



# Modeling Connectivity: Regression DCM for fMRI

*Imre Kertesz*

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

***Computational Psychiatry Course (CPC) 2024***  
*Thursday , 12.09.2024*



# THE HUMAN BRAIN



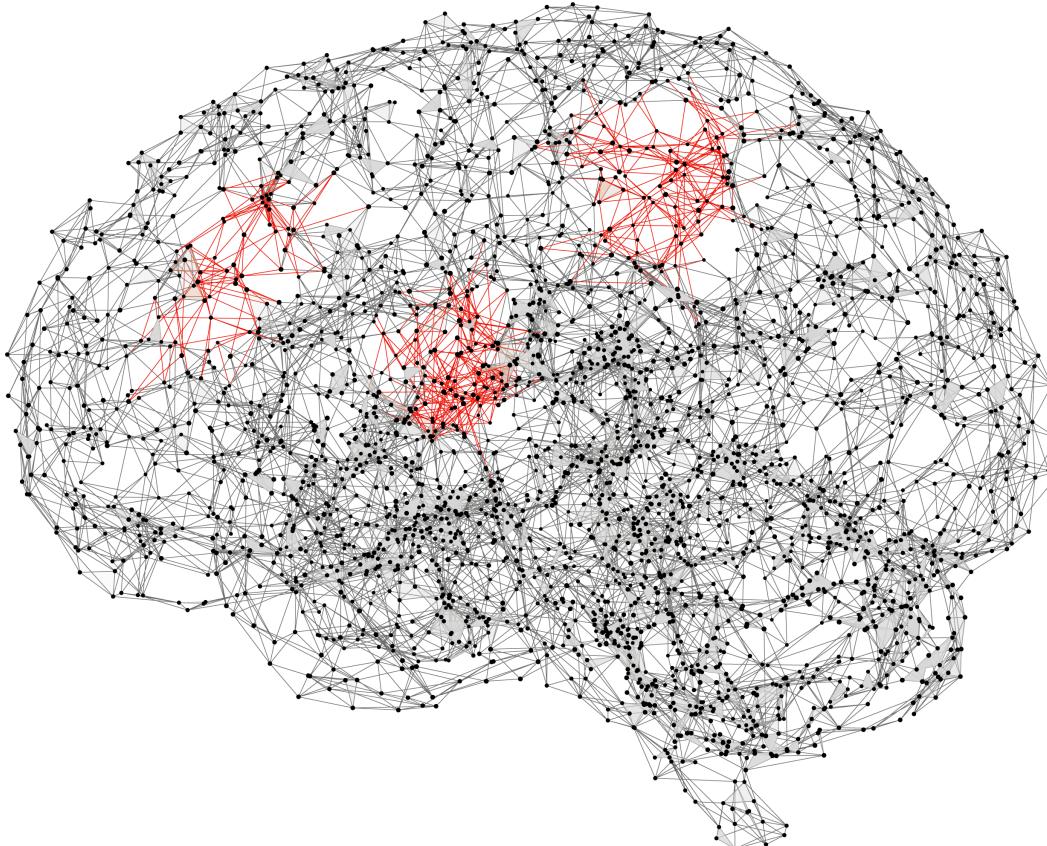
© www.dreamstime.com

autism



© www.leafscience.com

depression

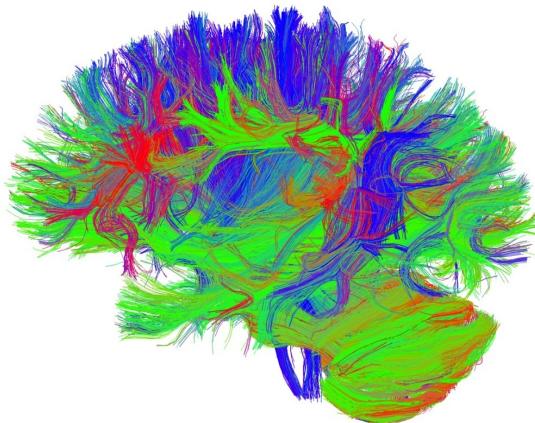


© www.blog.neuronup.com

schizophrenia

# DIFFERENT FORMS OF BRAIN CONNECTIVITY

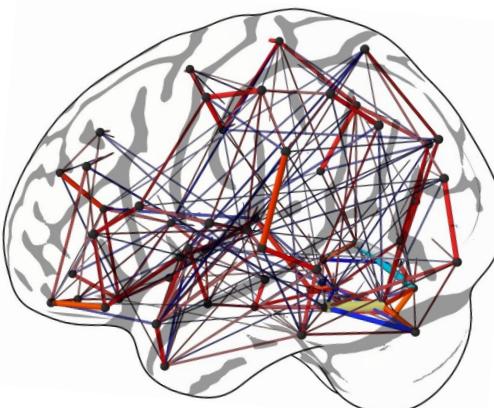
## structural connectivity



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

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

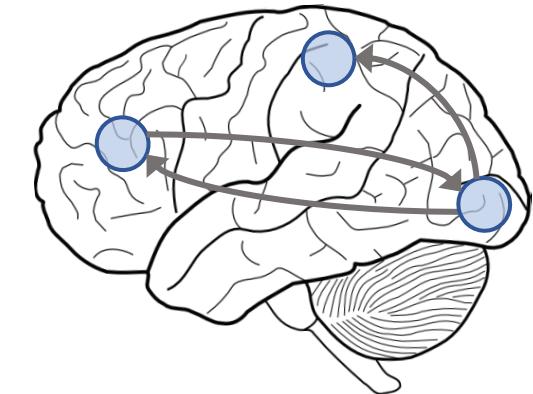
## functional connectivity



[https://team.inria.fr/parietal/files/2013/02/pc\\_dag.jpg](https://team.inria.fr/parietal/files/2013/02/pc_dag.jpg)

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

## effective connectivity



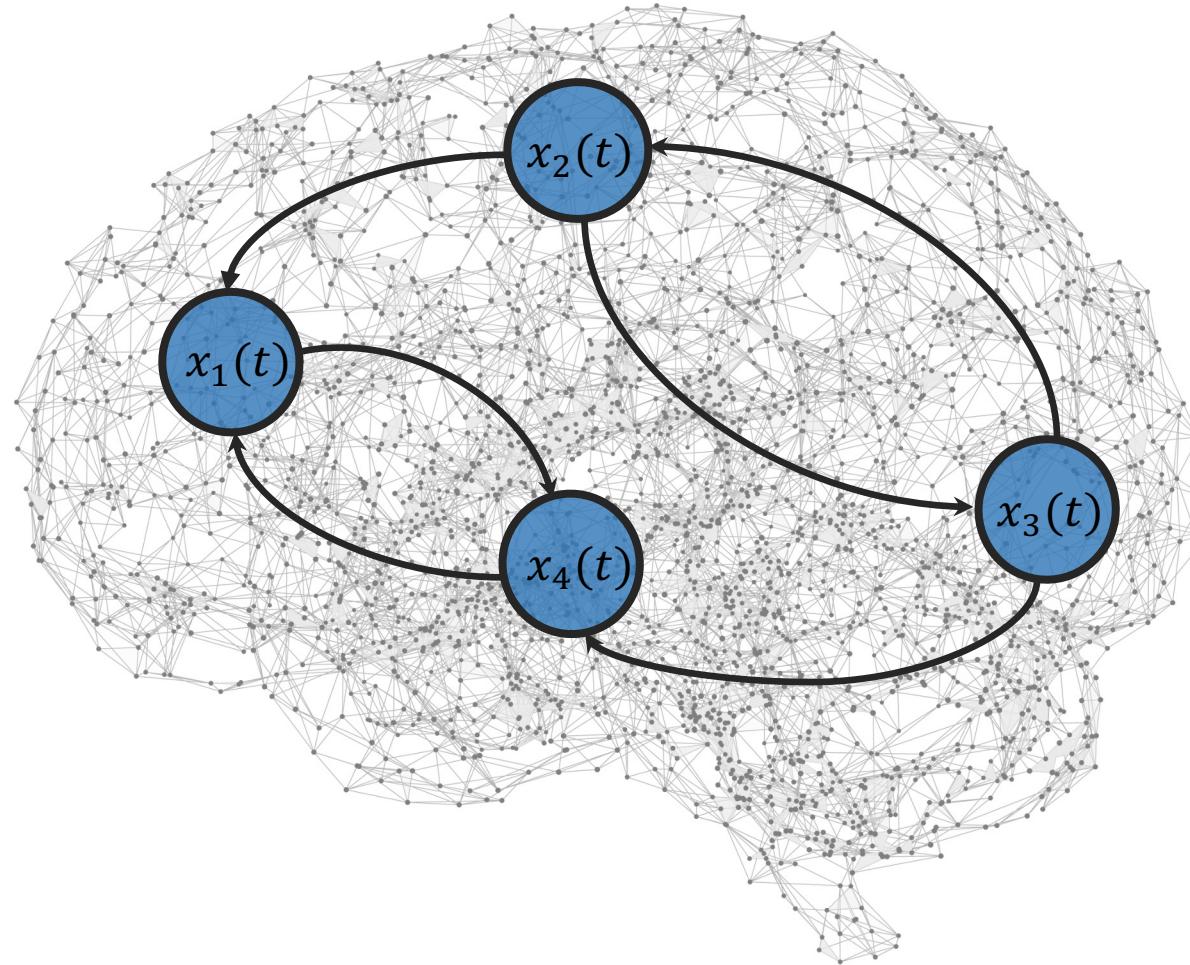
<http://www.clker.com/cliparts/e/5/Q/i/e/o/brain-line-drawing-md.png>

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

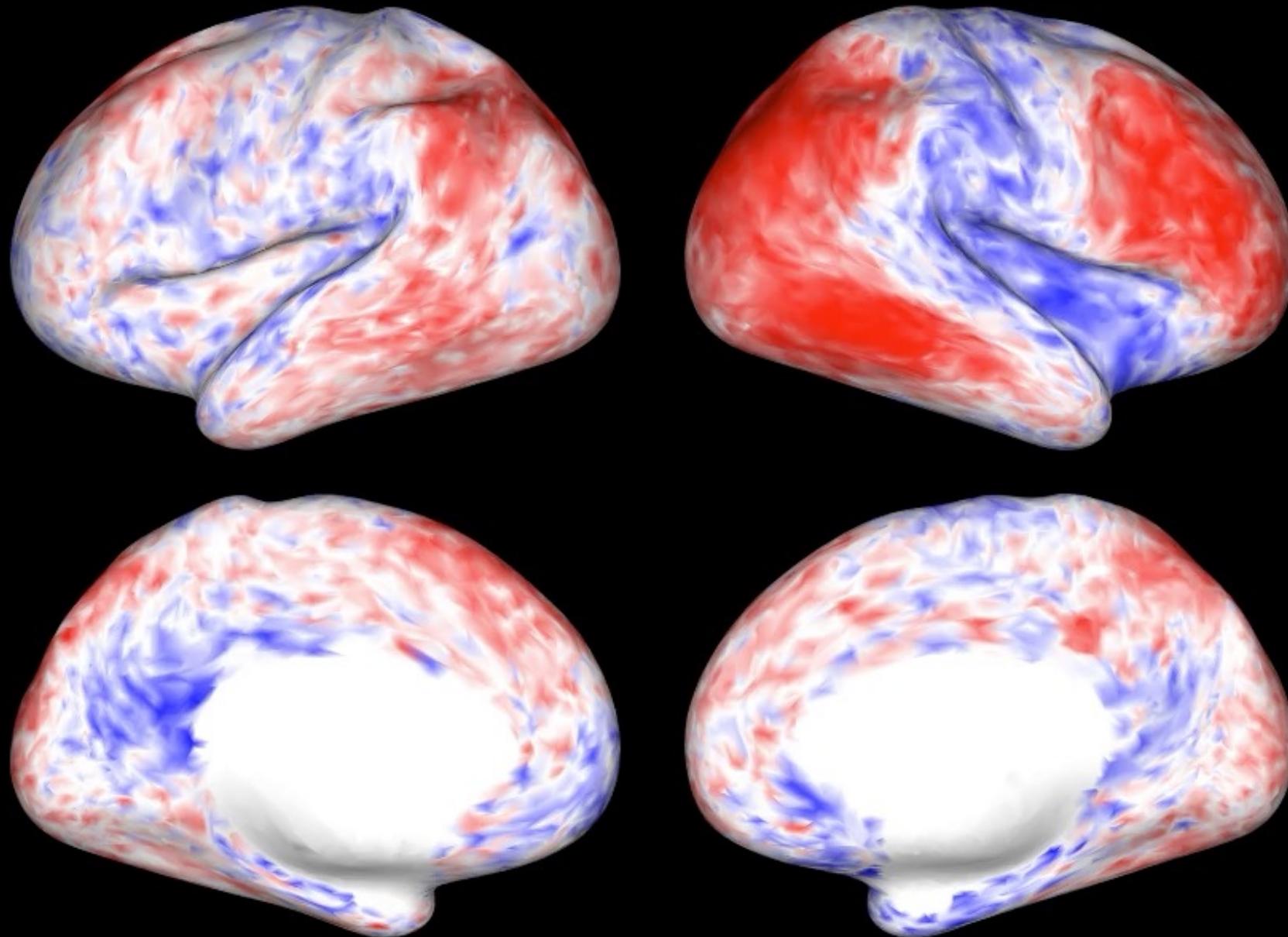
adapted from: Sporns, 2007, Scholarpedia

