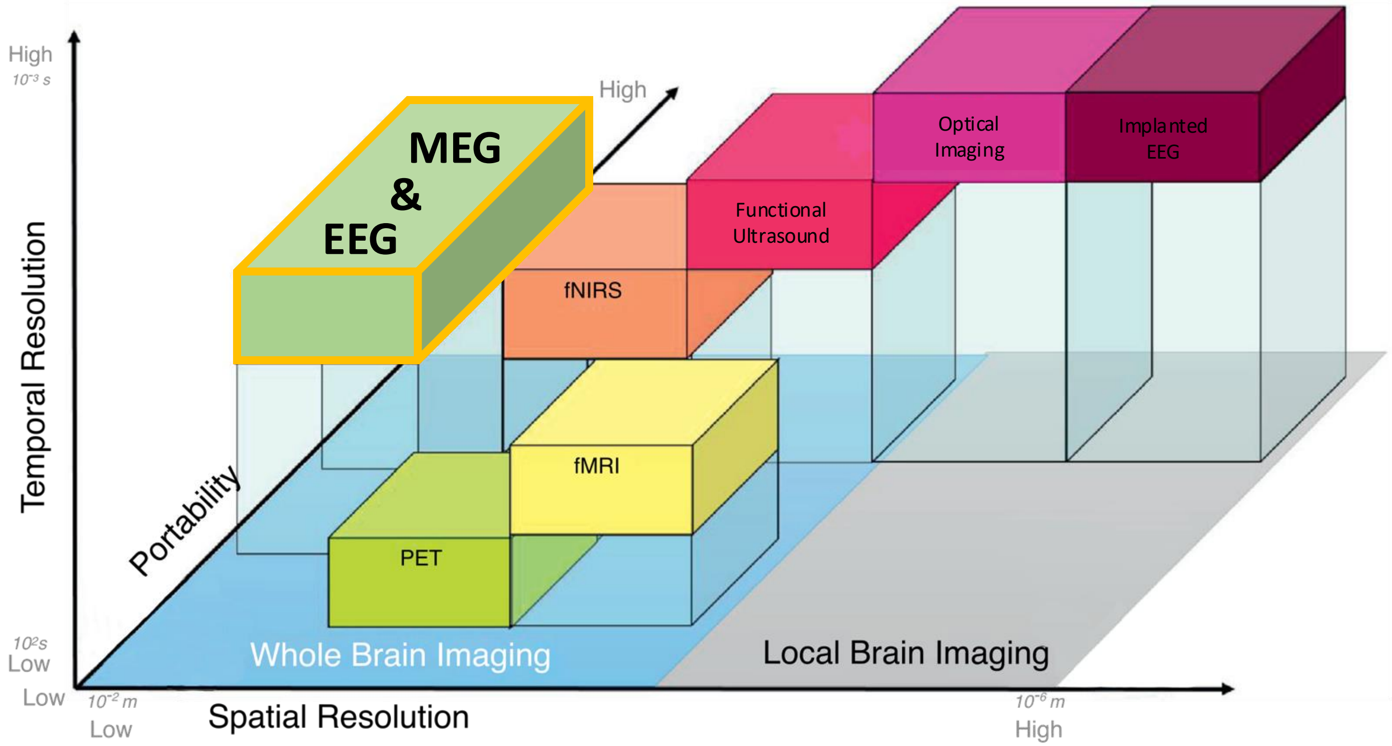
- Non-invasive scalp-level measurement of neuronal population dynamics



Magneto- / Electroencephalography
Properties

- Non-invasive scalp-level measurement of neuronal population dynamics

+ High temporal resolution
- Low spatial resolution
- Prone to artefacts

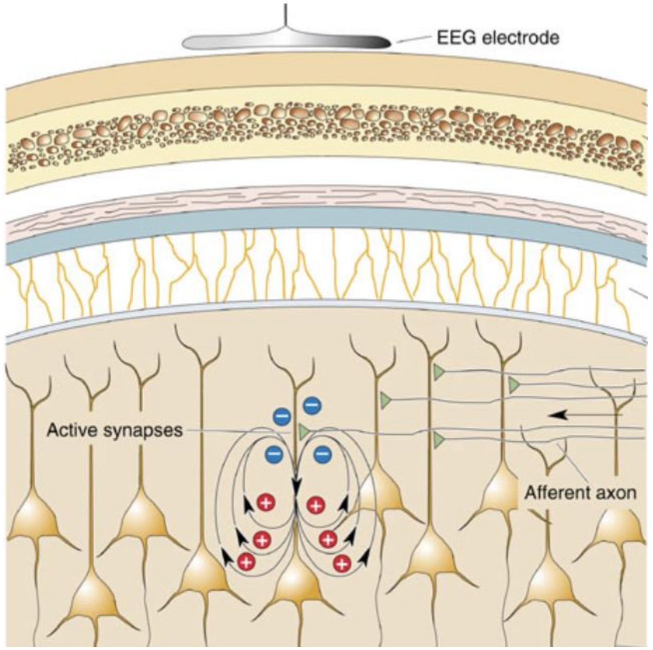


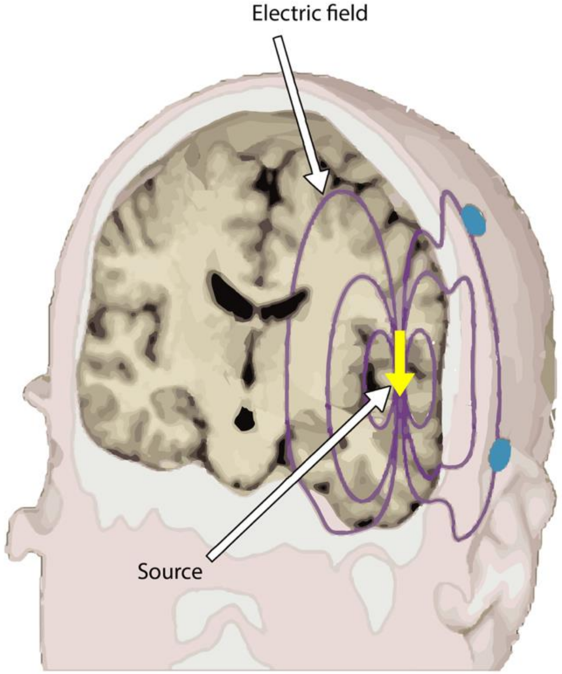
Adapted from Ramoo, 2021

Magneto- / Electroencephalography

Neurophysiological mechanisms

1. Depolarization of cell membrane due to change in distribution of charged ions
2. Accumulation of charge leads to dipole field and corresponding electrical current
3. Dipole fields manifest as differences of electrical potentials on the scalp (EEG)
4. Currents induce magnetic fields (MEG)





Figures from Bear et al., 2009 (left) and SPM M/EEG course (right)

MEG/EEG and model-based approaches

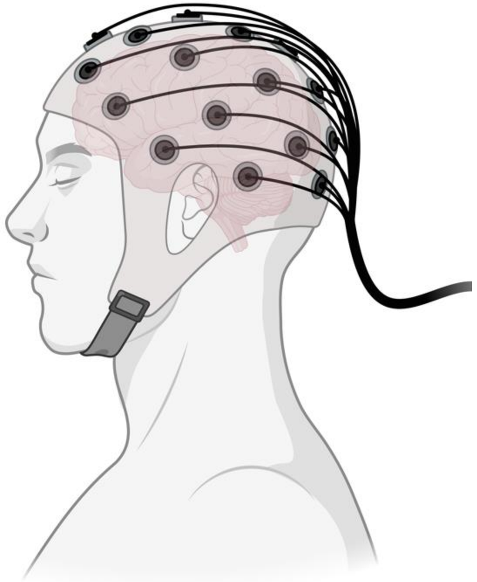
Traditional MEG/EEG analysis

- Based on frequency/waveform characteristics
- Limited (mechanistical) interpretability

Model-based MEG/EEG analysis

- Based on biophysiologically plausible model
- Increased interpretability
- Generative model allows simulation of data

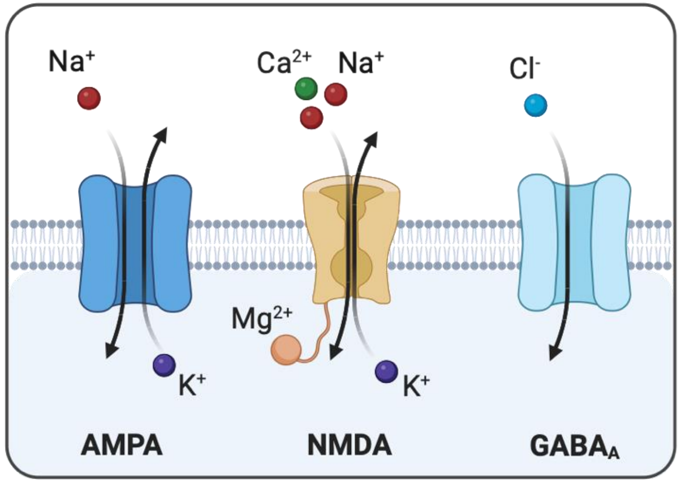
Dynamic causal modeling of MEG/EEG data



Observable measurements Y

Forward model

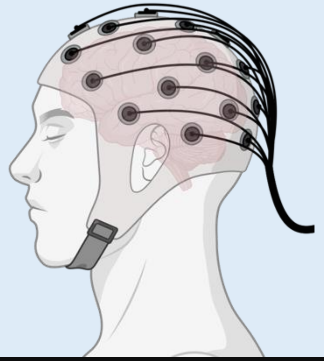
Model inversion (VB, MCMC)



Hidden states X

Adapted from Stephan et al., *Front. Hum. Neurosci.*, 2016

Dynamic causal modeling of MEG/EEG data



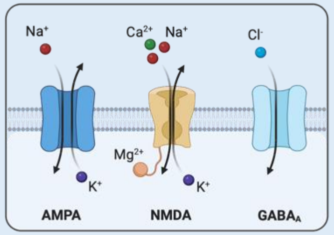
Observable measurements

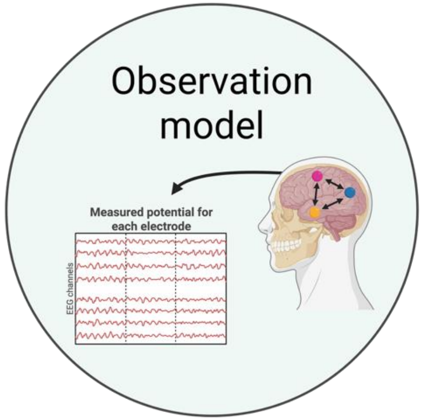
$Y \leftrightarrows X$

Forward model

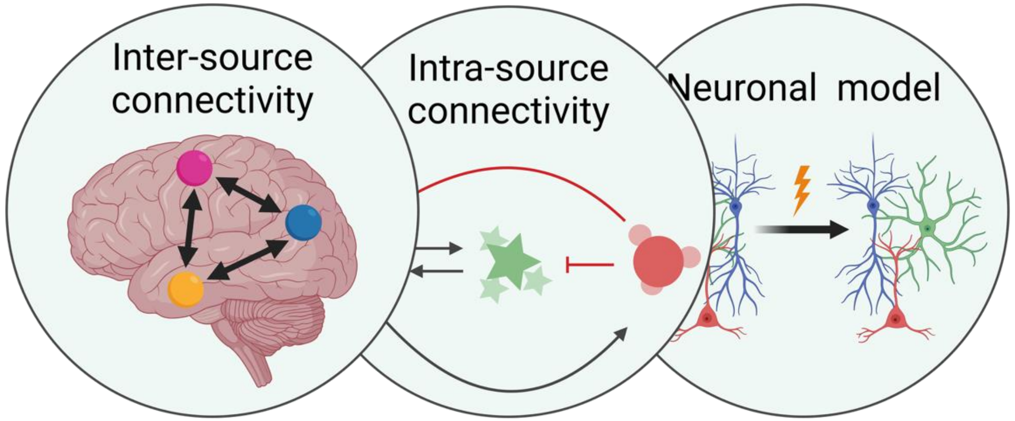
Model inversion

Hidden states





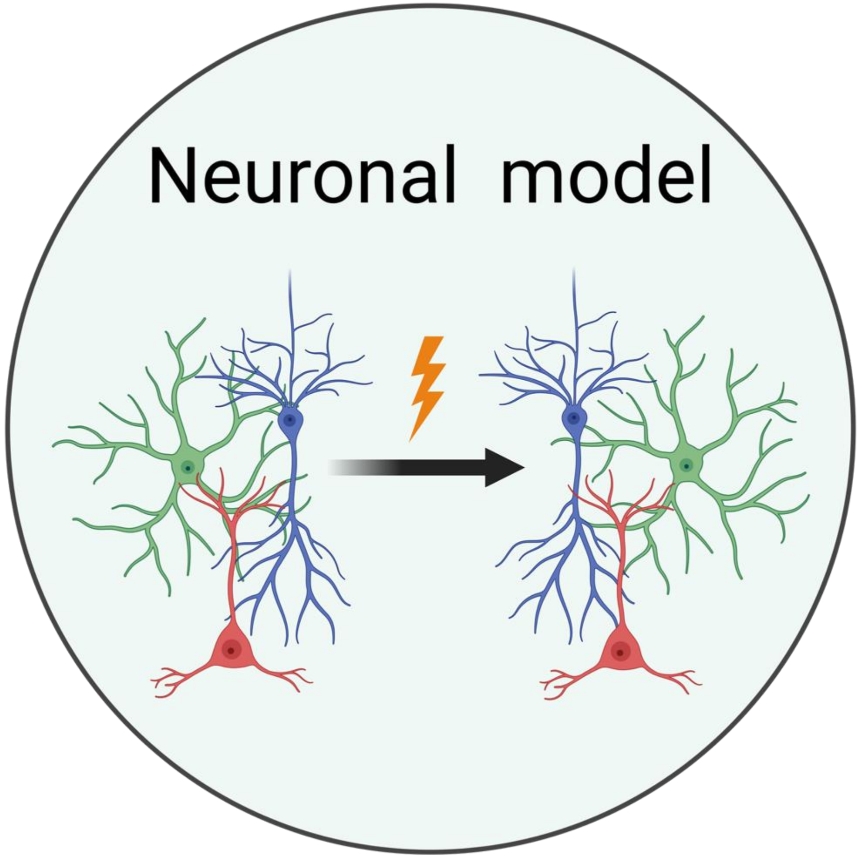
$$y = G(x, \vartheta) + \epsilon$$



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

DCM for MEG/EEG data

Neuronal Dynamics



DCM for MEG/EEG data

neuronal dynamics

Convolution-based DCM

- Neuronal population dynamics defined by convolution with impulse response function
- No direct representation of individual ion-channel dynamics

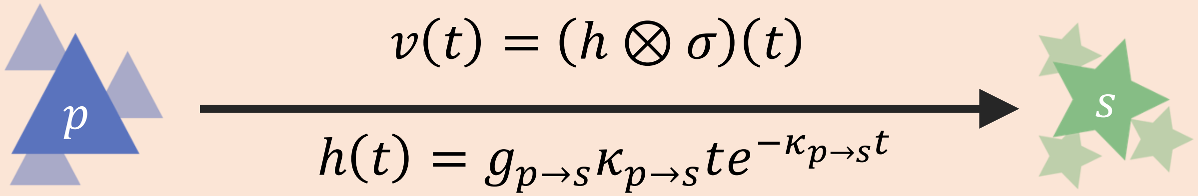
Conductance-based DCM

- Neuronal population dynamics defined by equivalent circuit model
- Detailed representation of different ion-channels
- Fokker-Planck for population dynamics

