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# Whole-brain models fitting and applications

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# Why using models?

- Proposing new **causal mechanisms**.
- Recover **latent information**.
- Create a **test bench** for biomedical interventions.
- **Guide** the development of useful experiments and **inspire** new technologies.

# Building a model



Research Article: Methods/New Tools | Novel Tools and Methods

## A how-to-model guide for Neuroscience

<https://doi.org/10.1523/ENEURO.0352-19.2019>

## A how-to-model guide for Neuroscience

G. Blohm<sup>1</sup>, K.P. Kording<sup>2</sup>, P.R. Schrater<sup>3</sup>



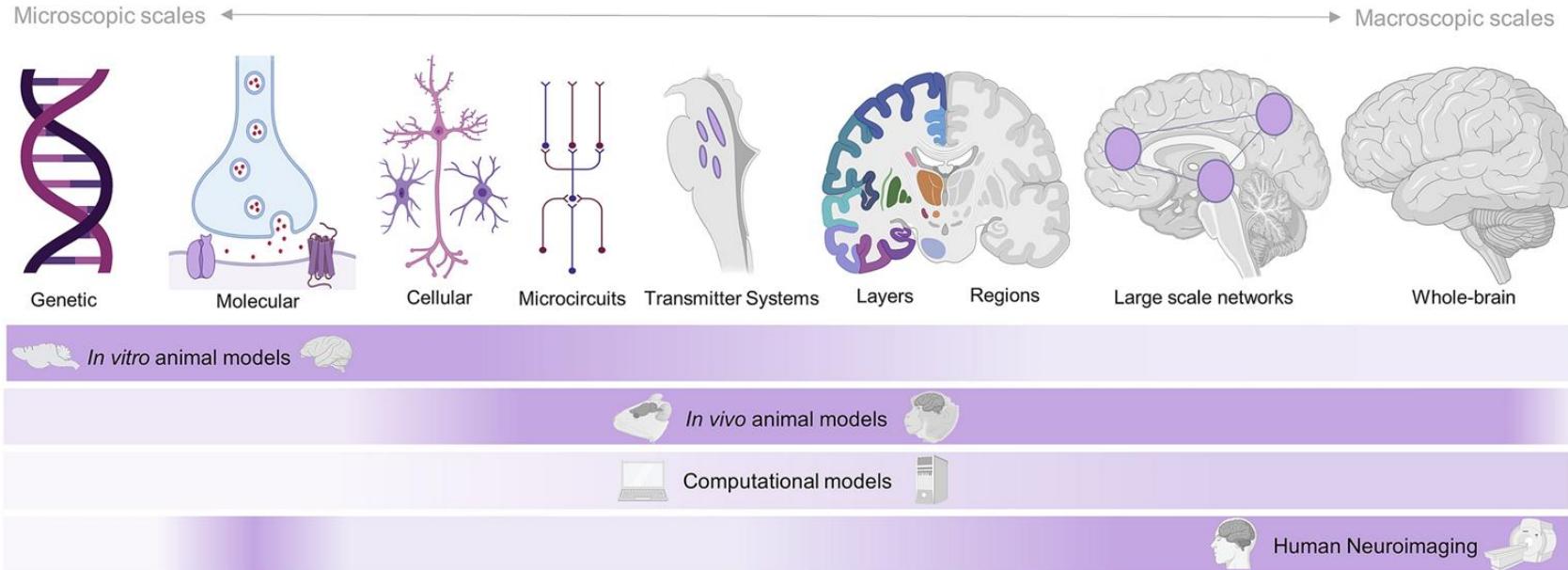
# Building a model

A good model should answer these three questions:

- **The what?:** The model must describe the experimental result.
- **The how?:** related to the mechanisms of the model that reproduce the data.
- **The why?:** explain what is the motivation of the "entity" (e.g., the brain) to function based on the proposed mechanisms.

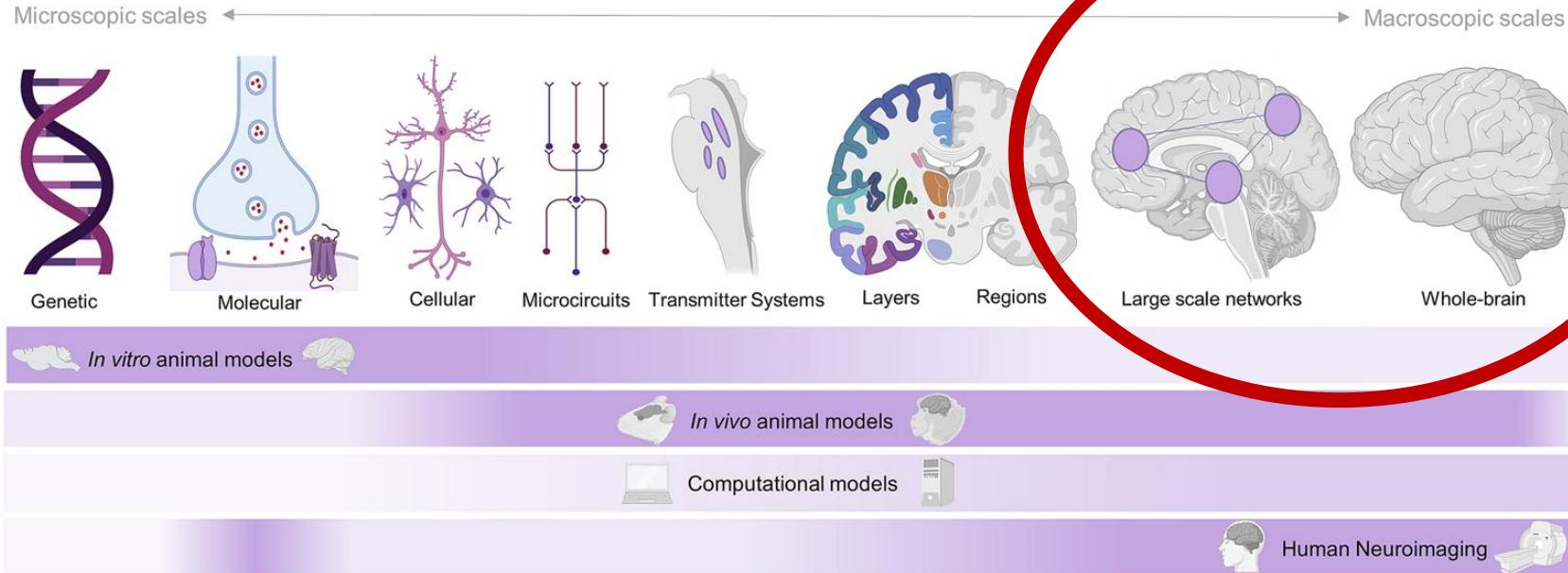


# Modeling Scales



Luppi et al. (2021)

# Modeling Scales



Luppi et al. (2021)

# Whole-brain models

**Basic elements** of whole-brain models:

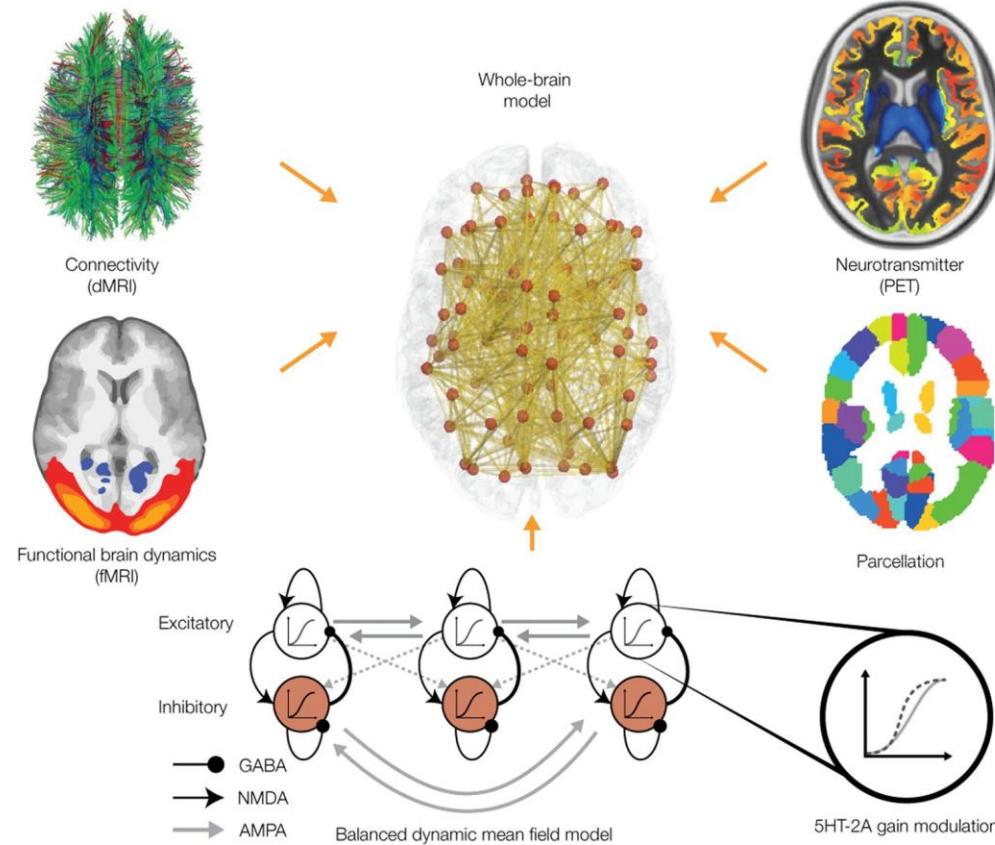
**Dynamic model:** A system of differential equations that describes the dynamics of a brain region.

**Structural connectivity:** A topology used to connect network elements.

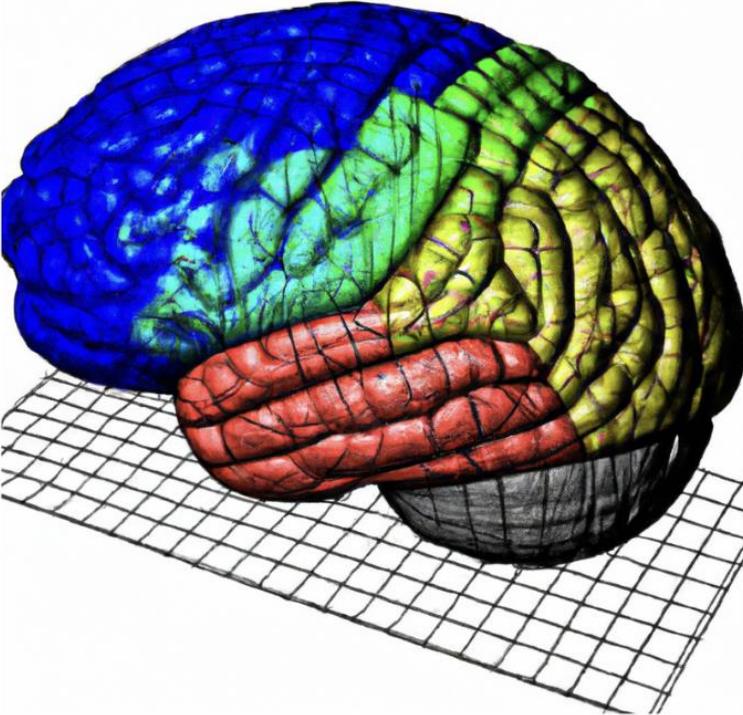
**Heterogeneities of the model:** depending on the research question to be answered, the model may include distance matrices, receptor density, and asymmetries in the assignment of parameters, among others.