# WHAT YOU HAVE SEEN SO FAR

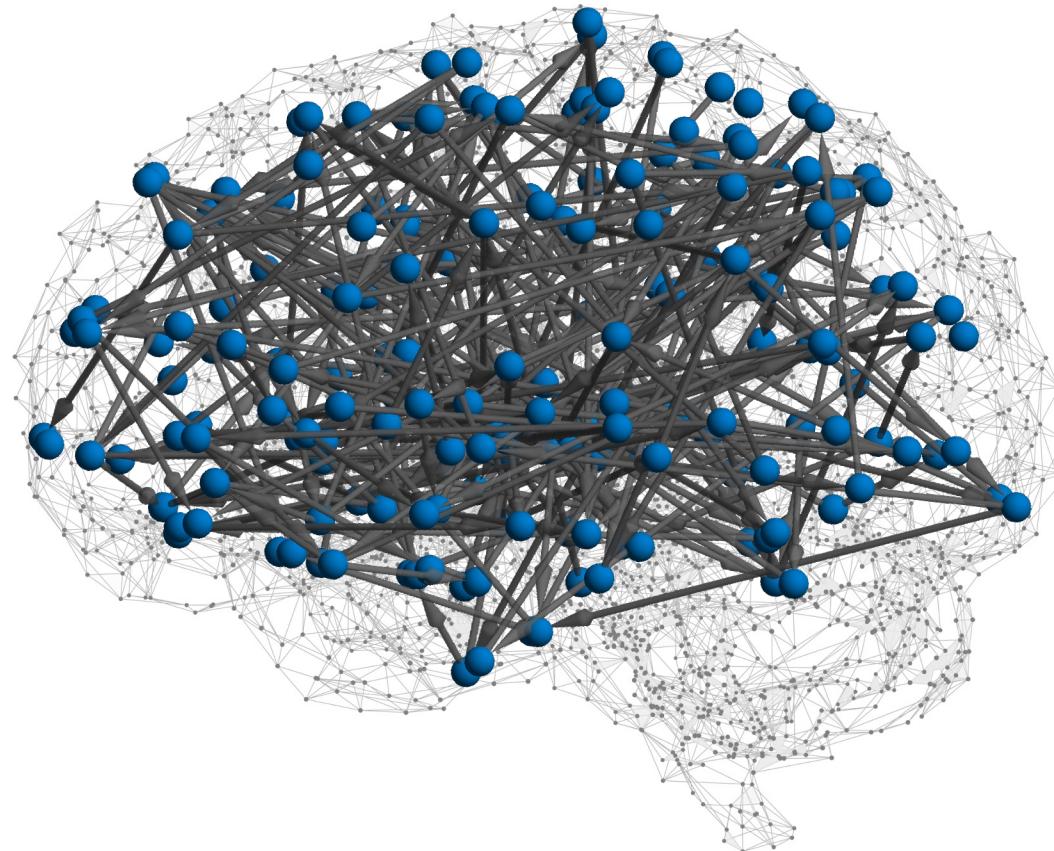
## DCM for fMRI



BUT...

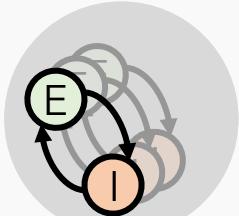


# WHAT WE WANT

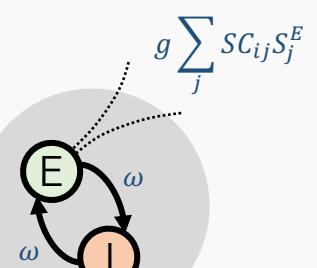


## biophysical network models (BNMs)

direct simulation



mean-field models



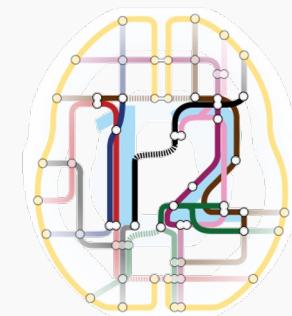
The Virtual Brain



THE VIRTUAL BRAIN.

## dynamic causal models (DCMs)

spectral DCM  
for large-scale network



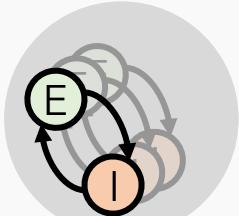
regression DCM



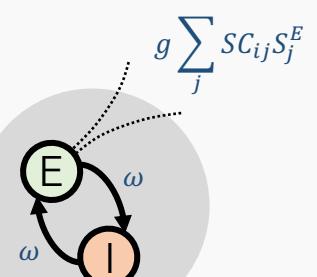
TAPAS

## biophysical network models (BNMs)

direct simulation



mean-field models



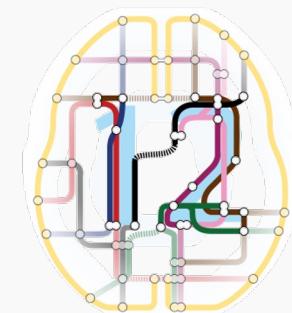
The Virtual Brain



THE VIRTUAL BRAIN.

## dynamic causal models (DCMs)

spectral DCM  
for large-scale network



regression DCM



TAPAS



E. Lomakina

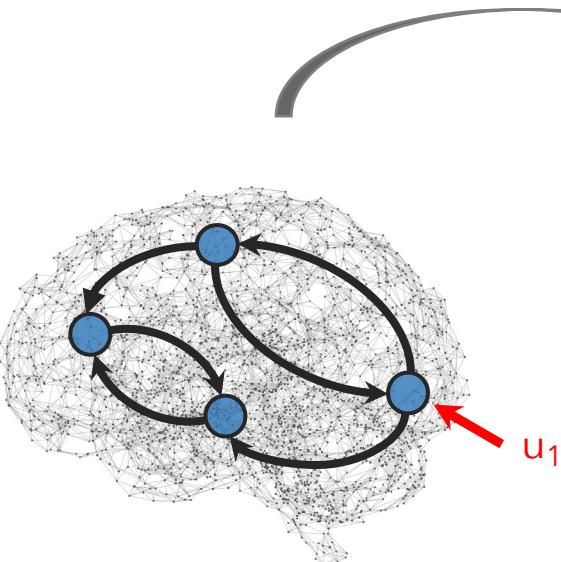


S. Frässle

# Regression dynamic causal modeling (rDCM)

Go simple, go big

# REGRESSION DCM – UNDER THE HOOD...



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

linear DCM in the time domain

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

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

$$X := [\widehat{y}_1, \dots, \widehat{y}_R, \widehat{h}\widehat{u}_1, \dots, \widehat{h}\widehat{u}_K]$$

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

GLM in the frequency domain

introduce priors

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

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

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

Bayesian linear regression in the frequency domain

→highly efficient VB inversion scheme with analytical update equations

# SPARSE REGRESSION DCM – UNDER THE HOOD...



Formulation for regression DCM

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

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

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

Bayesian linear regression in the frequency domain

Introduce binary indicator variables

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

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

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

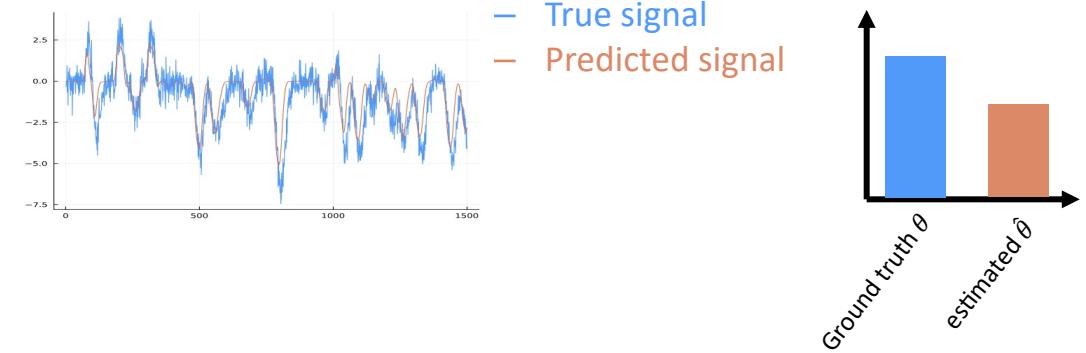
Sparse Bayesian linear regression in the frequency domain

→automatically prunes network as part of model inversion

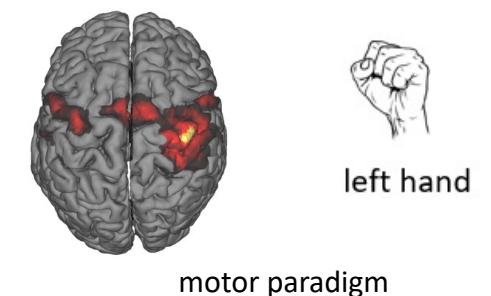


# MODEL VALIDITY (IN THE CONTEXT OF DCM)

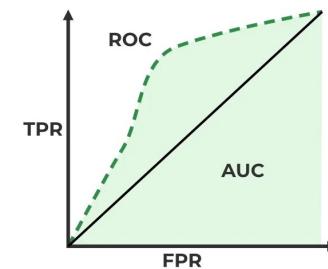
- **Face validity:** Is the model inferring what it is supposed to?



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

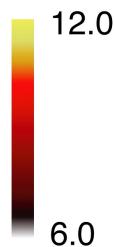
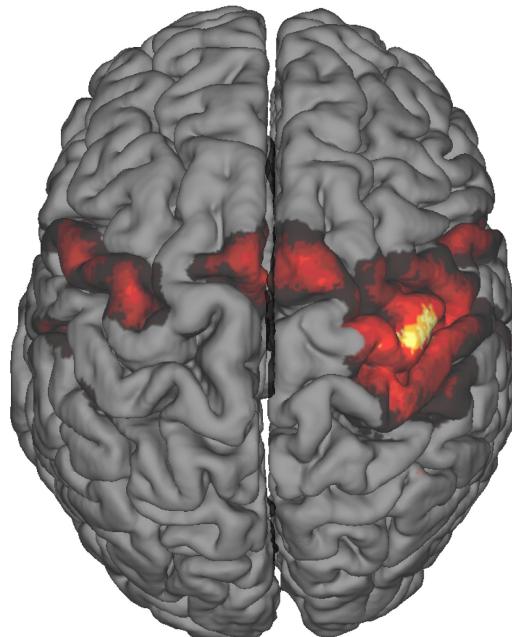


- **Predictive validity:** Ability to make accurate predictions
  - Prediction of independent data, e.g. treatment response





left hand

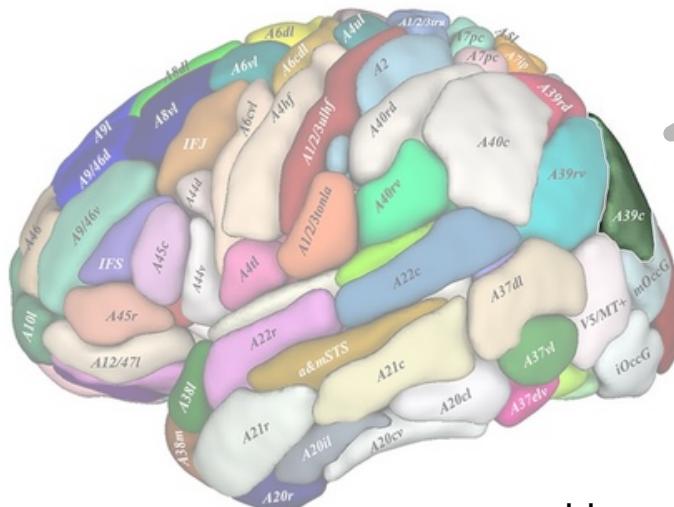
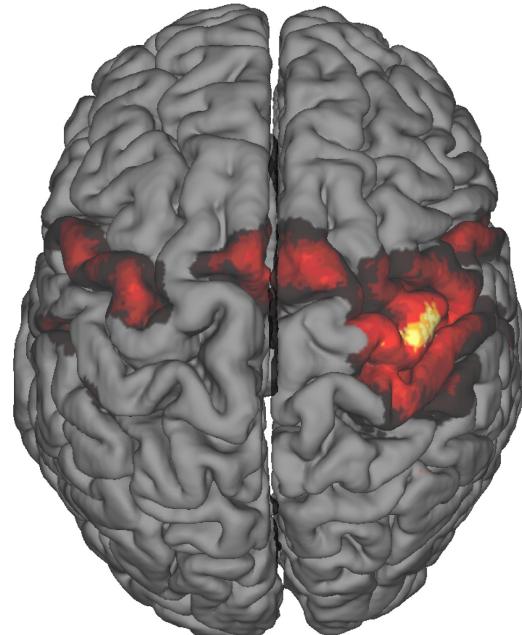


