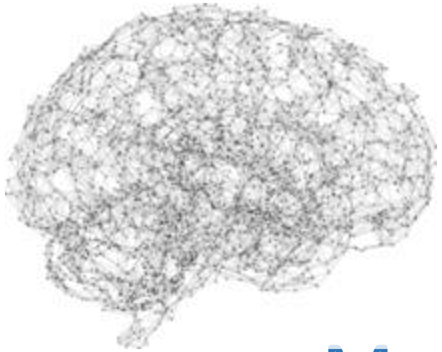


Modeling Connectivity: Regression DCM for fMRI

Imre Kertesz

Translational Neuromodeling Unit (TNU)
University of Zurich & ETH Zurich

Computational Psychiatry Course (CPC) 2025
Thursday , 04.09.2025

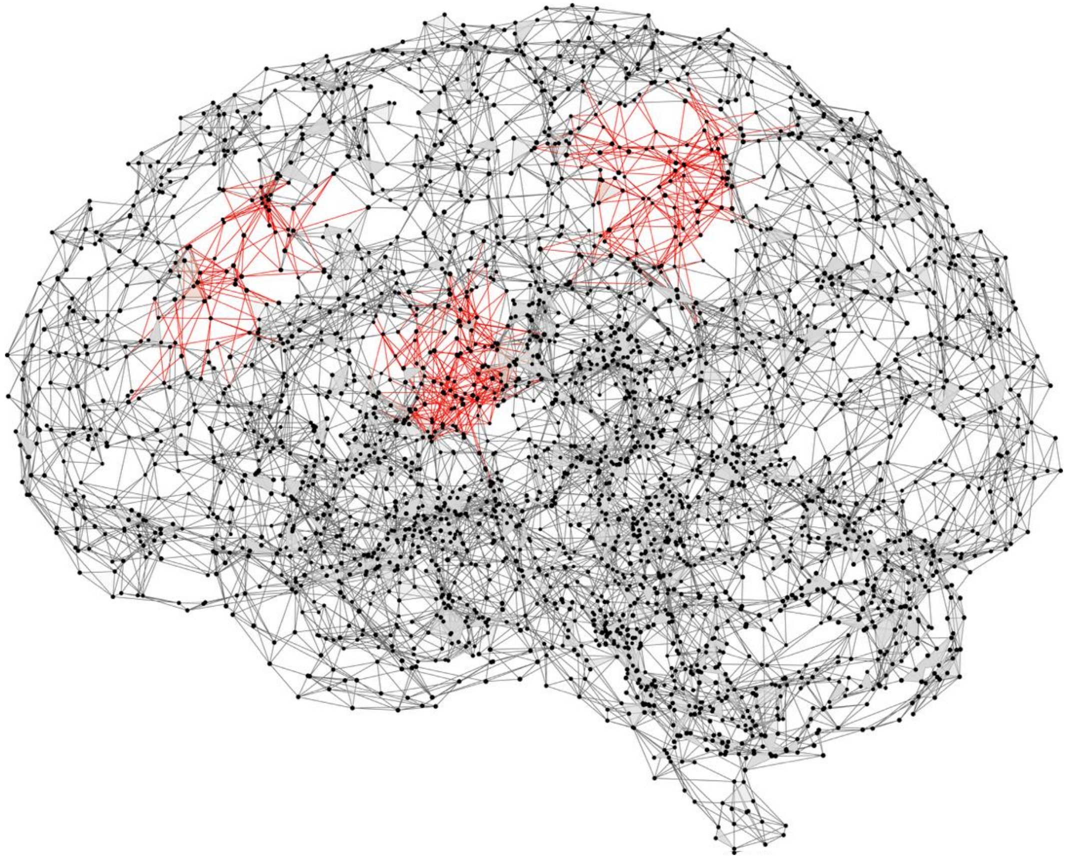
THE HUMAN BRAIN

© www.dreamstime.com

autism

© www.leafscience.com

depression



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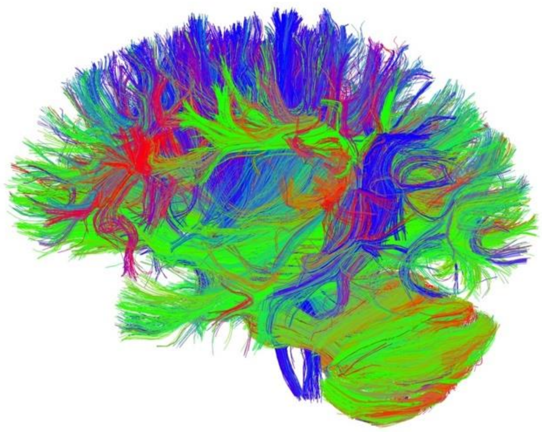
schizophrenia

DIFFERENT FORMS OF BRAIN CONNECTIVITY

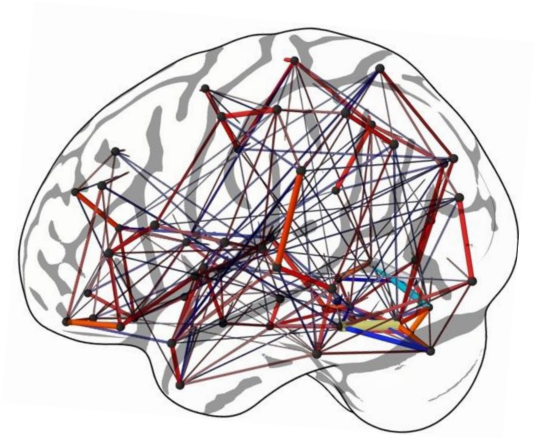
structural connectivity



https://optimalsurgerytle.weebly.com/imaging-and-dataset.html

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

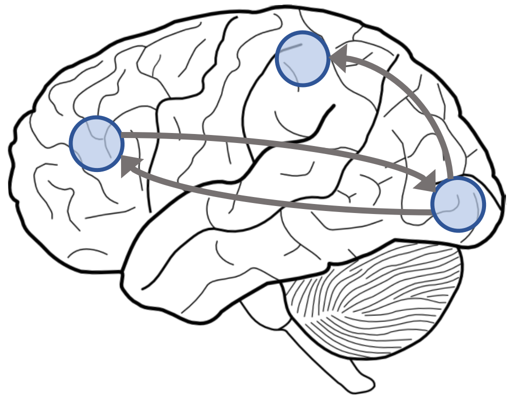
functional connectivity



https://team.inria.fr/parietal/files/2013/02/pc_dag.jpg

- statistical dependencies between regional time series
- correlations, Independent Component Analysis (ICA),…

effective connectivity



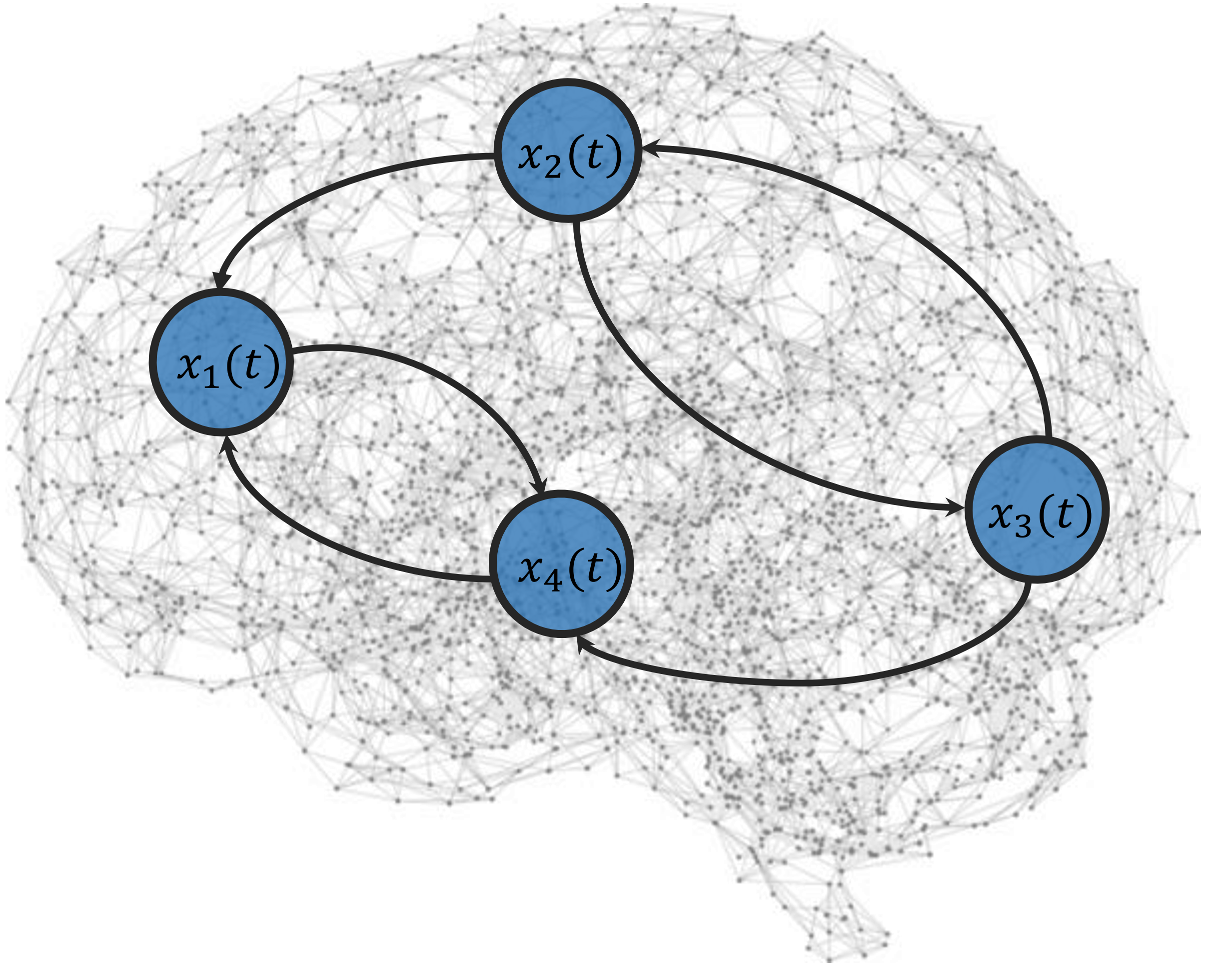
http://www.clker.com/cliparts/e/5/Q/i/e/o/brain-line-drawing-md.png

- directed influences between neuronal populations
- Dynamic causal modeling (DCM),…