DCM for MEG/EEG data

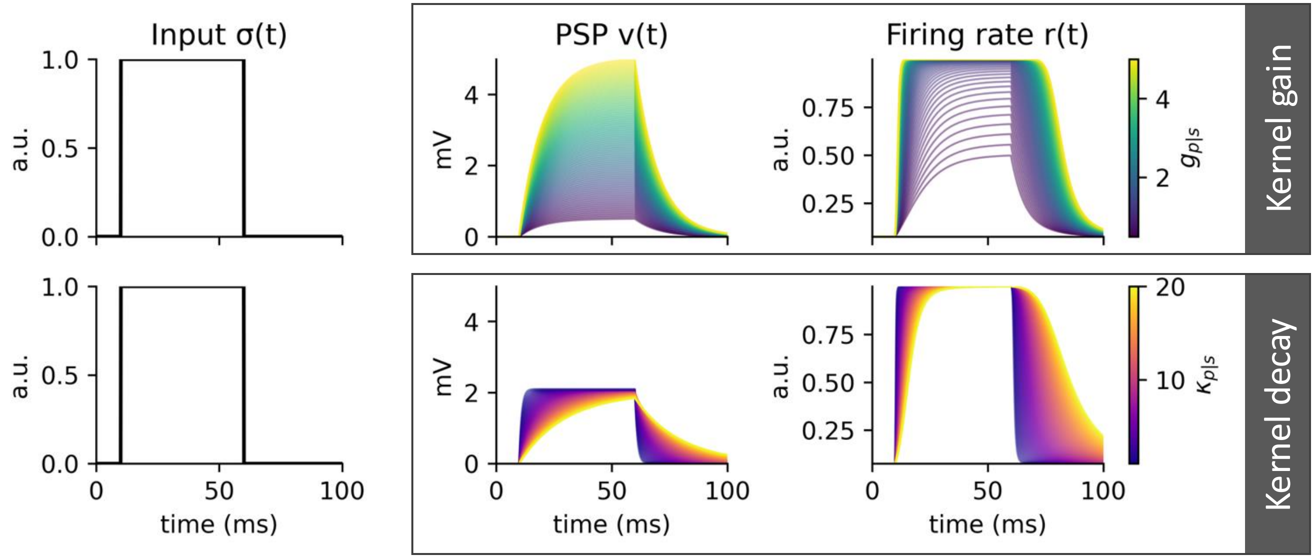
convolution-based neuronal model

- Convolution of presynaptic firing input $\sigma(t)$ with impulse response function $h(t)$ to produce post-synaptic membrane potential (PSP) $v(t)$
- Sigmoid transform of PSP to obtain post-synaptic firing rate r
- Kernel parameters for gain and decay



$$v(t) = (h \otimes \sigma)(t)$$

$$h(t) = g_{p \to s} \kappa_{p \to s} t e^{-\kappa_{p \to s} t}$$

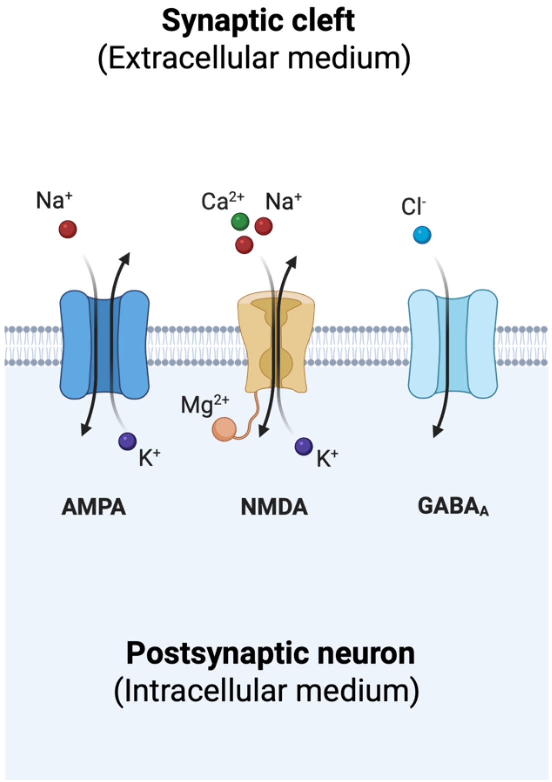


Jansen and Rit, *Biological Cybernetics*, 1995 | David et al., *NeuroImage*, 2006 | Moran et al., *Front Comput Neurosci*, 2013

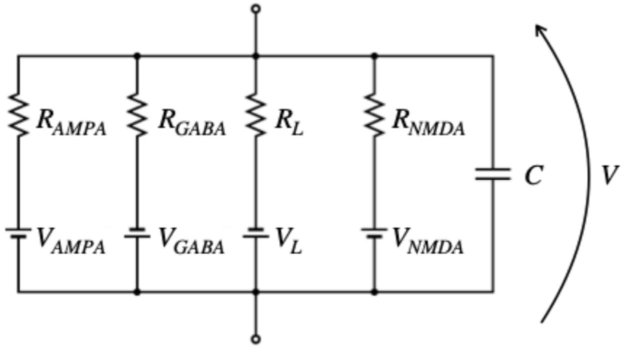
DCM for MEG/EEG data

conductance-based neuronal model

- Differential equation for membrane voltage
- Single neuron dynamics defined by equivalent circuit model
    - $I_C = -\sum_k I_k + u$
    - $I_C = C \cdot \frac{dV}{dt}$
    - $I_k = g_k(V - V_k)$



Circuit model
(Hodgkin-Huxley)



Change in cross-membrane voltage:

$$C\dot{V} = \left(\sum_k g_k(V_k - V)\right) + u$$

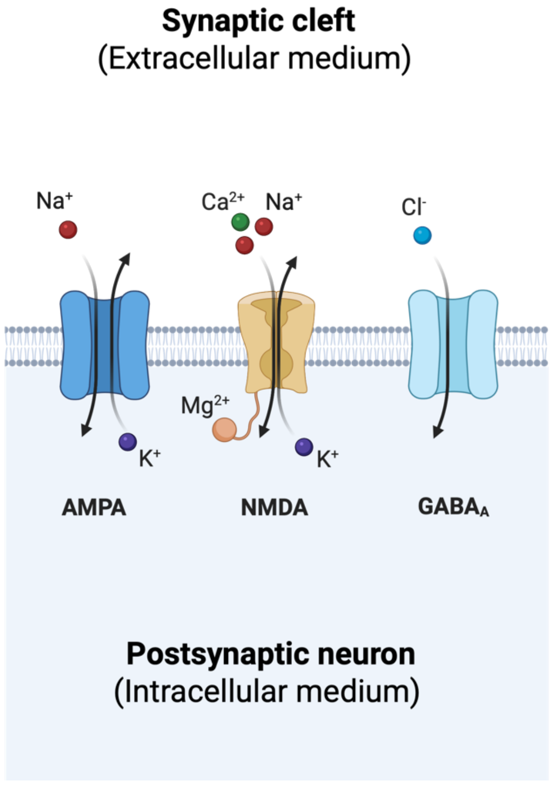
Hodgkin and Huxley, *J. Physiol.*, 1952 | Morris and Lecar, *Biophys. J.*, 1981 | Figure adapted from Pereira et al., *NeuroImage*, 2021

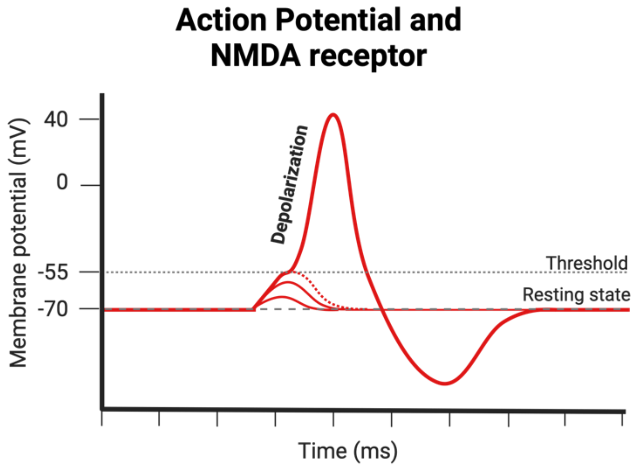
DCM for MEG/EEG data

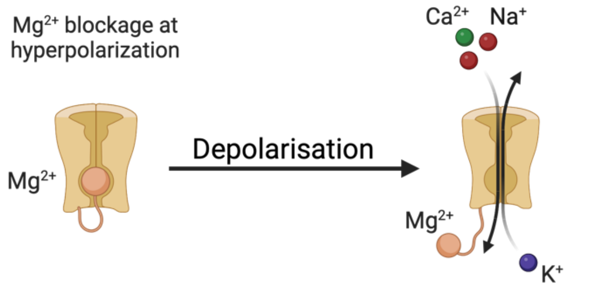
conductance-based neuronal model

- Differential equation for membrane voltage
- Single neuron dynamics defined by equivalent circuit model
- Non-linearity of NMDA receptor

$$m(V) = \frac{1}{1 + 0.2\exp(-\alpha_{NMDA}V)}$$







Jahr, *J. Neurosc.*, 1990 | Koch, Biophysics of Computation - Information Processing in Single Neurons | Moran et al., *Neuroimage* 2011

DCM for MEG/EEG data

conductance-based neuronal model

- Differential equation for membrane voltage
- Single neuron dynamics defined by equivalent circuit model
- Non-linearity of NMDA receptor

$$m(V) = \frac{1}{1 + 0.2\exp(-\alpha_{NMDA}V)}$$

Full model, including NMDA receptors:

$$C\dot{V} = \left(\sum_k g_k(V_k - V)\right) + g_{NMDA}\, m(V)(V_{NMDA} - V) + u + \Gamma_V$$

where $k \in L, \mathrm{AMPA}, \mathrm{GABA}$ and $\tilde{k} \in \mathrm{NMDA}, \mathrm{AMPA}, \mathrm{GABA}$

Hodgkin and Huxley, *J. Physiol.*, 1952 | Morris and Lecar, *Biophys. J.*, 1981 | Pereira et al., *NeuroImage*, 2021

DCM for MEG/EEG data

conductance-based neuronal model

- Differential equation for membrane voltage
- Single neuron dynamics defined by equivalent circuit model
- Non-linearity of NMDA receptor
- Differential equation for channel conductance

Full model, including NMDA receptors:

$$C\dot{V} = \left(\sum_k g_k(V_k - V)\right) + g_{NMDA}\, m(V)(V_{NMDA} - V) + u + \Gamma_V$$

$$\dot{g}_{\tilde{k}} = \kappa_{\tilde{k}}(\gamma_{aff} \cdot \sigma_{aff} - g_{\tilde{k}}) + \Gamma_g$$

time constant

coupling strength

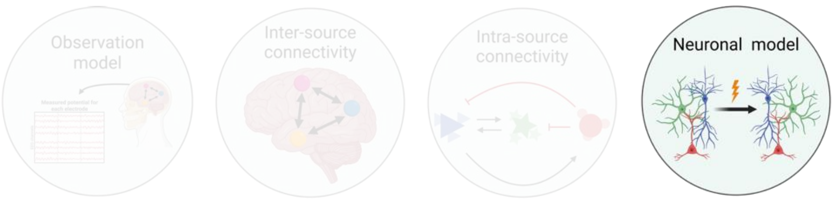
afferent firing

where $k \in L, \mathrm{AMPA}, \mathrm{GABA}$ and $\tilde{k} \in \mathrm{NMDA}, \mathrm{AMPA}, \mathrm{GABA}$

Hodgkin and Huxley, *J. Physiol.*, 1952 | Morris and Lecar, *Biophys. J.*, 1981 | Pereira et al., *NeuroImage*, 2021

DCM for MEG/EEG data

Fokker-Planck



- **Single neuron dynamics**
  stochastic differential equation considering state noise

Fokker-Planck equation

$$q(x) = \mathcal{N}(\mu, \Sigma)$$

$$\dot{\mu}_l^{(j)} = f_l^{(j)}(\mu) + \frac{1}{2} Tr\left(\Sigma^{(j)} \frac{\partial^2 f_l^{(j)}}{\partial x^2}\right)$$

$$\dot{\Sigma}^{(j)} = \frac{\partial f^{(j)}}{\partial x} \Sigma^{(j)} + \Sigma^{(j)} \frac{\partial f^{(j)^T}}{\partial x} + D^{(j)} + D^{(j)^T}$$

- **Population dynamics**
  deterministic differential equation for average voltage change of ensemble density

$$C\dot{V} = \left(\sum_k g_k (V_k - V)\right) + g_{NMDA}\, m(V)(V_{NMDA} - V) + u + \Gamma_V$$

$$\dot{g}_{\tilde{k}} = \kappa_{\tilde{k}}(\gamma_{aff} \cdot \sigma_{aff} - g_{\tilde{k}}) + \Gamma_g$$

State noise

where $k \in L, \mathrm{AMPA}, \mathrm{GABA}$ and $\tilde{k} \in \mathrm{NMDA}, \mathrm{AMPA}, \mathrm{GABA}$

Marreiros et al., *NeuroImage*, 2009 | Pereira et al., *NeuroImage*, 2021

DCM for MEG/EEG data

Fokker-Planck

Fokker-Planck equation

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  stochastic differential equation considering state noise

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- **Population dynamics**
  deterministic differential equation for average voltage change of ensemble density

Full neuronal population model (neural mass model)

$$C\dot{\mu}_V^{(j)} = \left(\sum_k \mu_{g_k}^{(j)} \left(V_k - \mu_V^{(j)}\right)\right) + \mu_{g_{NMDA}}^{(j)}\, m\left(\mu_V^{(j)}\right)\left(V_{NMDA} - \mu_V^{(j)}\right)$$

$$\dot{\mu}_{g_k}^{(j)} = \kappa_k^{(j)} \left(\zeta_k^{(j)} - \mu_{g_k}^{(j)}\right)$$

$$\zeta_k^{(j)} = \sum_i \gamma_{\tilde{k}}^{(j,i)} \sigma\left(\mu_V^{(i)} - V_R, \Sigma^{(i)}\right)$$

where $k \in L, \mathrm{AMPA}, \mathrm{GABA}$ and $\tilde{k} \in \mathrm{NMDA}, \mathrm{AMPA}, \mathrm{GABA}$

Marreiros et al., *NeuroImage*, 2009 | Pereira et al., *NeuroImage*, 2021

DCM for MEG/EEG data

Fokker-Planck

Fokker-Planck equation

- **Single neuron dynamics**
  stochastic differential equation considering state noise