know from literature what brain regions are involved





left hand



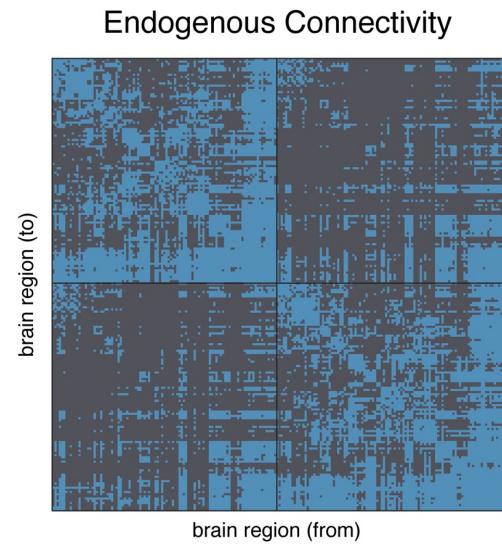
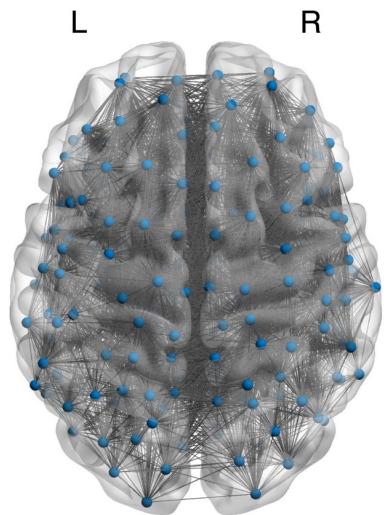
Human Brainnetome Atlas  
(parcellation of the brain)

208 brain regions

BOLD signal time  
series

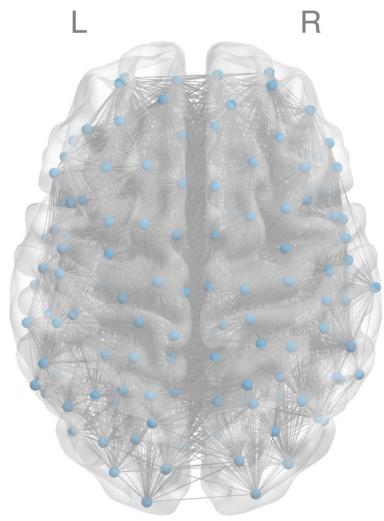


# WHOLE-BRAIN EFFECTIVE CONNECTIVITY

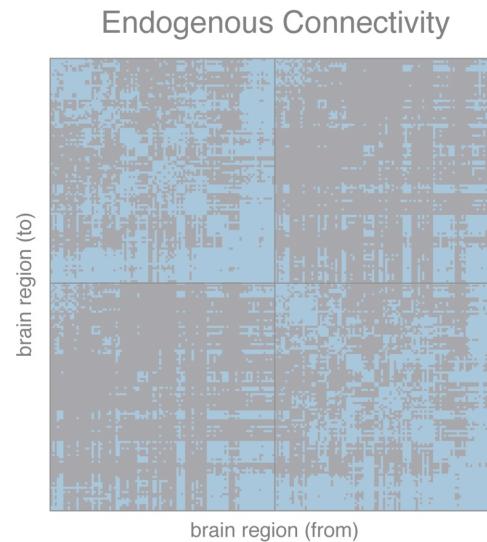


Human Brainnetome atlas  
(# parameter = 17.518)

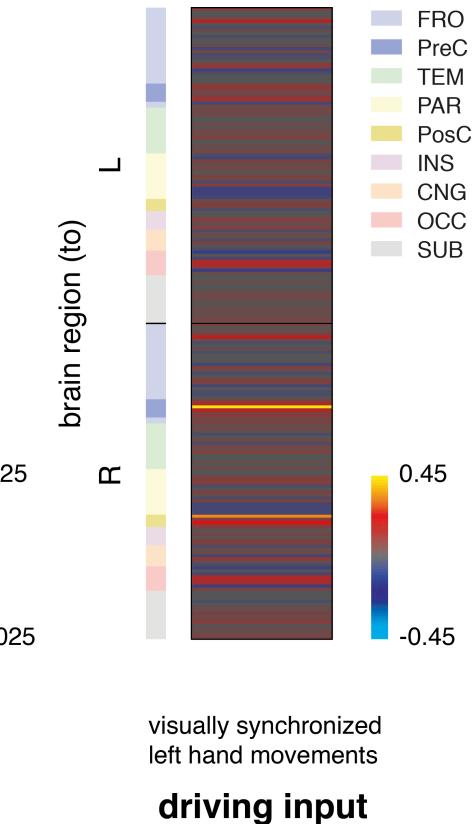
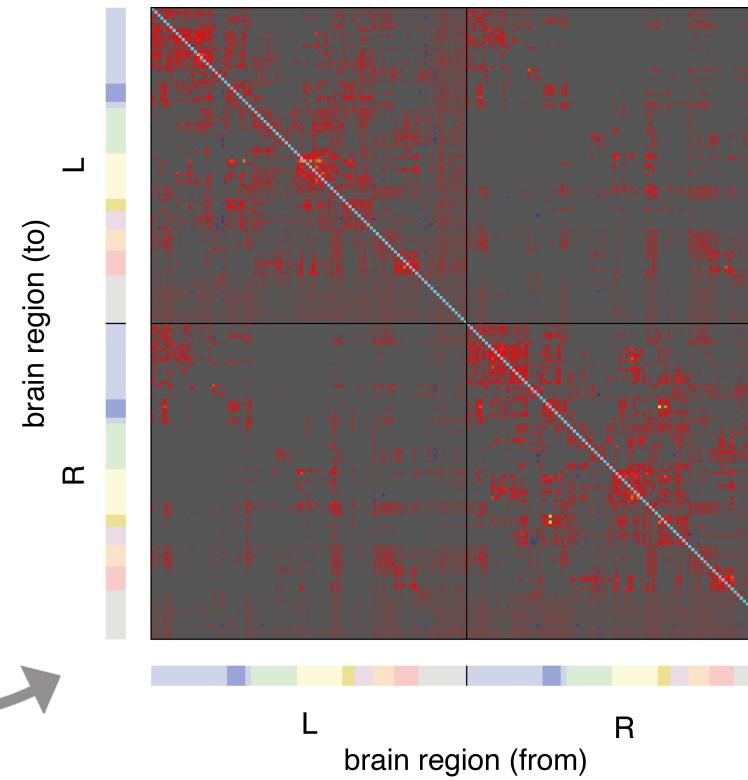
# WHOLE-BRAIN EFFECTIVE CONNECTIVITY



Human Brainnetome atlas  
(# parameter = 17.518)



~ 1 min



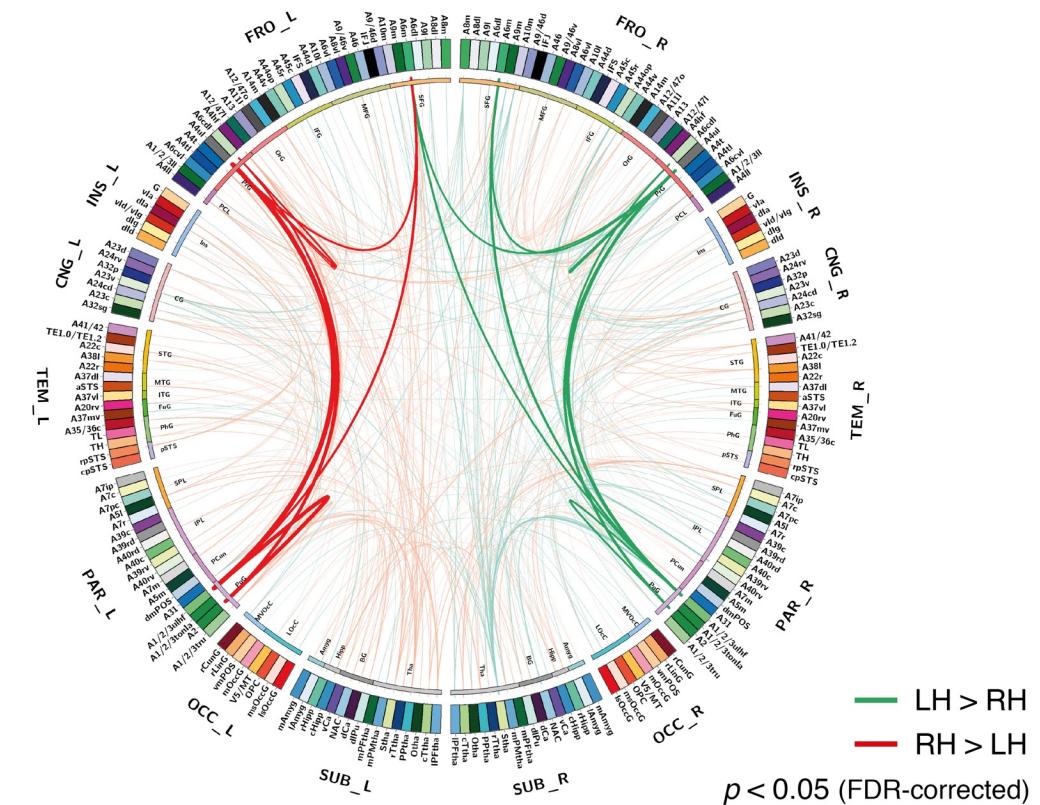
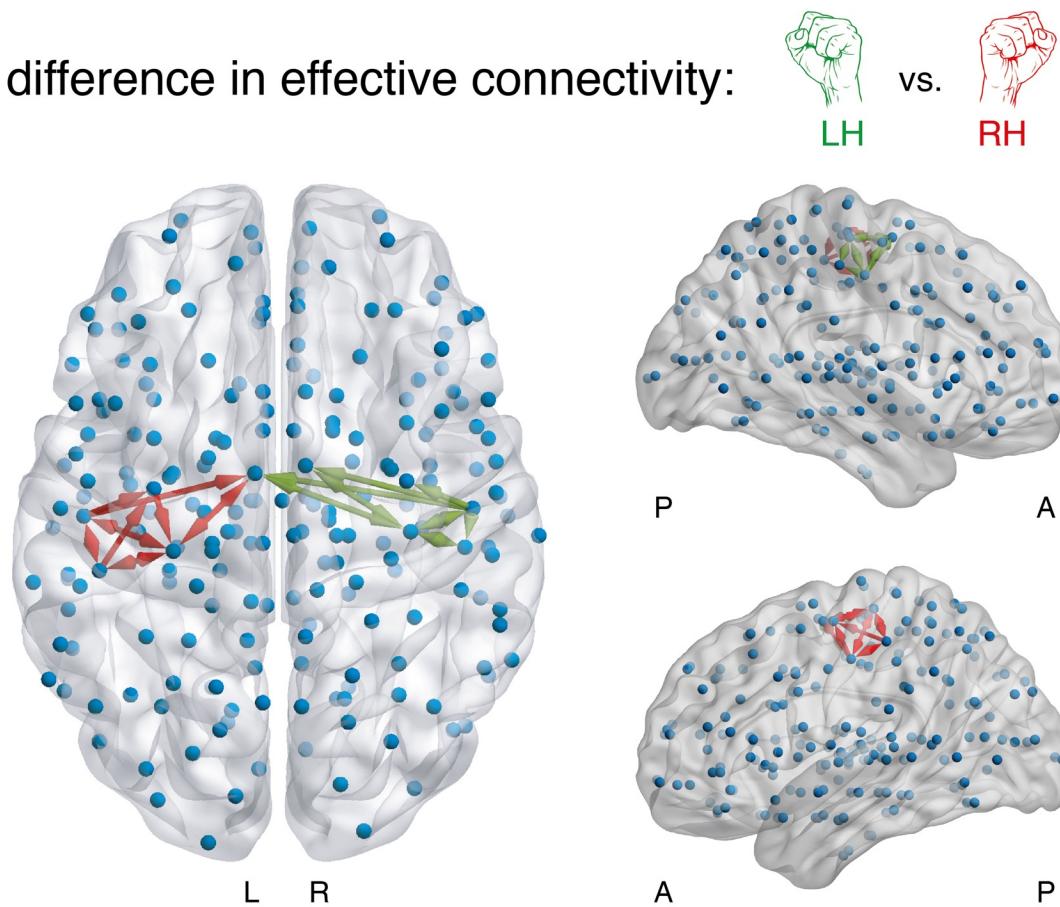
# WHOLE-BRAIN EFFECTIVE CONNECTIVITY

difference in effective connectivity:



# WHOLE-BRAIN EFFECTIVE CONNECTIVITY

difference in effective connectivity:



# SPARSE WHOLE-BRAIN EFFECTIVE CONNECTIVITY

# SPARSE WHOLE-BRAIN EFFECTIVE CONNECTIVITY

How to find optimal network structure?