adapted from: Sporns, 2007, *Scholarpedia*

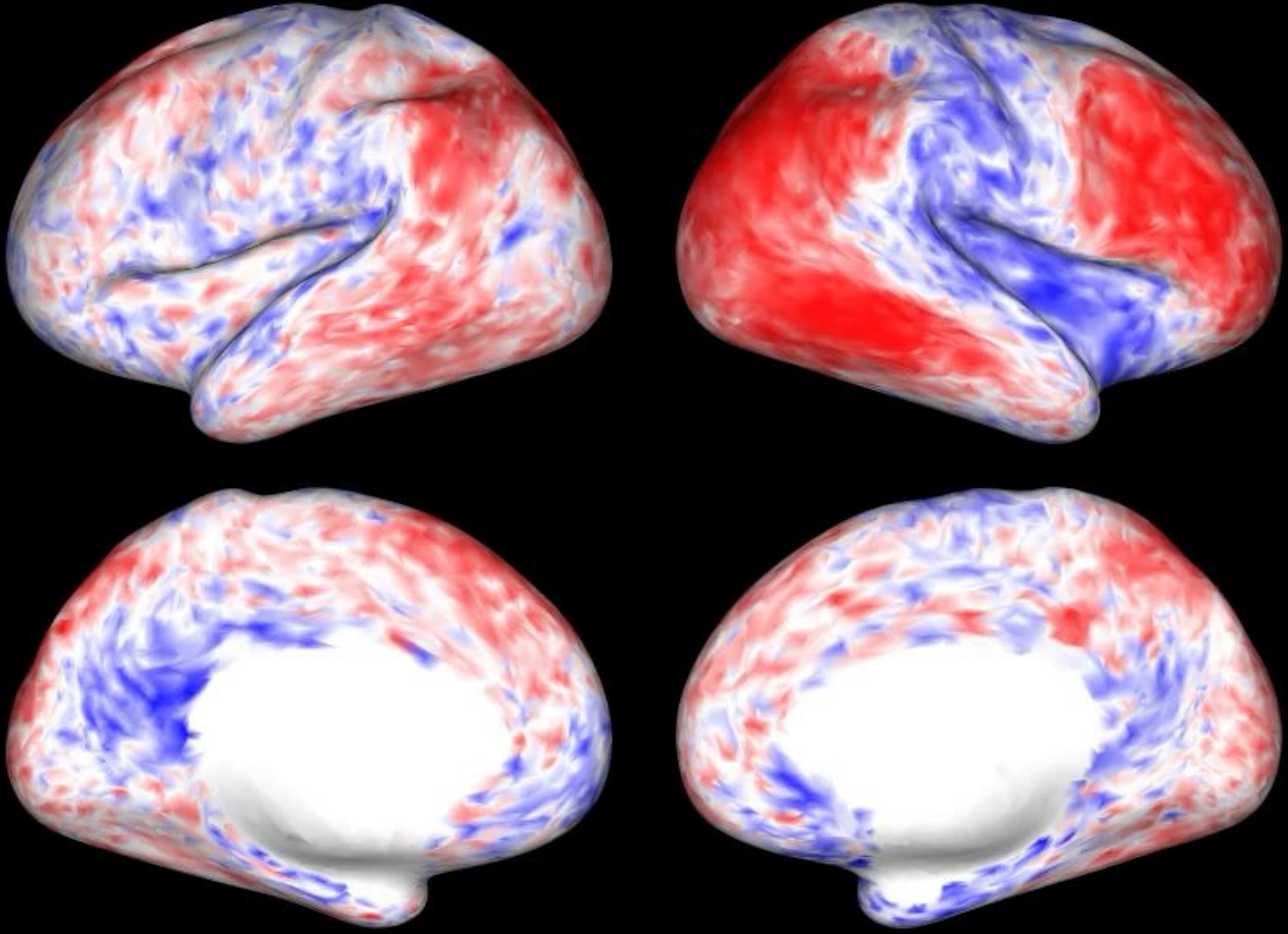
WHAT YOU HAVE SEEN SO FAR

DCM for fMRI



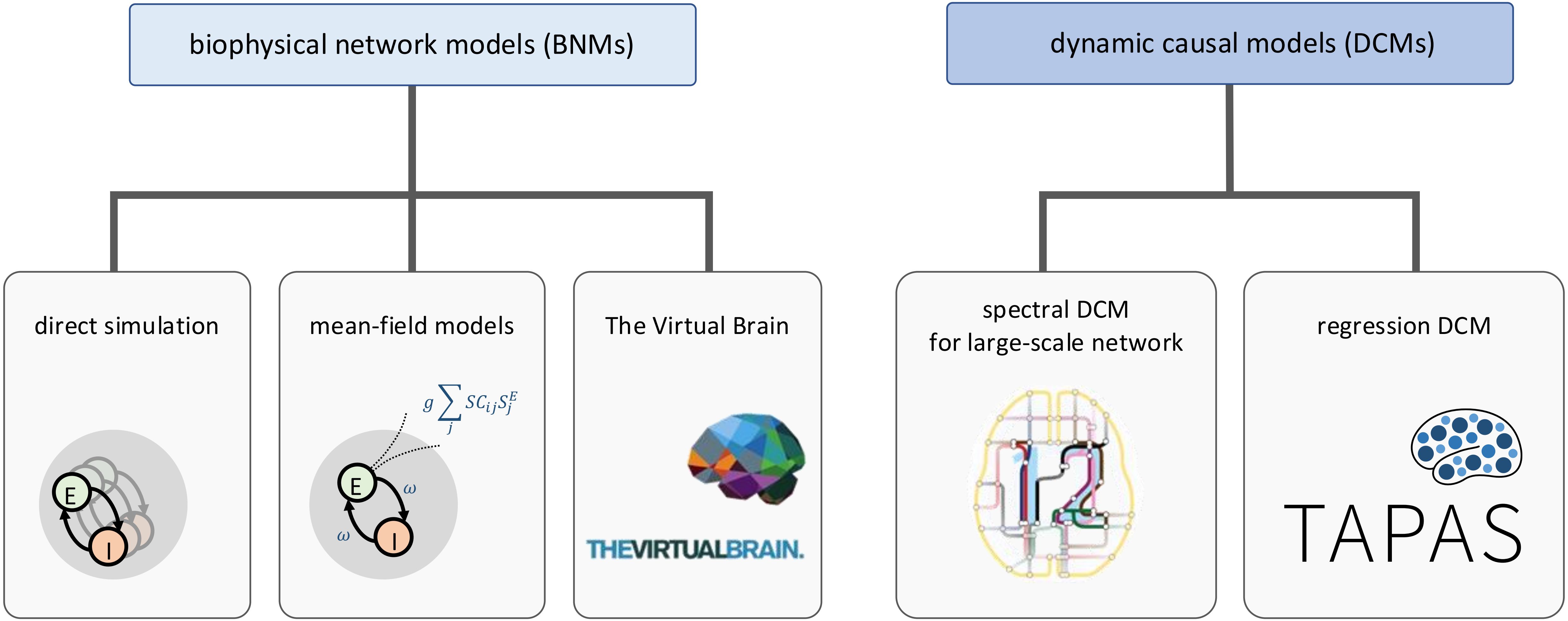
Friston et al., 2003, *NeuroImage*

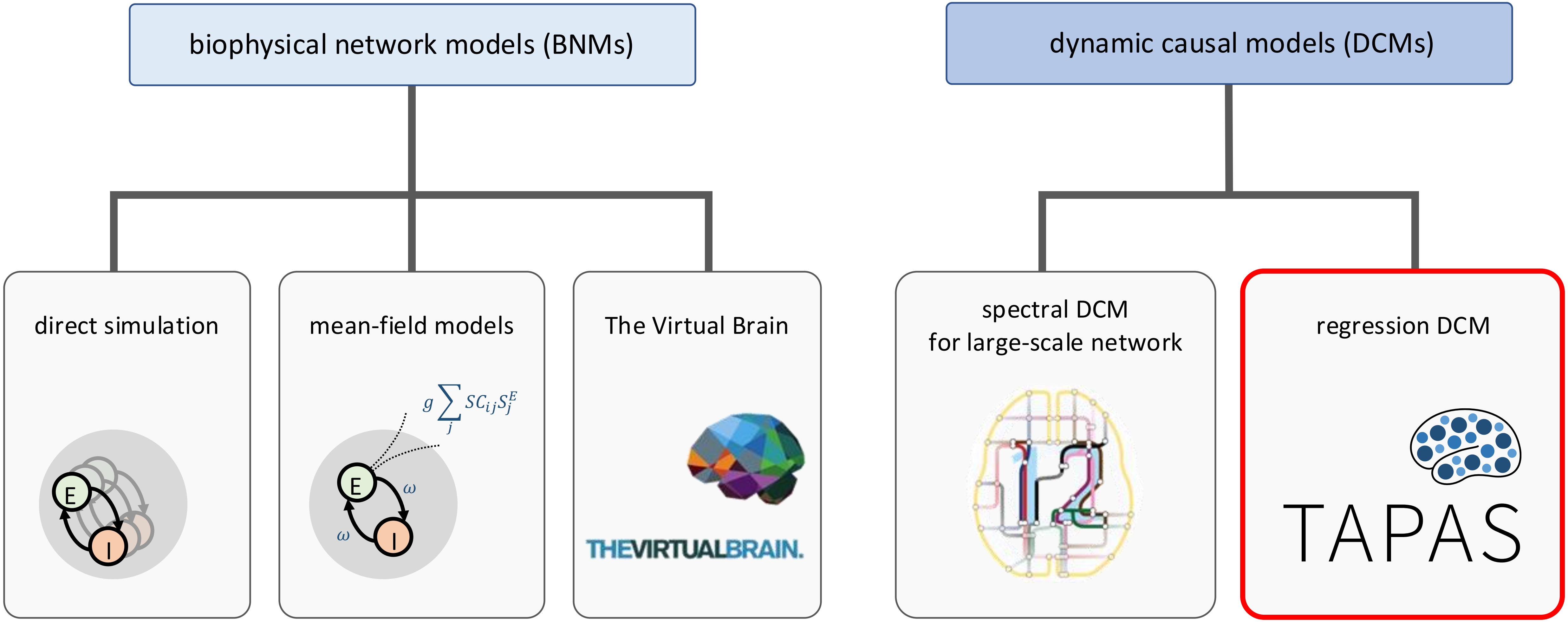
BUT…



Bhushan et al., 2016, *PLoS One*

What we want


biophysical network models (BNMs)
dynamic causal models (DCMs)
direct simulation
E
I
mean-field models
$g \sum_j SC_{ij} S_j^E$
E
I
ω
ω
The Virtual Brain
THEVIRTUALBRAIN.
spectral DCM
for large-scale network
regression DCM
TAPAS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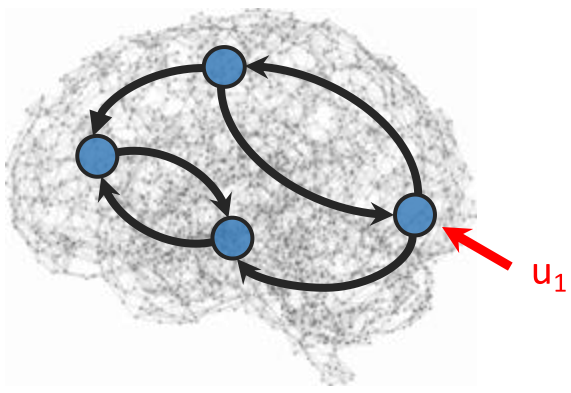
spectral DCM
for large-scale network
regression DCM
TAPAS

E. Lomakina

S. Frässle

Regression dynamic causal modeling (rDCM)

REGRESSION DCM – UNDER THE HOOD…



$$\frac{dx}{dt} = \boxed{Ax} + \boxed{Cu}$$

linear DCM in the
time domain

FFT, fixed HRF, mean field

$$p(Y|\theta, \tau, X) = \prod_{i=1}^{R} \mathcal{N}(Y_i; X\theta_i, {\tau_i}^{-1} I_{N\times N})$$

$$Y_i := \left(e^{2\pi i \frac{\boldsymbol{m}}{N}} - 1\right) \frac{\hat{y}_i}{T}$$

$$X := [\widehat{y_1}, \dots, \widehat{y_R}, \hat{h}\widehat{u_1}, \dots, \hat{h}\widehat{u_K}]$$

$$\theta_i := [a_{i1}, \dots, a_{iR}, c_{i1}, \dots, c_{iK}]$$

GLM in the
frequency domain

introduce priors

$$p(\theta_i) = \mathcal{N}\left(\theta_i; \mu_0^i, \Sigma_0^i\right)$$

$$p(\tau_i) = Gamma(\tau_i; \alpha_0, \beta_0)$$

$$p(\theta, \tau | Y, X) \propto \prod_{i=1}^{R} p(Y_i|X, \theta_i, \tau_i) \prod_{i=1}^{R} \left(p(\theta_i) p(\tau_i)\right)$$

Bayesian linear regression in the
frequency domain

→highly efficient VB inversion scheme with analytical update equations

Frässle et al., 2017, *NeuroImage*; Lomakina, 2016, *PhD thesis*

SPARSE REGRESSION DCM – UNDER THE HOOD…

Formulation for regression DCM

$$p(\theta_i) = \mathcal{N}\left(\theta_i; \mu_0^i, \Sigma_0^i\right)$$

$$p(\tau_i) = Gamma(\tau_i; \alpha_0, \beta_0)$$

$$p(\theta, \tau | Y, X) \propto \prod_{i=1}^{R} p(Y_i | X, \theta_i, \tau_i) \prod_{i=1}^{R} \left(p(\theta_i) p(\tau_i)\right)$$

Bayesian linear regression in the frequency domain

Introduce binary indicator variables

$$Z \in \mathbb{B}^{D \times D}$$

$$Z_{i,j} = \begin{cases} \xi_i, & \text{if } i = j \\ 0, & \text{otherwise} \end{cases} \qquad \xi_i \in \{0,1\}$$

$$p(\theta, \tau, \xi | Y, X) \propto \prod_{i=1}^{R} p(Y_i | X, \mathrm{Z}_i, \theta_i, \tau_i) \prod_{i=1}^{R} \left(p(\theta_i) p(\tau_i) \prod_{j=1}^{D} p\left(\xi_{i,j}\right) \right)$$

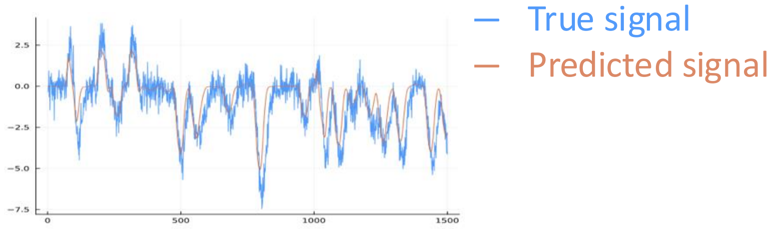
Sparse Bayesian linear regression in the frequency domain

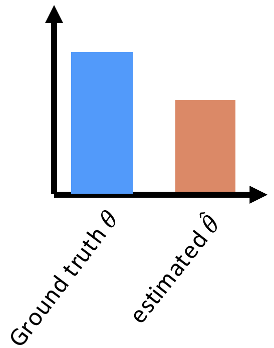
→automatically prunes network as part of model inversion

Frässle et al., 2018, *NeuroImage*; Lomakina, 2016, *PhD thesis*

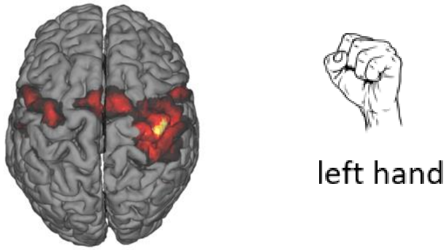
Model Validity (in the context of DCM)

- **Face validity**: Is the model inferring what it is supposed to?



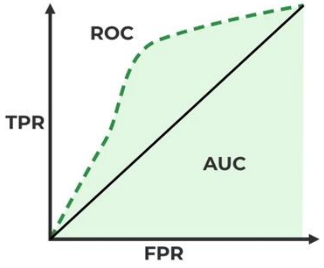


- **Construct validity**: Coherence with understanding of brain
  - Estimates should be consistent with known effects
  - How does it compare to alternative models of effective connectivity?



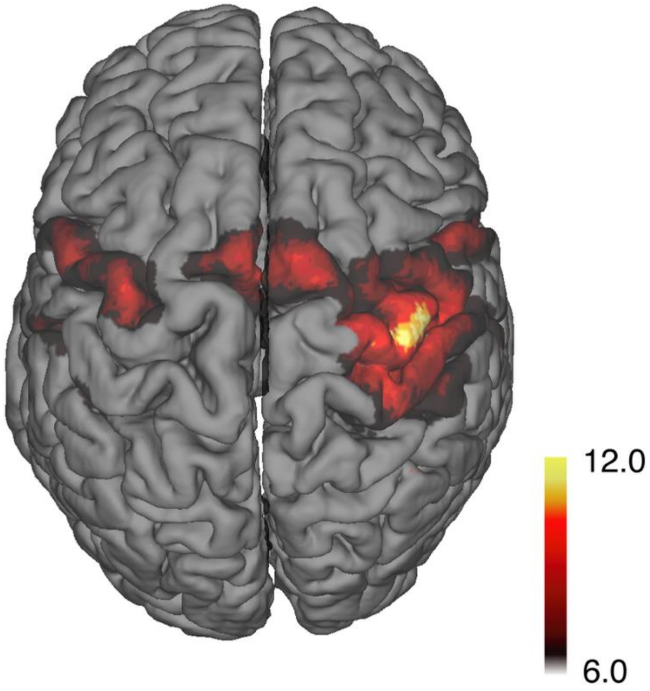
motor paradigm

- **Predictive validity**: Ability to make accurate predictions
  - Prediction of independent data, e.g. treatment response