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- **Population dynamics**
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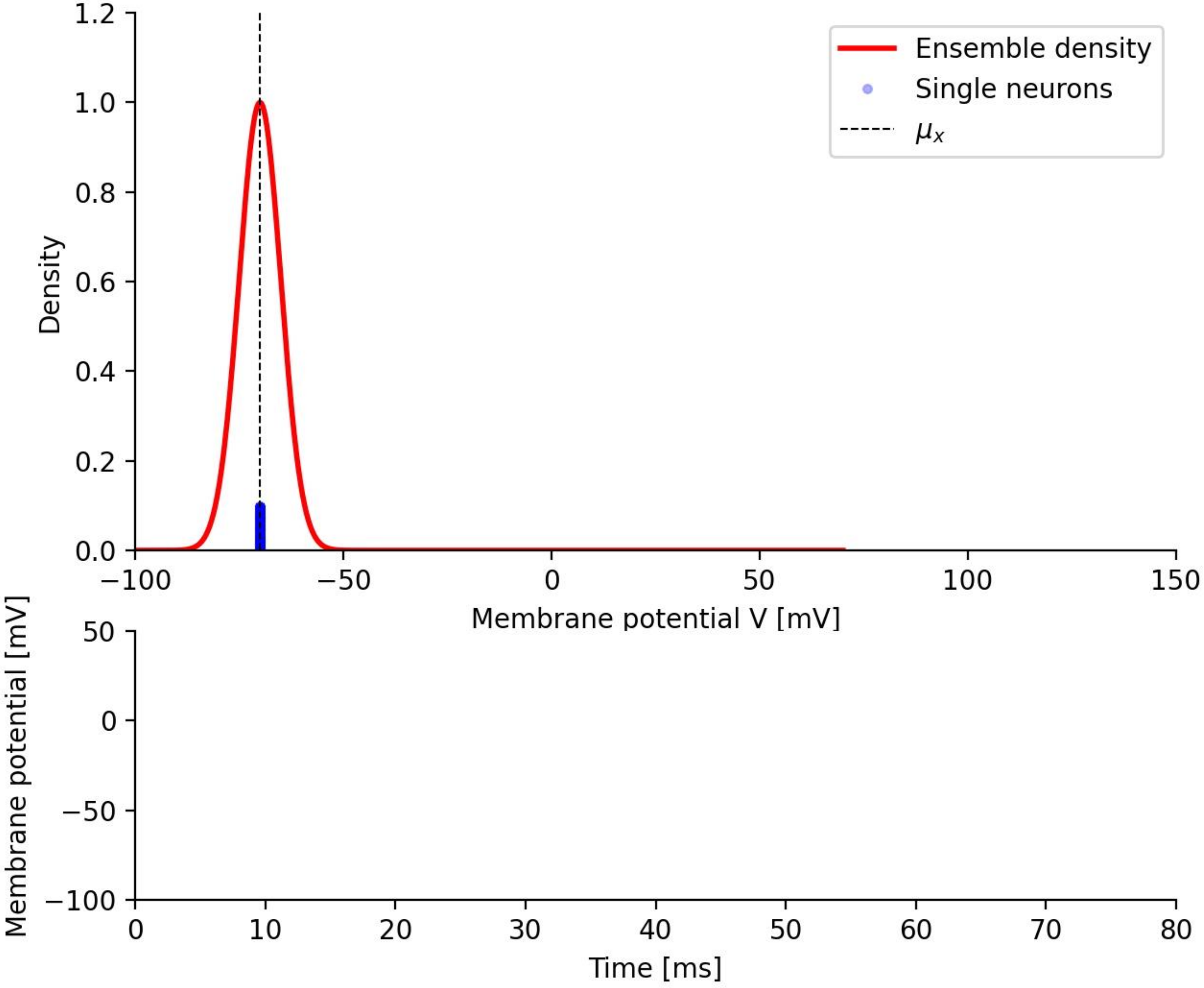

DCM for MEG/EEG data

Fokker-Planck

- **Single neuron dynamics**

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$$q(x) = \mathcal{N}(\mu, \Sigma)$$

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Fokker-Planck equation

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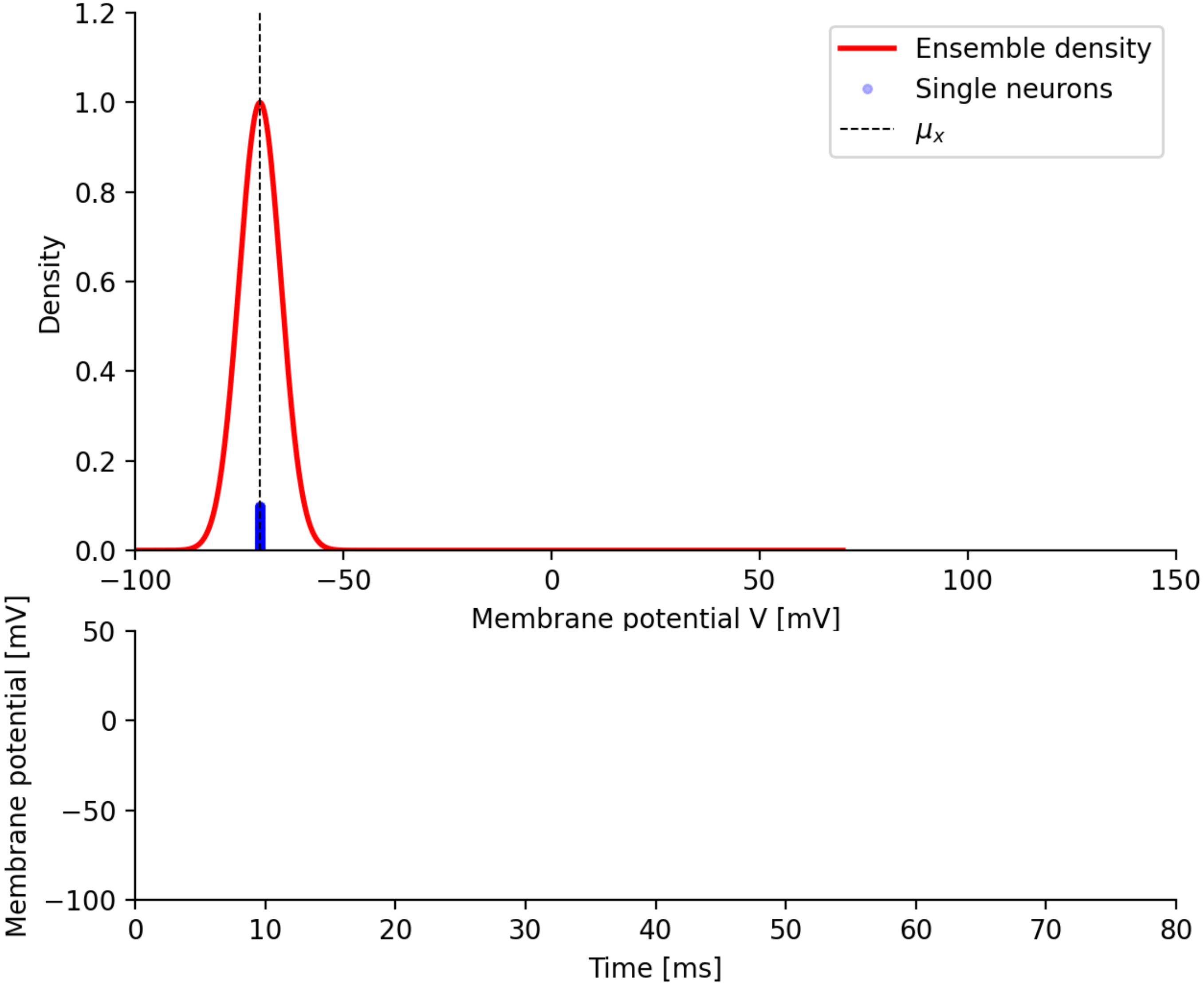
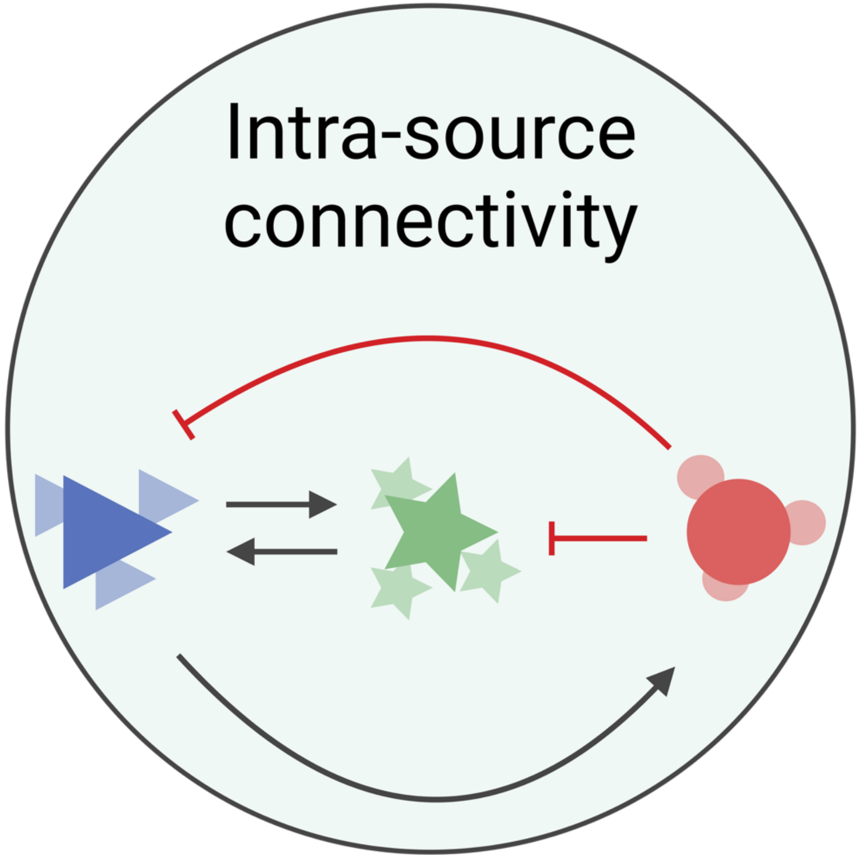