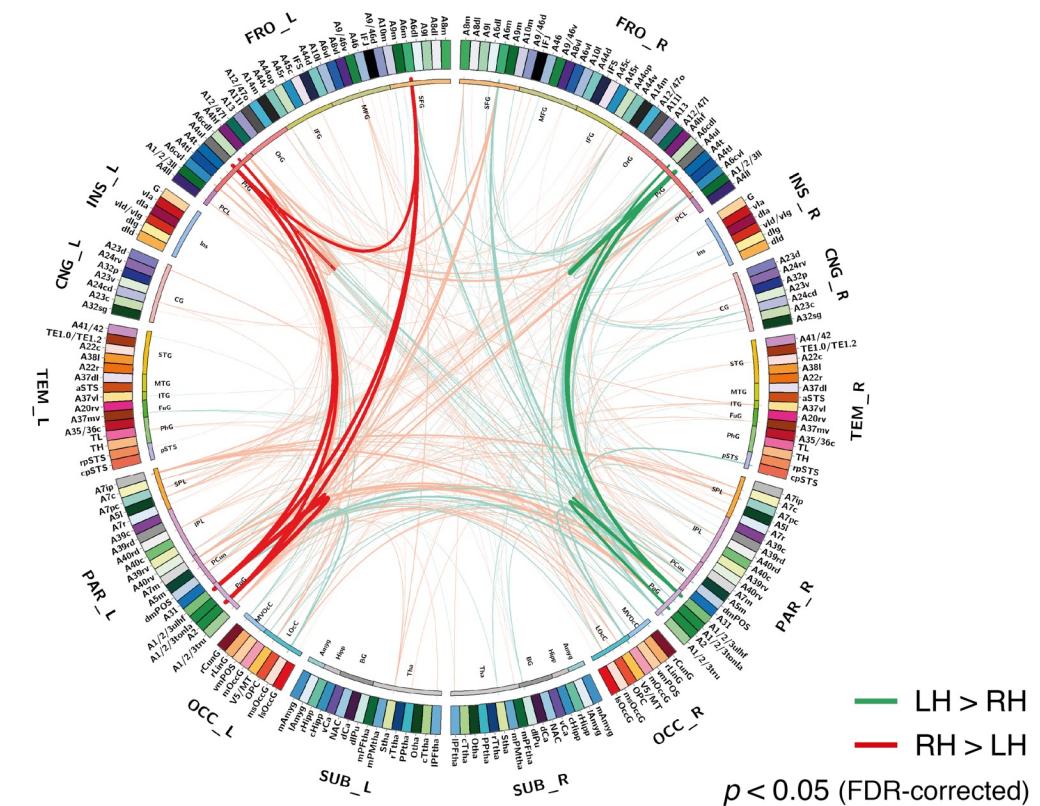
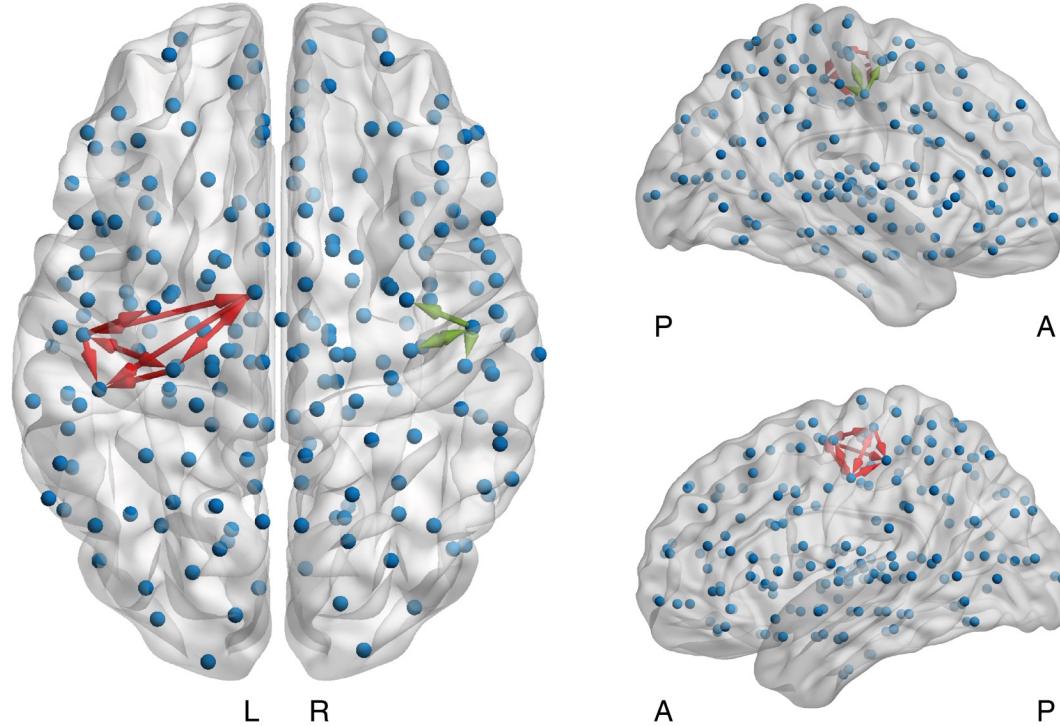
$$p(\theta, \tau, \xi | Y, X) \propto \prod_{i=1}^R p(Y_i | X, Z_i, \theta_i, \tau_i) \prod_{i=1}^R \left( p(\theta_i) p(\tau_i) \prod_{j=1}^D p(\xi_{i,j}) \right)$$

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

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

# SPARSE WHOLE-BRAIN EFFECTIVE CONNECTIVITY

difference in sparse effective connectivity:



... AND DURING THE RESTING STATE

## ... AND DURING THE RESTING STATE

Idea:

- Set driving inputs (C matrix) to zero

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

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

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

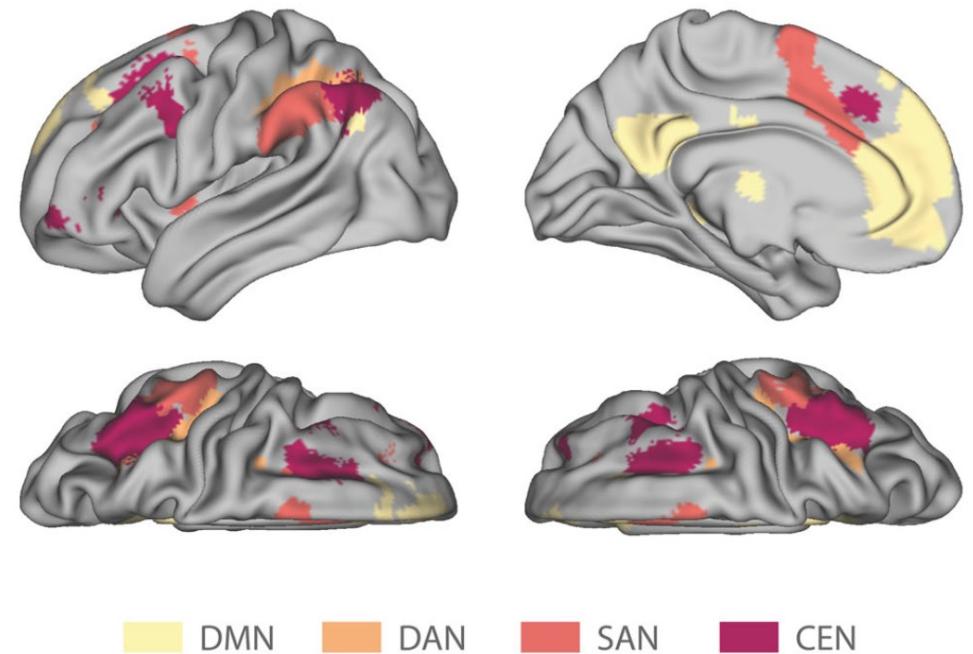
$$\theta_i := [a_{i1}, \dots, a_{iR}]$$

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

# Construct validity of rDCM in comparison to spectral DCM

Data:

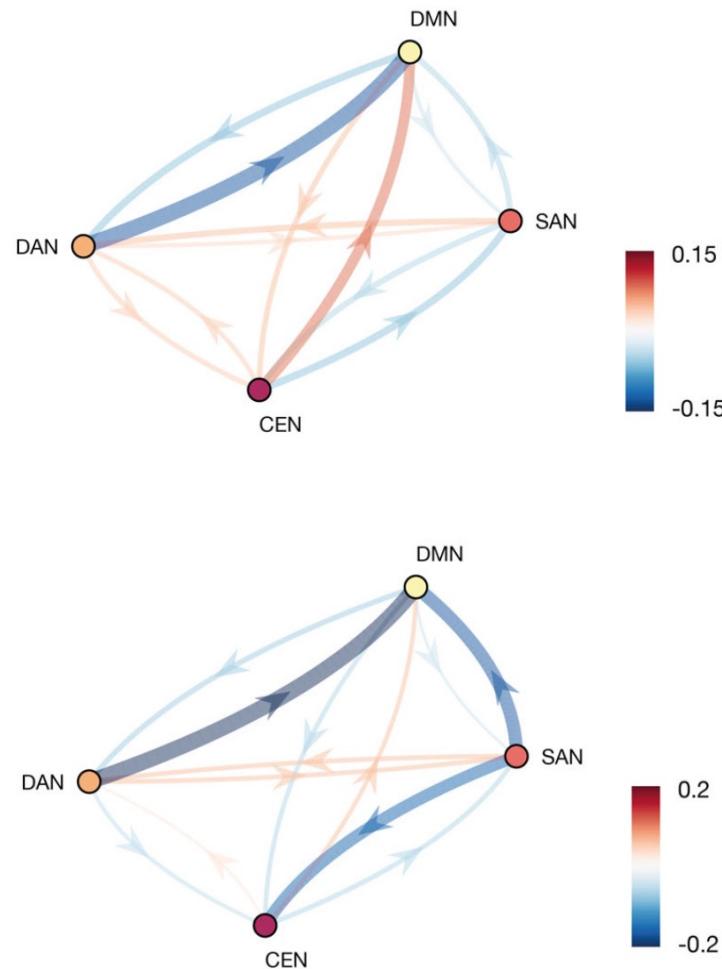
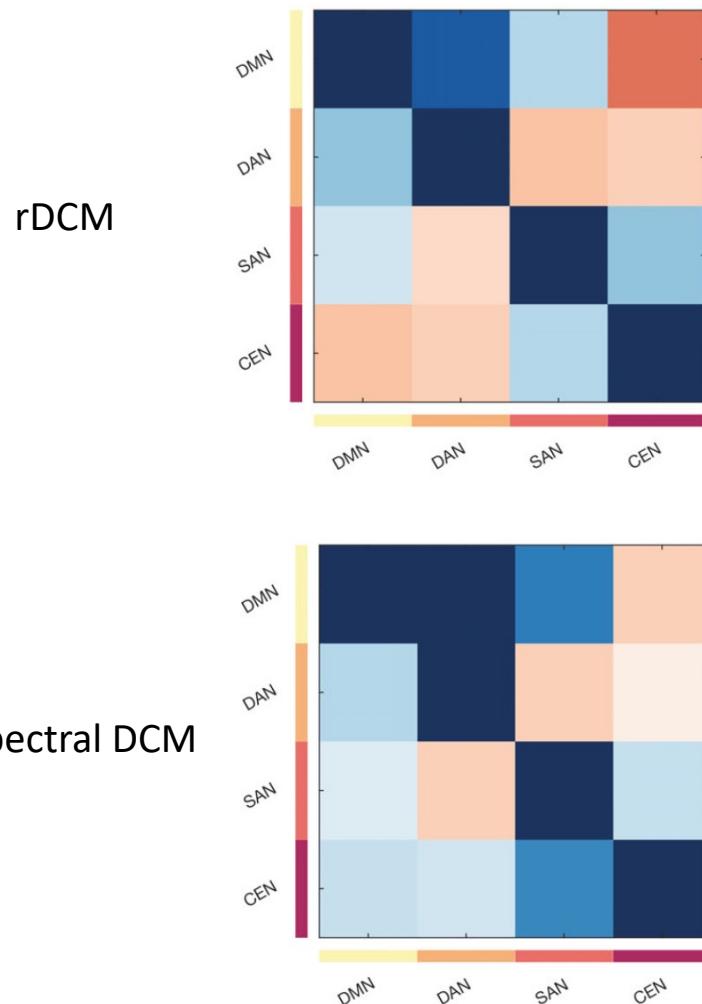
- 196 healthy participants (B-SNIP-1 resting state data)
- modes of 4 resting state networks:
  - Default mode network (DMN)
  - Dorsal attention network (DAN)
  - Salience network (SAN)
  - Central executive network (CEN)