Frässle et al., 2021, *NeuroImage*

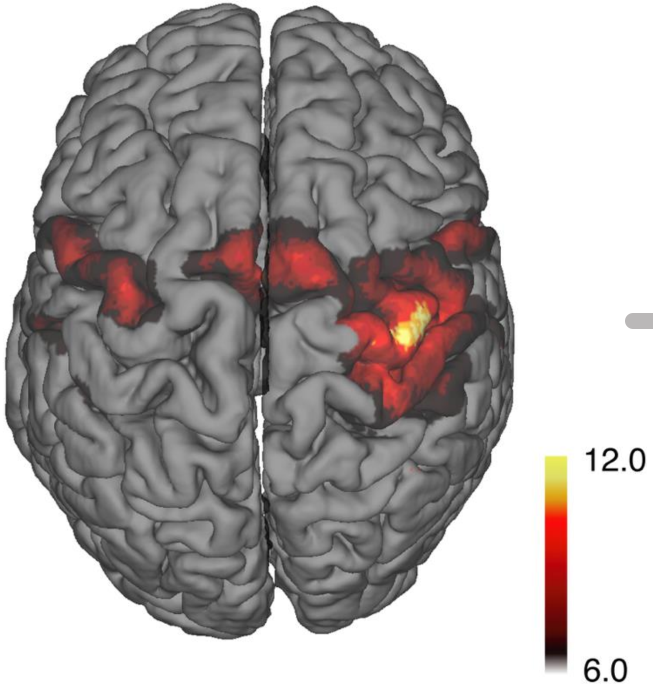
left hand

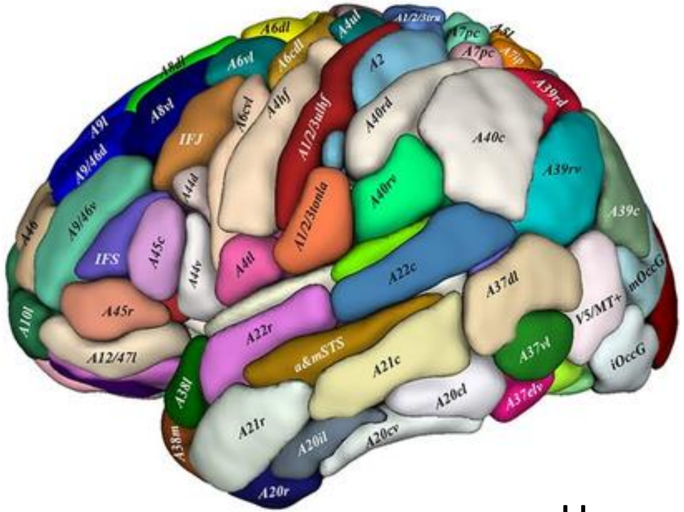


know from literature what brain regions are involved

Frässle et al., 2021, *NeuroImage*

left hand





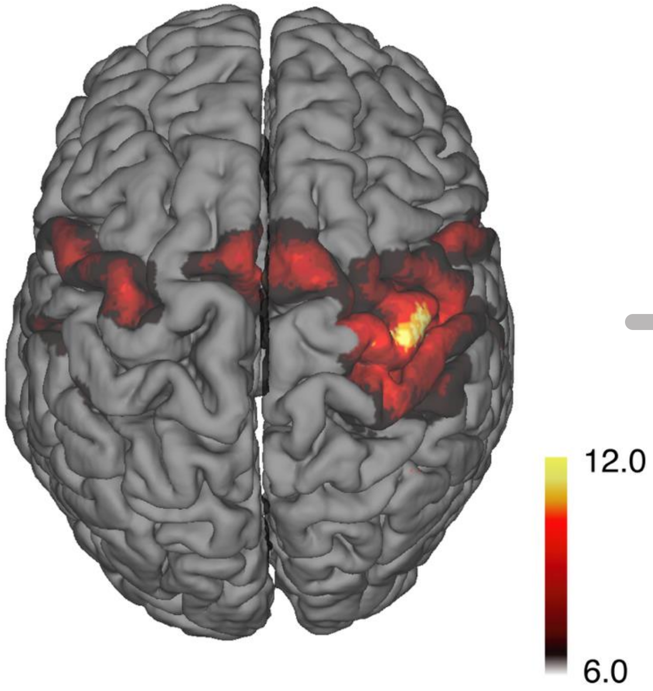
Human Brainnetome Atlas

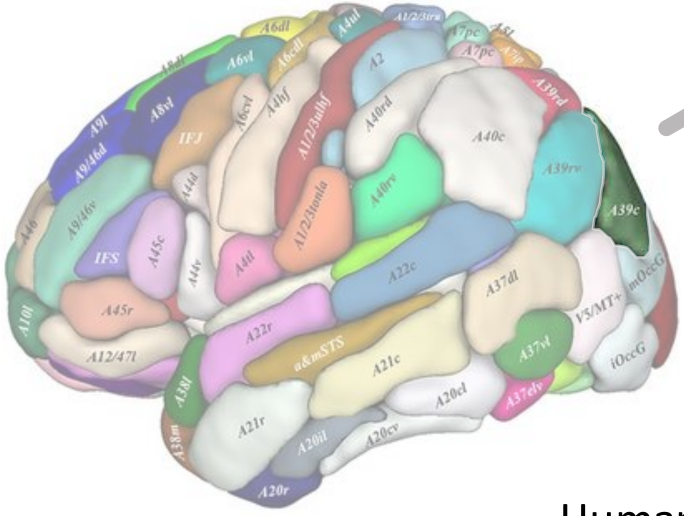
(parcellation of the brain)

<u>208 brain regions</u>

Frässle et al., 2021, *NeuroImage*

left hand





Human Brainnetome Atlas

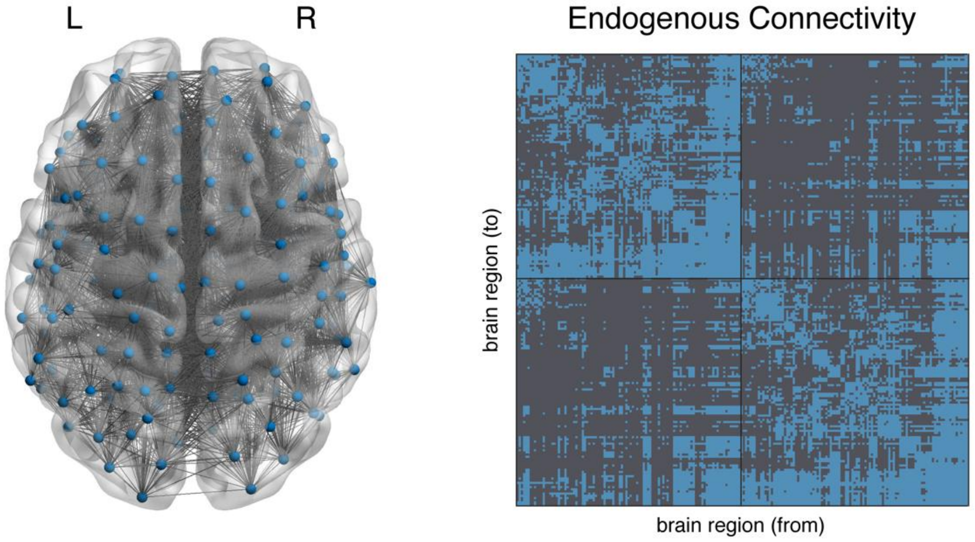
(parcellation of the brain)

<u>208 brain regions</u>

BOLD signal time series

Frässle et al., 2021, *NeuroImage*

Whole-brain effective connectivity

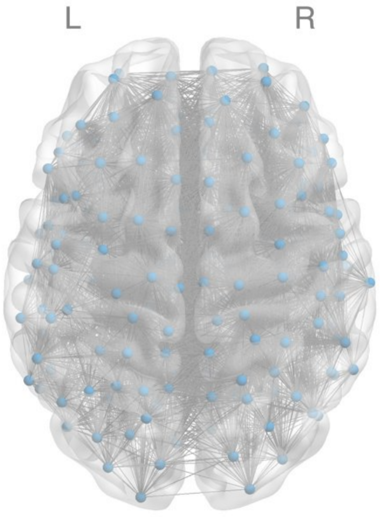


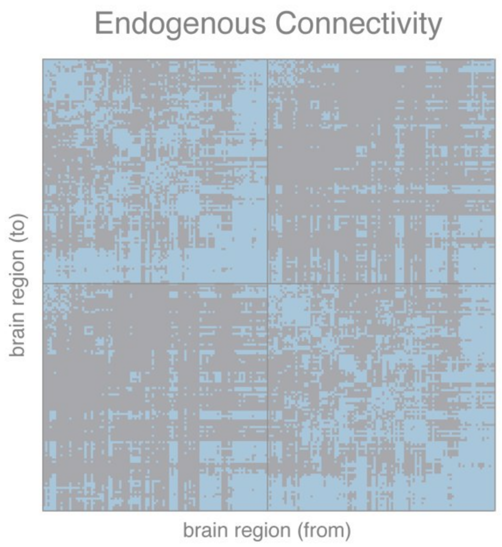
Human Brainnetome atlas

(# parameter = 17.518)

Frässle et al., 2021, *NeuroImage*

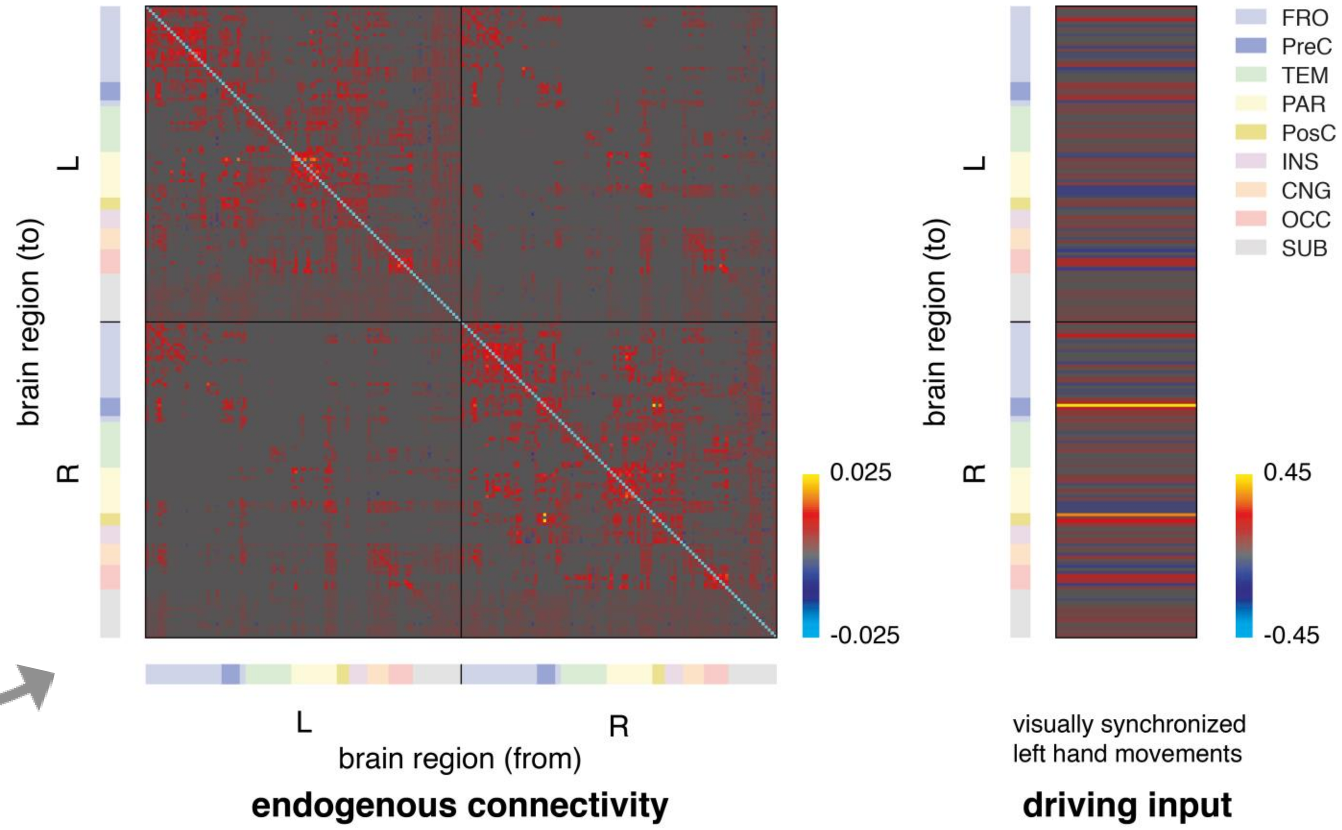
Whole-brain effective connectivity





Human Brainnetome atlas
(# parameter = 17.518)

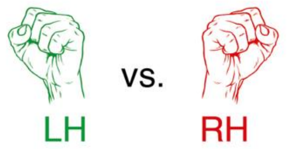
~ 1 min



Frässle et al., 2021, *NeuroImage*

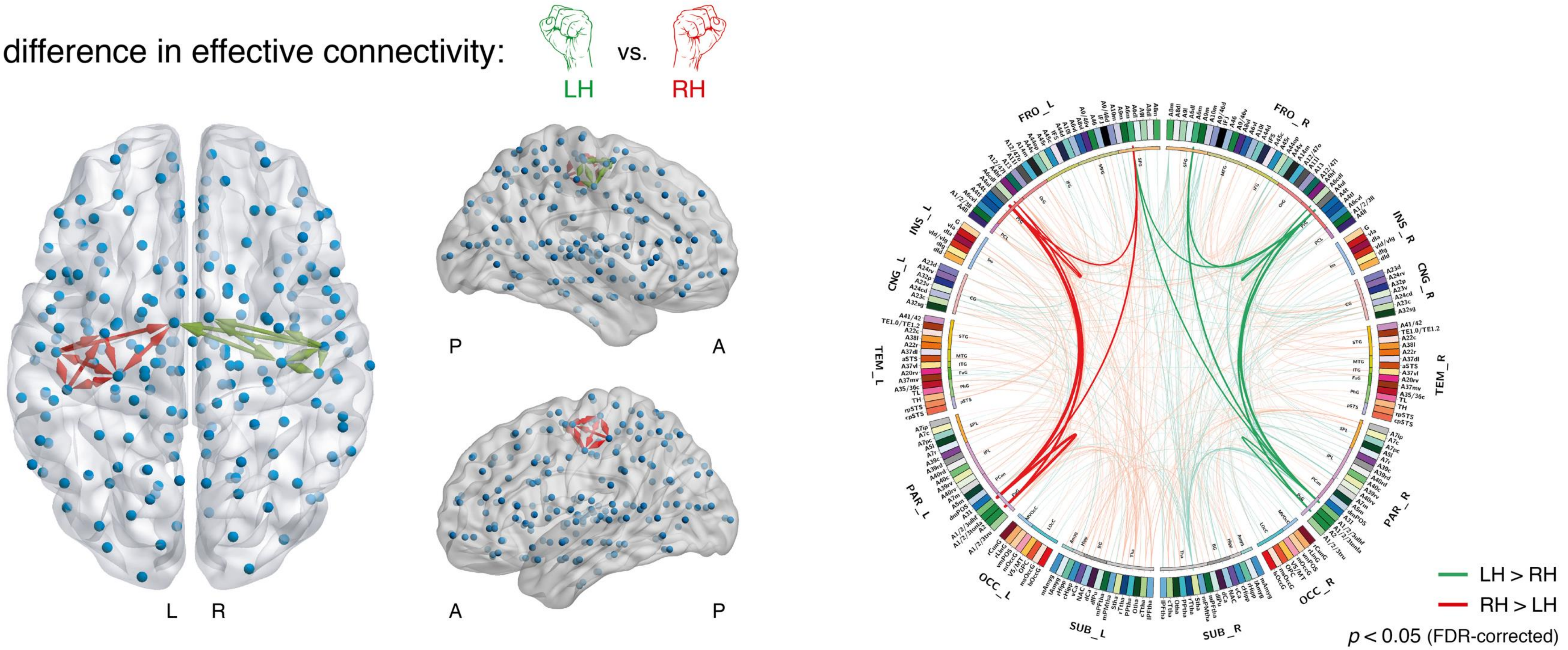
Whole-brain effective connectivity

difference in effective connectivity:



Frässle et al., 2021, *NeuroImage*

Whole-brain effective connectivity



Frässle et al., 2021, *NeuroImage*

Sparse whole-brain effective connectivity

Frässle et al., 2021, *NeuroImage*

SPARSE WHOLE-BRAIN EFFECTIVE CONNECTIVITY

How to find optimal network structure?

$$p(\theta, \tau, \xi | Y, X) \propto \prod_{i=1}^{R} p(Y_i | X, Z_i, \theta_i, \tau_i) \prod_{i=1}^{R} \left(p(\theta_i) p(\tau_i) \prod_{j=1}^{D} {\color{red} p(\xi_{i,j})} \right)$$