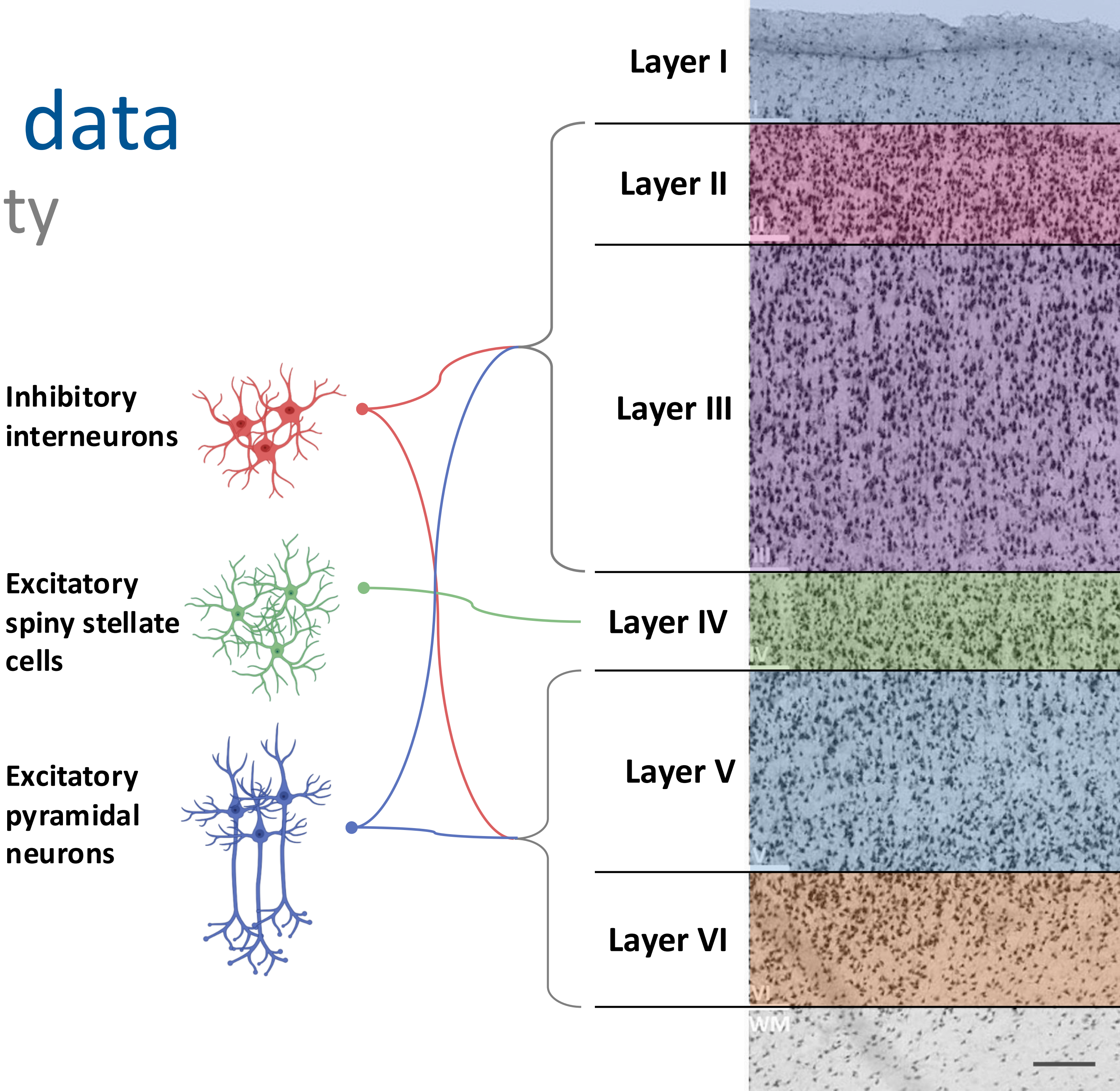
DCM for MEG/EEG data

Intra-source connectivity



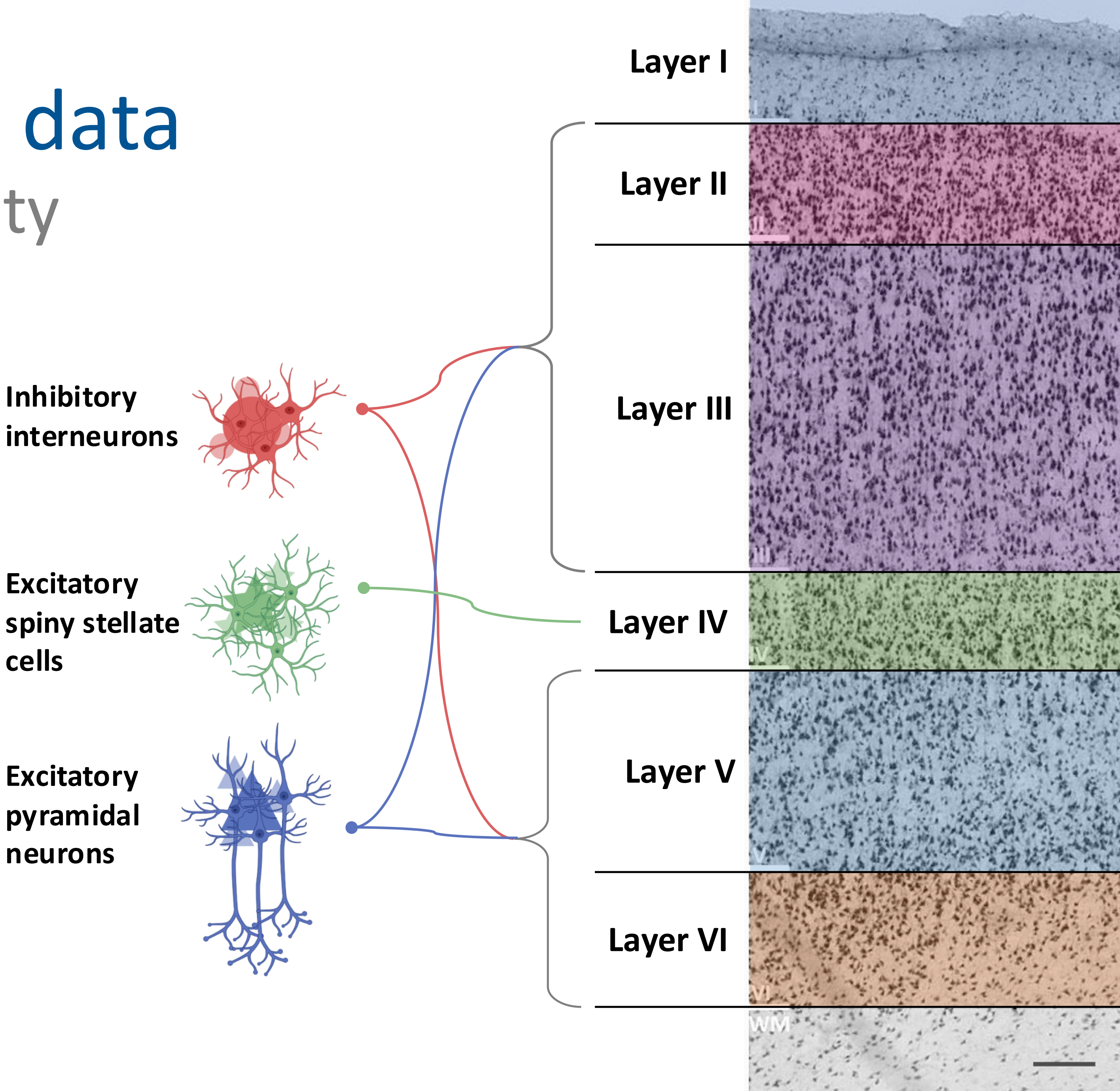
DCM for MEG/EEG data

intra-source connectivity



DCM for MEG/EEG data

intra-source connectivity



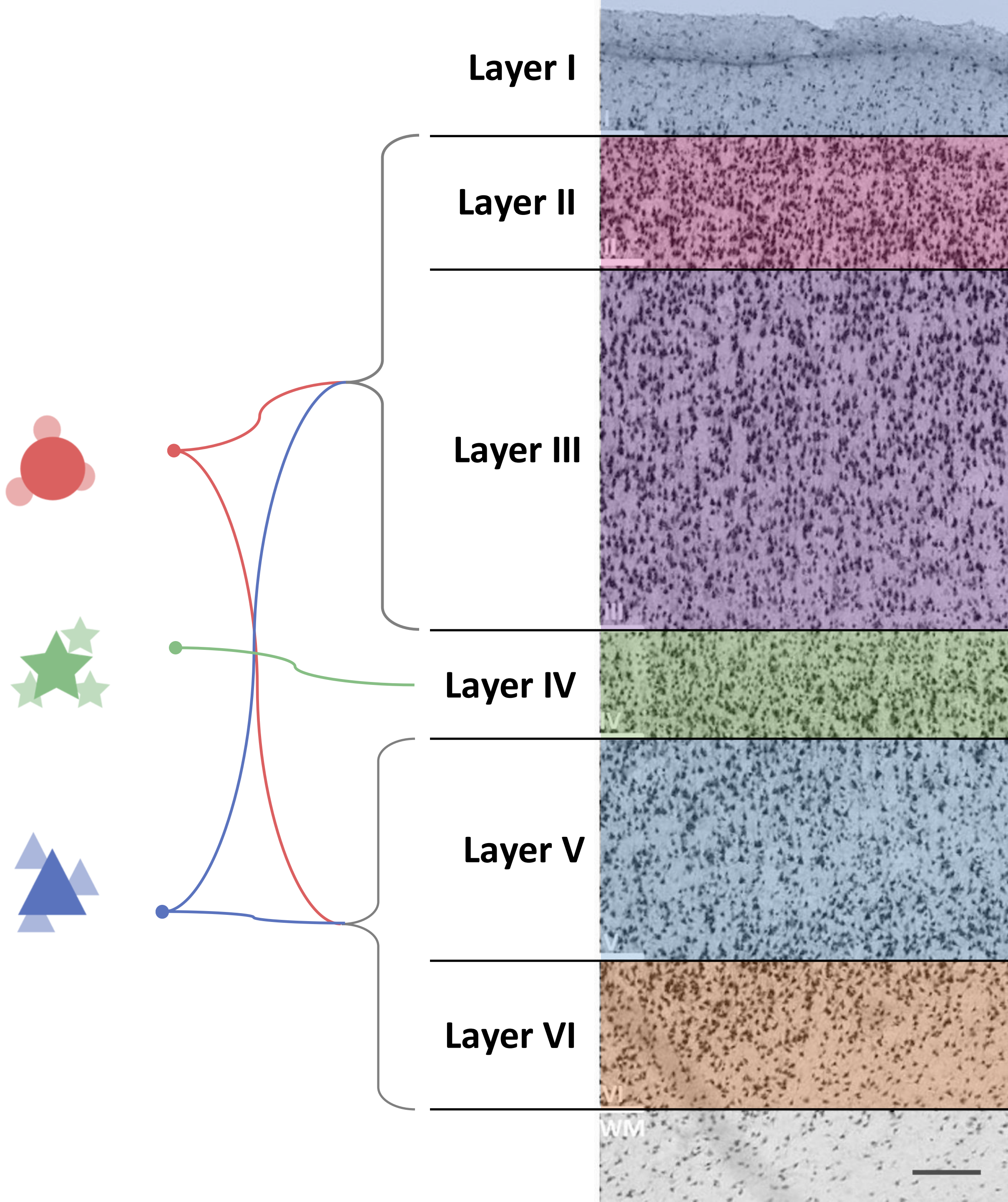
DCM for MEG/EEG data

intra-source connectivity

conductivity

$$\dot{\mu}_{g_k}^{(j)} = \kappa_k^{(j)} \left(\zeta_k^{(j)} - \mu_{g_k}^{(j)} \right)$$

$$\zeta_k^{(j)} = \sum_i \gamma_{\tilde{k}}^{(j,i)} \sigma \left(\mu_V^{(i)} - V_R, \Sigma^{(i)} \right)$$



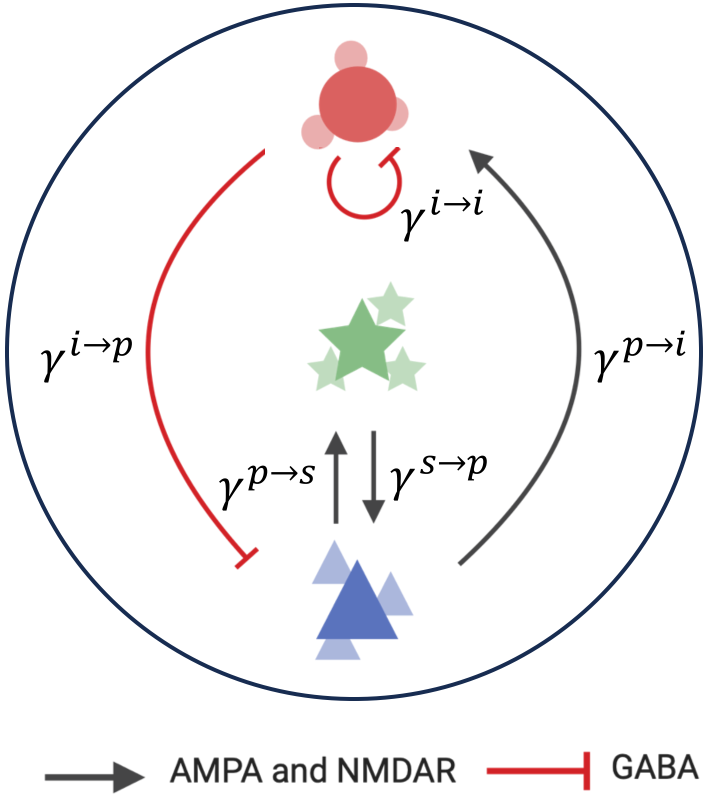
DCM for MEG/EEG data

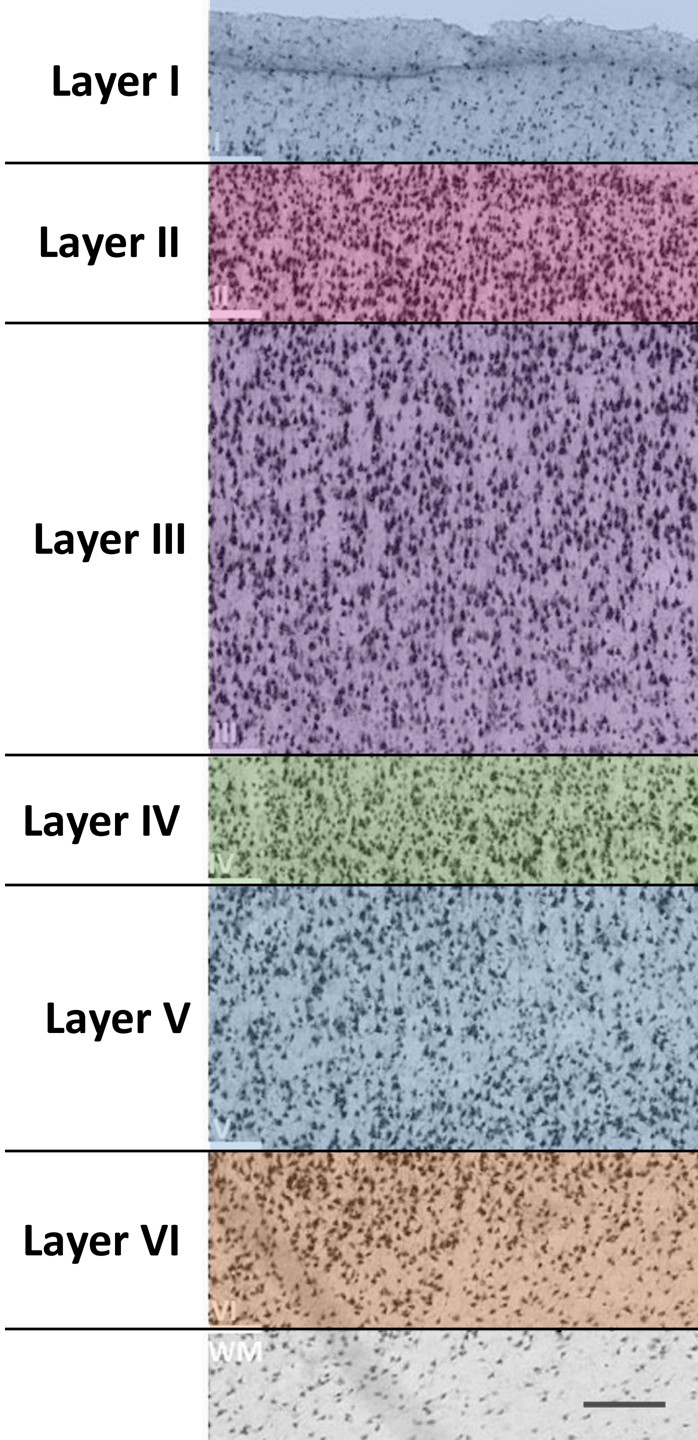
intra-source connectivity

conductivity

$$\dot{\mu}^{(j)}_{g_k} = \kappa^{(j)}_k \left(\zeta^{(j)}_k - \mu^{(j)}_{g_k}\right)$$

$$\zeta^{(j)}_k = \sum_i \gamma^{(j,i)}_{\tilde{k}} \sigma\left(\mu^{(i)}_V - V_R, \Sigma^{(i)}\right)$$





DCM for MEG/EEG data

intra-source connectivity

- Identifies most common classes of neurons
- Reflects the laminar structure of the cortex
- Defines connectivity of neuronal populations

conductivity

$$\dot{\mu}_{g_k}^{(j)} = \kappa_k^{(j)}\left(\zeta_k^{(j)} - \mu_{g_k}^{(j)}\right)$$

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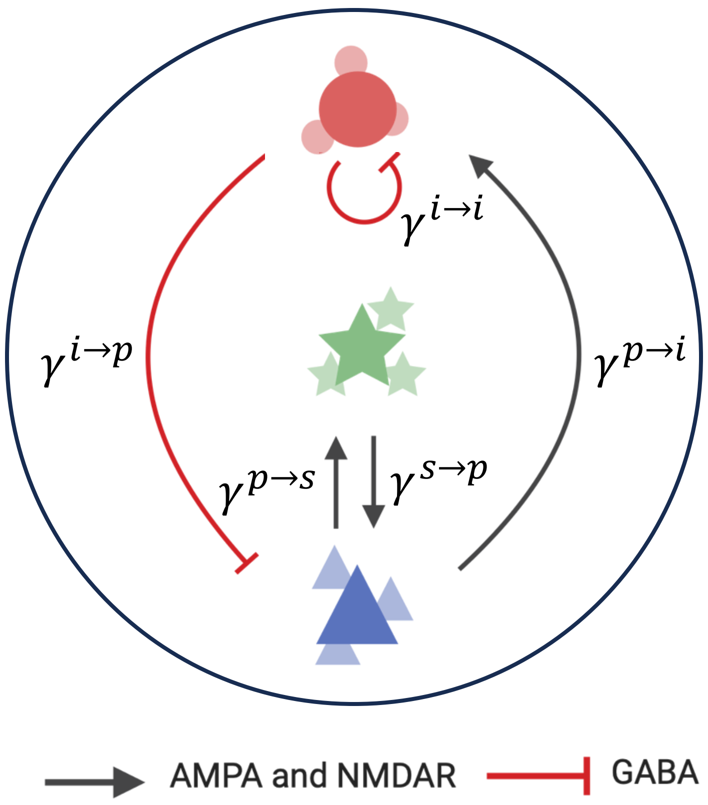