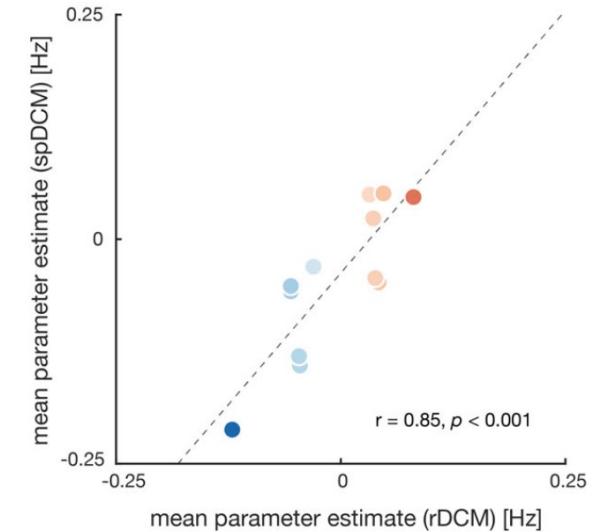
Masks comprising four key intrinsic networks of the resting state

# Results

## Average effective connectivity among modes



## Consistency of group level estimates



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



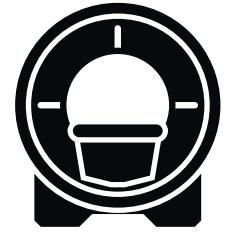


$t_0$

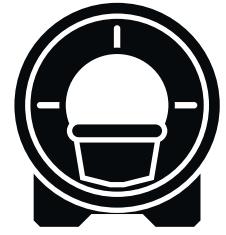


$t_1$

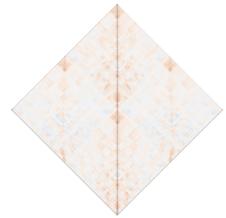


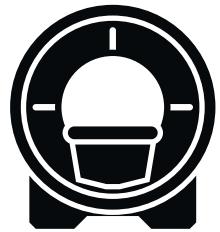


$t_0$



$t_1$

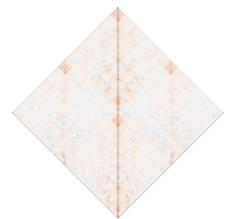




$t_0$



$t_1$



test-retest reliability





## 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**.

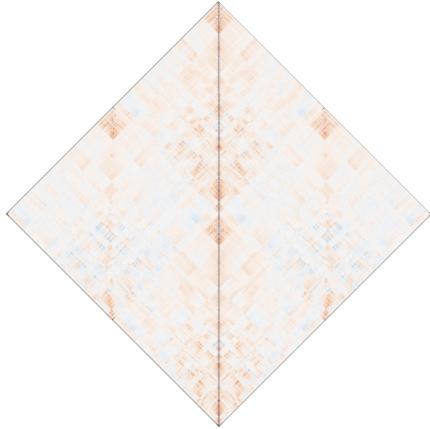
The CCF currently supports 20 human connectome studies. Scroll down to learn more.



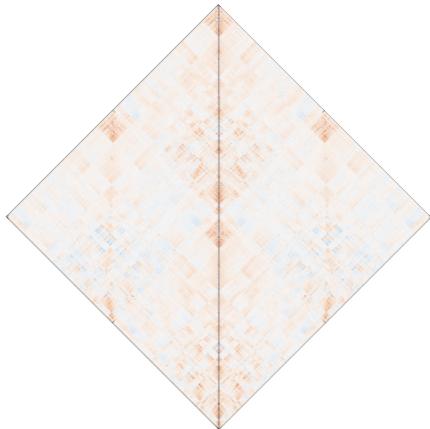
# TEST-RETEST RELIABILITY



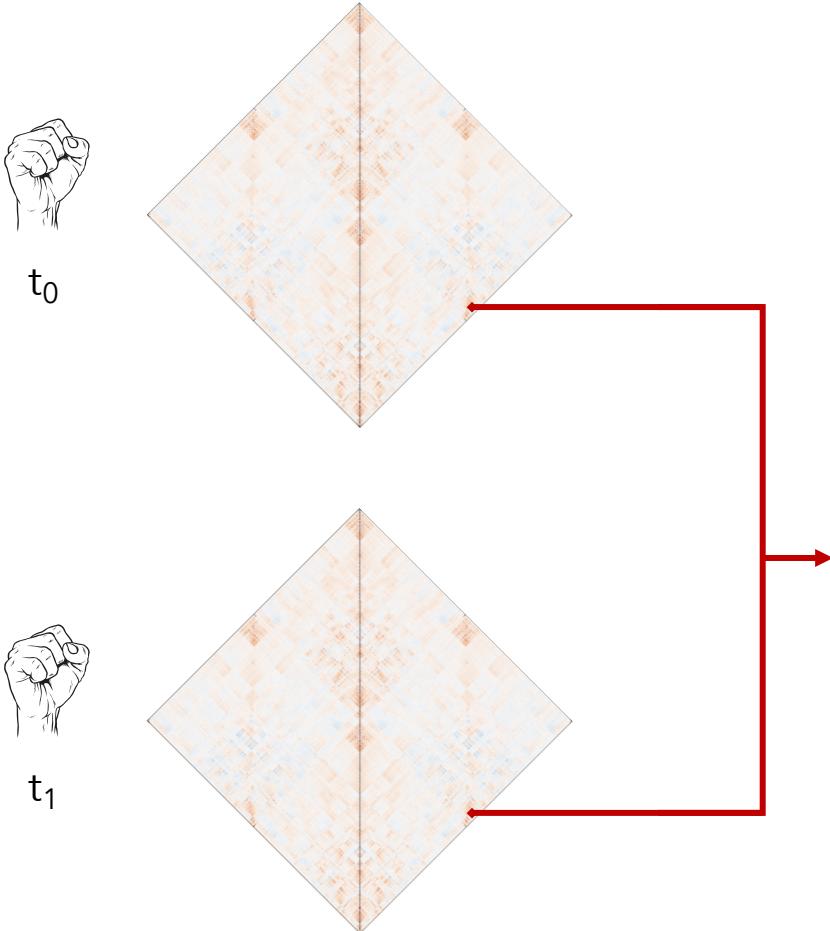
$t_0$



$t_1$



# TEST-RETEST RELIABILITY

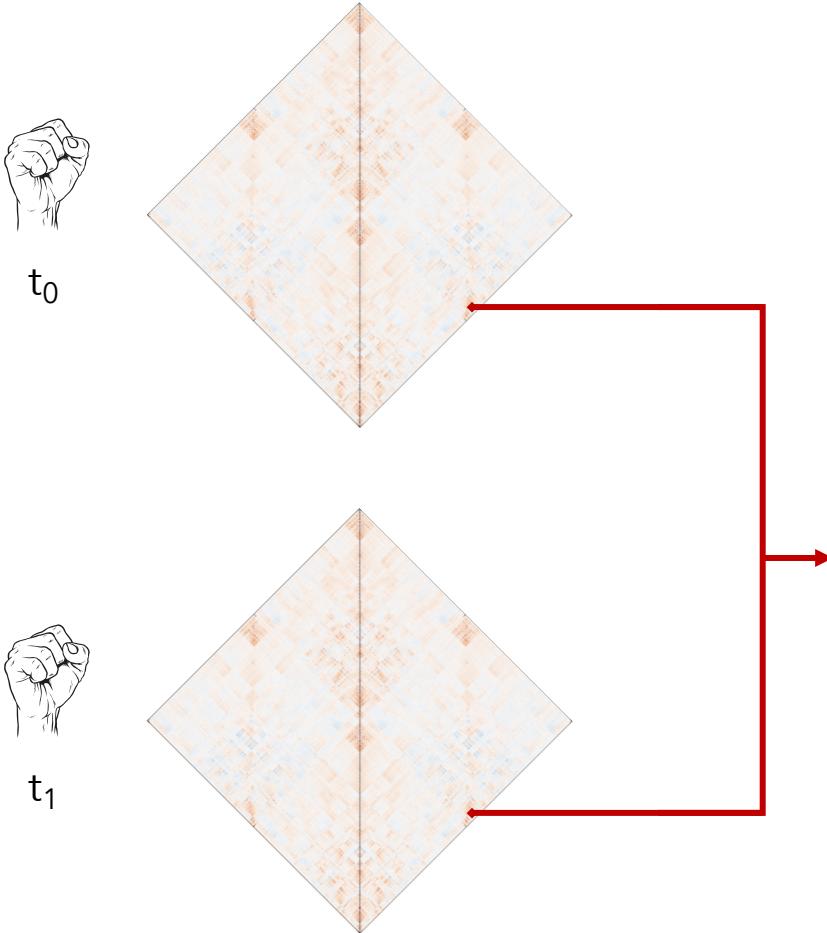


*between-subject*  
*within-subject*

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

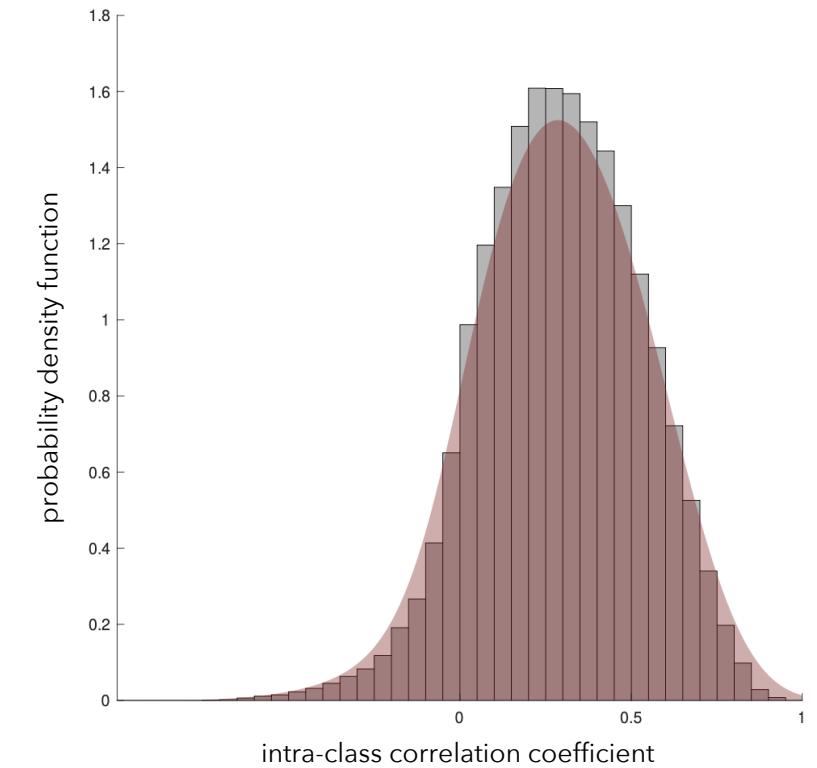
intra-class correlation coefficient  
(for each connection)