# Whole-brain models

Deco et al. (2018,  
Current Biology)

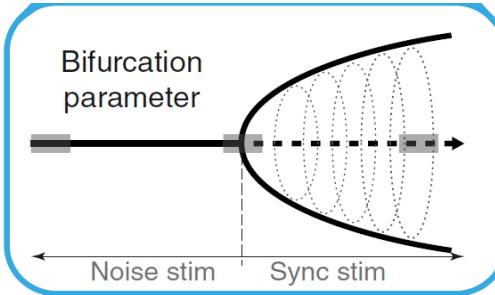


# What models?



# Phenomenological models

## Hopf Model



Deco et al. (2019)

Hopf: Local dynamics

$$\frac{dx_i(t)}{dt} = \boxed{a_i} x_i(t) - [x_i^2(t) - y_i^2(t)] x_i(t) - \boxed{w_i} y_i(t) + \boxed{\beta \eta_i(t)}$$

$$\frac{dy_i(t)}{dt} = \boxed{a_i} y_i(t) - [x_i^2(t) - y_i^2(t)] y_i(t) - \boxed{w_i} x_i(t) + \boxed{\beta \eta_i(t)}$$

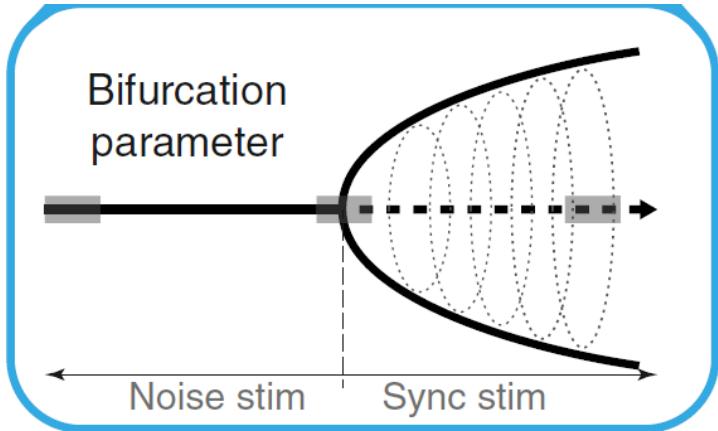
*Bifurcation parameter*

*Oscillatory frequency*

*Background noise*

# Phenomenological models

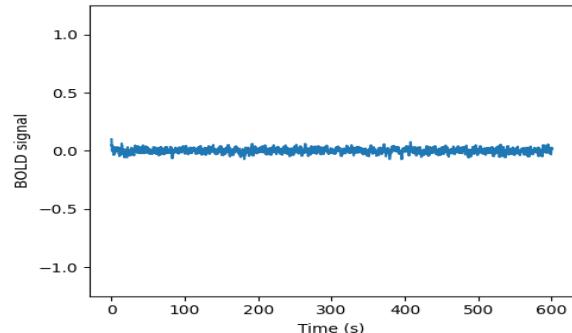
## Hopf Model



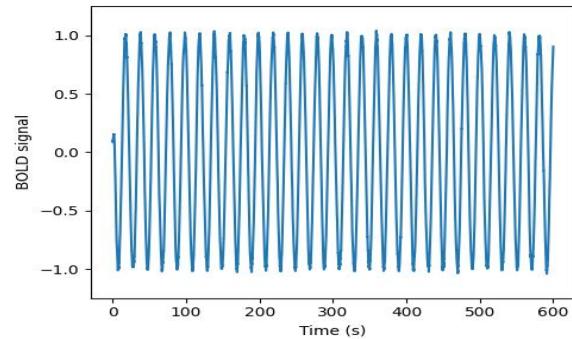
Hopf: Local dynamics

Deco et al. (2019)

$a = -1$  (noisy signals)



$a = 1$   
(Sustained oscillations)



# Phenomenological models

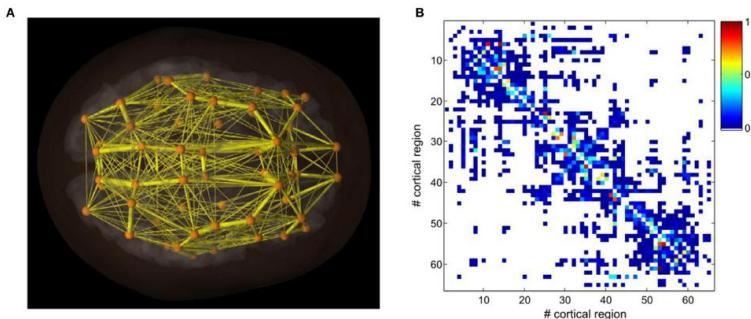
## Hopf Model

$$\frac{dx_i(t)}{dt} = a_i x_i(t) - [x_i^2(t) - y_i^2(t)] x_i(t) - w_i y_i(t) + G \sum_{j=1}^n M_{ij} (x_j(t) - x_i(t)) + \beta \eta_i(t)$$

$$\frac{dy_i(t)}{dt} = a_i y_i(t) - [x_i^2(t) - y_i^2(t)] y_i(t) - w_i x_i(t) + G \sum_{j=1}^n M_{ij} (y_j(t) - y_i(t)) + \beta \eta_i(t)$$

*Structural connectivity connections ( $M_{ij}$ )  
Scaled by a global coupling parameter*

**Deco et al. (2012)**



# Phenomenological models

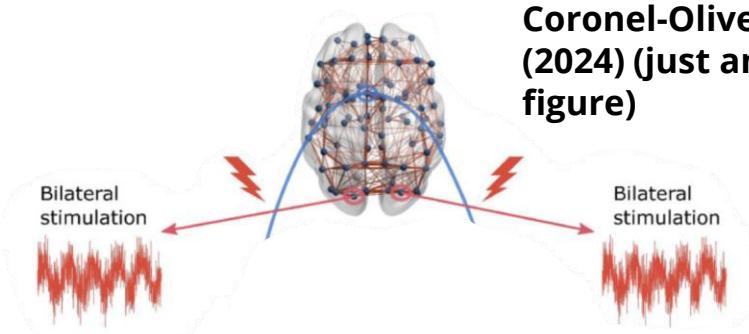
## Hopf Model

$$\frac{dx_i(t)}{dt} = a_i x_i(t) - [x_i^2(t) - y_i^2(t)] x_i(t) - w_i y_i(t) + G \sum_{j=1}^n M_{ij} (x_j(t) - x_i(t)) \\ + F_i(t) \cos(w_i t) + \beta \eta_i(t)$$

$$\frac{dy_i(t)}{dt} = a_i y_i(t) - [x_i^2(t) - y_i^2(t)] y_i(t) - w_i x_i(t) + G \sum_{j=1}^n M_{ij} (y_j(t) - y_i(t)) \\ + F_i(t) \sin(w_i t) + \beta \eta_i(t)$$

**External stimulation (perturbations)**

Wave stimulation  
 $+F_0 \cos(\omega_0 t)$

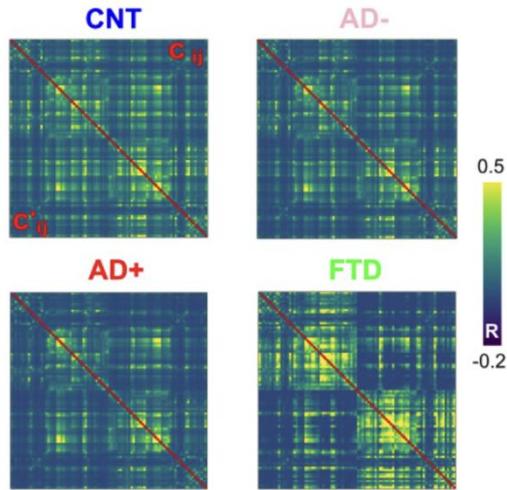


Coronel-Oliveros et al.  
(2024) (just an example  
figure)

# Phenomenological models

Sanz Perl et al.  
(2023)

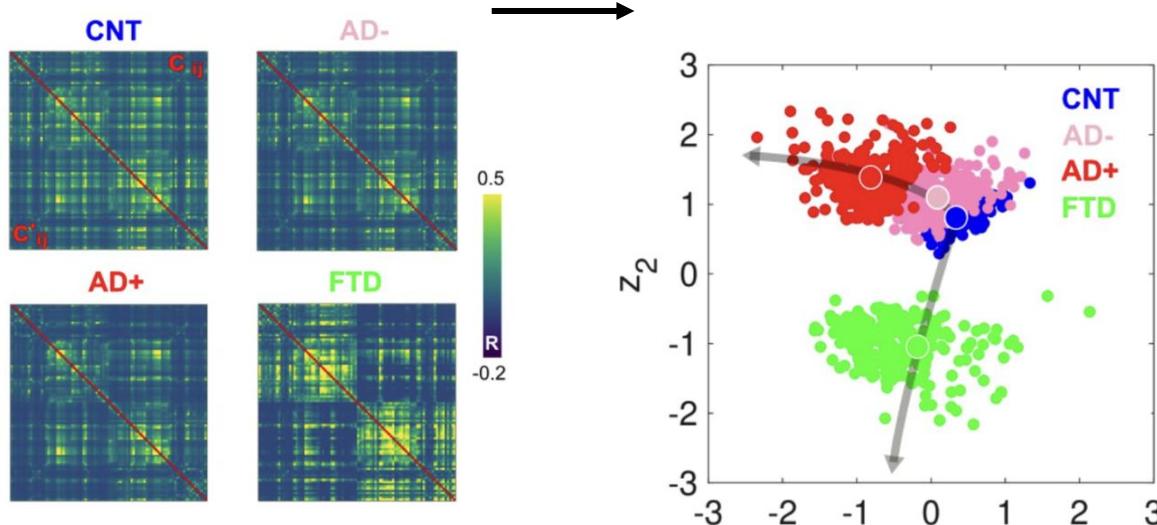
Simulated functional connectivity



# Phenomenological models

Sanz Perl et al.  
(2023)

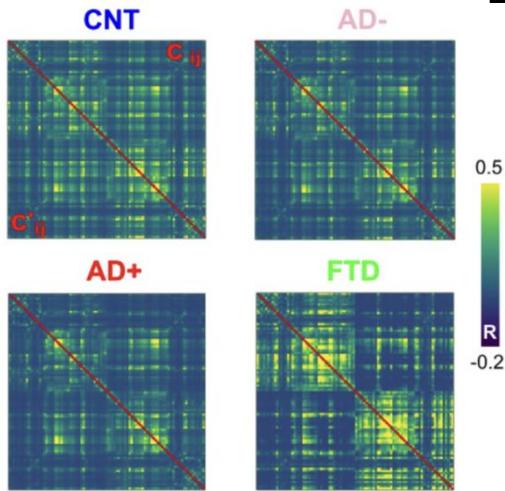
Simulated functional connectivity      Dimensionality reduction



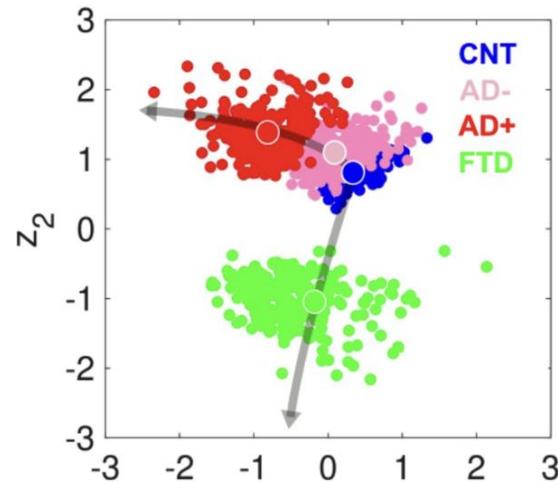
# Phenomenological models

Sanz Perl et al.  
(2023)

## Simulated functional connectivity



## Dimensionality reduction

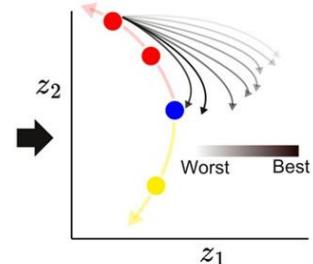


## Stimulation

Wave stimulation  
+  $F_0 \cos(\omega_0 t)$

Sync stimulation  
 $a_i \rightarrow a_i + \Delta a_i$

Noise stimulation  
 $a_i \rightarrow a_i - \Delta a_i$



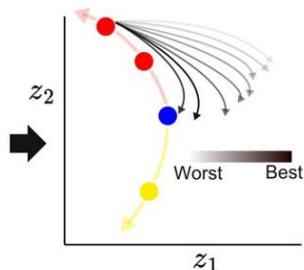
# Phenomenological models

Sanz Perl et al.  
(2023)