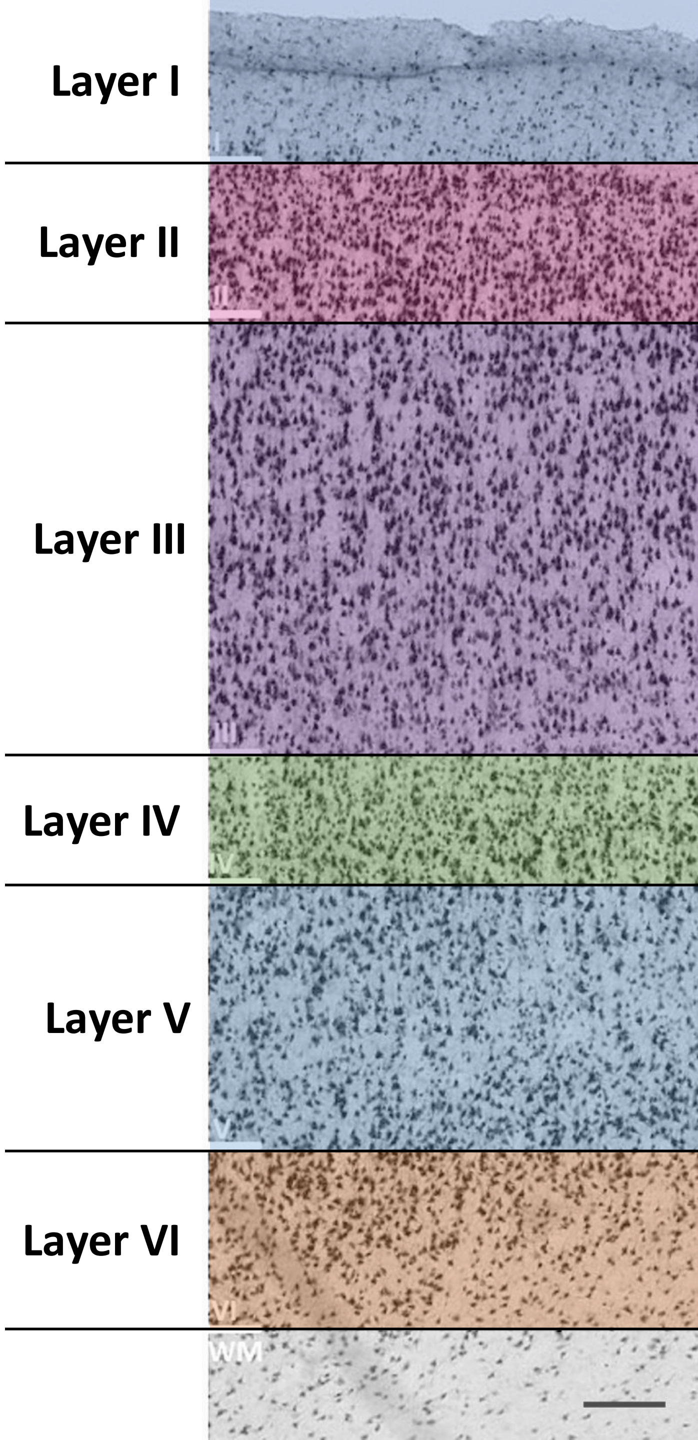

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intra-source connectivity

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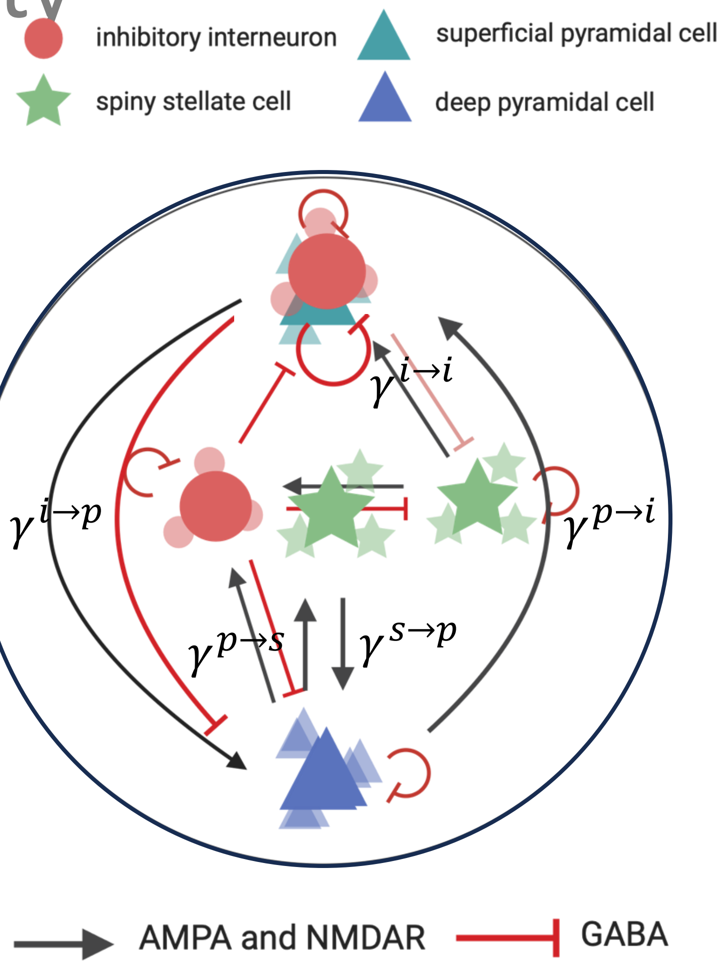
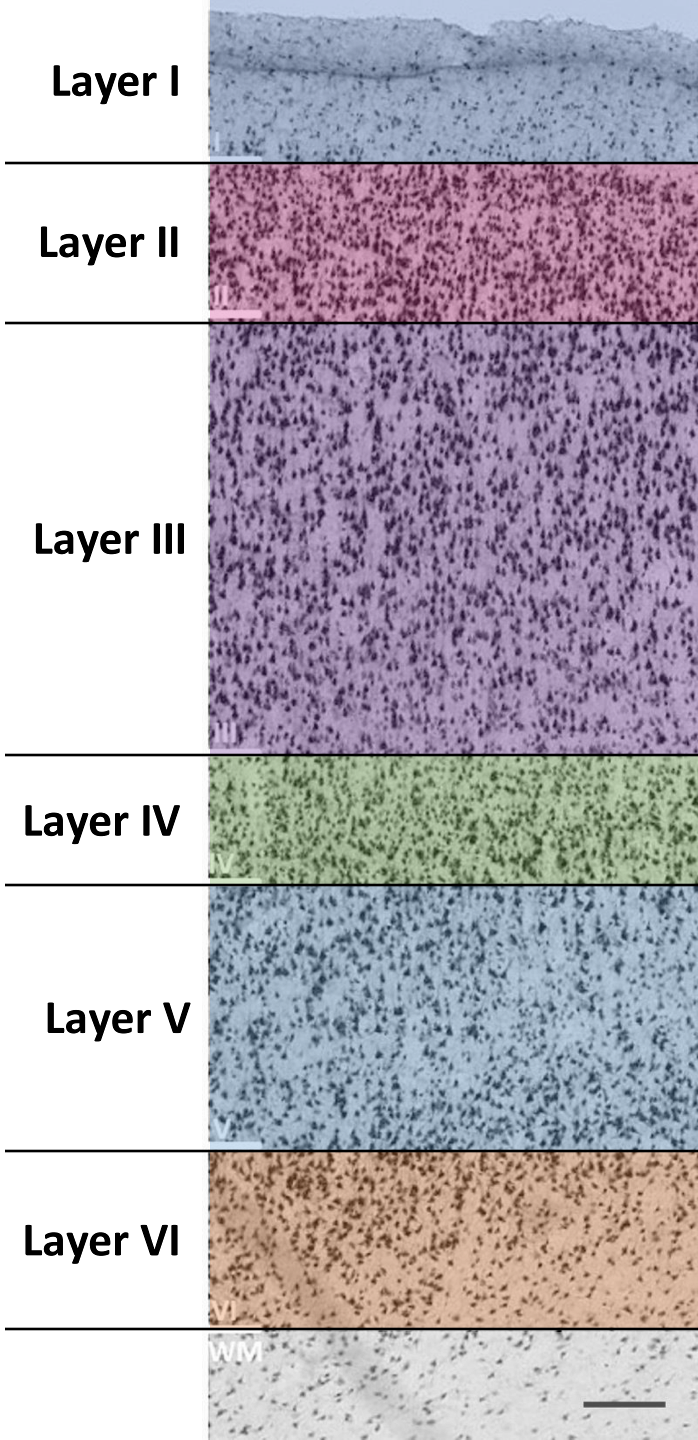
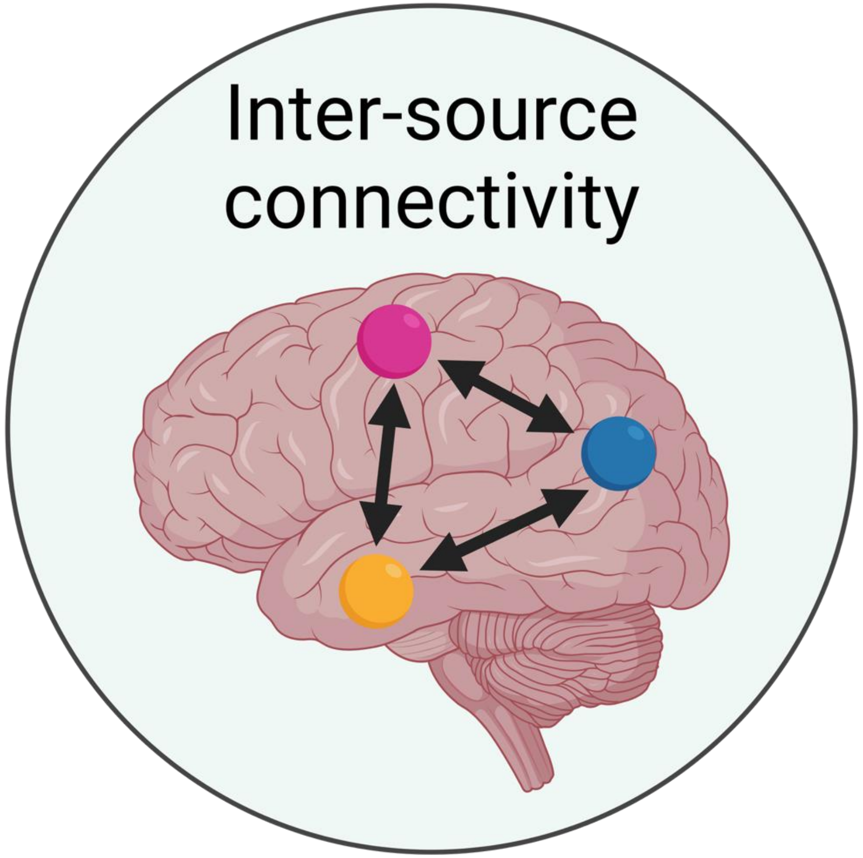
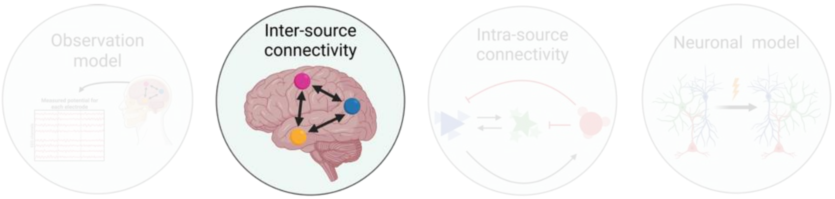