# TEST-RETEST RELIABILITY

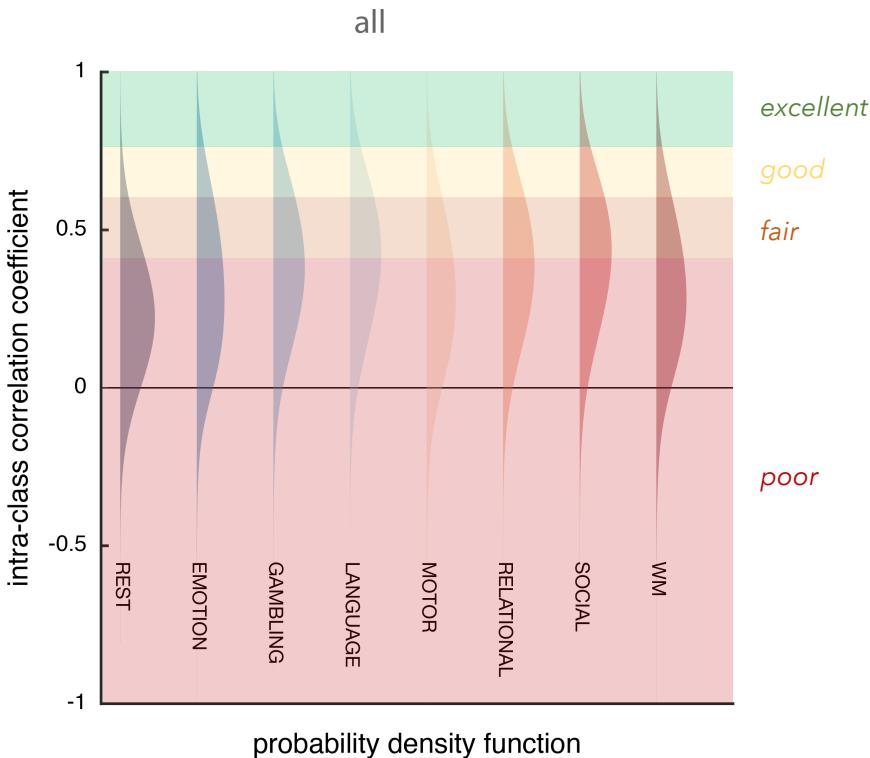


$$ICC(3,1) = \frac{\sigma_b^2 - \sigma_w^2}{\sigma_b^2 + \sigma_w^2}$$

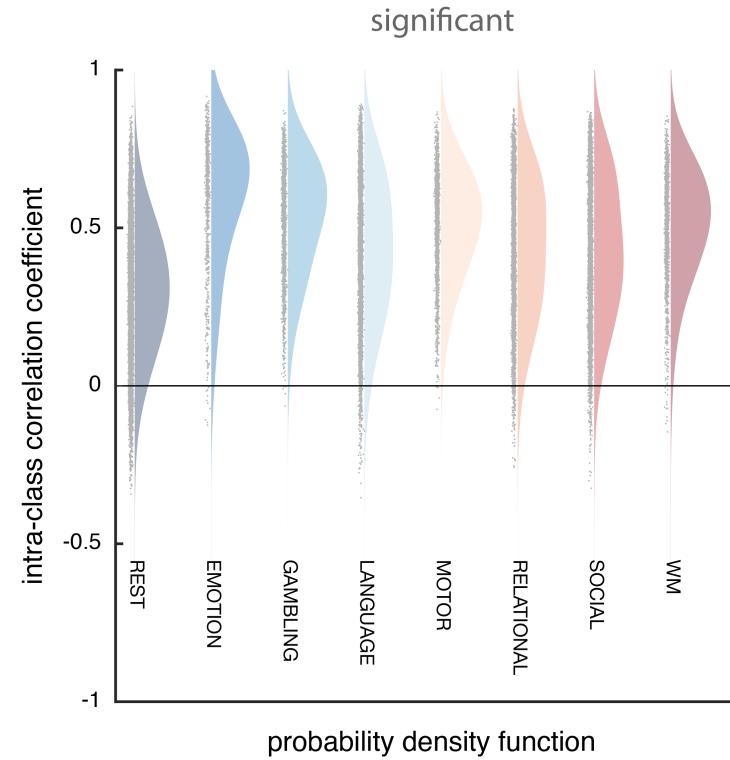
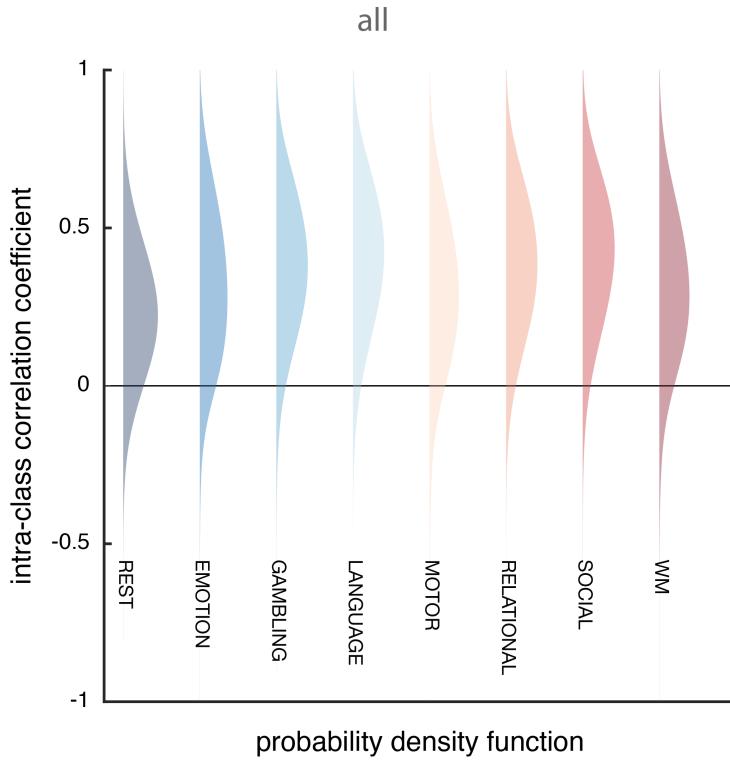
intra-class correlation coefficient  
(for each connection)



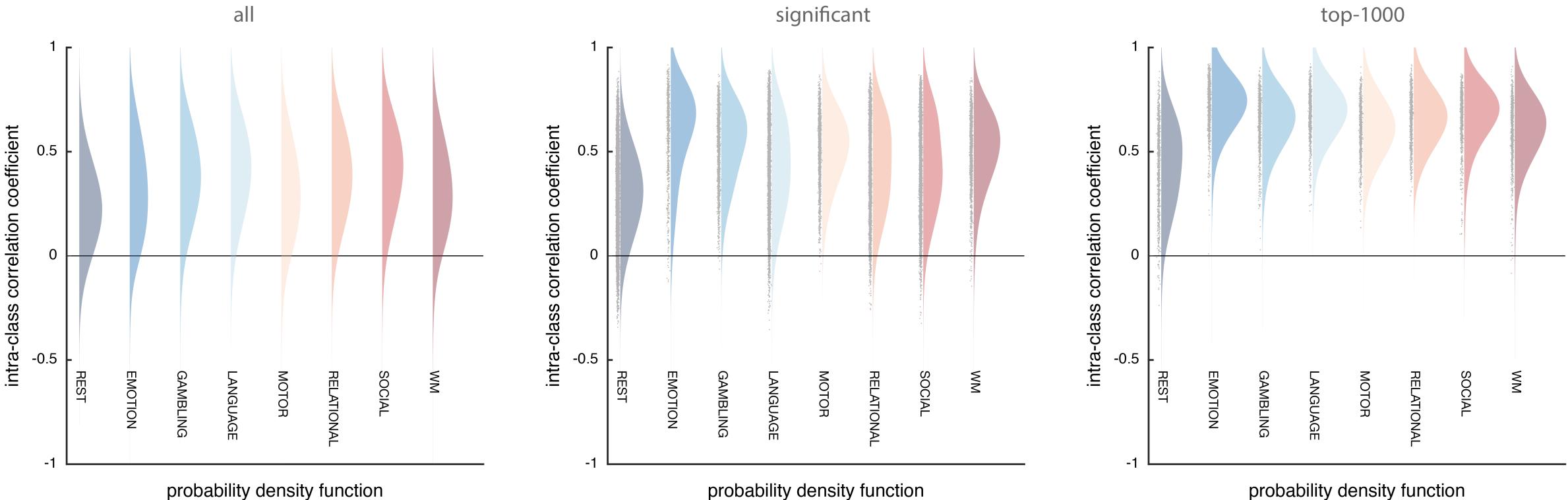
# TEST-RETEST RELIABILITY



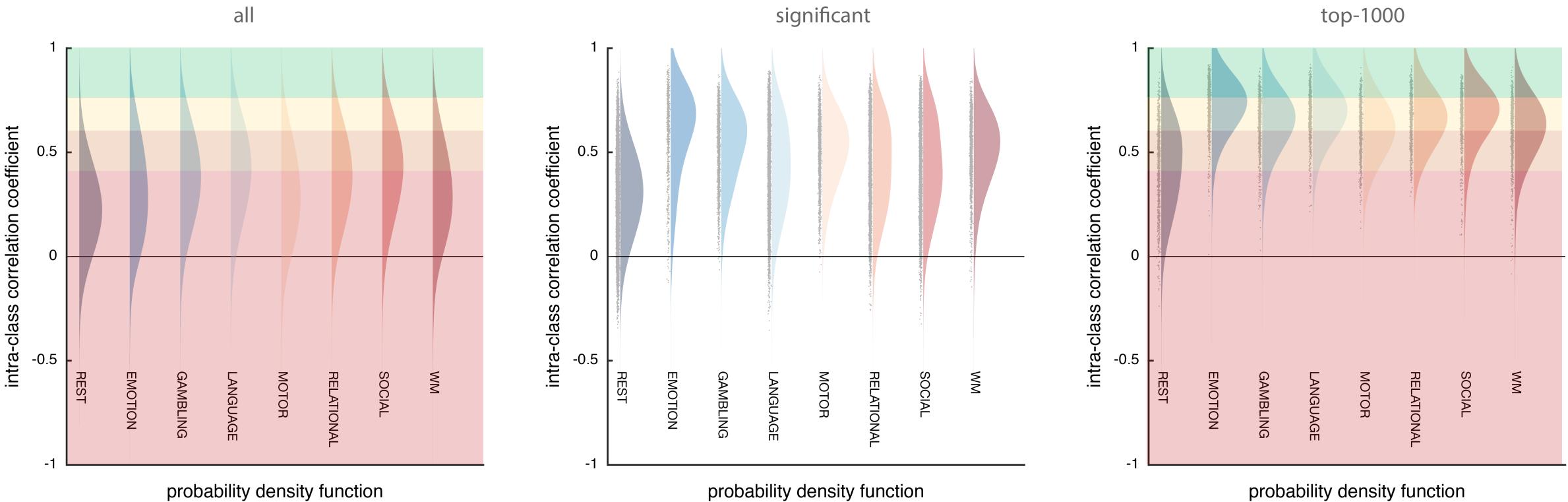
# TEST-RETEST RELIABILITY



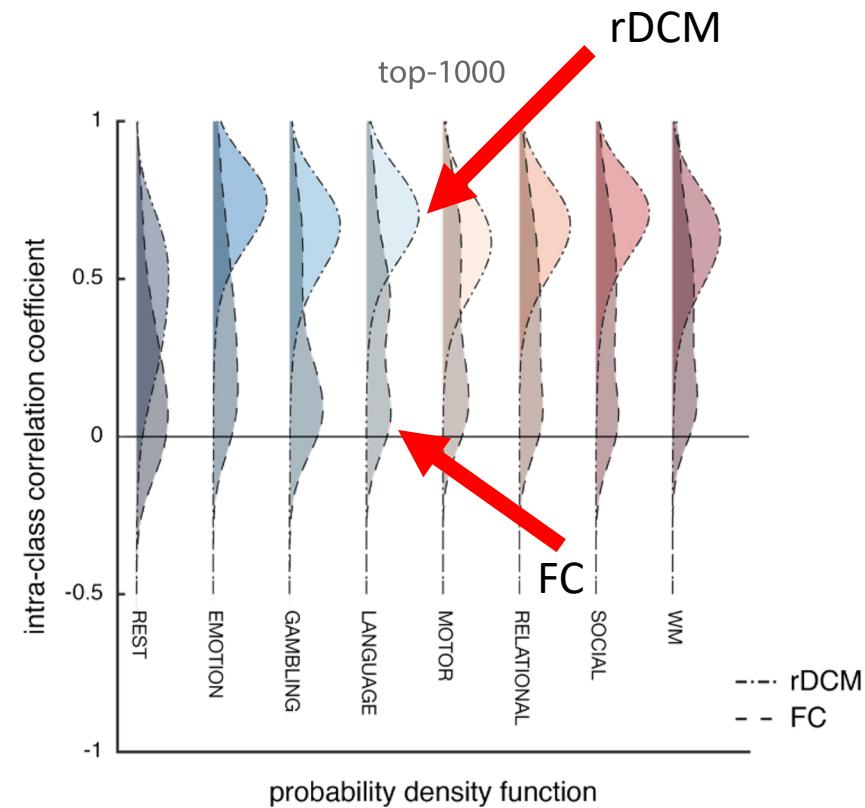
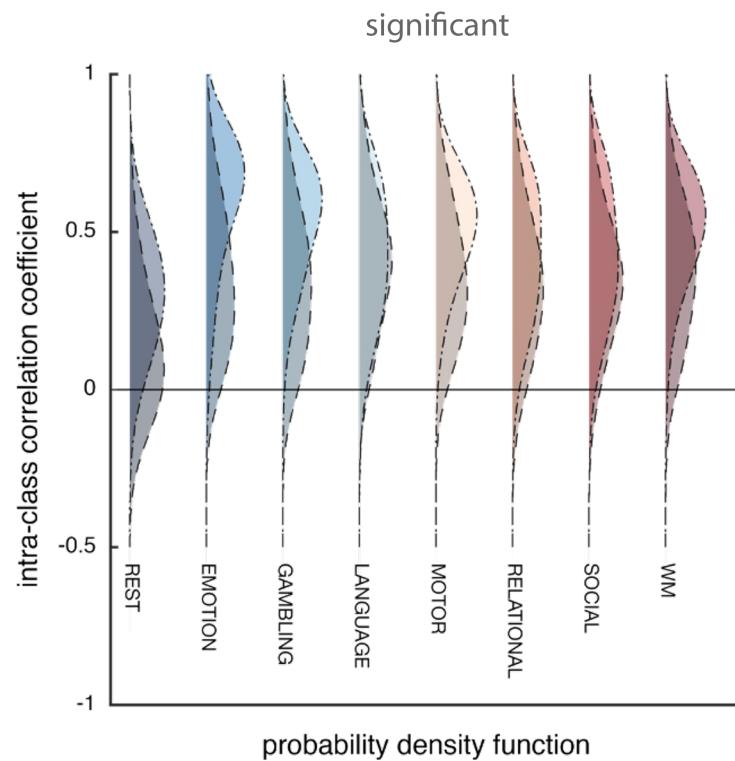
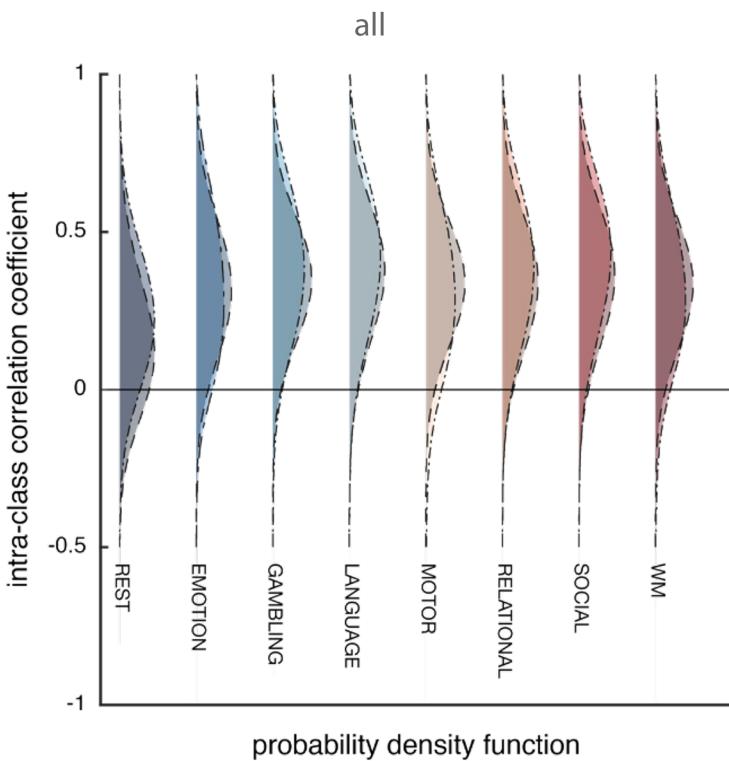
# TEST-RETEST RELIABILITY