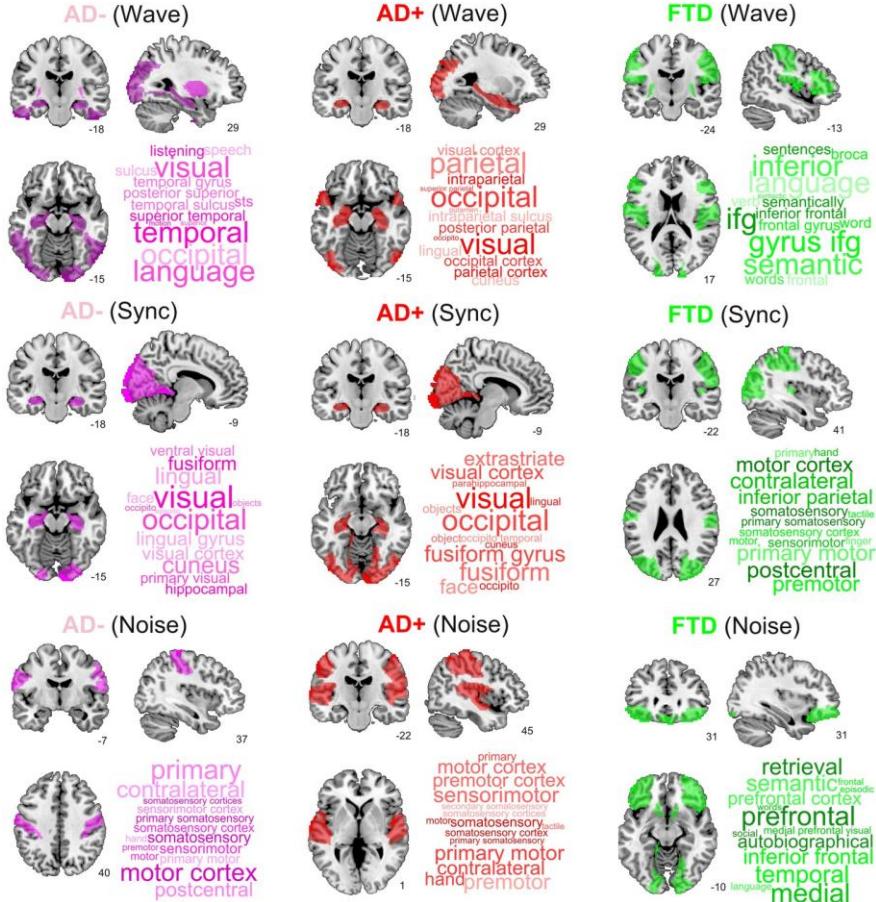
Wave stimulation  $+F_0 \cos(\omega_0 t)$

Sync stimulation  $a_i \rightarrow a_i + \Delta a_i$

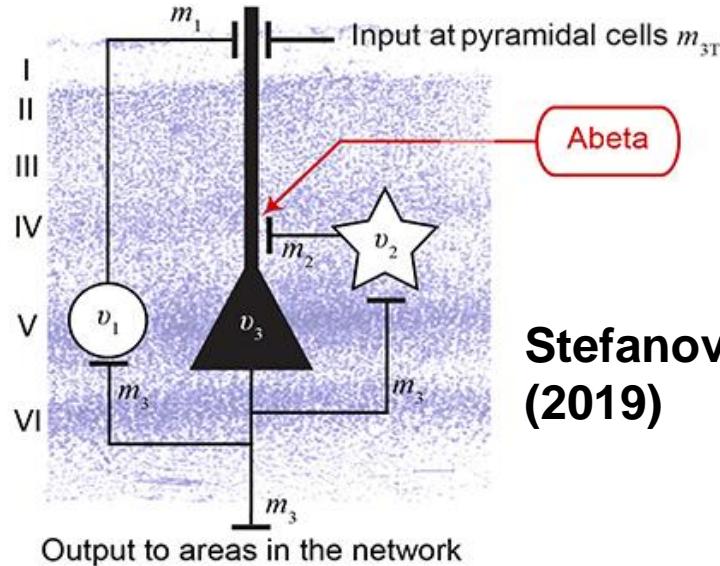
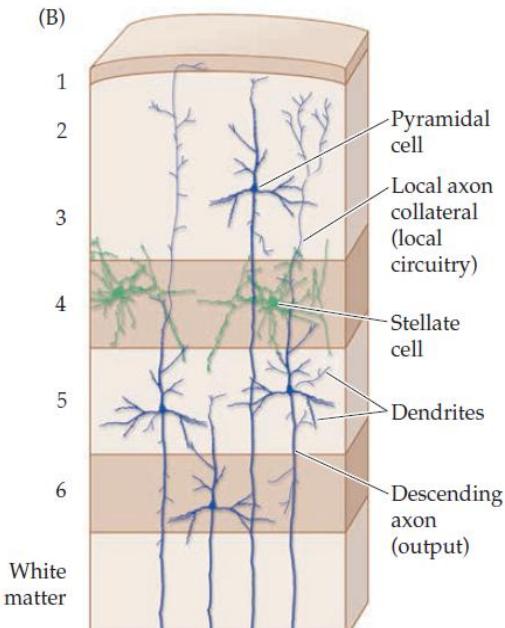
Noise stimulation  $a_i \rightarrow a_i - \Delta a_i$



Best stimulation targets



# Neural mass models: Jansen & Rit

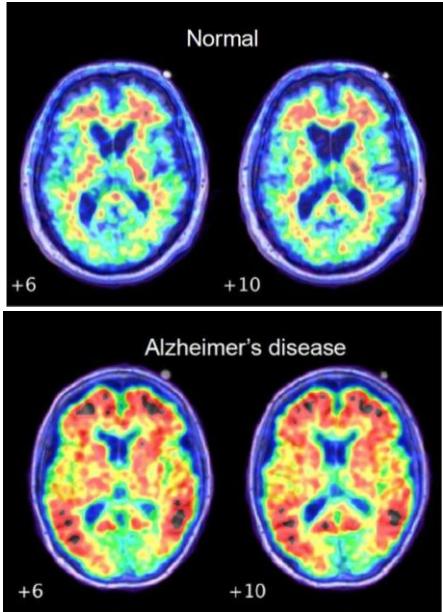


**Stefanovski et al.  
(2019)**

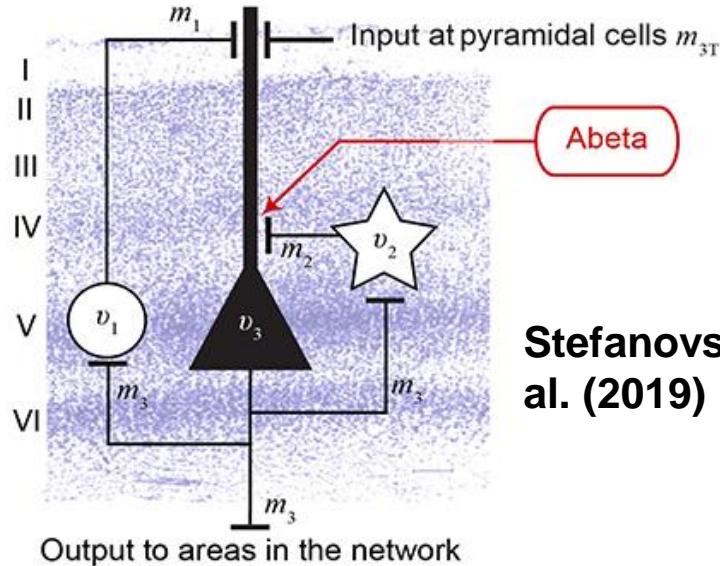
- $v_1$ : Excitatory interneurons.
- $v_2$ : inhibitory interneurons.
- $v_3$ : pyramidal neurons.

# Neural mass models: Jansen & Rit

## Amyloid beta aggregation (PET) in AD dementia



Chapleau et al. (2022)



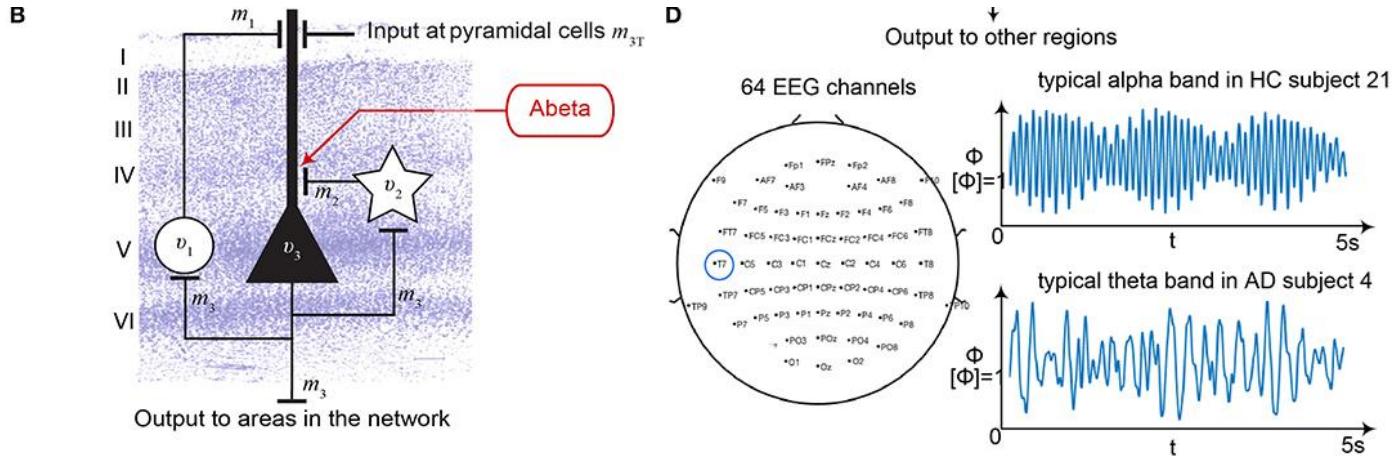
Stefanovski et al. (2019)

$v_1$ : Excitatory interneurons.  
 $v_2$ : inhibitory interneurons.  
 $v_3$ : pyramidal neurons.

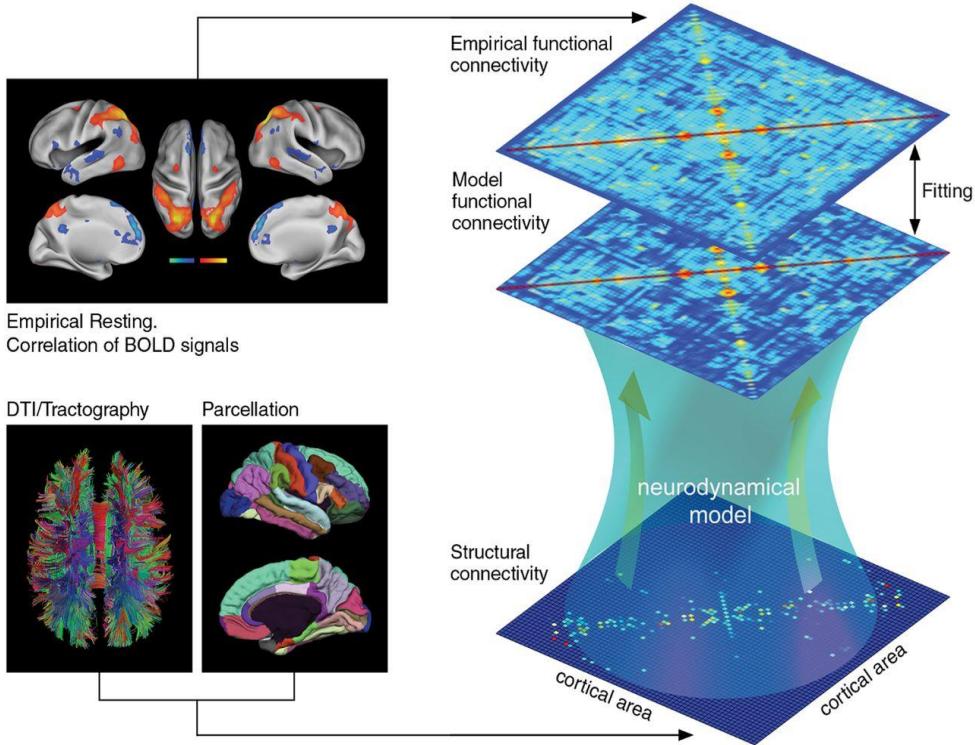
# Neural mass models: Jansen & Rit

**Stefanovski et al. (2019)** can reproduce changes in brain activity in Alzheimer's patients.

**Stefanovski et al. (2019)**



# Model fitting



*Deco et al. (2013)*

# Target Function

The **target function** corresponds to the function that you want to optimize (minimize or maximize) during model tuning.