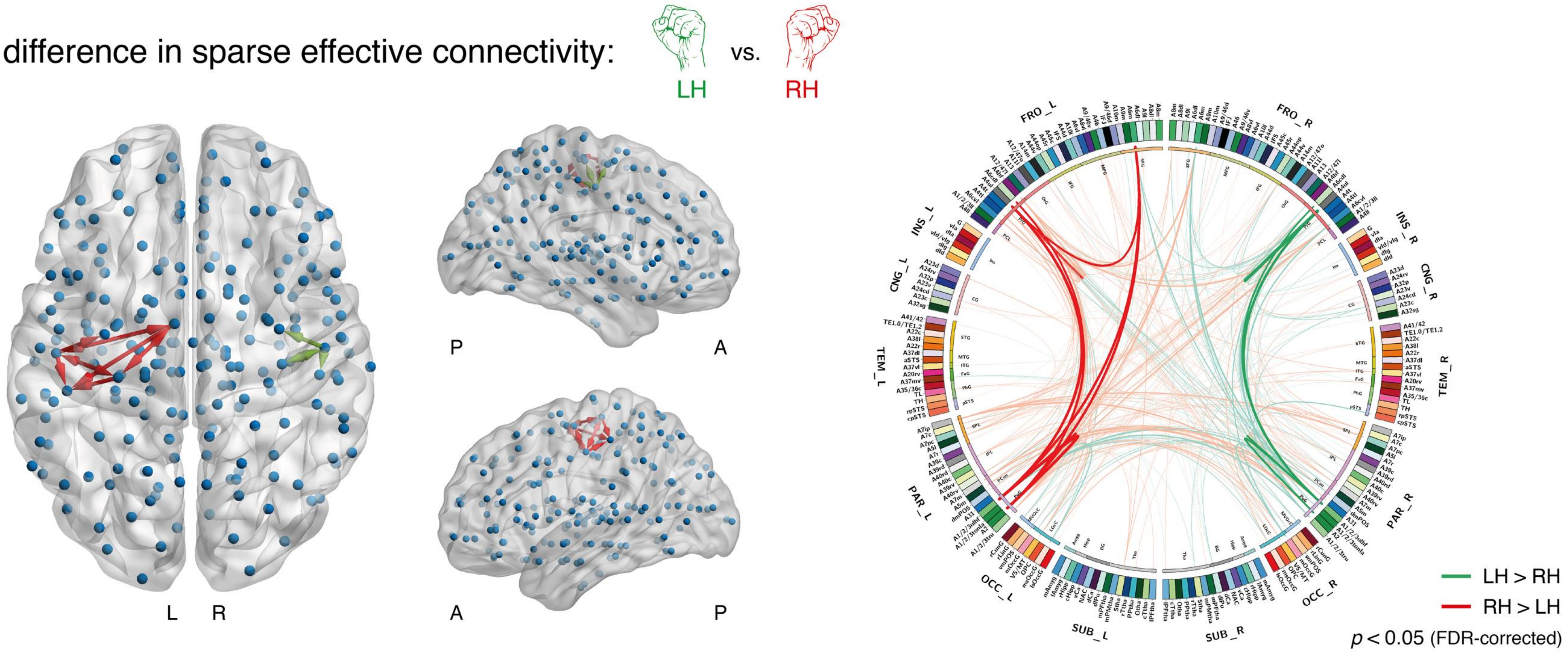
$$\Downarrow$$

$$p(\xi_{i,j}) = Bernoulli(\xi_{i,j}; p_0) = p_0^{\xi_{i,j}} (1 - p_0)^{1-\xi_{i,j}}$$

Initialize model with various p_0 (prior belief about network sparseness)
→ select p_0 that yields highest negative free energy

Frässle et al., 2021, *NeuroImage*

SPARSE WHOLE-BRAIN EFFECTIVE CONNECTIVITY



Frässle et al., 2021, *NeuroImage*

… AND DURING THE RESTING STATE

Frässle et al., 2021, *Human Brain Mapping*

… AND DURING THE RESTING STATE

Idea:

- Set driving inputs (C matrix) to zero

$$
\begin{aligned}
p(Y|\theta,\tau,X) &= \prod_{i=1}^{R} \mathcal{N}(Y_i; X\theta_i, {\tau_i}^{-1} I_{N\times N}) \\
Y_i &:= \left(e^{2\pi i\frac{\boldsymbol{m}}{N}} - 1\right)\frac{\hat{y}_i}{T} \\
X &:= [\widehat{y_1}, \dots, \widehat{y_R}\,] \\
\theta_i &:= [a_{i1}, \dots, a_{iR}]
\end{aligned}
$$

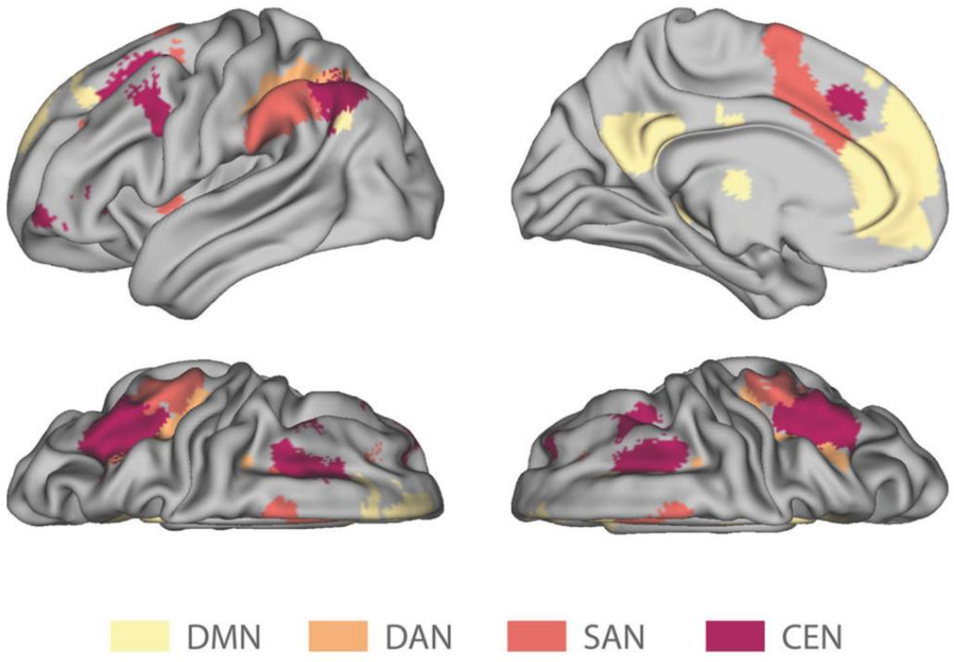
→ no explicit representation of endogenous fluctuations, instead fluctuations of BOLD signal explained as **linear mixture** of intrinsic fluctuations

Frässle et al., 2021, *Human Brain Mapping*

Construct validity of rDCM in comparison to spectral DCM

Data:

- 196 healthy participants (B-SNIP-1 resting state data)
- modes of 4 resting state networks:
    - Default mode network (DMN)
    - Dorsal attention network (DAN)
    - Salience network (SAN)
    - Central executive network (CEN)



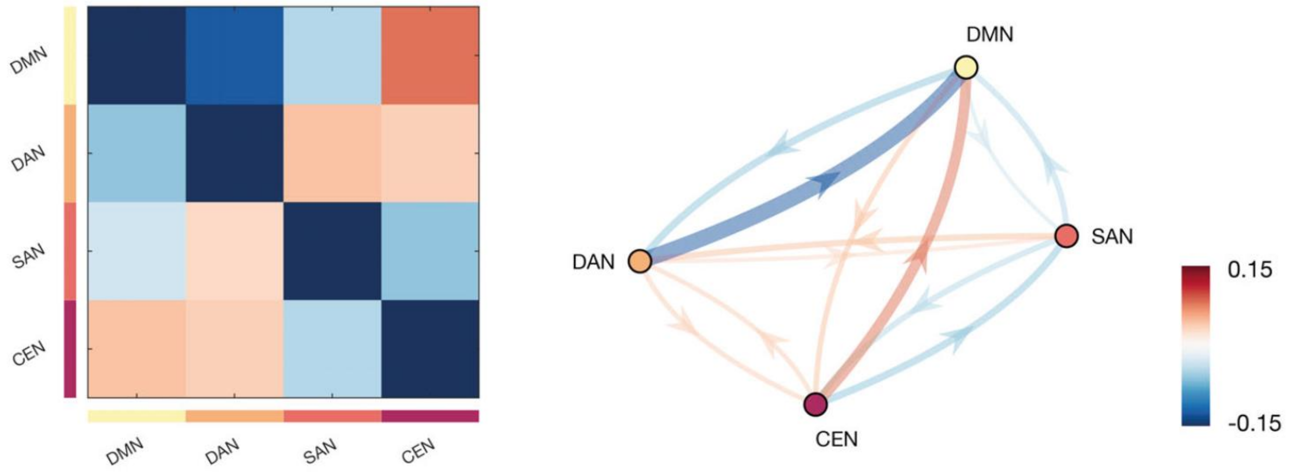
Masks comprising four key intrinsic networks of the resting state

Frässle et al., 2021, *Human Brain Mapping*

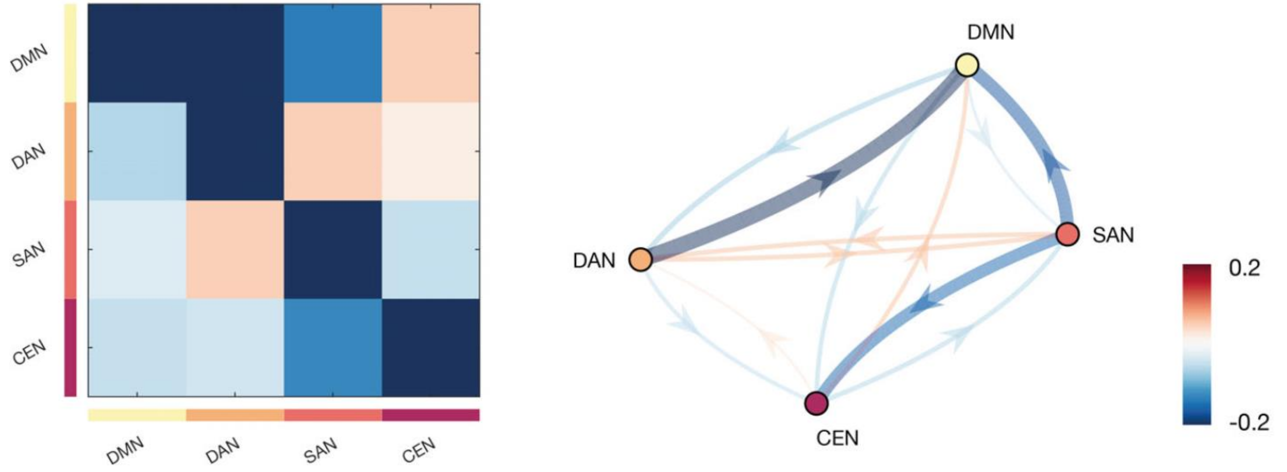
Results

Average effective connectivity among modes

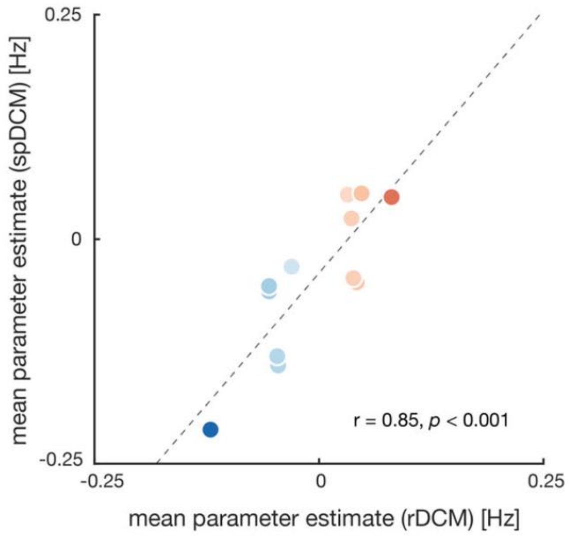
rDCM



spectral DCM



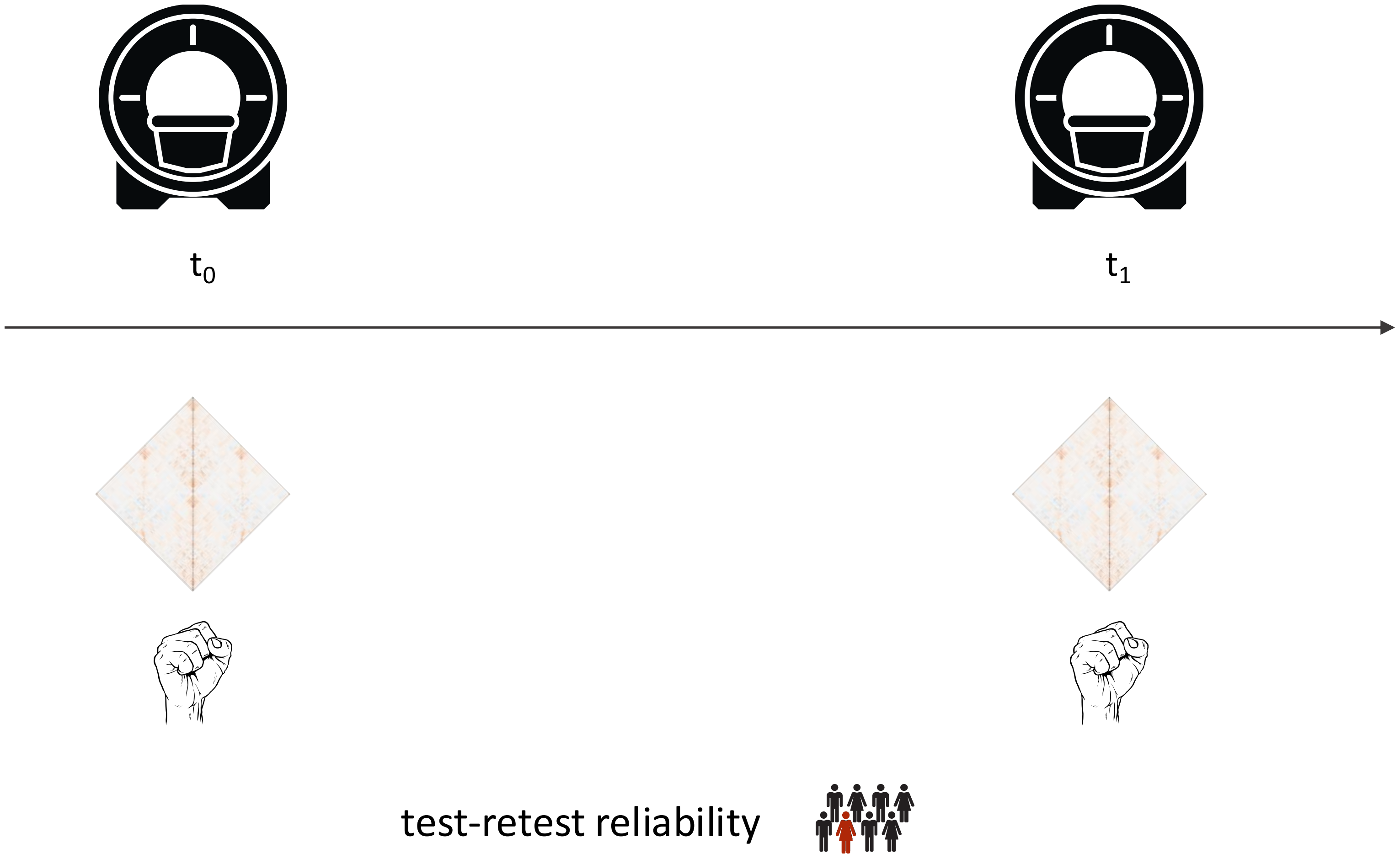
Consistency of group level estimates



Frässle et al., 2021, *Human Brain Mapping*


t_0
t_1

t_0
t_1


t_0
t_1
test-retest reliability

CONNECTOME
COORDINATION FACILITY

Studies | Software | Resources | News & Events | About CCF

What is the Connectome Coordination Facility?