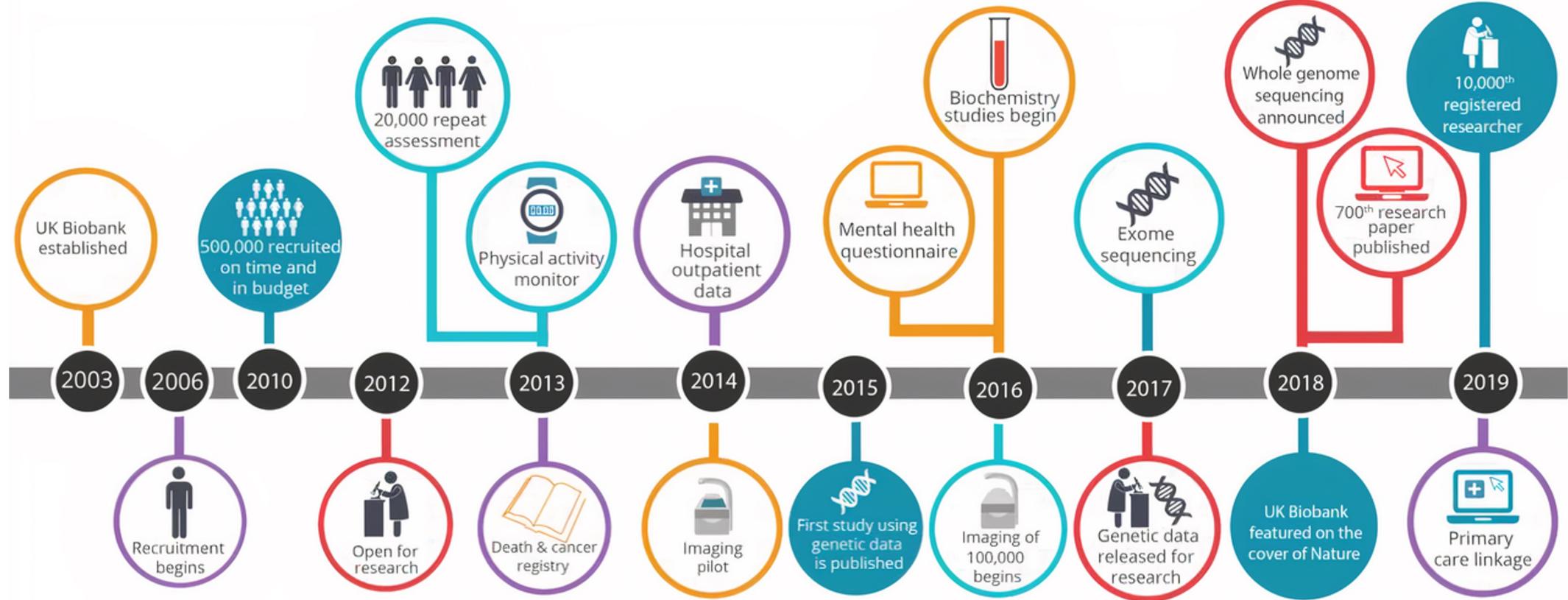
# TEST-RETEST RELIABILITY

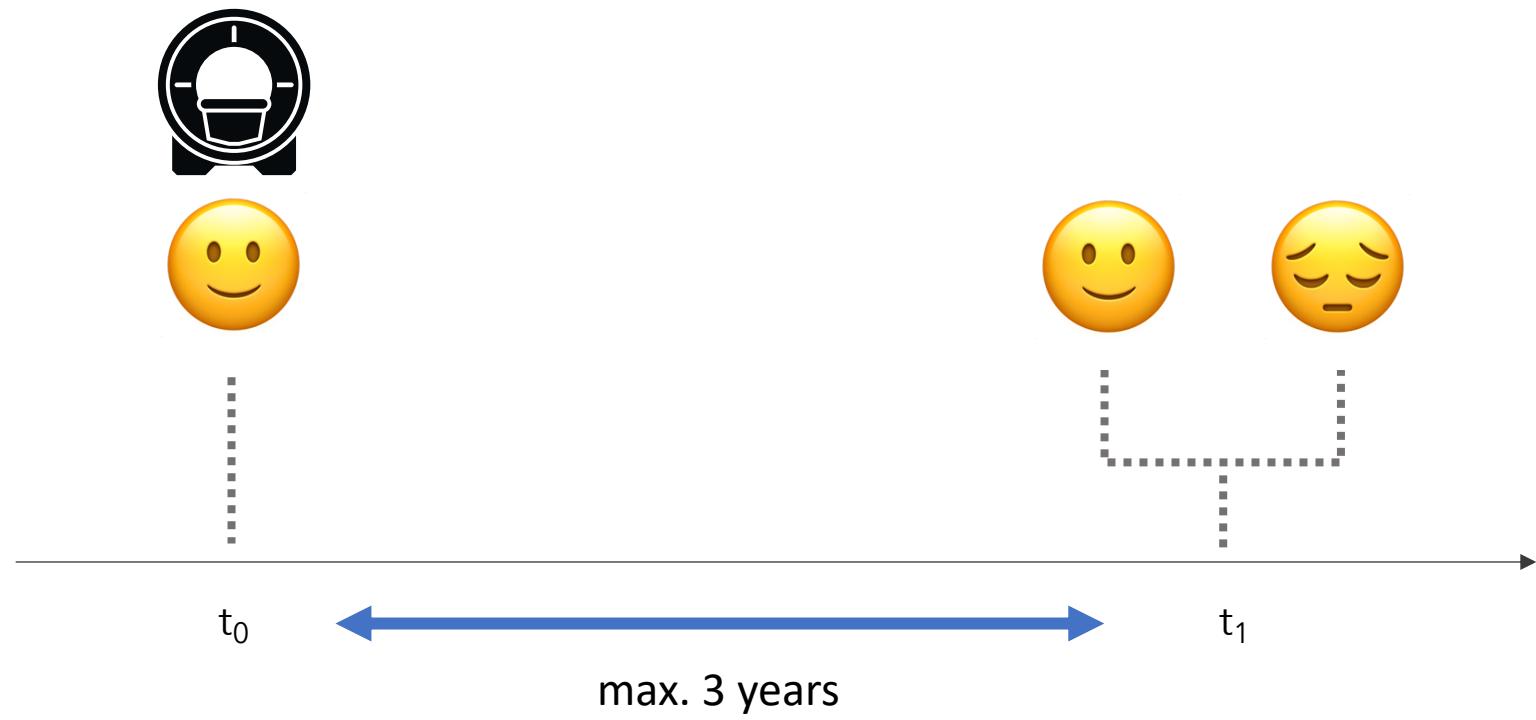
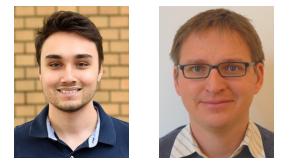