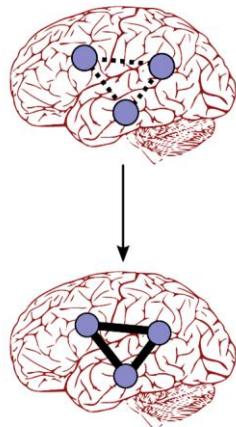
Some **output of the model** that has a direct correlation with the experimental data is used.

If experimental data are not available, a value taken from the literature can be used as a **reference** (e.g., firing rates, postsynaptic potential amplitude, among others).

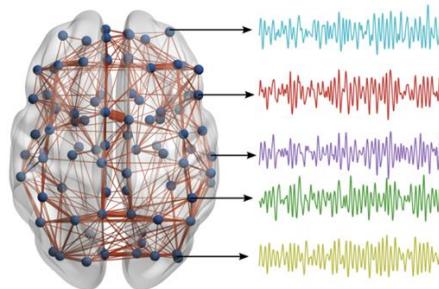
# Target Function

## Fitting functional connectivity (FC)

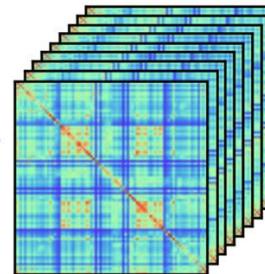
Global coupling modulation



Simulated BOLD-like signals

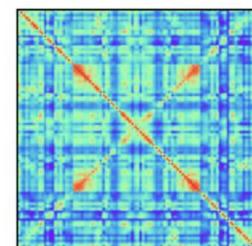


Simulated FCs



SSIM

HCP empirical FC

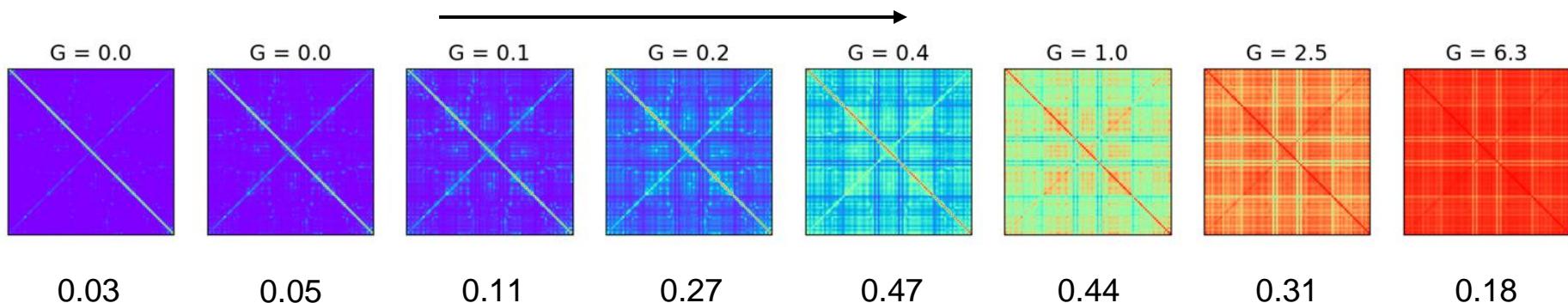


SSIM: structural similarity index.  
SSIM = 1: perfect fit.  
SSIM = 0: poor fit.

# Target Function

## Fitting functional connectivity (FC)

Increasing connectivity strength in the model

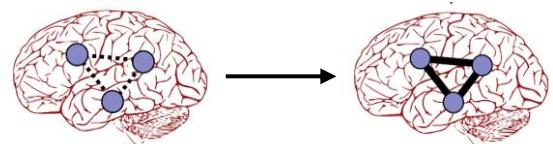


Simulated FC matrices using the Hopf model

**SSIM**

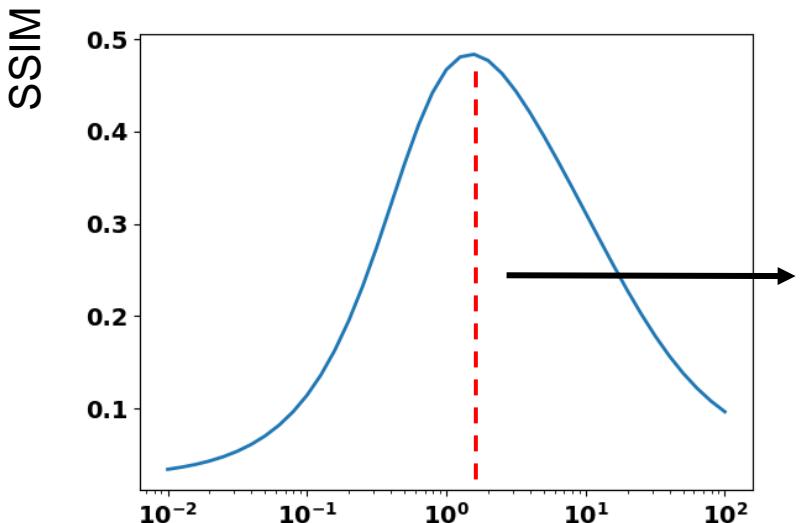
SSIM: structural similarity index.  
SSIM = 1: perfect fit.  
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Global coupling modulation

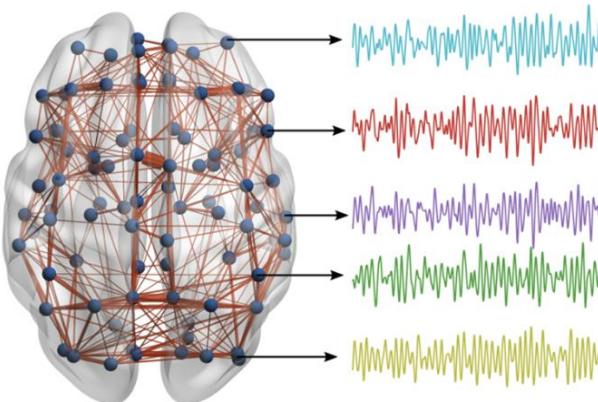


# Target Function

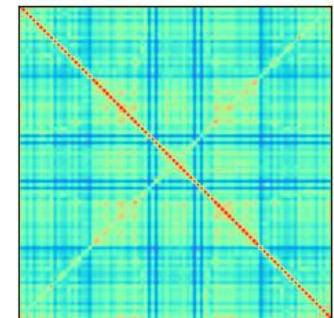
## Fitting functional connectivity (FC)



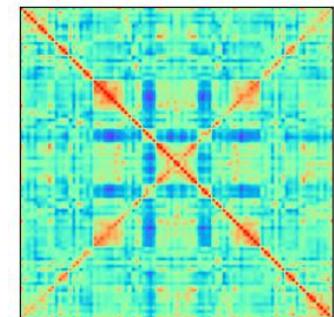
Global Coupling



Simulated FC



Empirical FC



# Brain clocks and biophysical modeling using EEG



# How can we measure “brain health”?



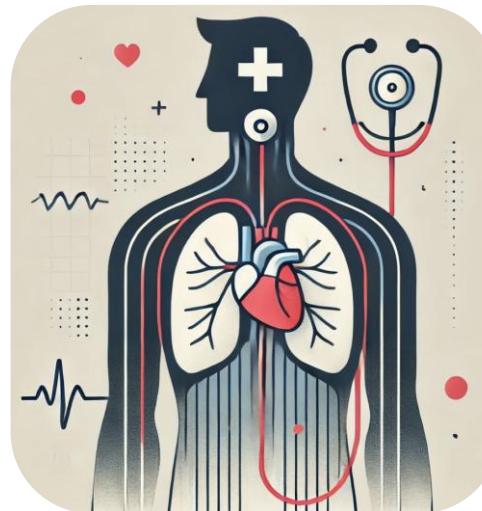
**Blood pressure:**  $>120/80 \text{ mm}$ : *hypertension*.  
You can use just a single pair of numbers  $<90/60 \text{ mm}$ : *hypotension*.

# How can we measure “brain health”?



**Blood pressure:**  
You can use just a single pair of numbers

$>120/80 \text{ mm}$ : *hypertension.*  
 $<90/60 \text{ mm}$ : *hypotension.*



**Overall health:**  
Frailty index:

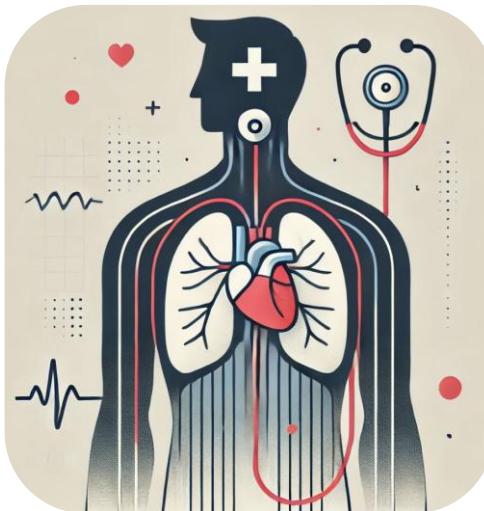
- Physical health.
- Cognitive function.
- Psychological health.
- Social factors.

# How can we measure “brain health”?



**Blood pressure:**  
You can use just a single pair of numbers

*>120/80 mm: hypertension.  
<90/60 mm: hypotension.*



**Overall health:**  
Frailty index:

- Physical health.
- Cognitive function.
- Psychological health.
- Social factors.



**Brain health:**



# How can we measure “brain health”?



**Brain health:**

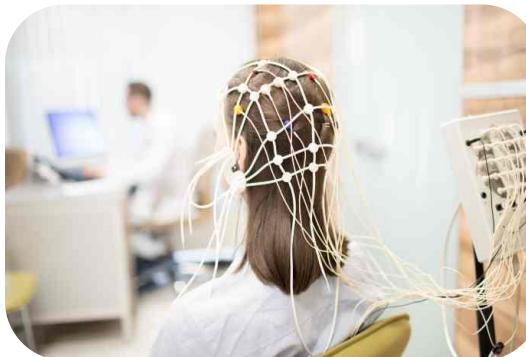


## **Neuroimaging:**

PET: Positron Emission Tomography

MRI: Magnetic Resonance Imaging

fMRI: Functional Magnetic Resonance Imaging



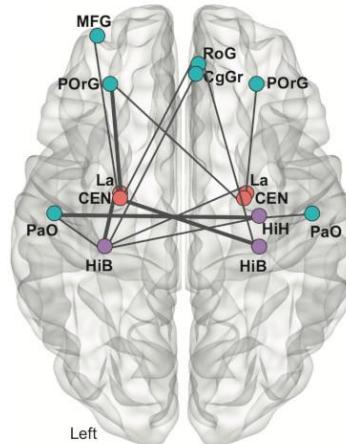
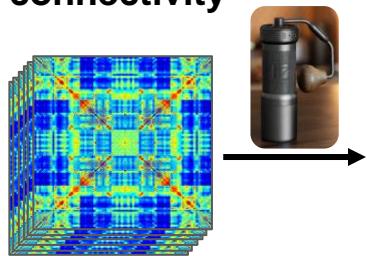
## **Electrophysiology:**