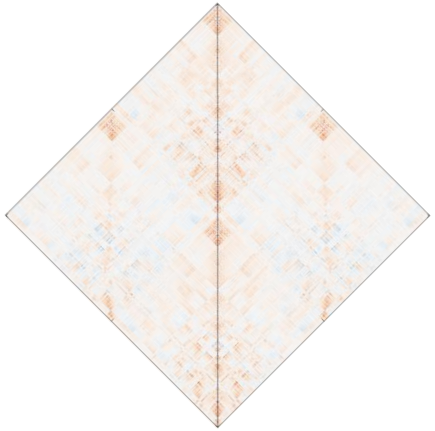
The Connectome Coordination Facility (CCF) houses and distributes public research data for a series of studies that focus on the connections within the human brain. These are known as **Human Connectome Projects**.

The CCF currently supports 20 human connectome studies. Scroll down to learn more.

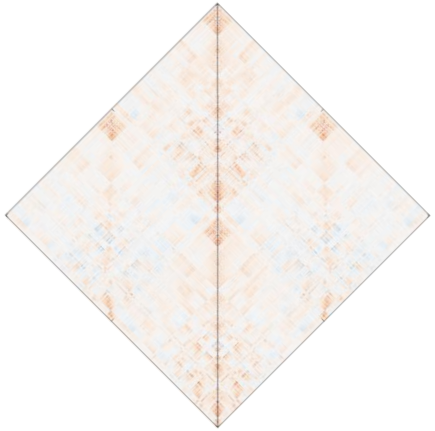
CCF STUDIES AND SOFTWARE

Van Essen et al., 2013, *NeuroImage*; Glasser et al., 2013, *NeuroImage*

Test-retest reliability

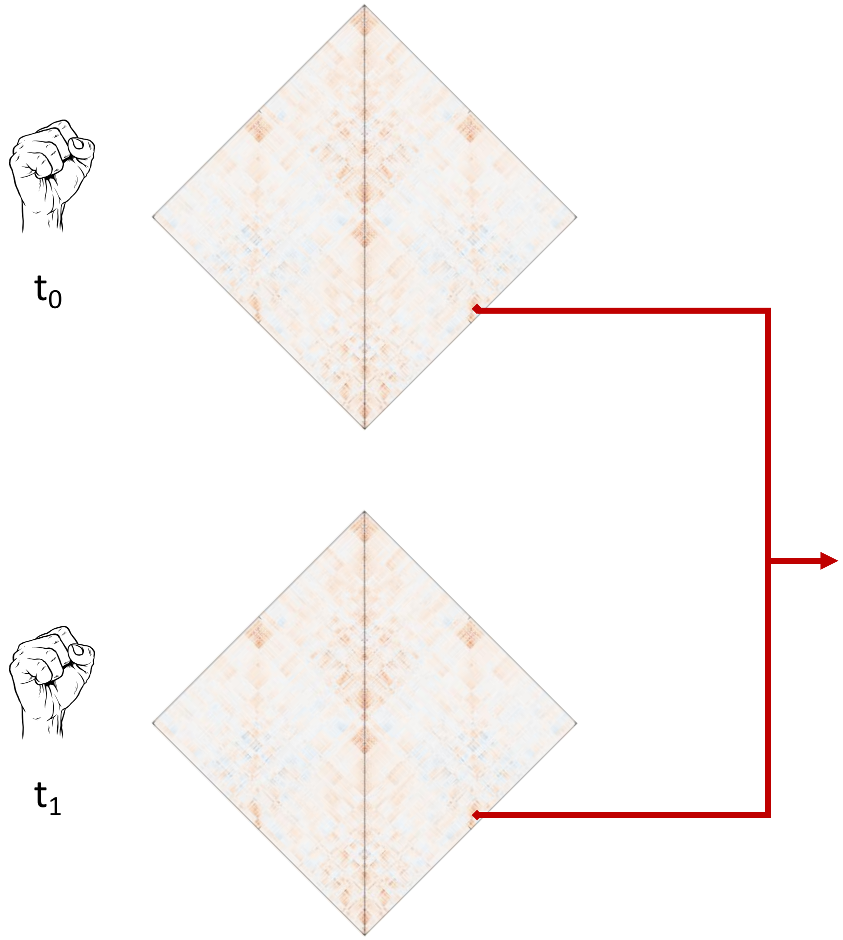
t_0

t_1

Frässle & Stephan, 2022, *Network Neuroscience*

TEST-RETEST RELIABILITY



between-subject

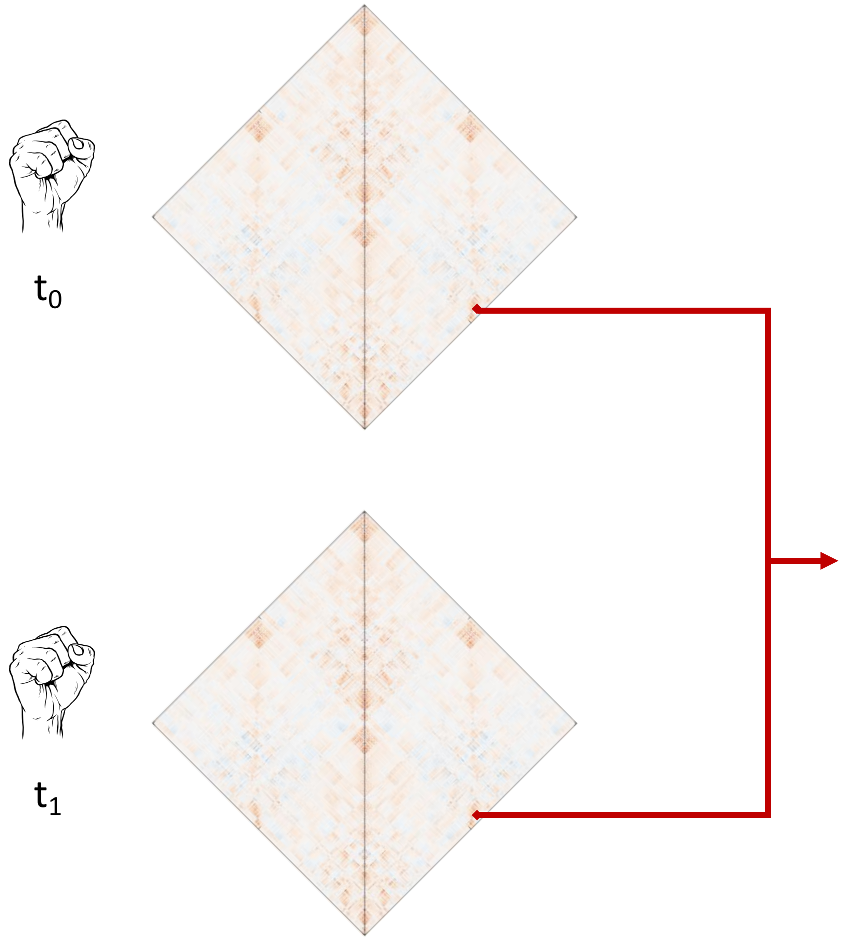
within-subject

$$ICC(3,1) = \frac{\boxed{\sigma_b^2} - \boxed{\sigma_w^2}}{\sigma_b^2 + \sigma_w^2}$$

intra-class correlation coefficient
(for each connection)

Frässle & Stephan, 2022, *Network Neuroscience*

TEST-RETEST RELIABILITY



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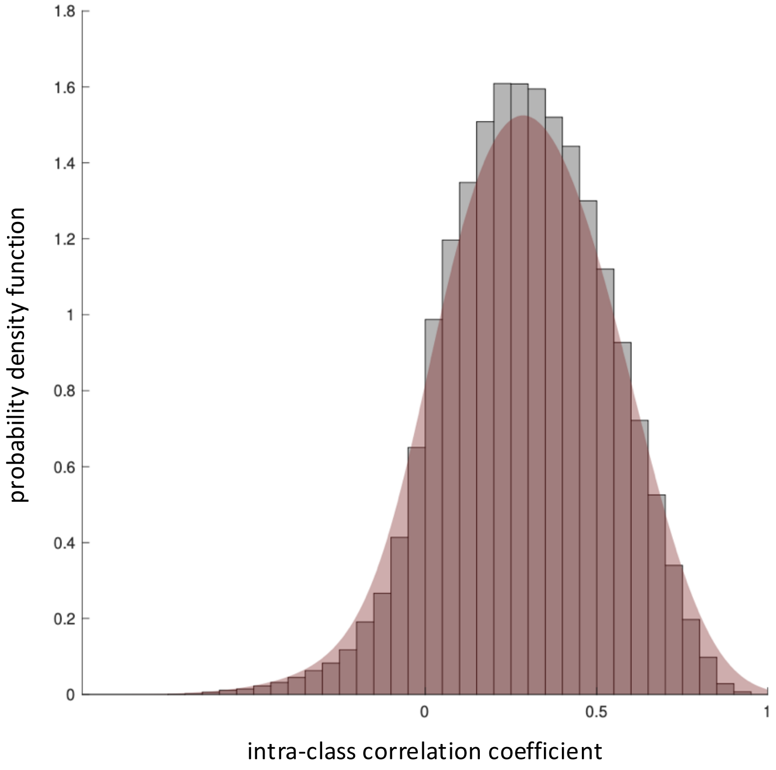
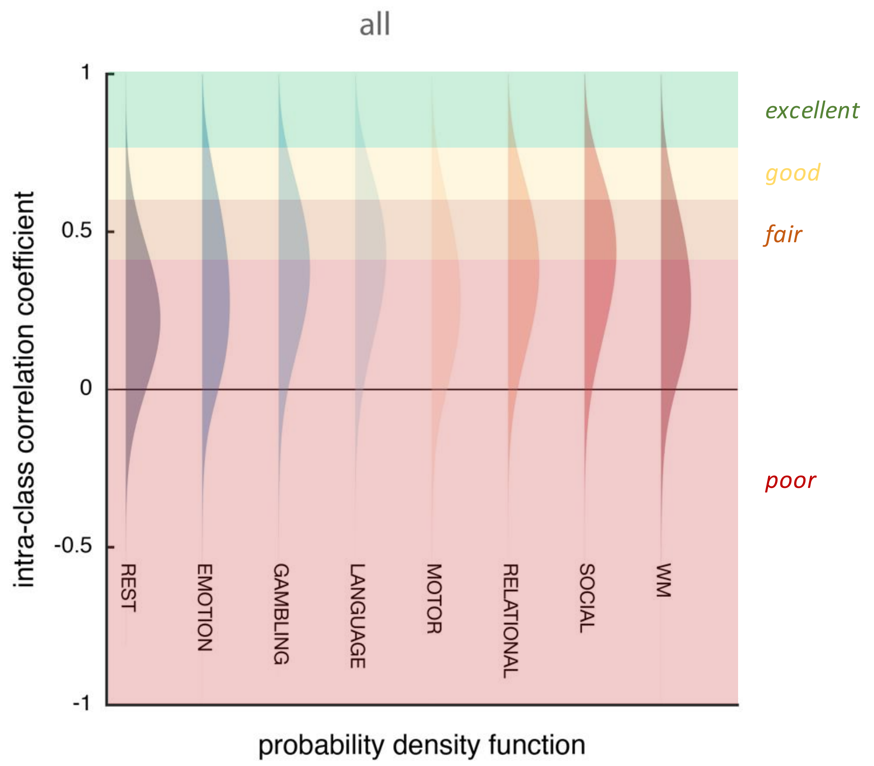
intra-class correlation coefficient
(for each connection)



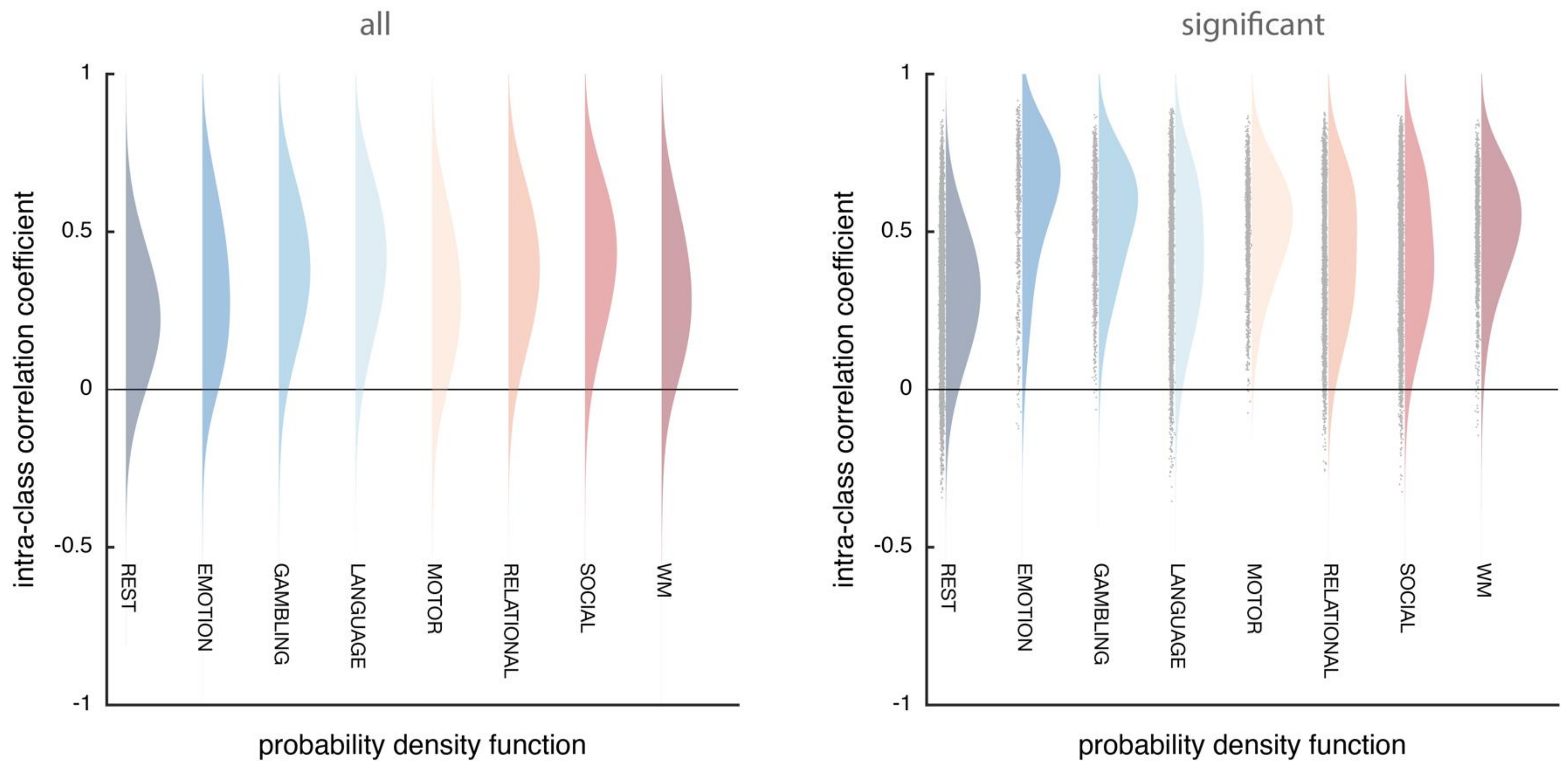
Frässle & Stephan, 2022, *Network Neuroscience*