DCM for MEG/EEG data

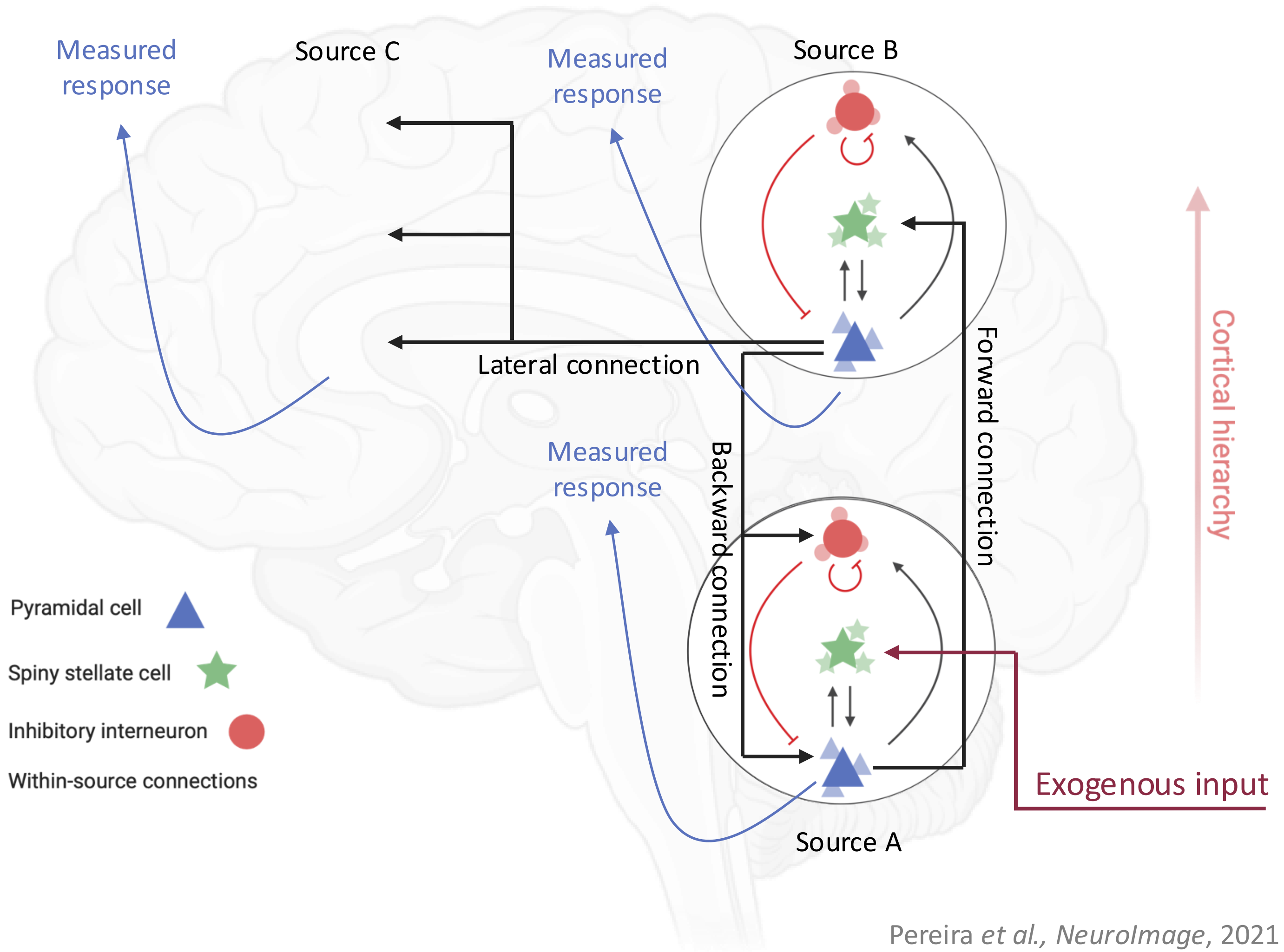
Inter-source connectivity





DCM for MEG/EEG data

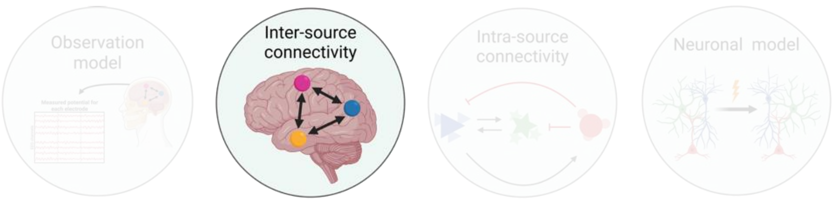
inter-source connectivity



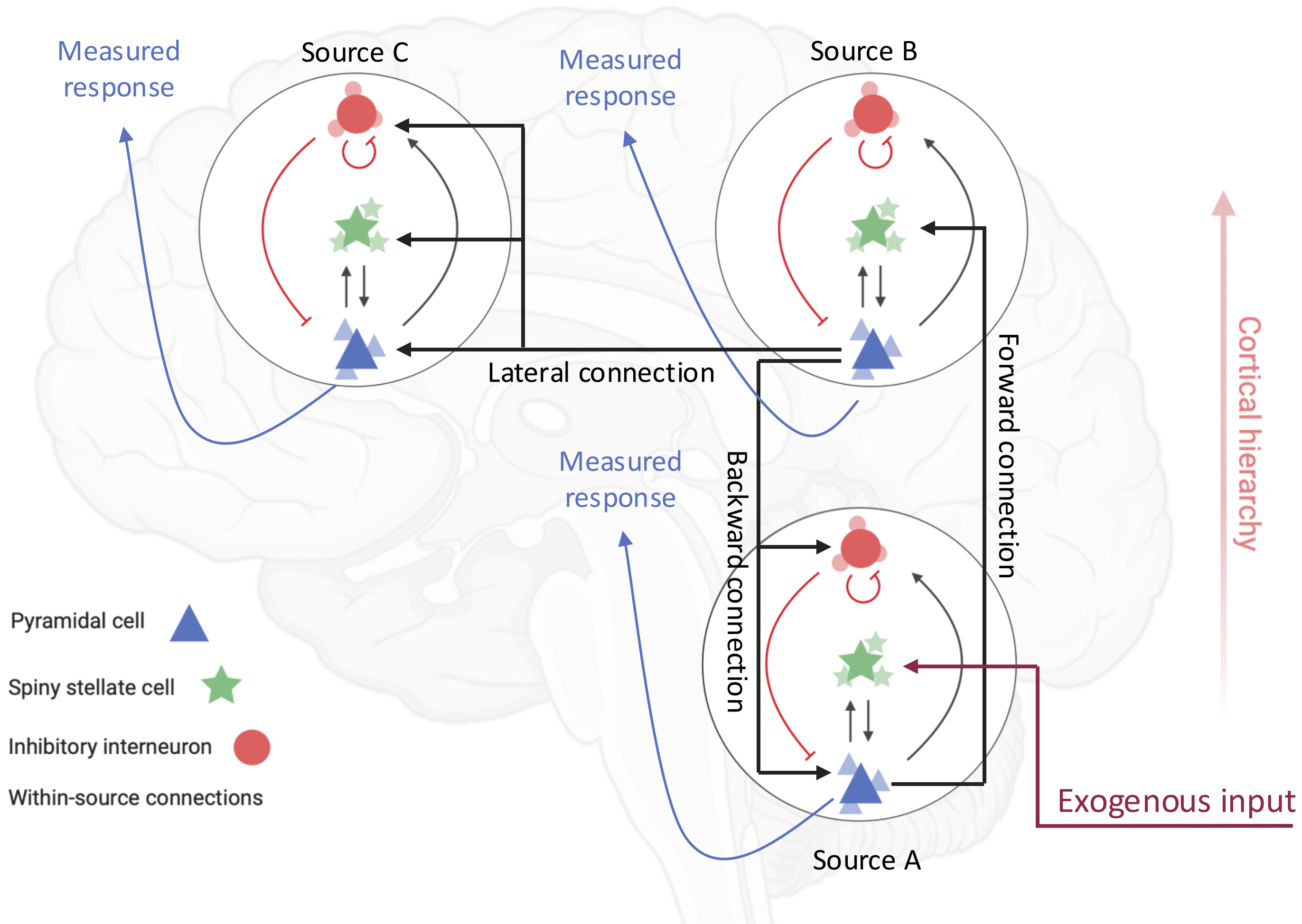
Pereira *et al.*, *NeuroImage*, 2021

DCM for MEG/EEG data

inter-source connectivity



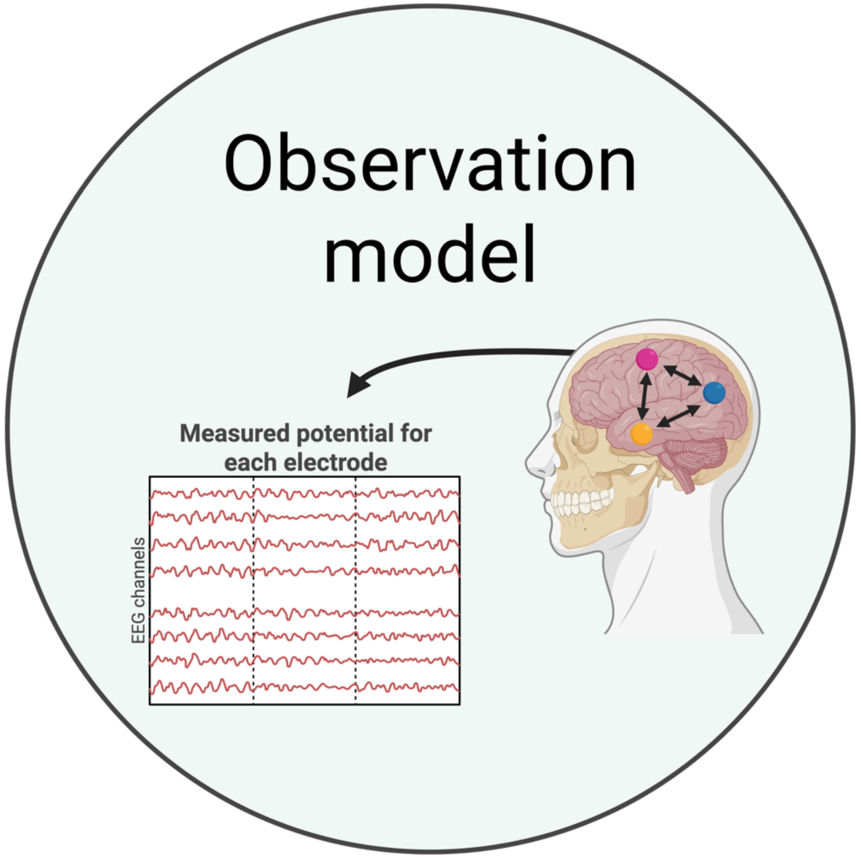
- Defines how multiple sources connect to each other
- Defined by dipole location and extrinsic synaptic connections
- Reflects cortical laminar structure
- Reflects cortical hierarchy and sequential processing



Pereira *et al.*, *NeuroImage*, 2021

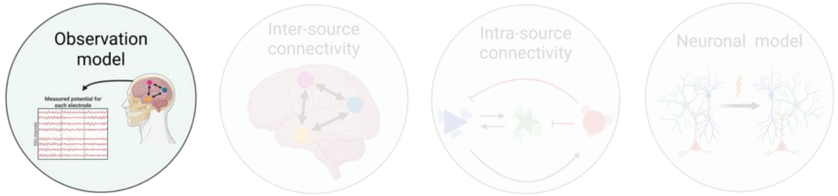
DCM for MEG/EEG data

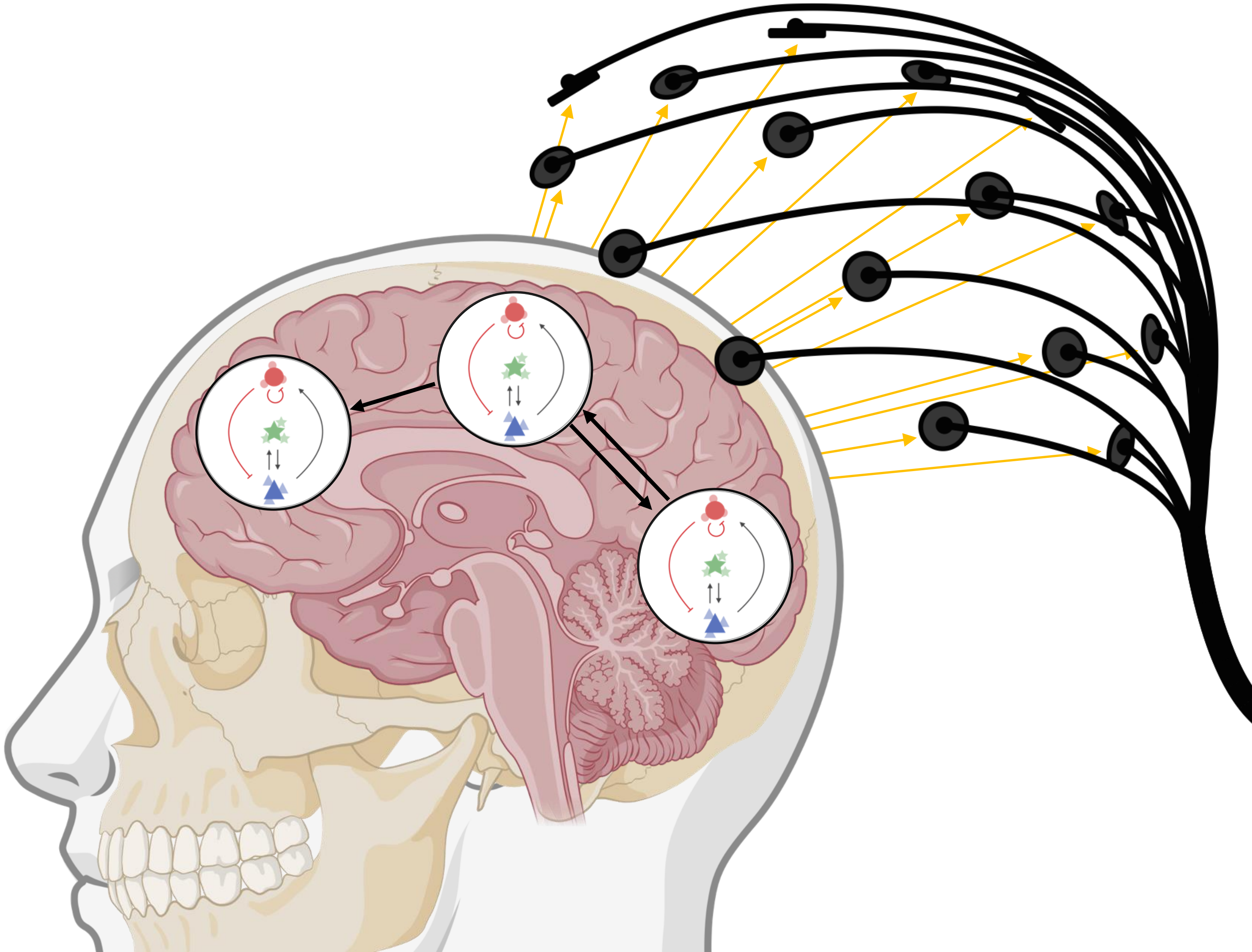
Observation model



DCM for MEG/EEG data

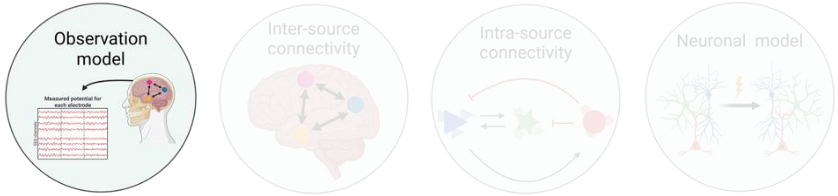
observation model





DCM for MEG/EEG data

observation model

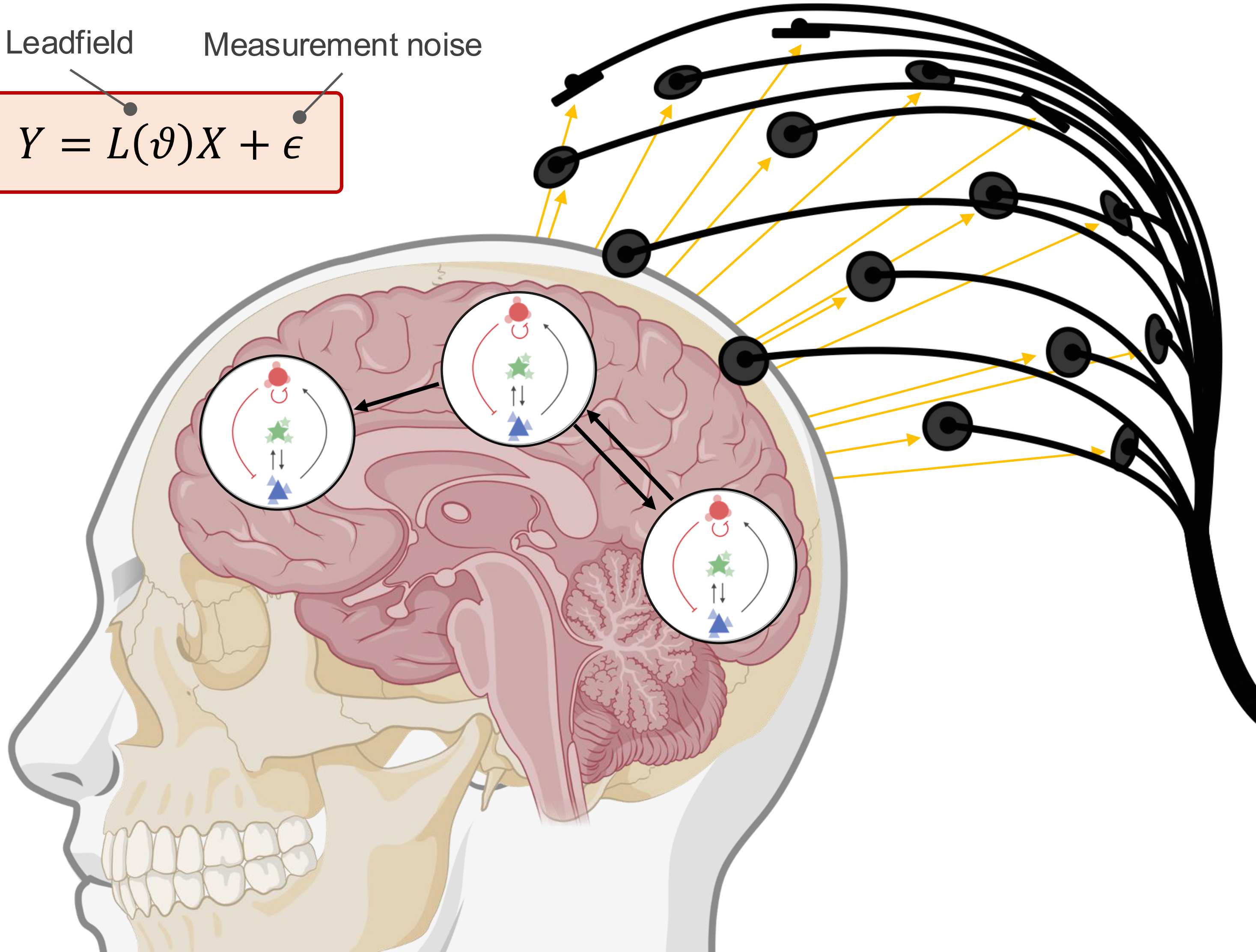


- Describes how electrical source activity propagates through biological tissue
- Is a linear model based on a gain matrix (lead field) L and current dipoles X