EEG: Electroencephalography

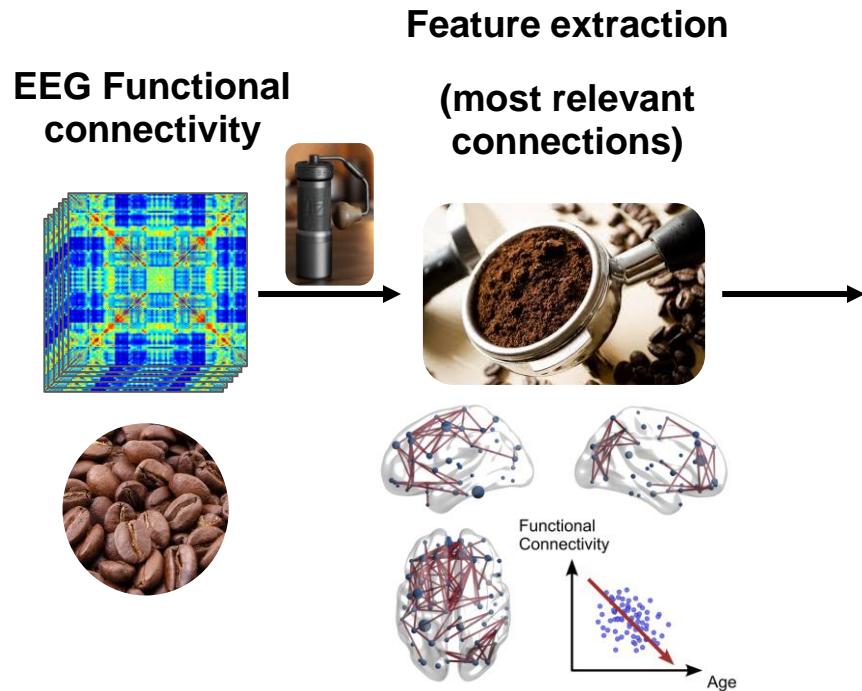
MEG: Magnetoencephalography

# Dataset and brain clock model

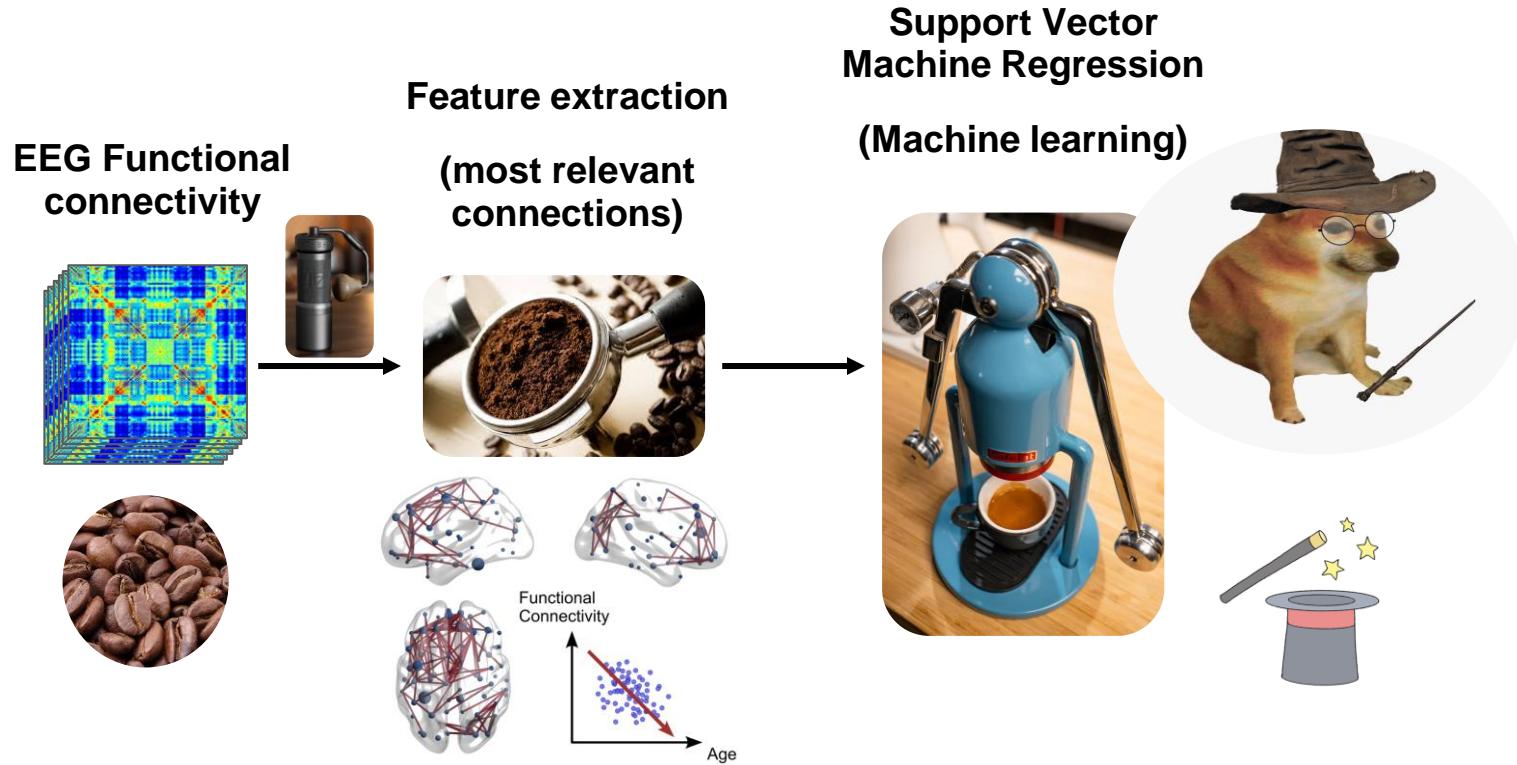
**EEG Functional connectivity**



# Dataset and brain clock model

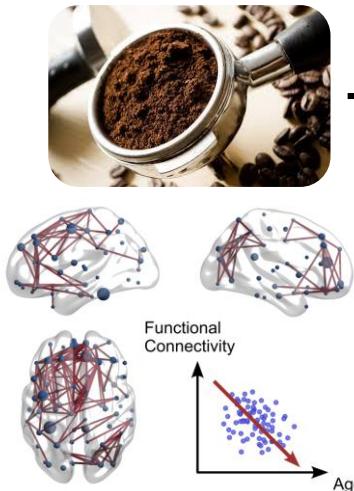


# Dataset and brain clock model



# Dataset and brain clock model

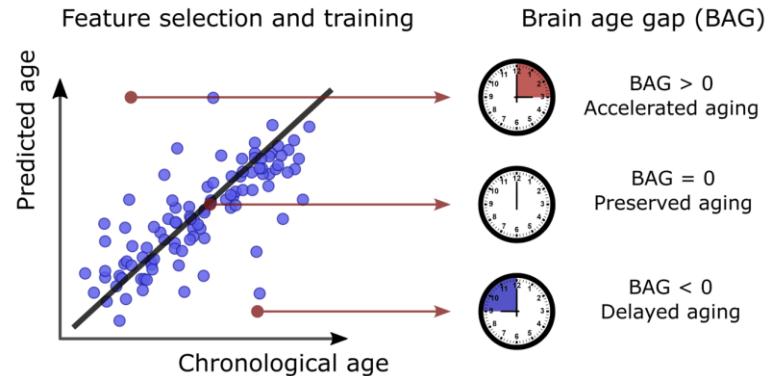
Feature extraction  
(most relevant connections)



Support Vector  
Machine Regression  
(Machine learning)



Predictions



# Brain clocks using EEG

Brain age gap (BAG)



BAG > 0  
Accelerated aging



BAG = 0  
Preserved aging



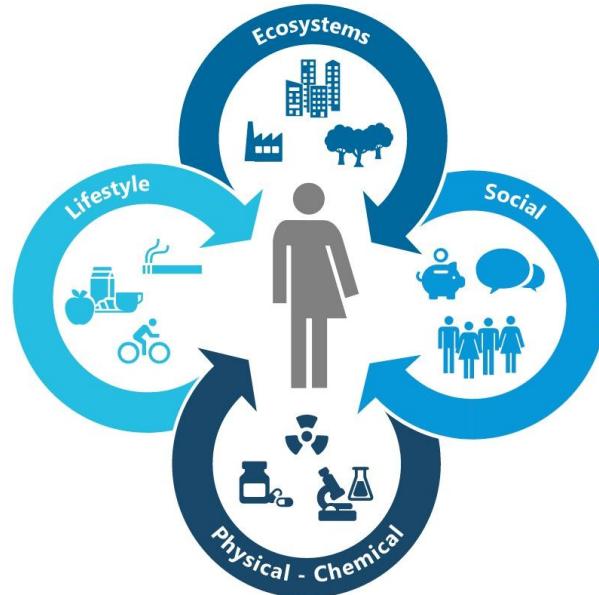
BAG < 0  
Delayed aging



DEMENTIA



Social exposome



# Brain clocks using EEG

## Brain age gap (BAG)



BAG > 0  
Accelerated aging



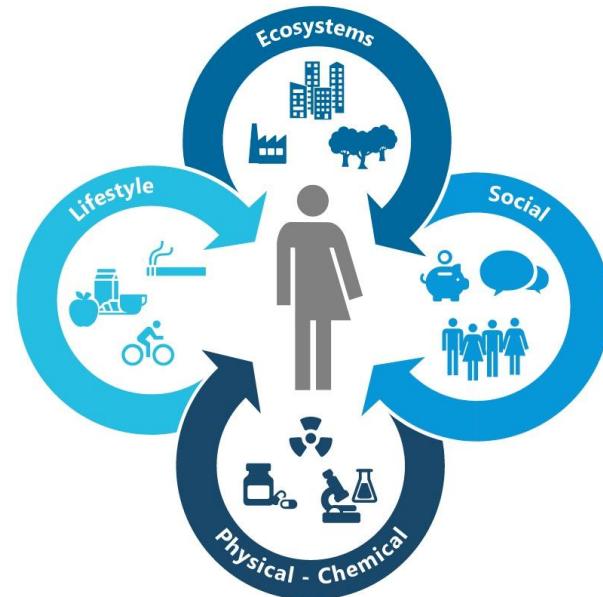
BAG = 0  
Preserved aging



BAG < 0  
Delayed aging



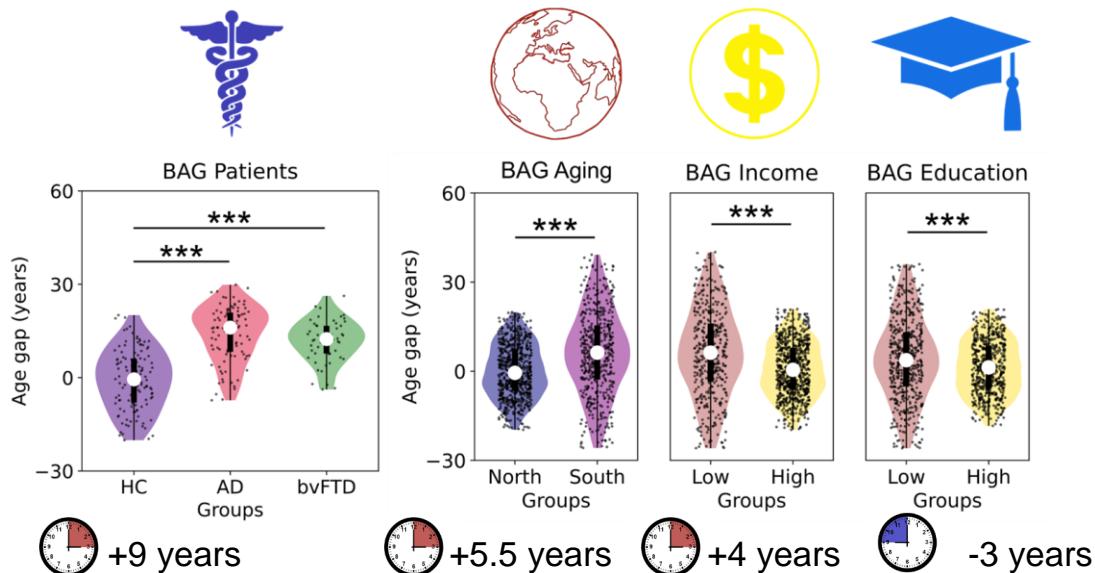
## Social exposome



# BAGs in aging and dementia

Normative models of healthy aging can be used to predict the brain age gaps (BAGs) in health and disease.