TEST-RETEST RELIABILITY



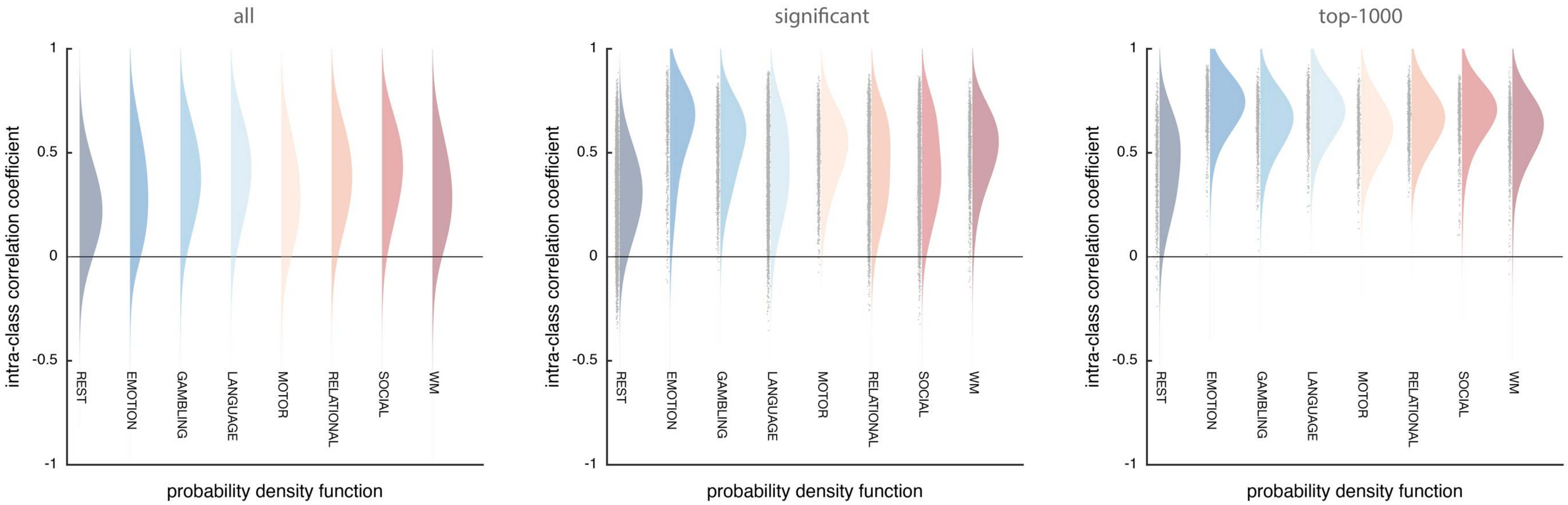
Frässle & Stephan, 2022, *Network Neuroscience*

TEST-RETEST RELIABILITY



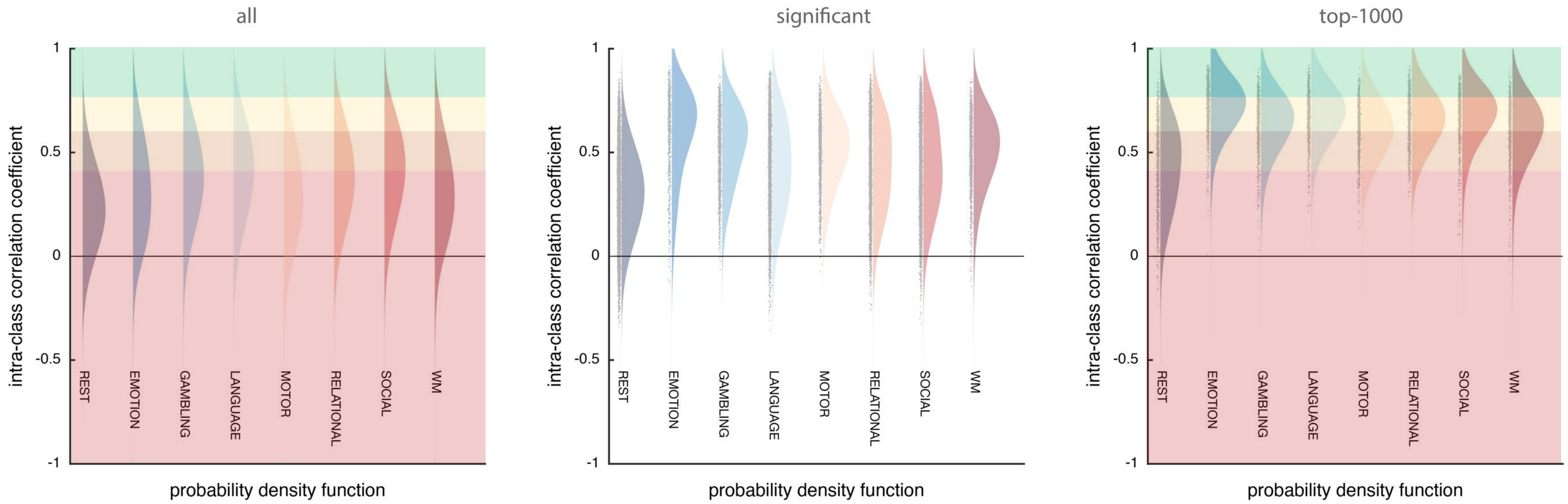
Frässle & Stephan, 2022, *Network Neuroscience*

Test-retest reliability



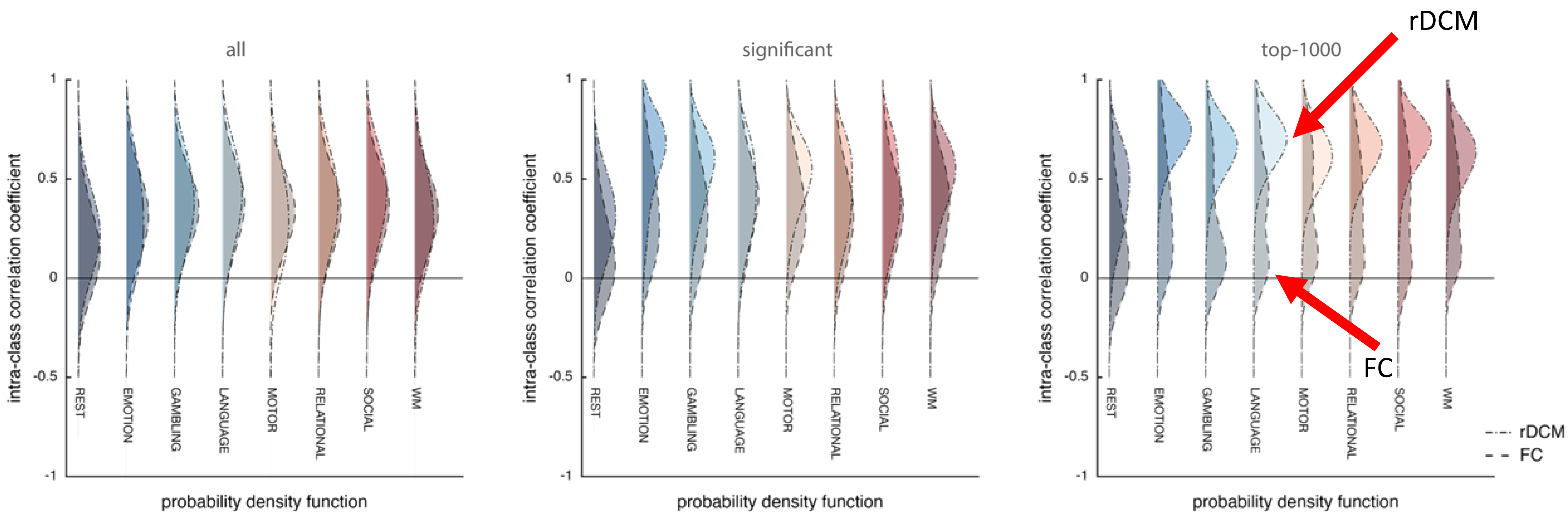
Frässle & Stephan, 2022, *Network Neuroscience*

TEST-RETEST RELIABILITY

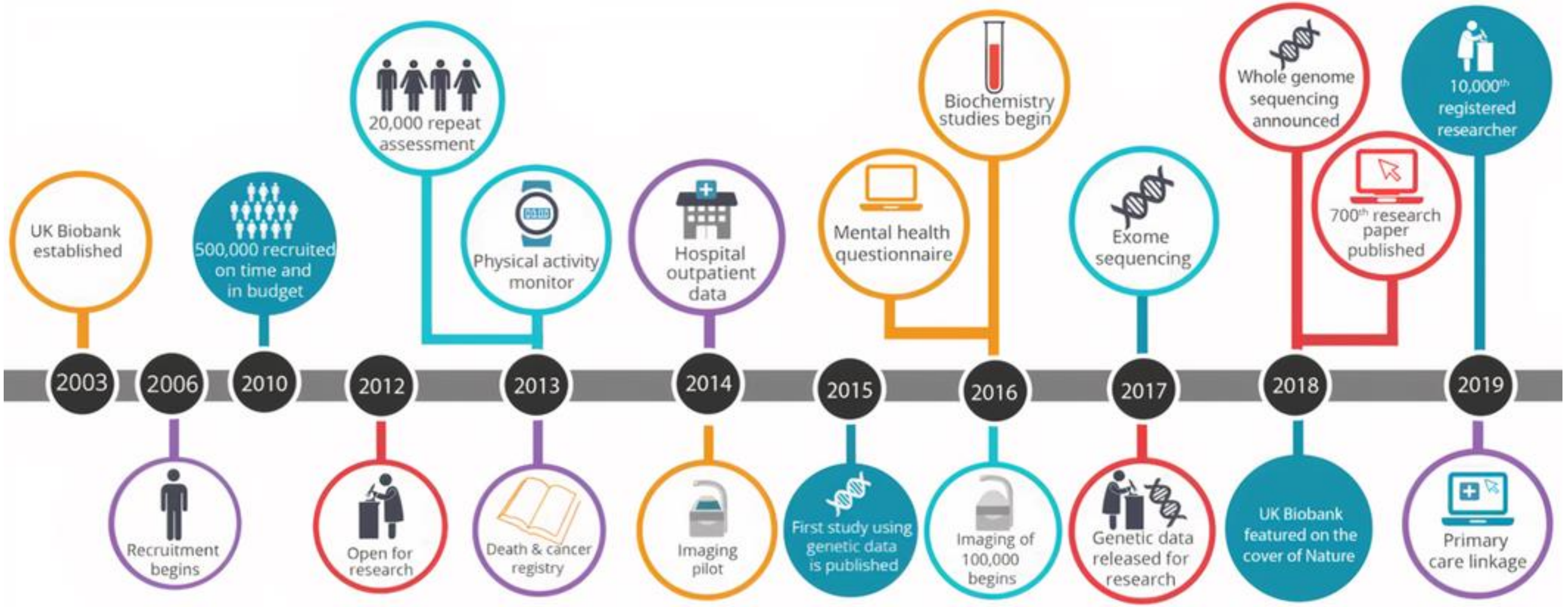


Frässle & Stephan, 2022, *Network Neuroscience*

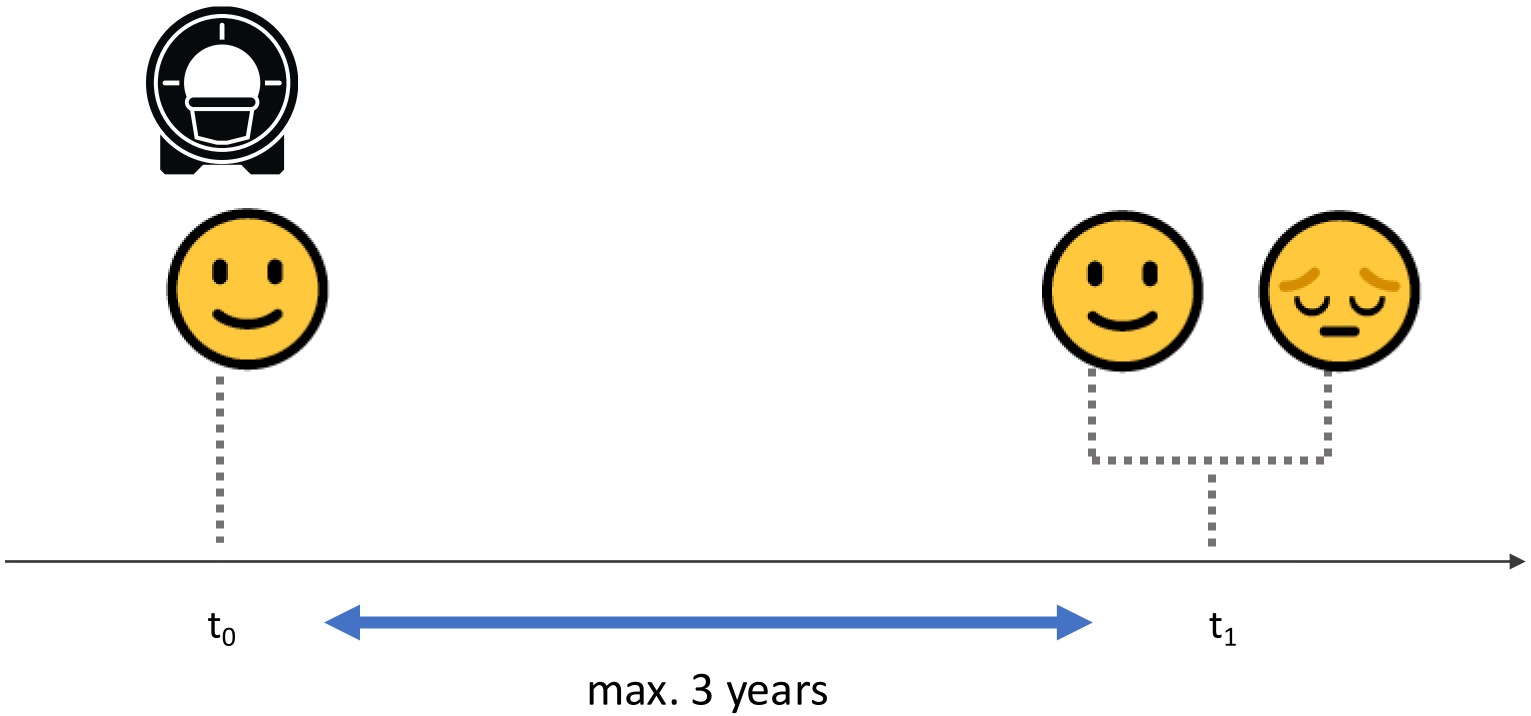
Test-retest reliability



Frässle & Stephan, 2022, *Network Neuroscience*



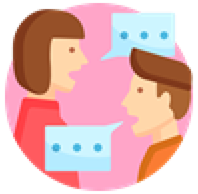
Effingham (2019)