Leadfield

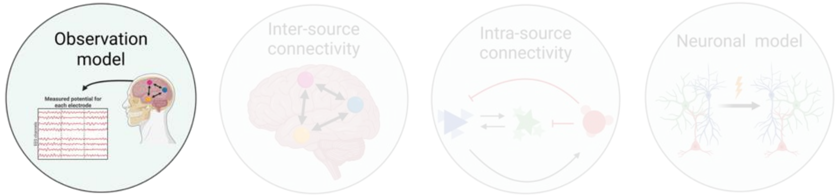
Measurement noise

$$Y = L(\vartheta)X + \epsilon$$



DCM for MEG/EEG data

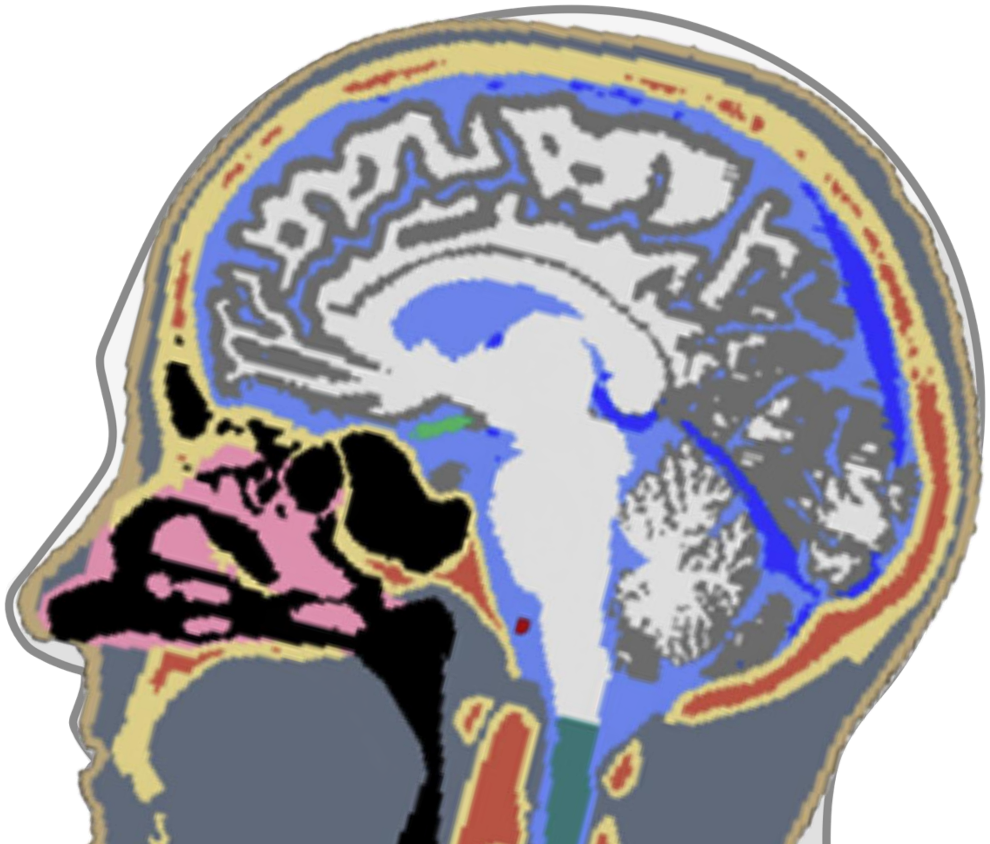
observation model



- Describes how electrical source activity propagates through biological tissue
- Is a linear model based on a gain matrix (lead field) L and current dipoles X
- L based on structural MRI or template
- Different for EEG and MEG

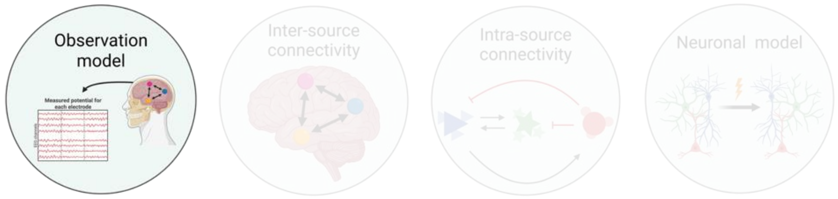
Leadfield　　Measurement noise

$$\boxed{Y = L(\vartheta)X + \epsilon}$$



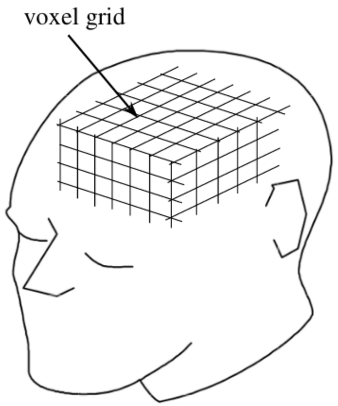
DCM for MEG/EEG data

source reconstruction



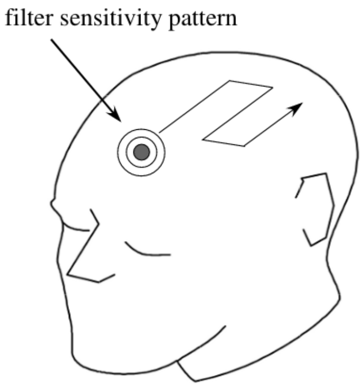
Dipole fitting

- Obtain a sparse solution by jointly optimizing the source activity at predefined locations
- Solution at one location is heavily dependent on source space



Spatial filtering

- Sequential scanning through the search volume by location-specific spatial filters
- Solution at each location is independent from source space



DCM for MEG/EEG data

review paper

Review of underlying principles and classification according to:

- Estimation of source data
- Description of cortical column
- Representation of hidden-states
- Presence of exogenous input

ELSEVIER

NeuroImage
Volume 245, 15 December 2021, 118662

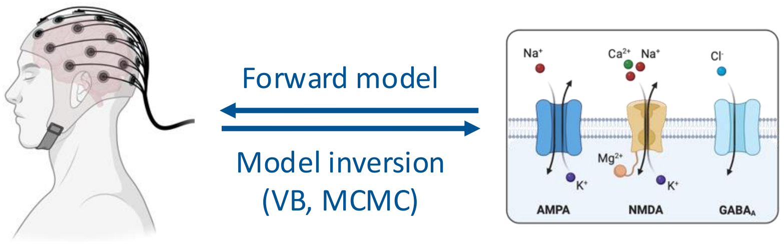
Conductance-based dynamic causal modeling: A mathematical review of its application to cross-power spectral densities

Inês Pereira [a], Stefan Frässle [a], Jakob Heinzle [a], Dario Schöbi [a], Cao Tri Do [a], Moritz Gruber [a], Klaas E. Stephan [a b]

Pereira et al., *NeuroImage*, 2021

DCM for MEG/EEG data

model inversion



Bayes Theorem

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

Likelihood $p(y|\theta, \vartheta, m)$:

- evolution of states (given by neuronal dynamics)

  $$\frac{dx}{dt} = F(x, u, \theta) \quad \text{with} \quad x = \{V, g_k\}$$

- observation model (given by leadfield)

  $$y = G(x, \vartheta) + \epsilon \quad \text{with} \quad G(x, \vartheta) = L(\vartheta)X$$

- distributional form given by assumptions about noise ϵ

Prior $p(\theta, \vartheta | m)$:

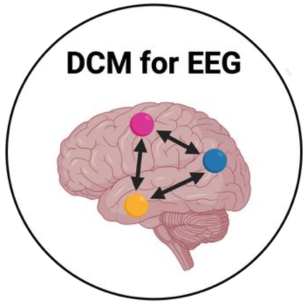
- neuronal parameters θ (time constants, kernel parameters, connection strength, etc.)
- observation model parameters ϑ (dipole location, etc.)

DCM for MEG/EEG data

application studies

Bayes Theorem

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



DCM for MEG/EEG data

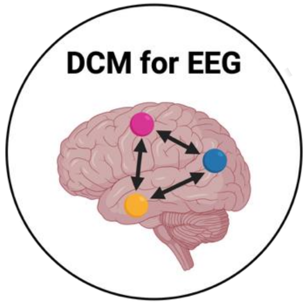
application studies

Bayes Theorem

$$\color{red}{p(\theta, \vartheta | y, m)} = \frac{p(y|\theta, \vartheta, m)\, p(\theta, \vartheta | m)}{p(y|m)}$$

<u>Test for differences</u>

- Delineation of subgroups and inference of receptor function based on posterior parameter estimates



DCM for MEG/EEG data

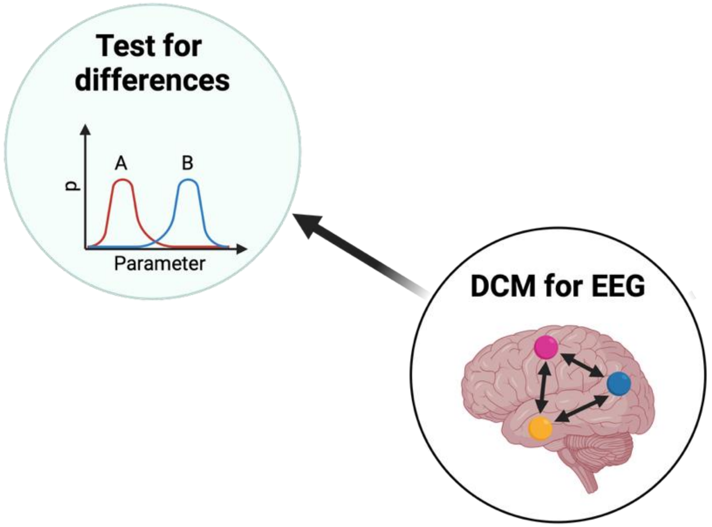
application studies

Bayes Theorem

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

<u>Test for dose-dependent effects</u>

- Identification/prediction of pharmacological efficacy based on posterior parameter estimates



DCM for MEG/EEG data

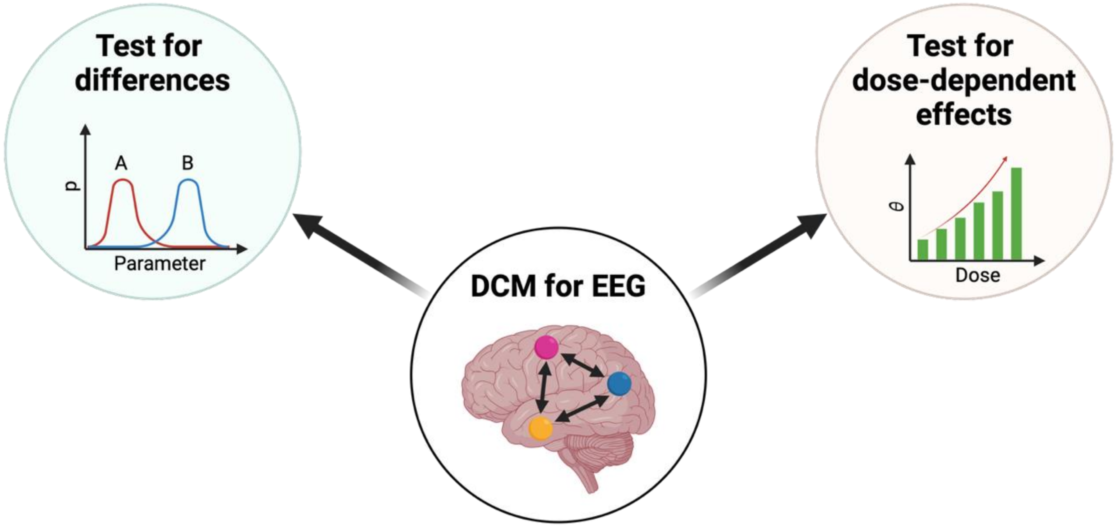
application studies

Bayes Theorem

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

Model selection

- Inference of network circuitry based on model selection



DCM for MEG/EEG data

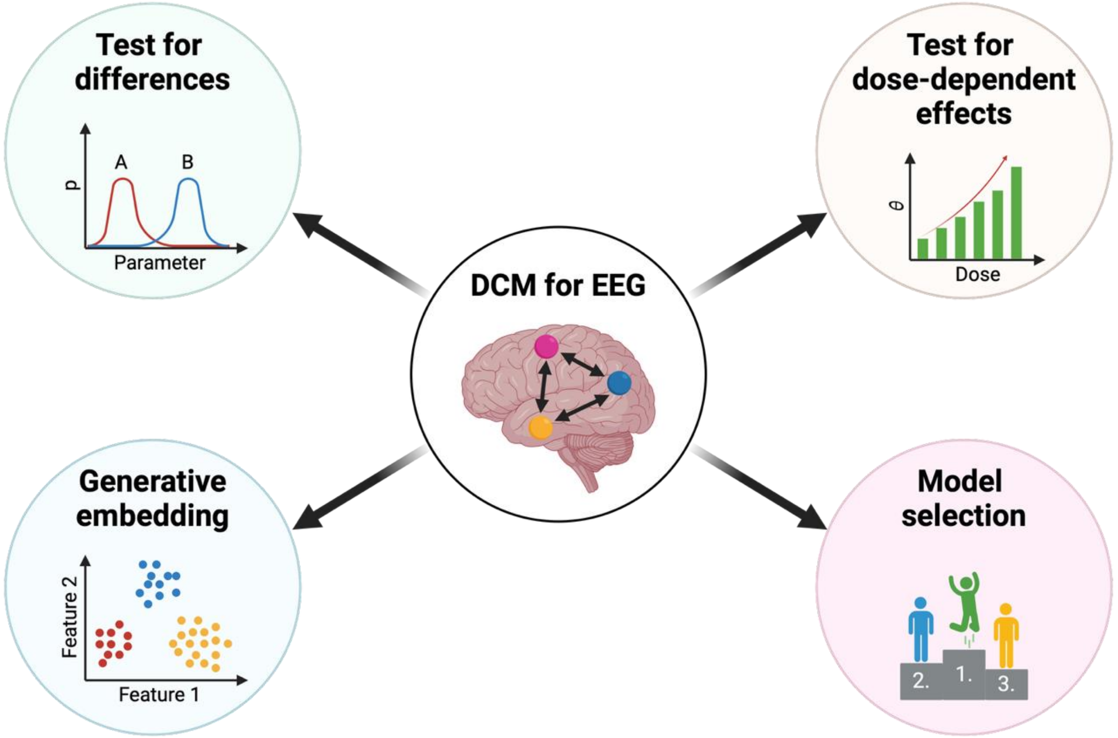
application studies

Bayes Theorem

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

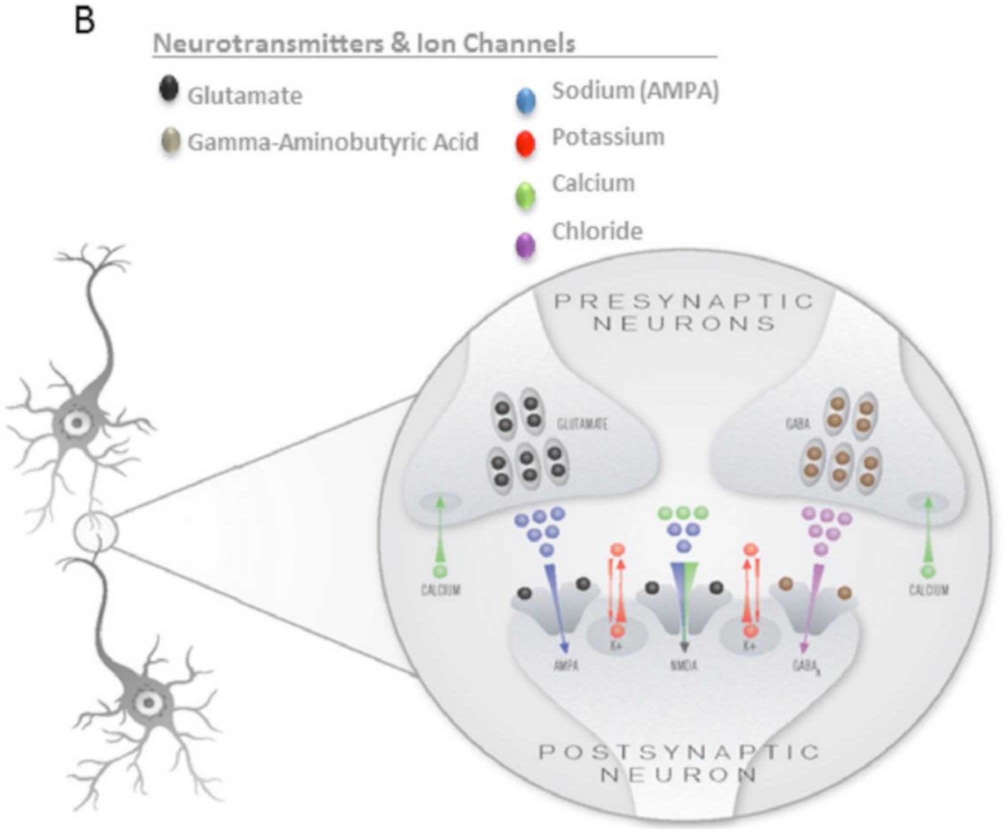
Generative embedding

- Feature engineering by mechanistically interpretable dimensionality reduction



Profiling neuronal ion channelopathies with non-invasive brain imaging and dynamic causal models