BAGs in healthy aging and dementia: accelerated aging in South and in dementia, and protective effects of education



## Comparisons:

- Patients and matched healthy controls.
- South vs North.
- Income: GDP per capita.
- Education: years education

# Mechanisms in aging and dementia

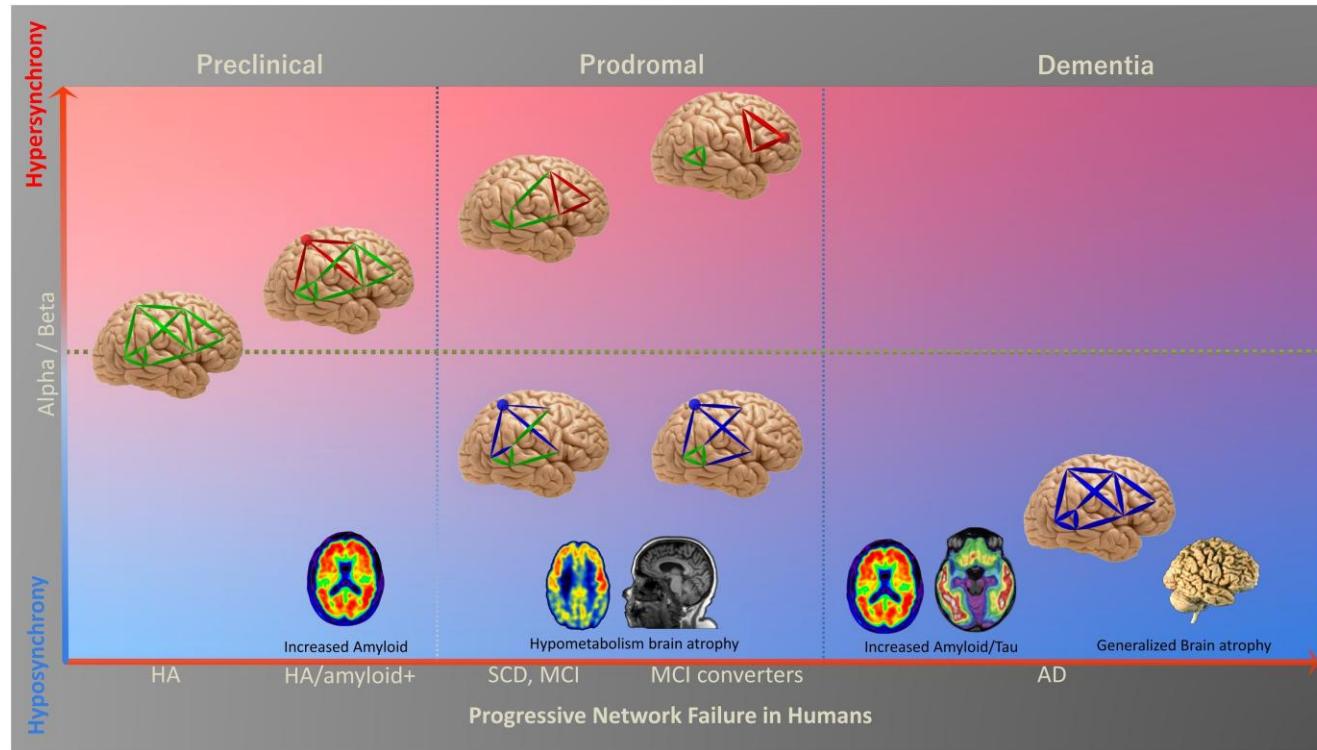
Ageing Research Reviews

Volume 69, August 2021, 101372

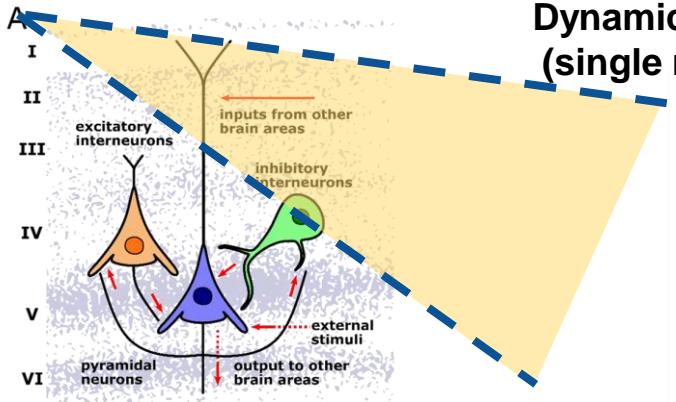
Review

Neuronal excitation/inhibition imbalance: core element of a translational perspective on Alzheimer pathophysiology

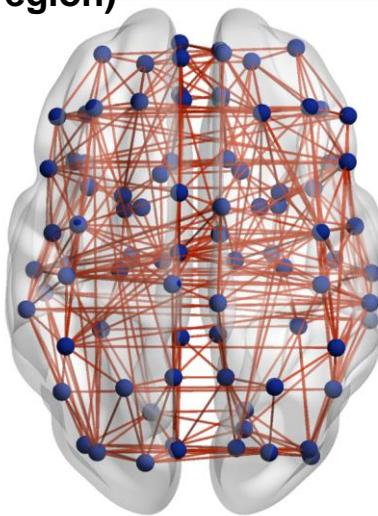
Fernando Maestú <sup>a b c</sup>   , Willem de Haan <sup>d</sup> , Marc Aurel Busche <sup>e</sup> , Javier DeFelipe <sup>f g h</sup>



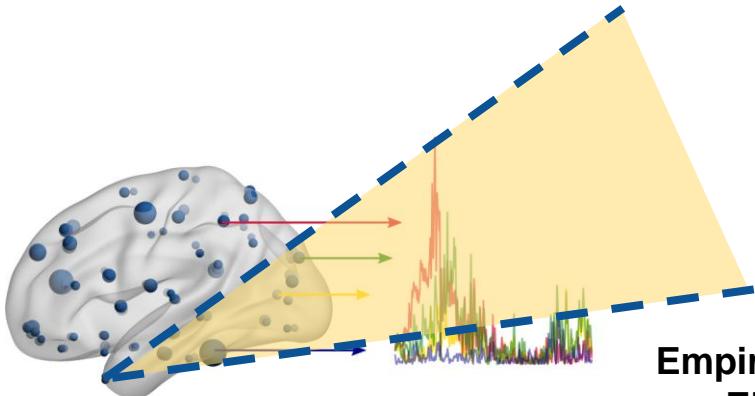
# Biophysical modeling



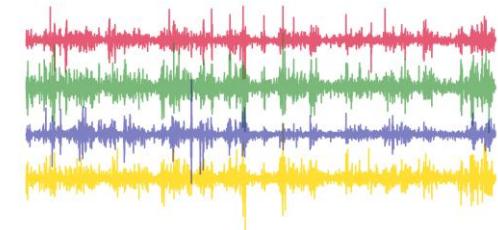
Dynamic model  
(single region)



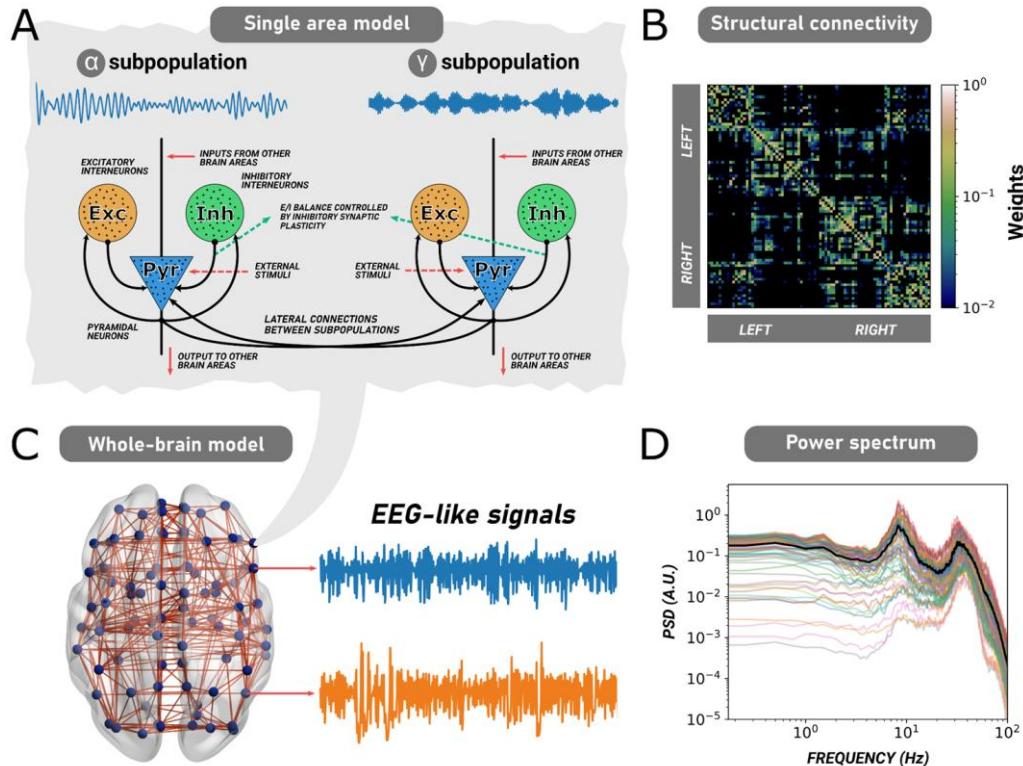
Human  
Connectome



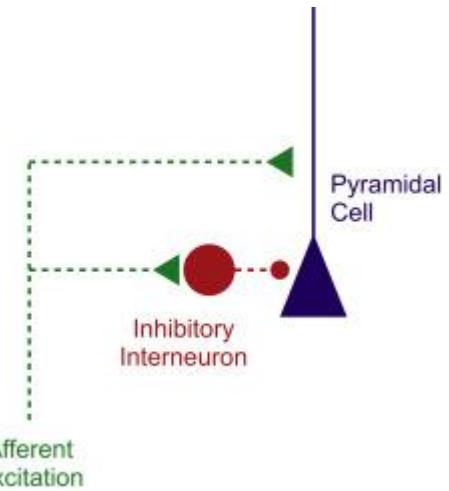
Empirical Source  
EEG data



# Neural mass model (Jansen-Rit)

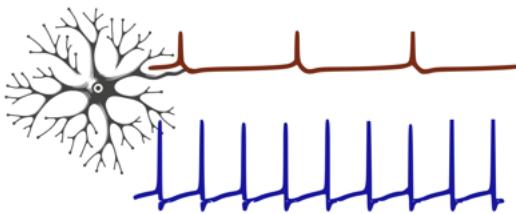


Modified Jansen & Rit model with **Inhibitory synaptic plasticity**



# Mechanisms in aging and dementia

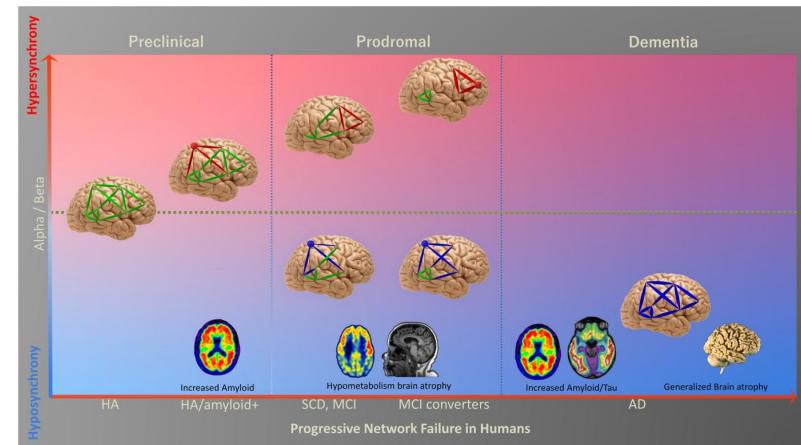
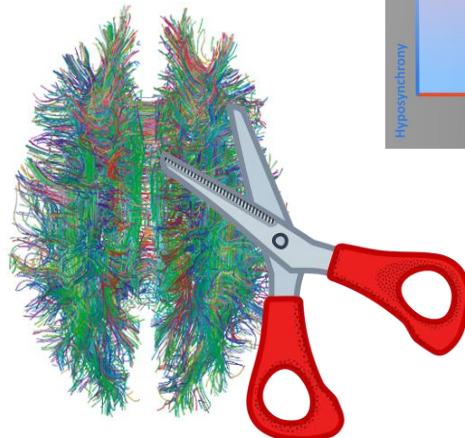
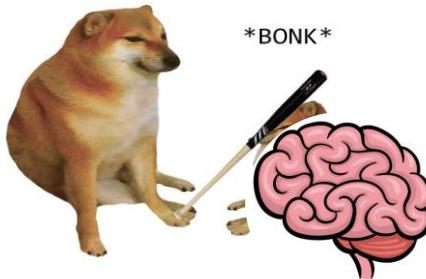
## Local E/I balance estimation