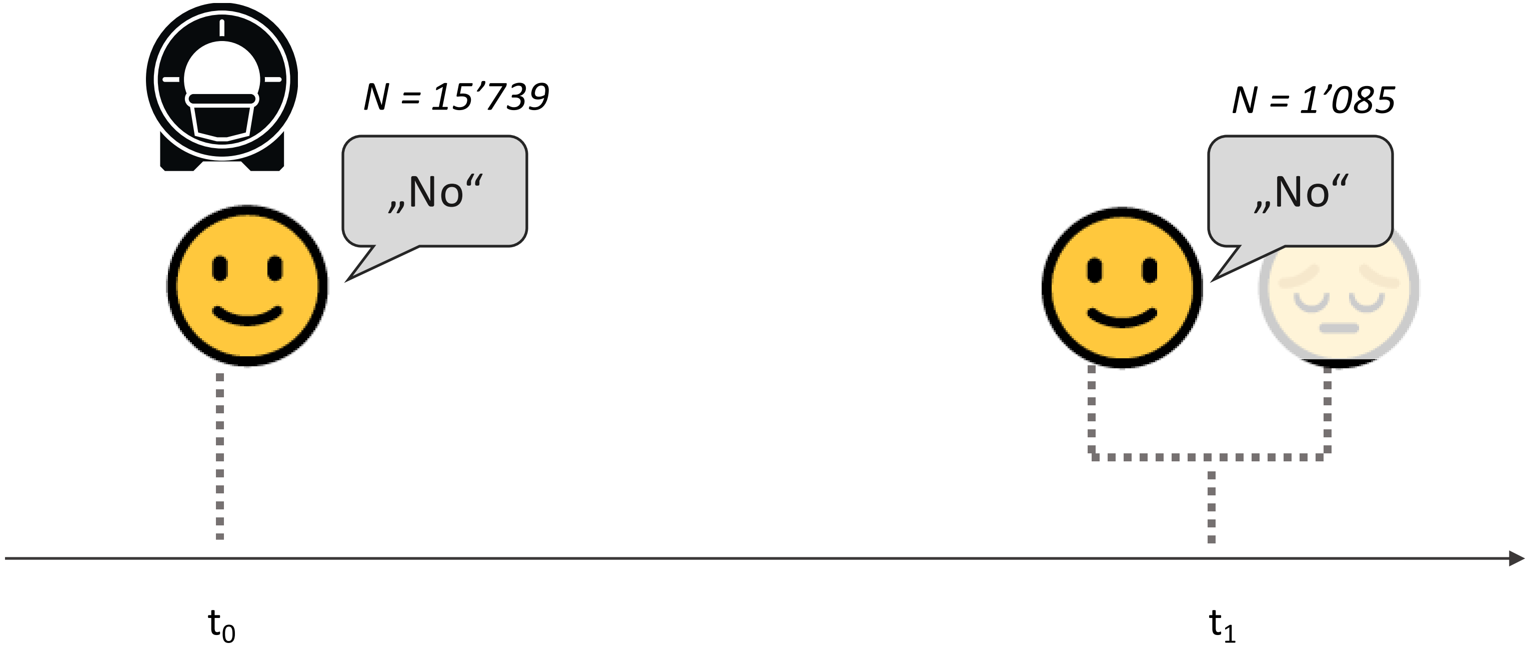
Galioulline et al., 2023, *NeuroImage*


DATASET: D-

Felt Depressed

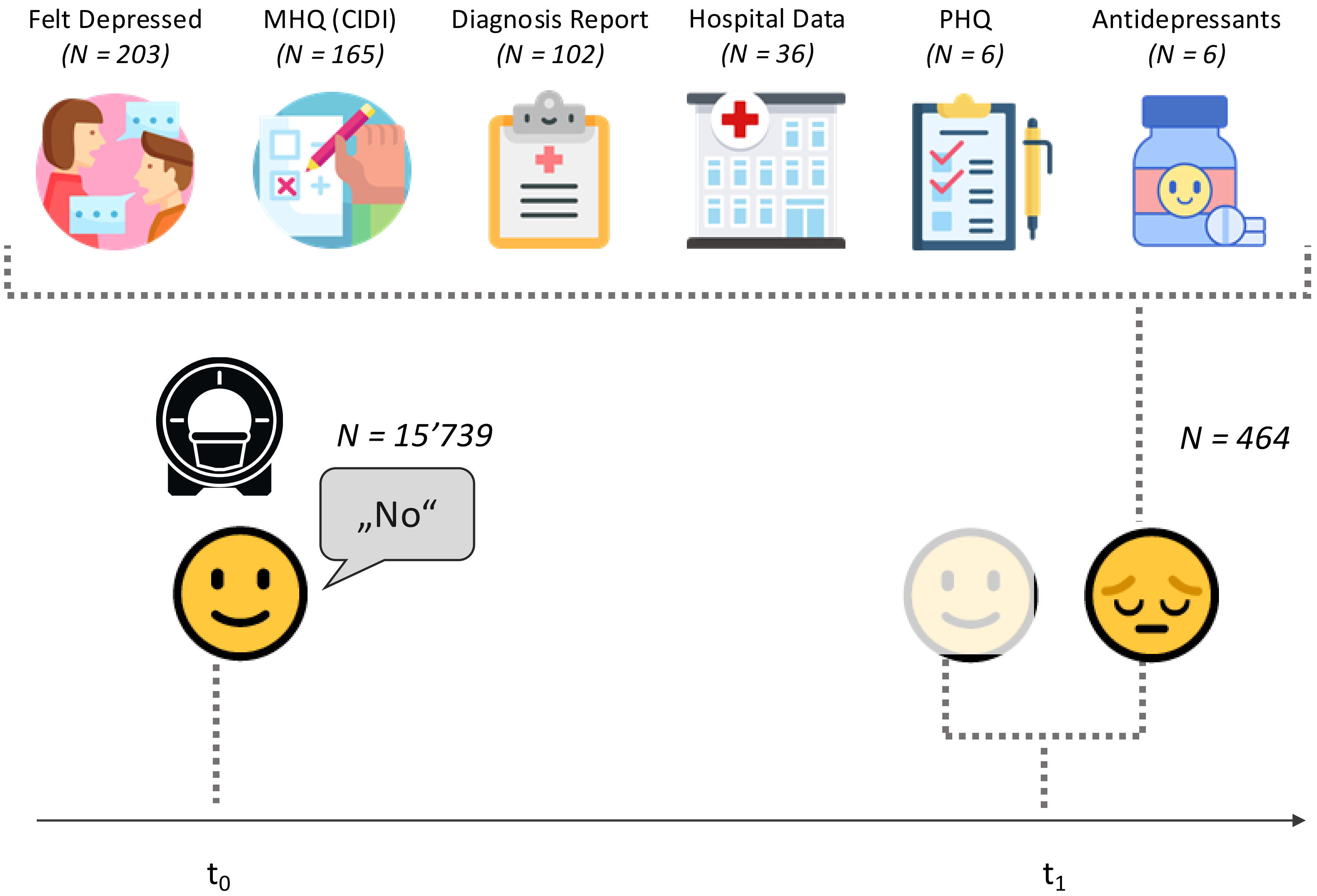


Looking back over your life, have you ever had a time when you were feeling depressed or down for at least a whole week?



Galioulline et al., 2023, *NeuroImage*

Dataset: D+



Galioulline et al., 2023, *NeuroImage*

N = 906

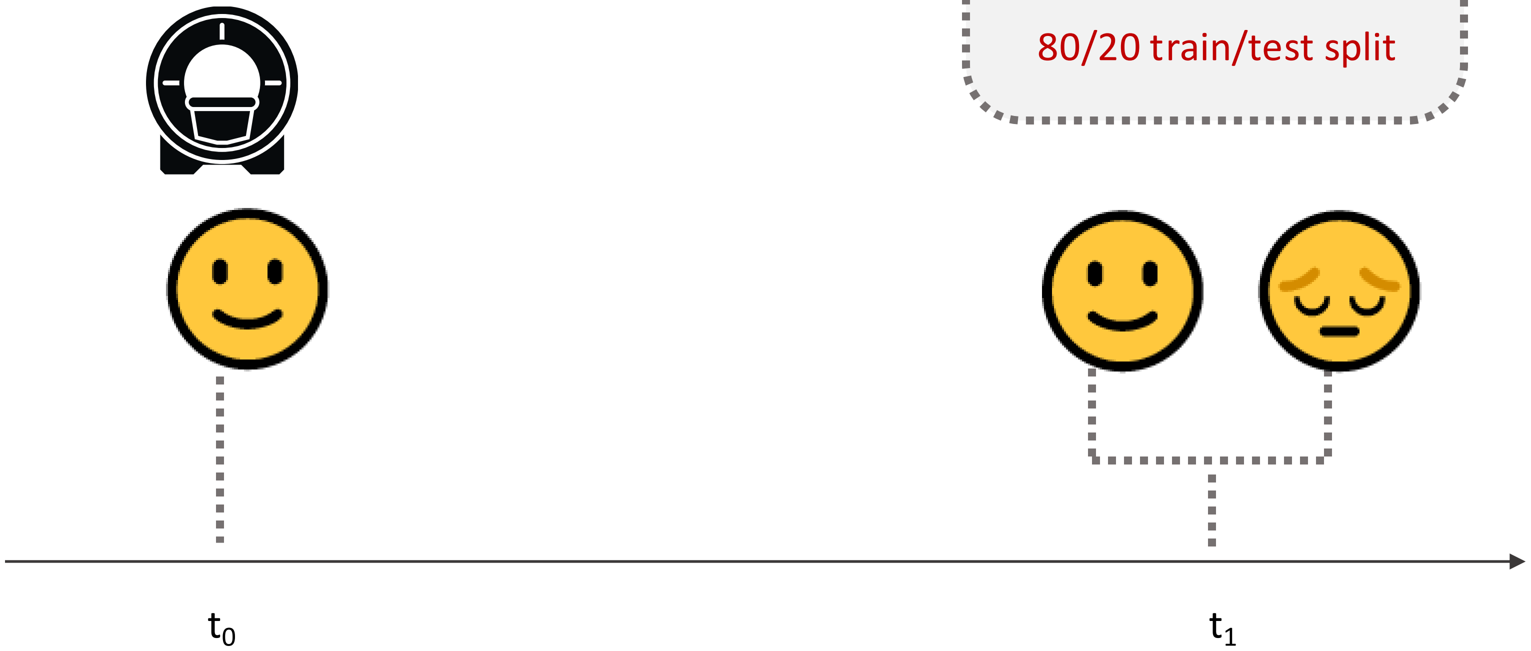
453 D+

453 D-

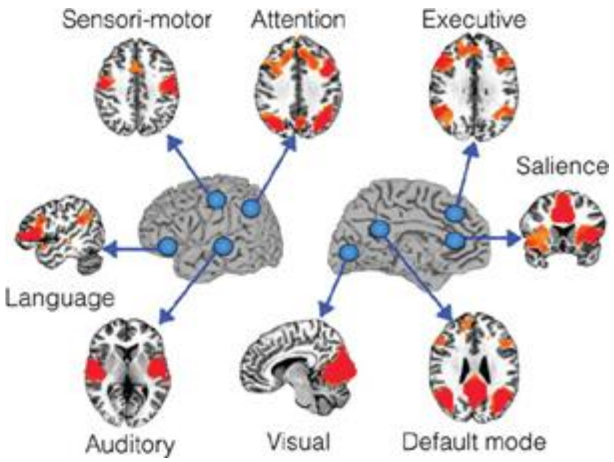
80/20 train/test split

matched for confounds

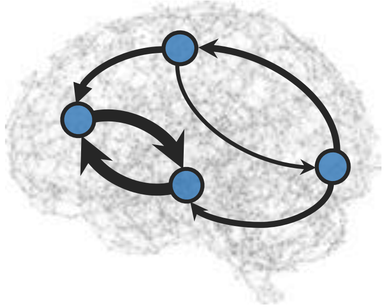
- age
- gender
- handedness
- …



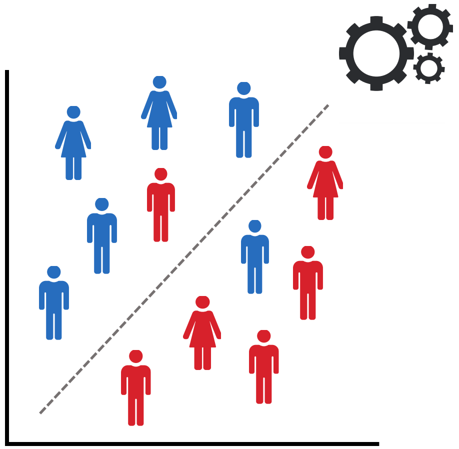
Galioulline et al., 2023, *NeuroImage*



inference on brain connectivity



classification



- 6 (major/selected) RSN
- 21 IC / RSN
- 55 IC / RSN

- Pearson's correlations
- Stochastic DCM
- Spectral DCM
- Regression DCM

- AdaBoost
- Decision Tree
- Gradient Boosting
- Gaussian Naïve Bayes
- k-Nearest Neighbor
- SVM, various kernels
- Logistic Regression
- Quadratic discriminant analysis
- Neural Network (1, 2 , or 3 layers)