- Assay synaptic-level channel communication non-invasively
- Two patients with single-gene mutations:
  1. Potassium rectifying channel
  2. Calcium transmitter release
- 94 controls



Gilbert et al., *NeuroImage*, 2015

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- 94 controls

$$C\dot{\mu}_V^{(j)} = \left(\sum_k \alpha_k \mu_{g_k}^{(j)} \left(V_k - \mu_V^{(j)}\right)\right) + \left(\sum_{k'} \alpha_{k'} \mu_{g_{k'}}^{(j)} m_{k'}\left(\mu_V^{(j)}\right)\left(V_{k'} - \mu_V^{(j)}\right)\right)$$

$$\dot{\mu}_{g_k}^{(j)} = \kappa_k^{(j)}\left(\zeta_k^{(j)} - \mu_{g_k}^{(j)}\right)$$

$$\zeta_k^{(j)} = \sum_i \gamma_{\tilde{k}}^{(j,i)} \sigma\left(\mu_V^{(i)} - V_R, \omega^{(i)}\right)$$

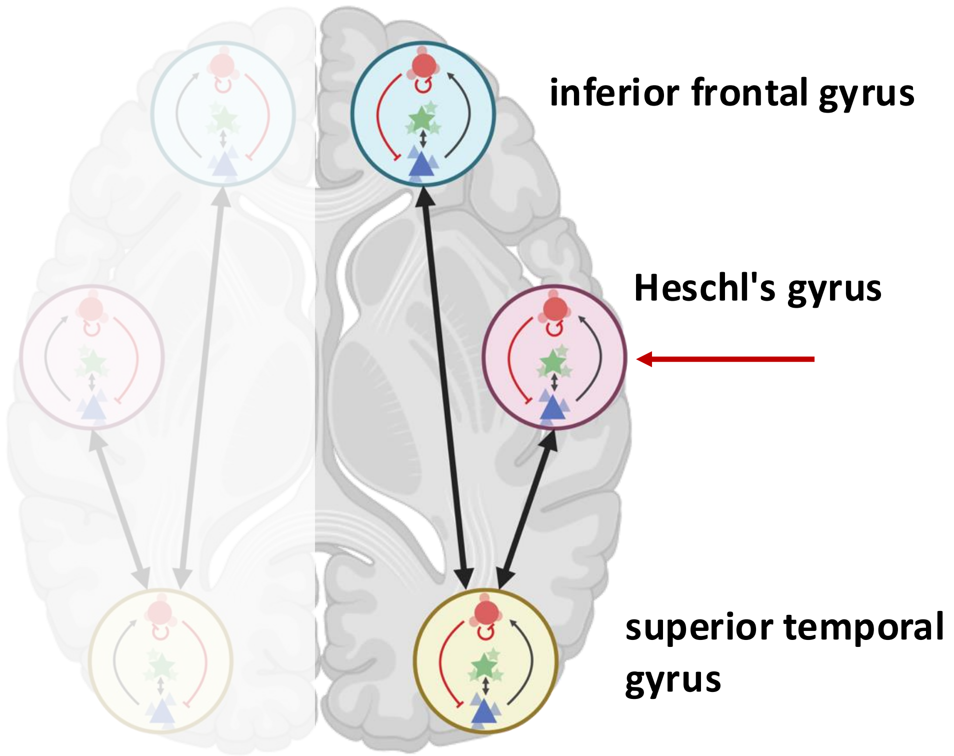
where $k \in L, \mathrm{AMPA}, \mathrm{GABA}$ and $\mathrm{k}' \in \mathrm{NMDA}, \mathrm{KIR}$

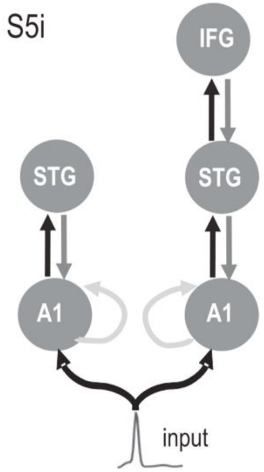
α_{KIR} : weight of potassium rectifying channel
ω : inverse of afferent firing variance

Gilbert et al., *NeuroImage*, 2015

Profiling neuronal ion channelopathies with non-invasive brain imaging and dynamic causal models

- Conductance-based neural mass model DCM
- Three neuronal populations
- Six bilateral source regions
- Auditory oddball paradigm
- SQUID MEG measurements

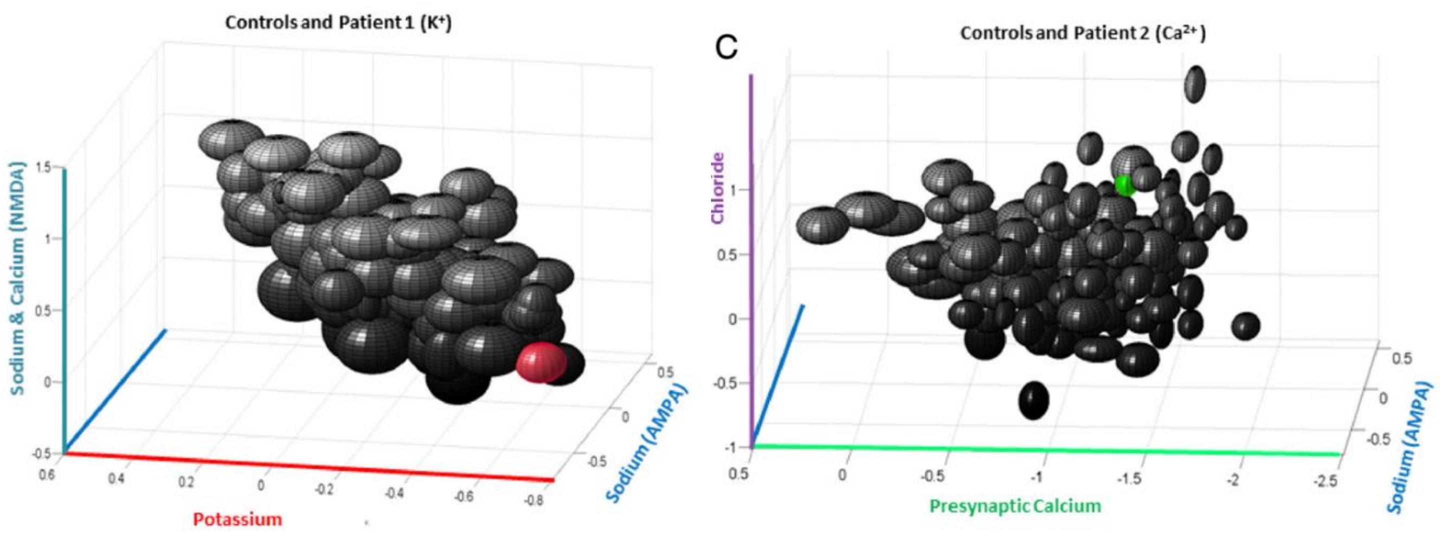




Gilbert et al., *NeuroImage*, 2015, Garrido et al., *J. Neurophysiol.*, 2009

Profiling neuronal ion channelopathies with non-invasive brain imaging and dynamic causal models

- Two patients with single-gene mutations:
  1. Potassium rectifying channel
  2. Calcium transmitter release
- Test for differences in posterior parameter estimates reflecting channel dynamics



$\alpha_{K\ Leak}$

ω_{Ca}

Gilbert et al., *NeuroImage,* 2015

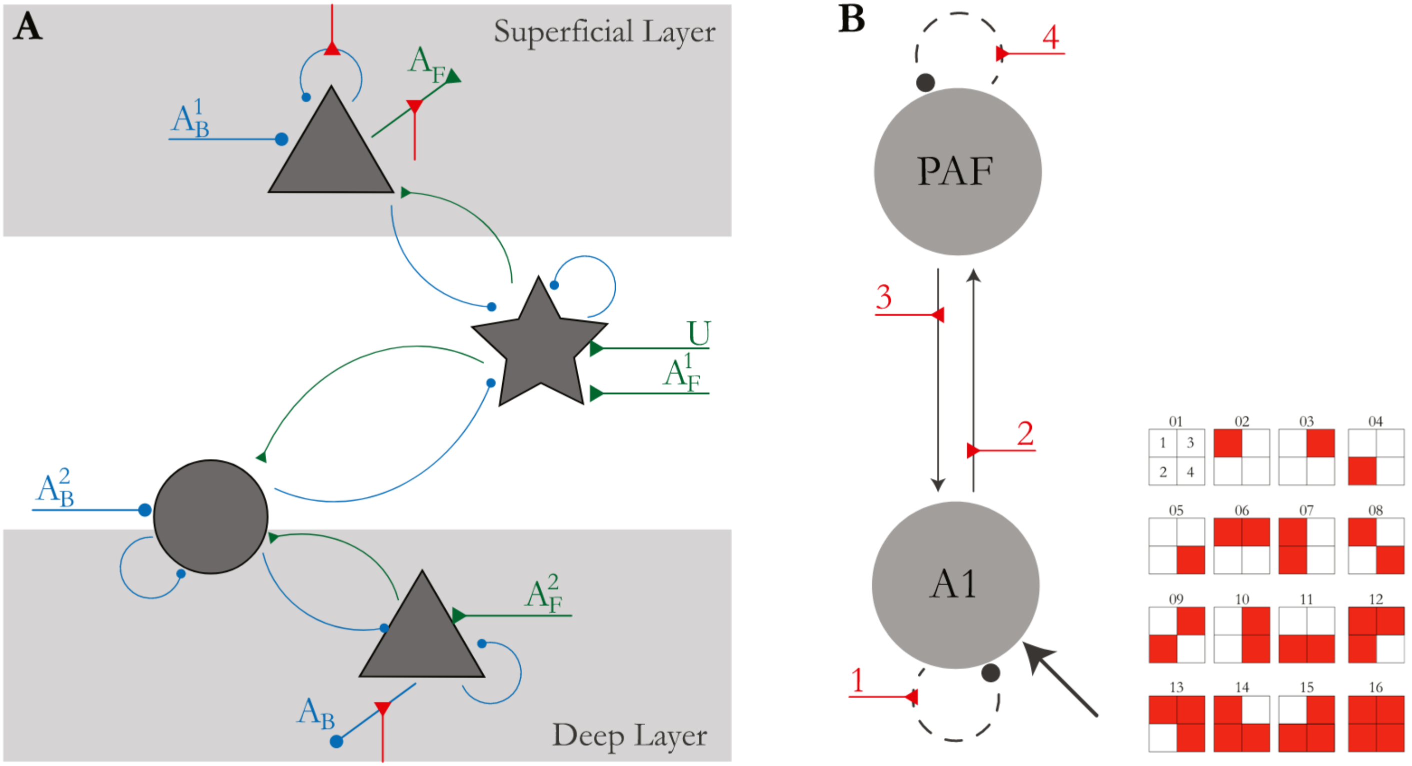
Model-based prediction of muscarinic receptor function from auditory mismatch negativity responses

- Pharmacological treatments affect actions of neuromodulatory transmitters
- Infer functional state of cholinergic receptors
- Intraperitoneal injections of:
  - Scopolamine (muscarinic receptor antagonist, different doses)
  - Pilocarpine (muscarinic receptor agonist, different doses)
  - 0.6 % NaCl-solution (vehicle)

Schöbi et al., *NeuroImage*, 2021

Model-based prediction of muscarinic receptor function from auditory mismatch negativity responses

- Convolution-based DCM
- Auditory stimulus
- Model-space comprising different modulatory connections
- Generative embedding:
  - 1000 datapoints per recording to 30 parameter estimates
  - Linear SVM with LOOCV
  - Permutation testing to assess significance



Schöbi et al., *NeuroImage*, 2021

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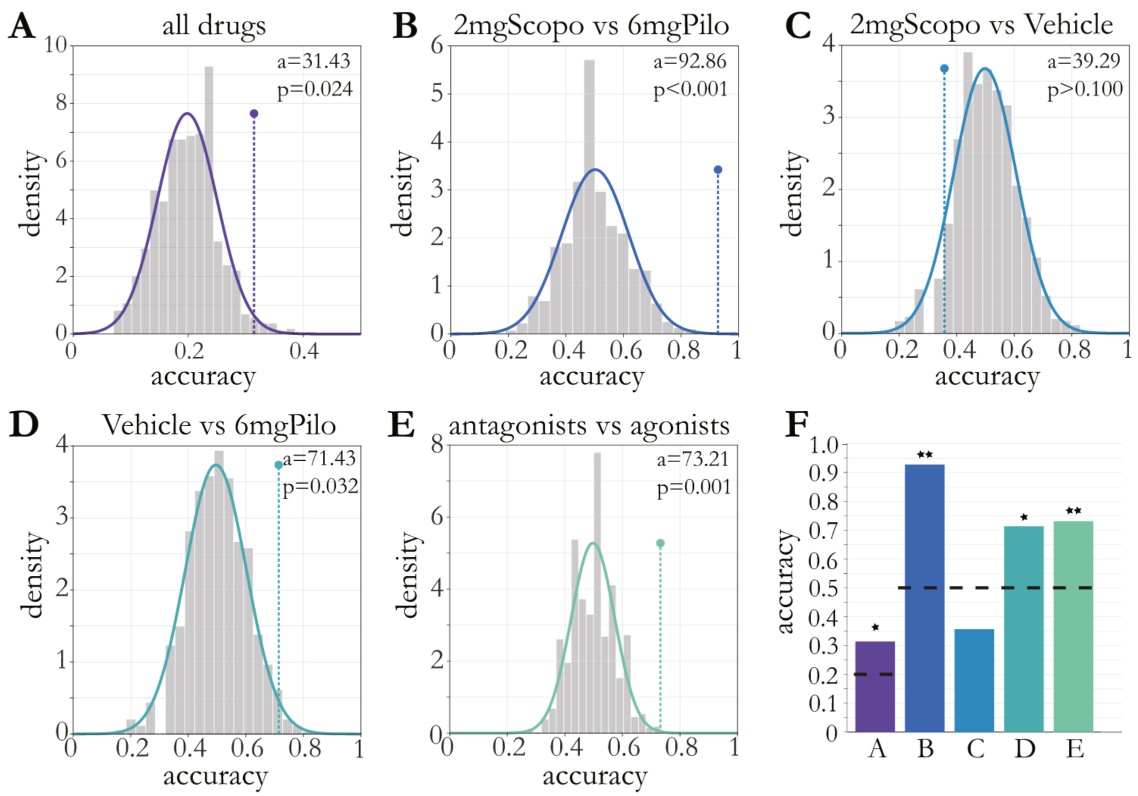

Schöbi et al., *NeuroImage*, 2021

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