Low excitation

High excitation

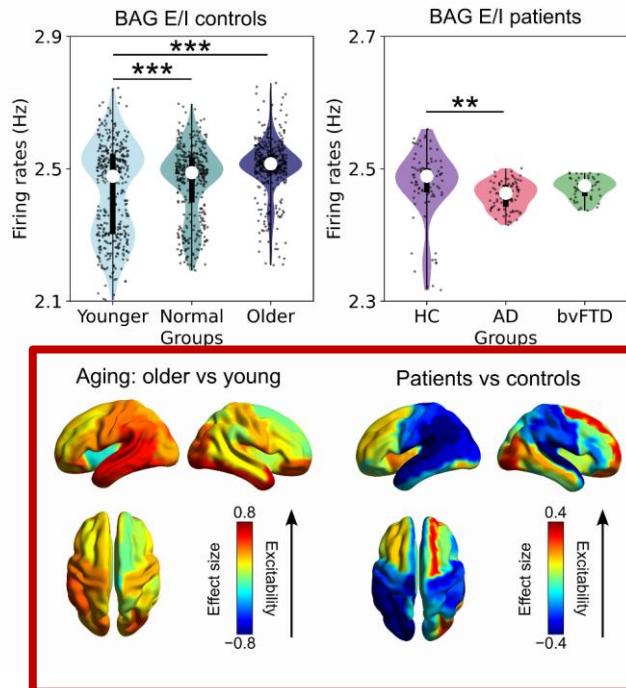
## Connectome “disintegration”



Maestú et al., 2021

# BAGs in modeling

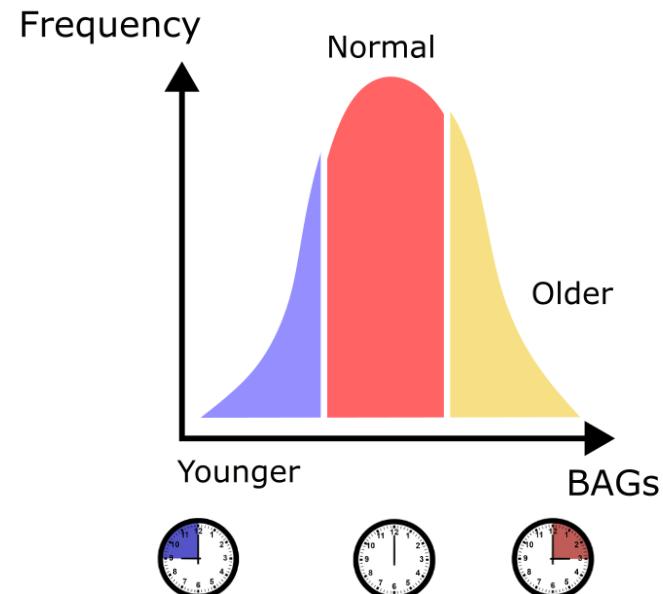
## A) Excitation/inhibition balance



**Hyperexcitation** in accelerated aging.

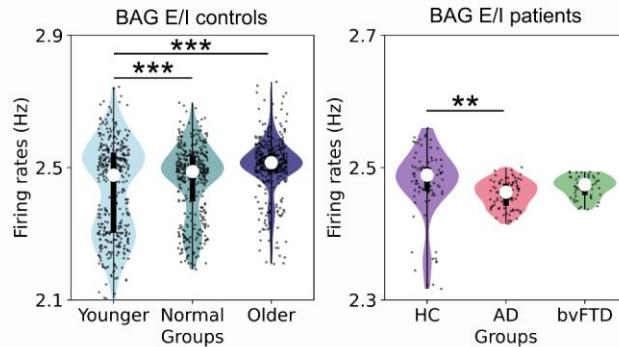
**Hypoexcitation** in dementia.

Specific E/I balance cortical patterns in aging and dementia.

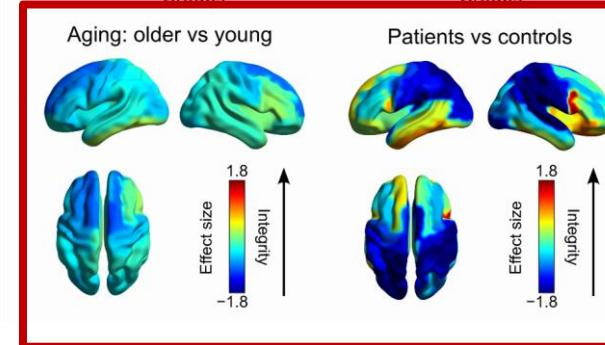
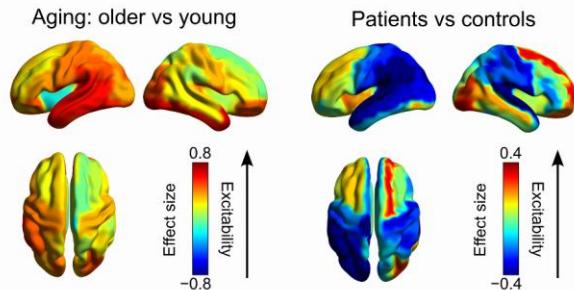
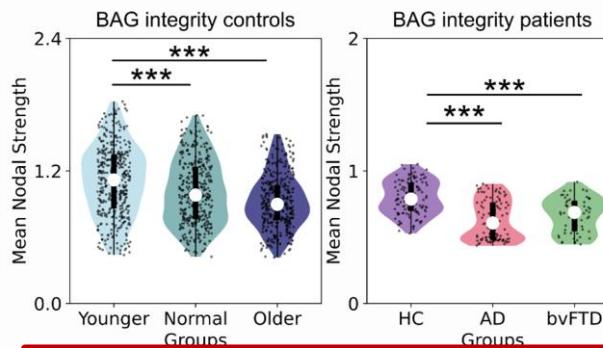


# BAGs in modeling

A) Excitation/inhibition balance



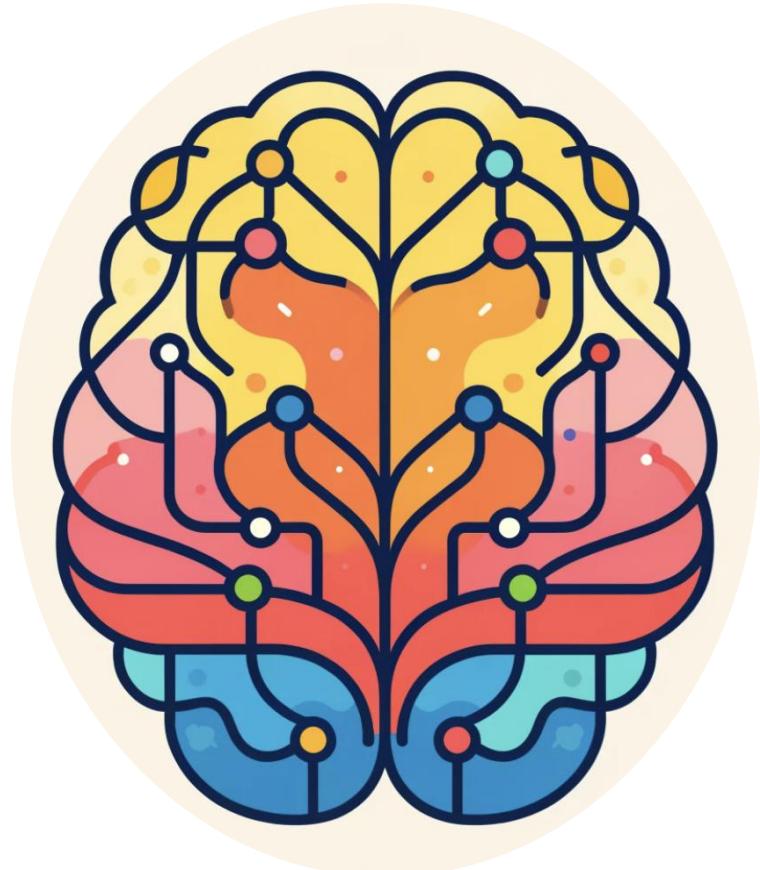
B) Structural integrity



**Reduced structural connectivity in aging and dementia**

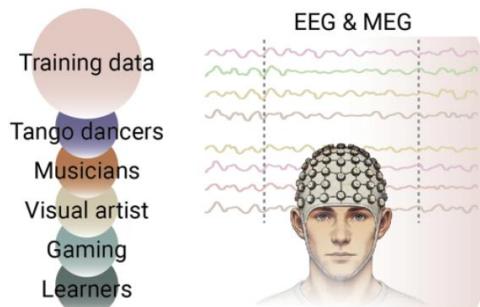
Specific connectivity differences in aging and dementia.

# Aging Gracefully: How Our Brains Bend but Don't Break

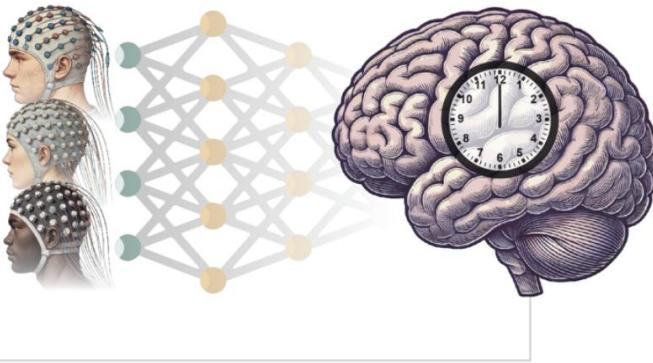


# Expertise and neural plasticity

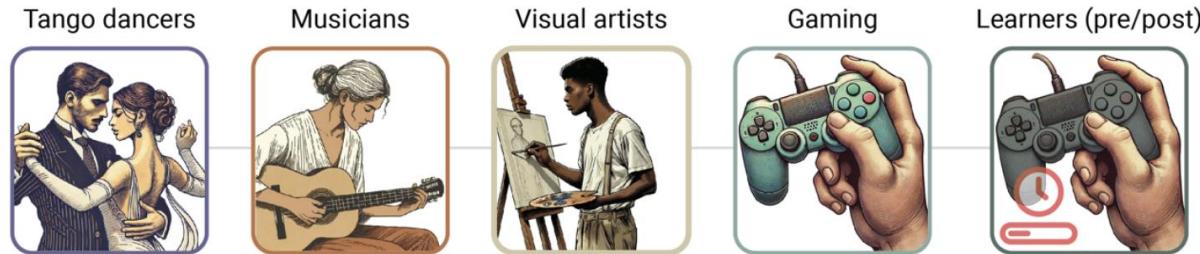
## A. Datasets (N = 1,467)



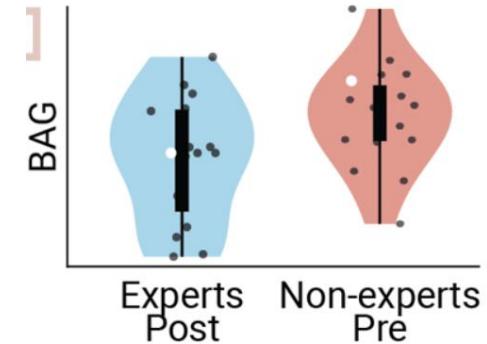
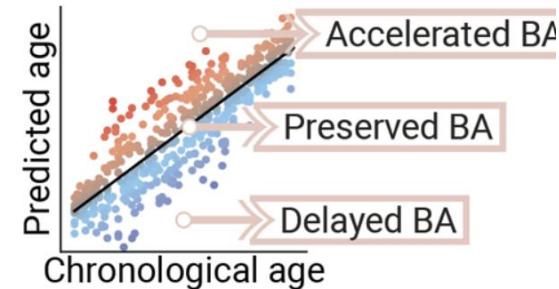
## B. Brain age model training (N = 1,240)



## C. Domains (N = 227)



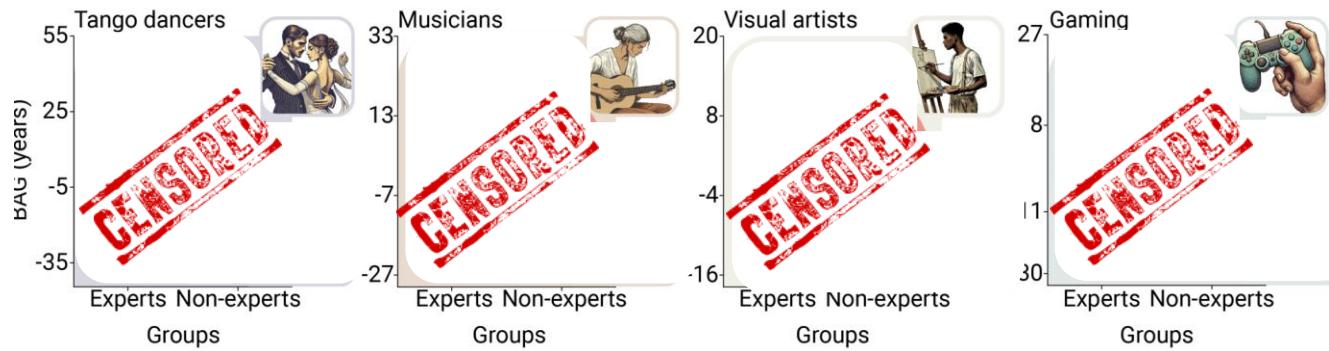
**Compared BAGs in different creative domains**