Galioulline et al., 2023, *NeuroImage*

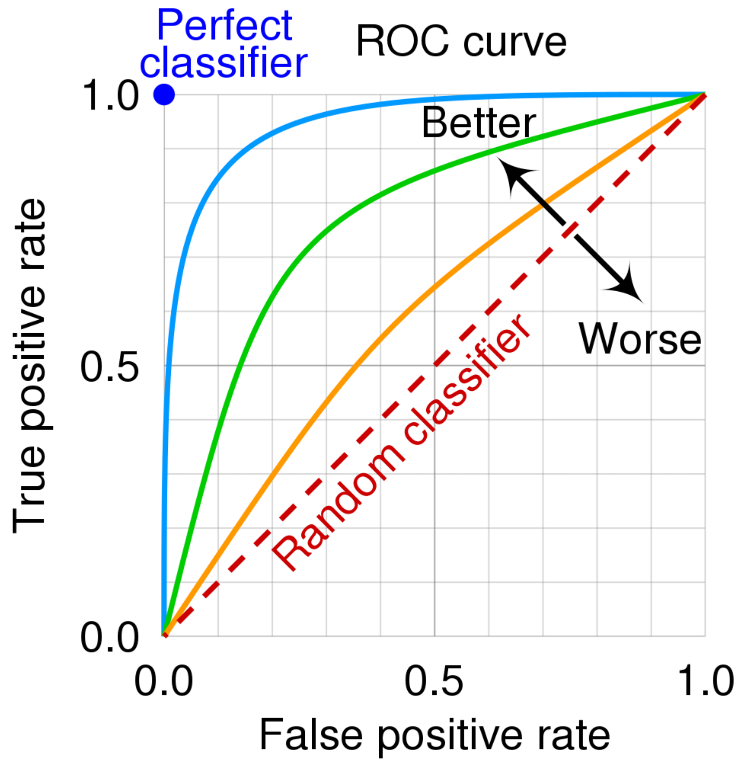
RECEIVER OPERATING CHARACTERISTIC CURVE (ROC)

True Positive Rate (sensitivity)

$$TPR = \frac{TP}{P} = \frac{TP}{TP + FN}$$

False Positive Rate

$$FPR = \frac{FP}{N} = \frac{FP}{FP + TN}$$



Martin Thoma from ROC Wikipedia

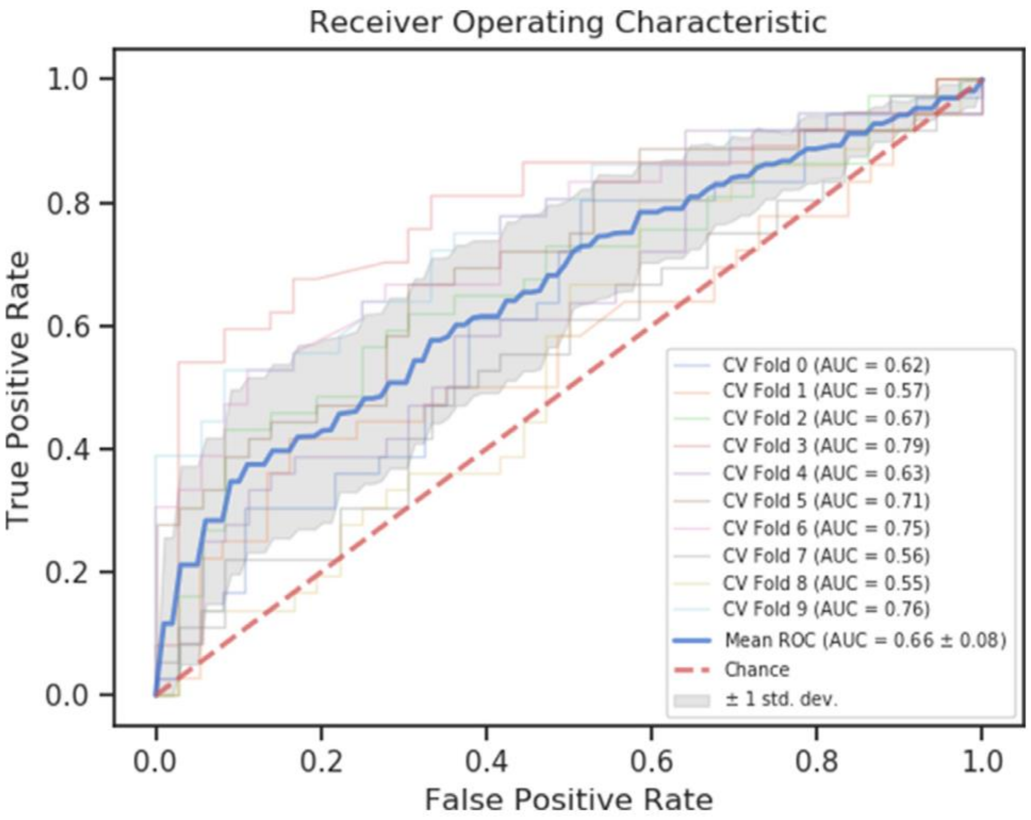
PREDICTING FUTURE DEPRESSIVE SYMPTOMS (TRAINING SET)

Classifiers	Features							
	FC (6)	FC (21)	FC (55)	St. DCM	Sp. DCM	rDCM (6)	rDCM (21)	rDCM (55)
Ada	0.52	0.49	0.56	0.49	0.47	0.55	0.54	0.56
DTC	0.49	0.49	0.52	0.50	0.51	0.51	0.53	0.52
GBC	0.51	0.50	**0.57**	0.49	0.45	0.60*	0.60*	0.64*
GNB	0.53	**0.54**	0.54	0.50	0.49	**0.61***	0.61*	0.63*
kNN	0.52	**0.54**	0.51	0.49	0.47	0.53	0.58	0.59
LR	**0.54**	0.52	0.55	0.51	0.51	0.59	0.58	0.58
NN (1)	0.47	0.52	0.55	0.47	**0.55**	0.50	0.60*	0.61*
NN (2)	0.47	0.52	0.54	0.48	0.53	0.50	0.58	0.63*
NN (3)	0.48	0.52	0.55	0.50	0.54	0.53	0.59	0.62*
QDA	0.47	0.52	0.50	**0.52**	0.53	0.52	0.48	0.51
RF	0.51	0.52	0.56	0.49	0.47	0.57	0.63*	**0.66***
SVM (lin)	**0.54**	0.50	0.55	0.51	0.48	0.58	0.58	0.56
SVM (3)	0.47	0.49	0.52	**0.52**	**0.55**	0.59	0.61*	0.65*
SVM (4)	0.49	0.50	0.47	0.50	0.47	0.49	0.46	0.47
SVM (5)	0.49	0.47	0.47	0.49	**0.55**	0.56	0.47	0.46
SVM (rbf)	0.51	0.51	0.55	0.50	0.50	0.60*	0.63*	0.65*
SVM (sig)	0.52	0.52	0.47	0.48	0.48	**0.61***	**0.64***	**0.66***

Summary table of AUROC for each feature/classifier combination

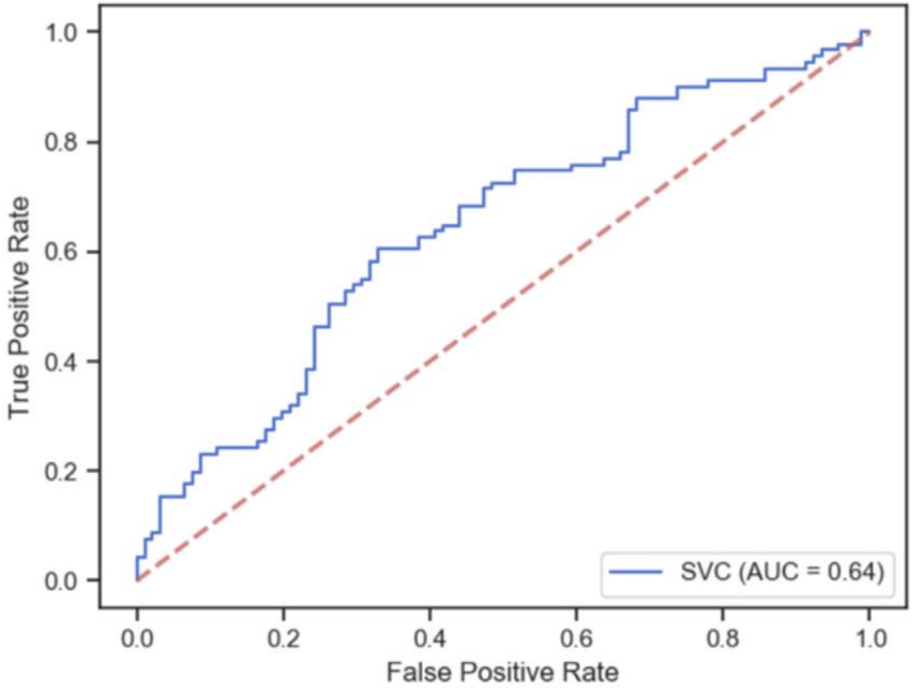
Galioulline et al., 2023, *NeuroImage*

Predicting future depressive symptoms (Training set)

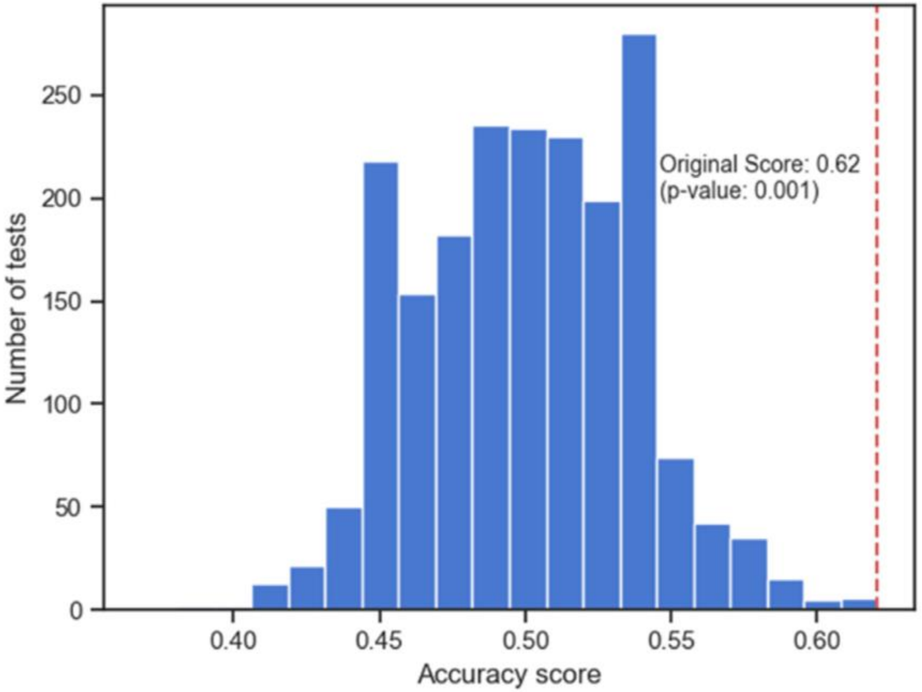


Galioulline et al., 2023, *NeuroImage*

PREDICTING FUTURE DEPRESSIVE SYMPTOMS (**TEST SET**)



ROC curve of rDCM (55ICs) with sigmoid SVM run on test data.



Permutation test (n=2,000) run on test data with accuracy as metric.

Galioulline et al., 2023, *NeuroImage*

Future developments

Future developments

Time domain formulation

$$iw\hat{y} = A\hat{y} + C\begin{bmatrix}\hat{u}_1\hat{h} \\ \vdots \\ \hat{u}_K\hat{h}\end{bmatrix} \quad \Longrightarrow \quad \frac{dy}{dt} = Ay + C\begin{bmatrix}u_1 * h \\ \vdots \\ u_K * h\end{bmatrix}$$

Refined noise formulation

$$\Sigma = \quad I \quad \Longrightarrow \quad \begin{bmatrix} \frac{2}{T^2} + (a_{rr}^0)^2 & -\frac{1}{T^2} + (a_{rr}^0)^2 & & \\ -\frac{1}{T^2} + (a_{rr}^0)^2 & \ddots & \ddots & -\frac{1}{T^2} + (a_{rr}^0)^2 \\ & \ddots & -\frac{1}{T^2} + (a_{rr}^0)^2 & \frac{2}{T^2} + (a_{rr}^0)^2 \end{bmatrix}$$

SOFTWARE

TAPAS

Translational Algorithms for Psychiatry-Advancing Science (TAPAS)

https://github.com/ComputationalPsychiatry

rDCM (Matlab version)

rDCM (Julia version)

TUTORIAL

Tutorial J: Regression DCM Using Tapas

When: AM: 08:15 – 11:45 [CEST]
PM: 13:00 – 16:30 [CEST]

Where: Zurich

Who: Imre Kertesz, Herman Galioulline

Programming Language:

Materials:

In this tutorial, you will learn how to use the regression dynamic causal modeling (rDCM) toolbox to perform effective (directed) connectivity analyses in whole-brain networks. We will provide you with the necessary theoretical background of the rDCM approach and detail practical aspects that are relevant for whole-brain connectivity analyses. After having laid the foundation, a hands-on part will familiarize you with the code and provide in-depth training on how to apply the model to empirical fMRI data. The goal of this tutorial is to familiarize you with the theoretical and practical aspects of rDCM, which will allow you to seamlessly integrate the approach into your own research. We will provide clear instructions on how to perform the analyses. However, experience with the analysis of fMRI data (already some experience with classical DCM for fMRI would be ideal) as well as experience with Julia or MATLAB are beneficial.

THANK YOU FOR YOUR ATTENTION !

Imre Kertesz

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Many thanks to Stefan Frässle, Klaas Enno Stephan, Herman Galioulline, Inês Pereira and Jakob Heinzle for many of the slides and inputs!

Further Readings

- Daunizeau J, Stephan KE, Friston KJ (2012) Stochastic Dynamic Causal Modelling of fMRI data: Should we care about neural noise? *NeuroImage* 62:464-481.
- Friston KJ, Harrison L, Penny W (2003) Dynamic causal modelling. *NeuroImage* 19:1273-1302.
- Friston KJ, Kahan J, Biswal B, Razi A (2014) A DCM for resting state fMRI. *Neuroimage* 94:396-407.
- Frässle S, Lomakina EI, Razi A, Friston KJ, Buhmann JM, Stephan KE (2017) Regression DCM for fMRI. *NeuroImage* 155:406-421.
- Frässle S, Lomakina EI, Kasper L, Manjaly ZM, Leff A, Pruessmann KP, Buhmann JM, Stephan KE (2018) A generative model of whole-brain effective connectivity. *NeuroImage* 179:505-529.
- Frässle S, Harrison SJ, Heinzle J, Clementz BA, Tamminga CA, Sweeney JA, Gershon ES, Keshavan MS, Pearlson GD, Powers A, Stephan KE (2021) Regression dynamic causal modeling for resting-state fMRI. *Human Brain Mapping* 42:2159-2180.
- Frässle S, et al. (2021) TAPAS: an open-source software package for Translational Neuromodeling and Computational Psychiatry. *Frontiers in Psychiatry* 12: 857
- Frässle S & Stephan KE (2022) Test-retest reliability of regression dynamic causal modeling. *Network Neuroscience* 6(1):135-160.
- Galioulline H, Frässle S, Harrison SJ, Pereira I, Heinzle J, Stephan KE (2023) Predicting future depressive episodes from resting-state fMRI with generative embedding. *NeuroImage* 273:119986
- Woolrich MW, Stephan KE (2013) Biophysical network models and the human connectome. *NeuroImage* 80:330-338
- Glasser MF, et al. (2013) The minimal preprocessing pipelines for the Human Connectome Project. NeuroImage 80:105-124
- Van Essen DC, et al. (2013) The WU-Minn Human Connectome Project: an overview. NeuroImage 80:62-79