# Expertise and neural plasticity

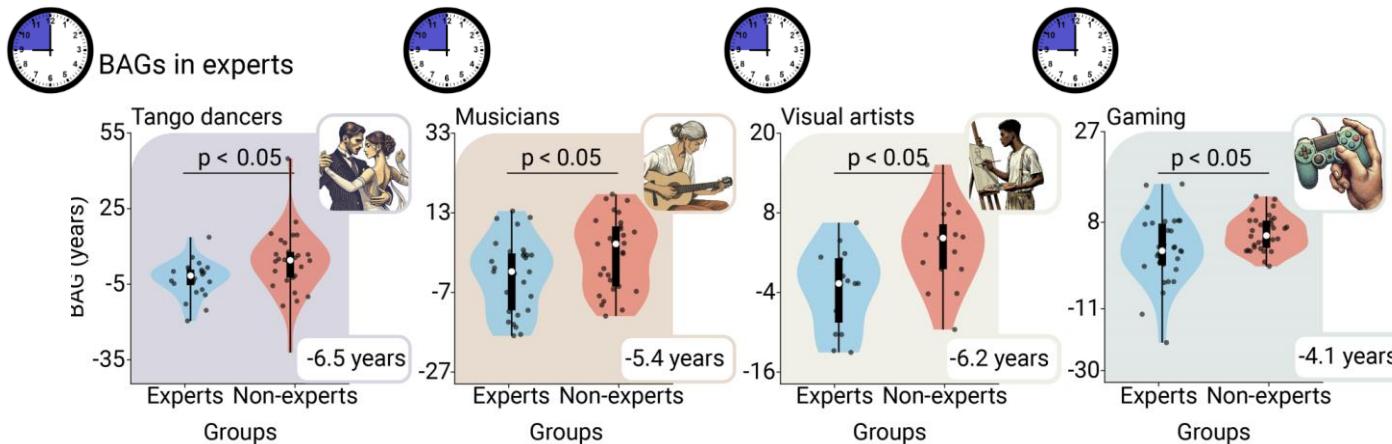
Lower BAGs across creativity domains (**expertise**)

)) BAGs in experts



# Expertise and neural plasticity

Lower BAGs across creativity domains (**expertise**)

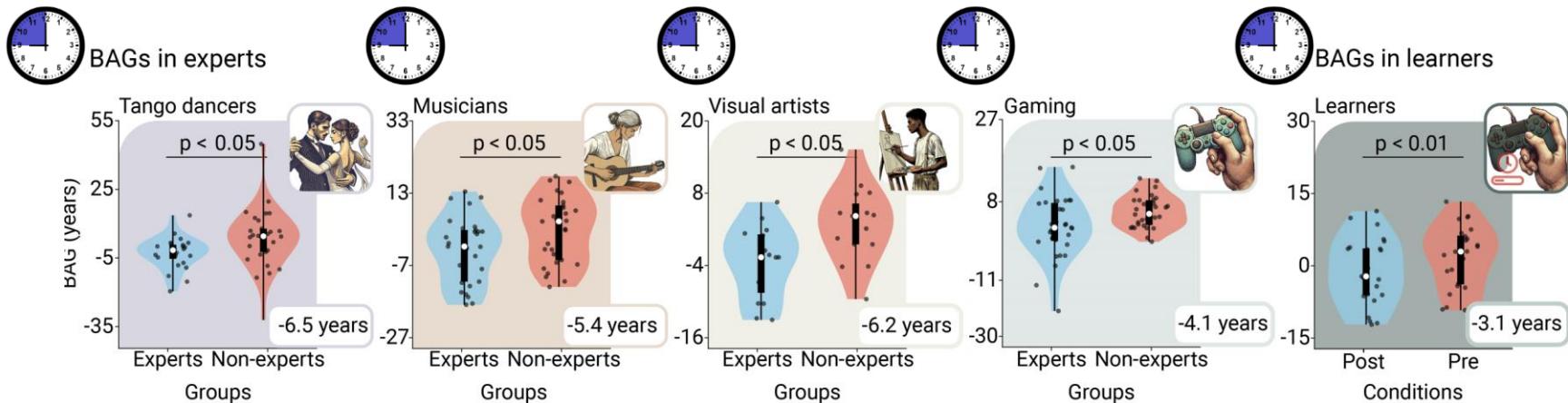


Coronel-Oliveros et al. 2025b (Not rejected... yet)

Personal disclaimer: this is not a recommendation about what you should do to improve your brain health. I'm not recommending anyone, for example, playing videogames for hours and hours (without doing anything else) as a healthy habit. The same applies to music and drawing or whatever. Do exercise and sleep well ☺

# Expertise and neural plasticity

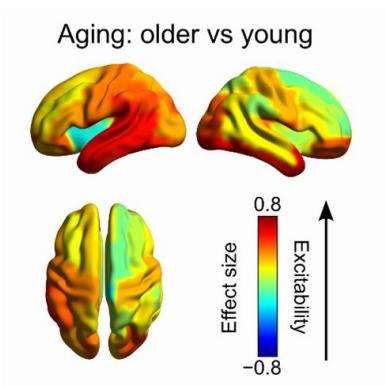
Lower BAGs across creativity domains (**expertise**)



**Scalable effects:** stronger effect in experts than learners.

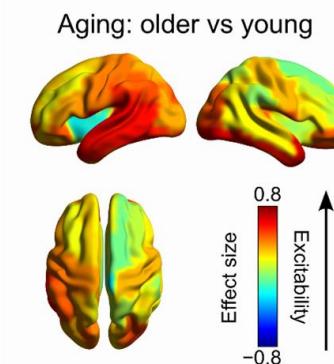
# Expertise and neural plasticity

**From part II:** accelerated aging is characterized by hyperexcitability



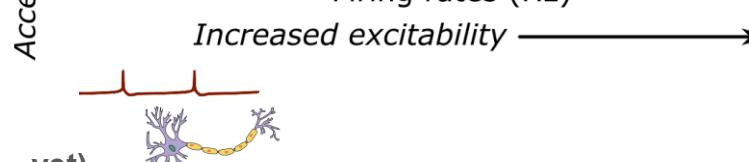
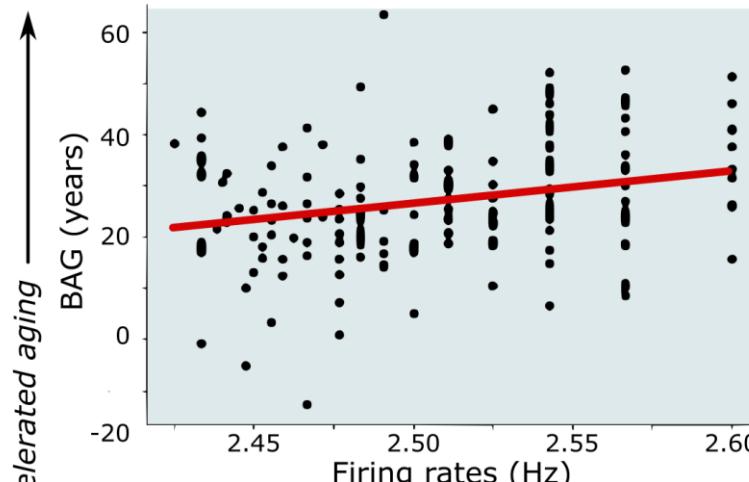
# Expertise and neural plasticity

**From part II:** accelerated aging is characterized by hyperexcitability

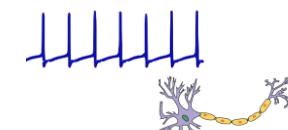


Neural excitability in the Expertise Design

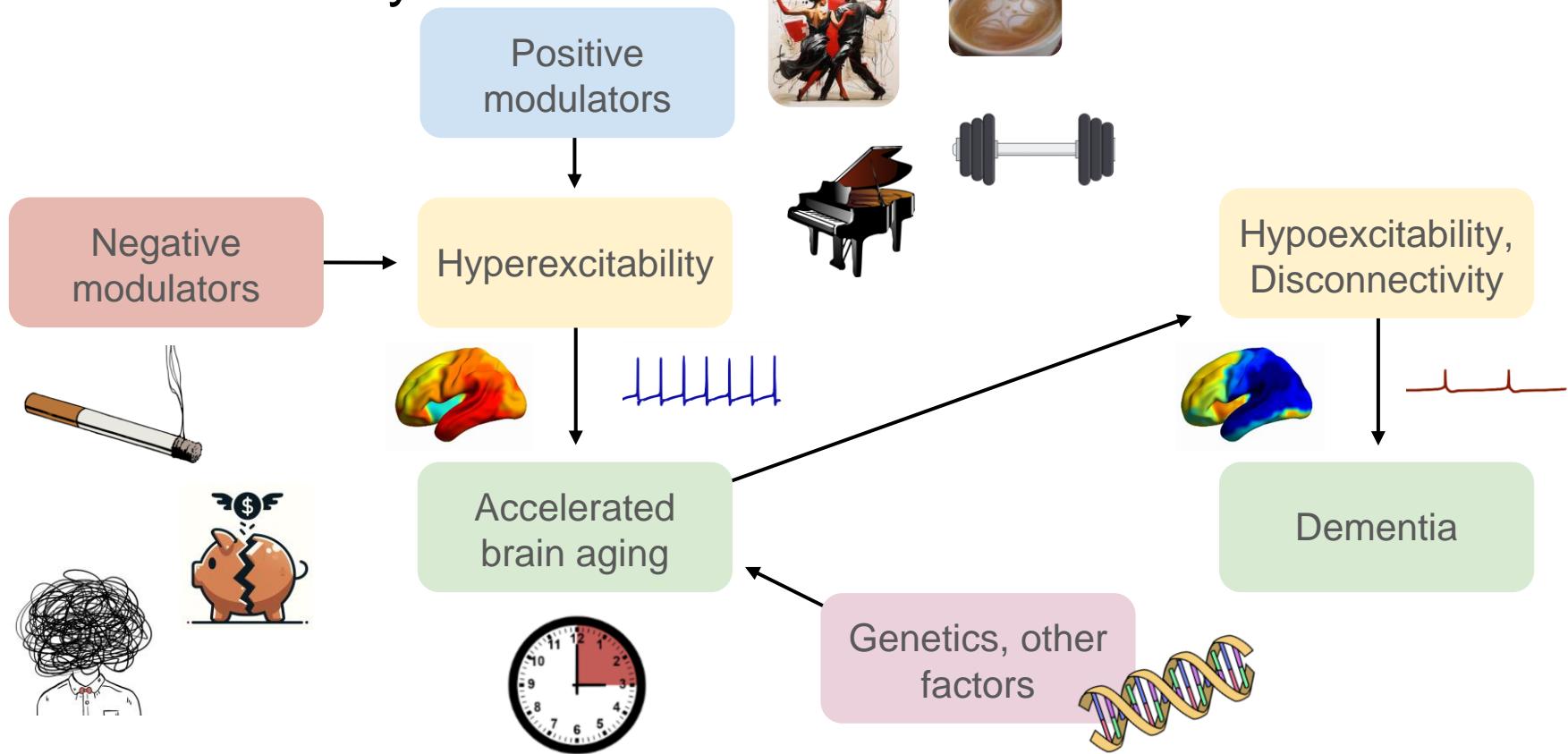
$$r = 0.261, p < 0.001$$



**Here:** lower BAGs by creativity are associated with less excitability



# Final summary



# Acknowledgments



**Agustín Ibáñez**



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**Sol Fittipaldi**



**Raúl González**



**Sebastián Moguilner**



**Vicente Medel**



**Agustina Legaz**

# Open to collaborations



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## RedLat and Eurolad

>14000 functional recordings: fMRI, EEG, MEG.

Structural MRI.

Plasma biomarkers.

Cognitive assessments.

Genetics.

Alzheimer's disease, frontotemporal dementia, mild cognitive impairment, Down syndrome.



Trinity  
College  
Dublin

The University of Dublin



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BRAIN HEALTH  
INSTITUTE



UAI  
UNIVERSIDAD ADOLFO IBÁÑEZ



# Whole-brain models fitting and applications

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May, 2025