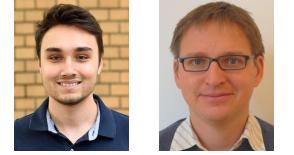
# TEST-RETEST RELIABILITY











# 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?*



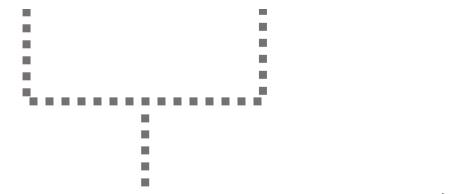
$N = 15'739$



„No“

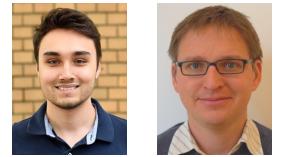


$N = 1'085$

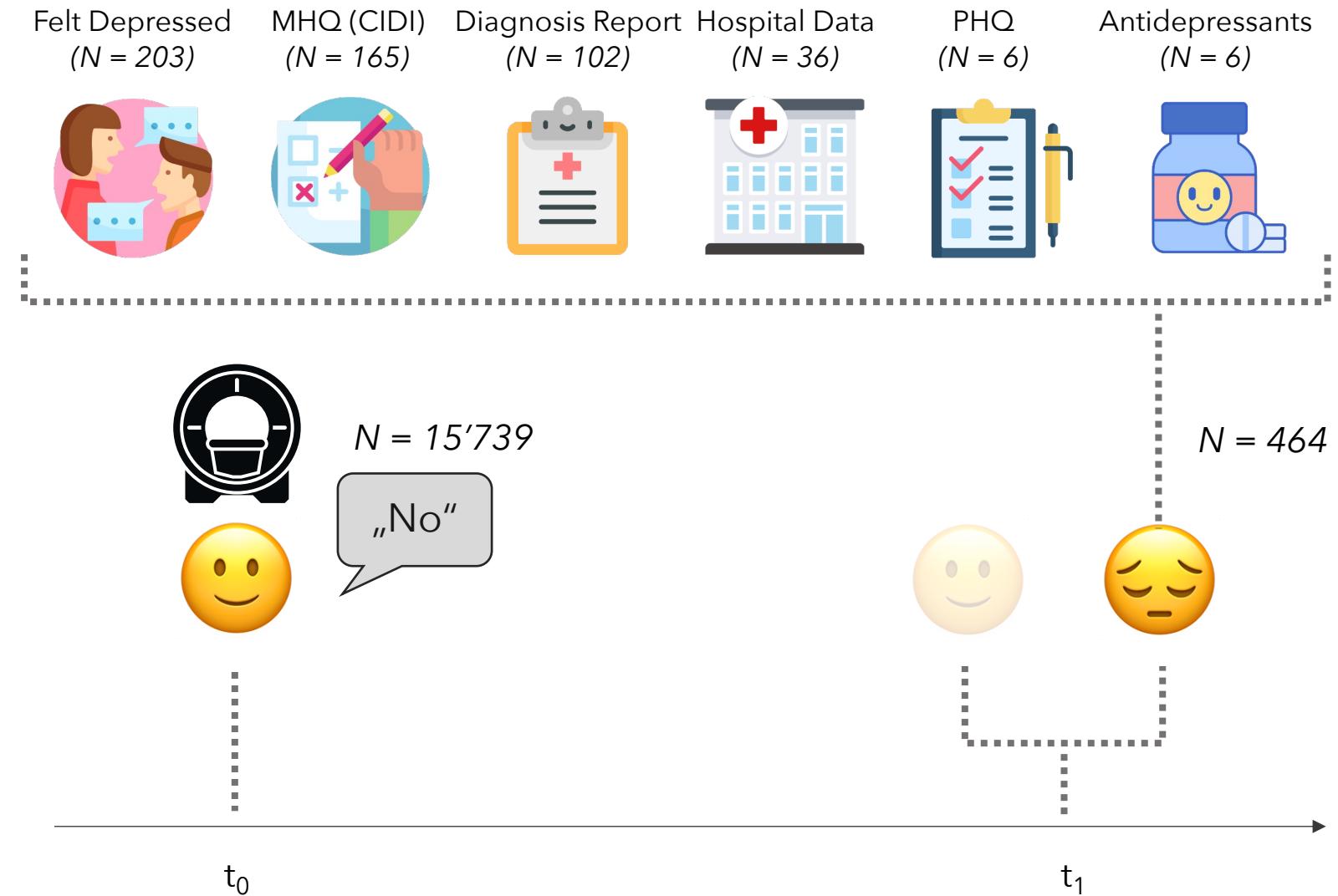


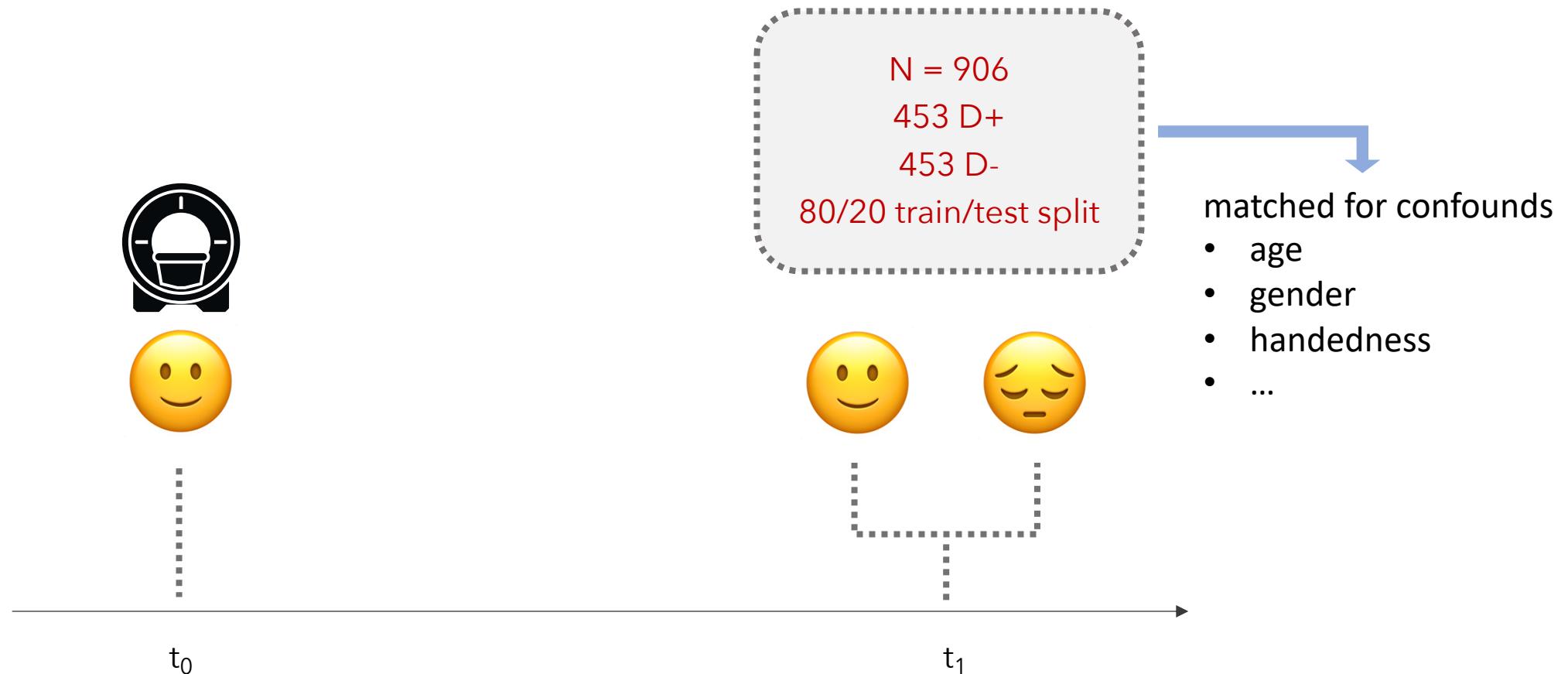
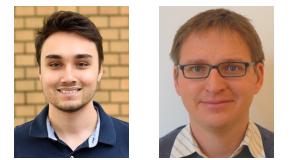
$t_0$

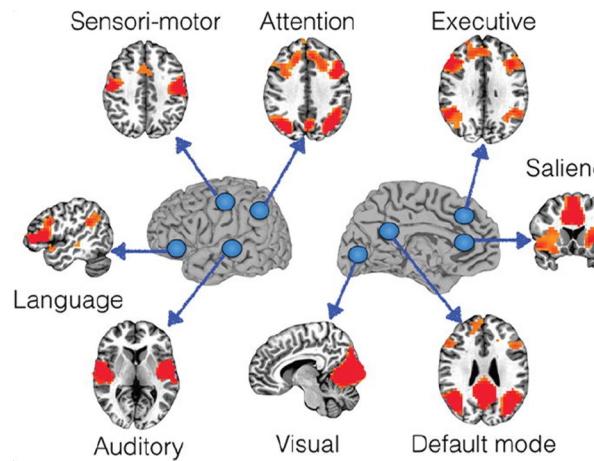
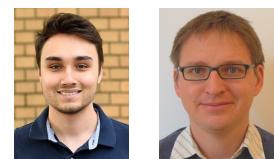
$t_1$



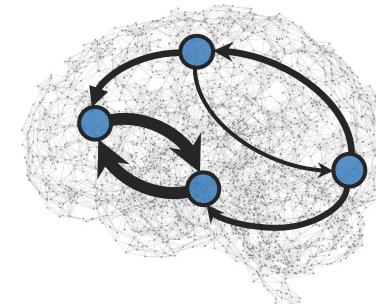
# DATASET: D+



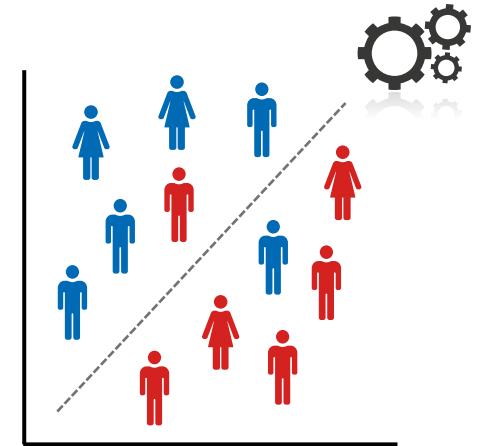




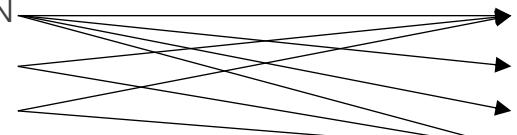
*inference on  
brain connectivity*



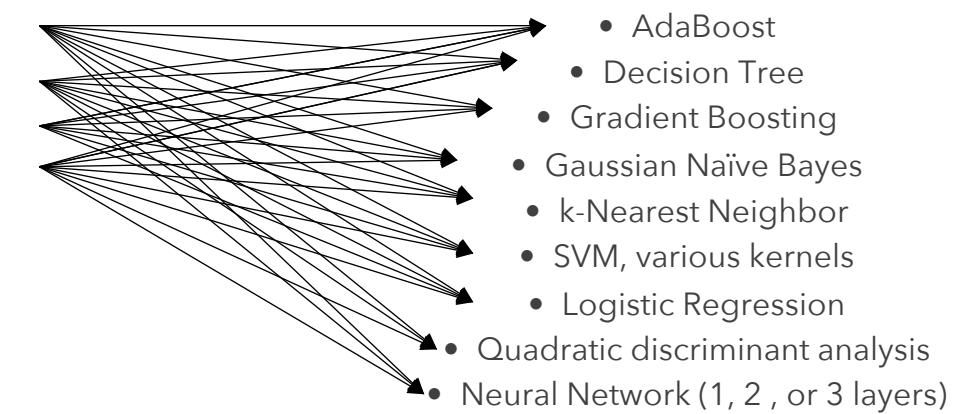
*classification*



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



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



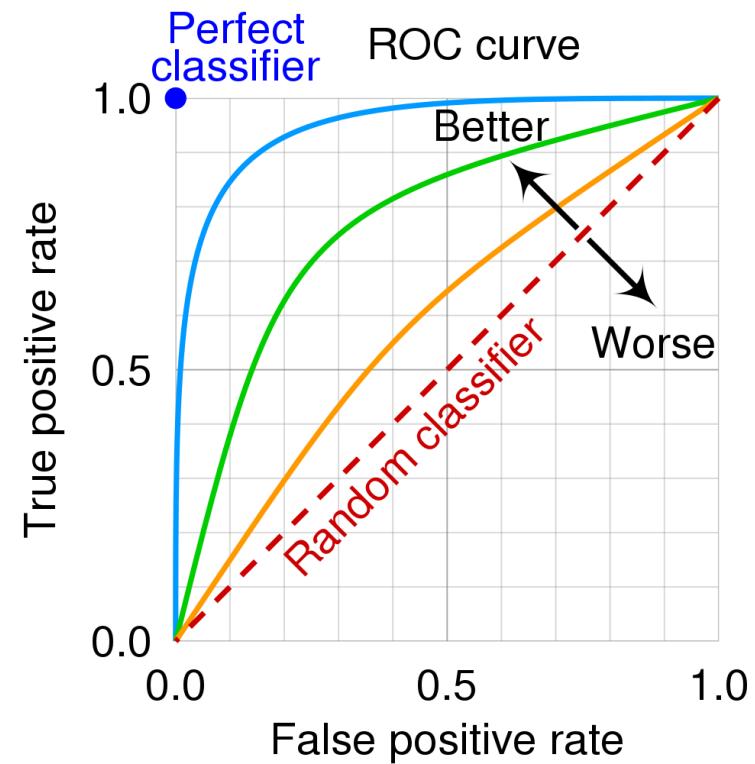
# RECEIVER OPERATING CHARACTERISTIC CURVE (ROC)

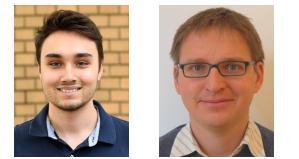
True Positive Rate (sensitivity)

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

False Positive Rate

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

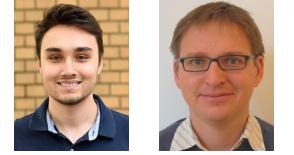




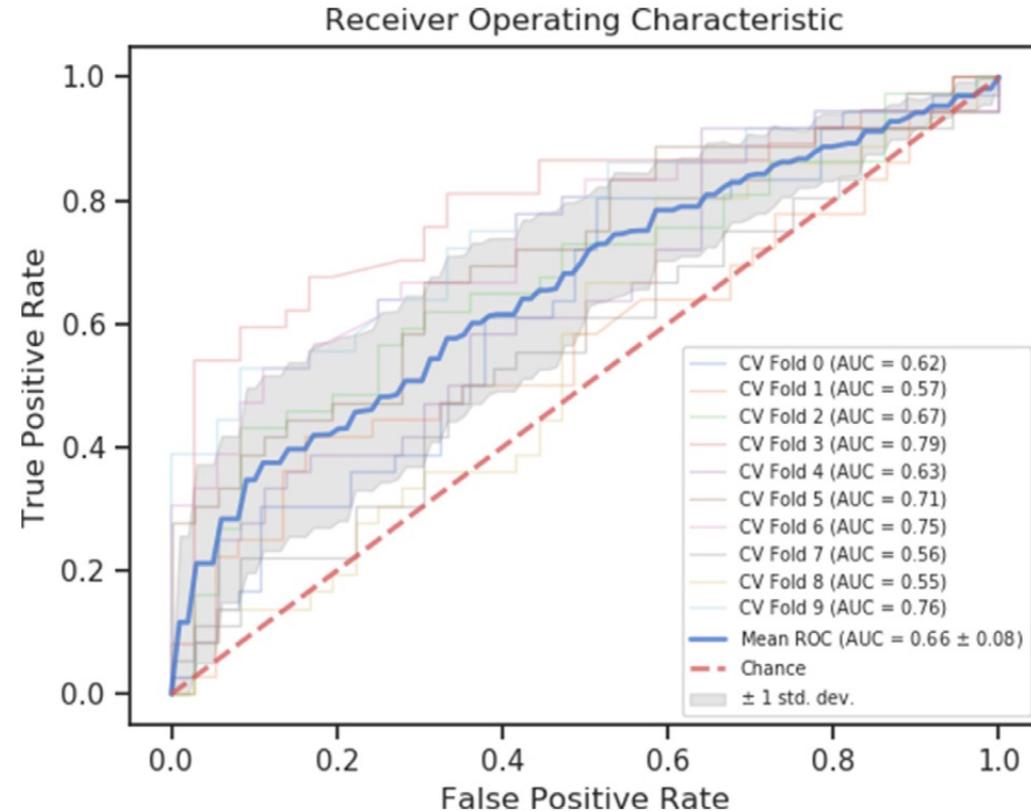
# PREDICTING FUTURE DEPRESSIVE SYMPTOMS (TRAINING SET)

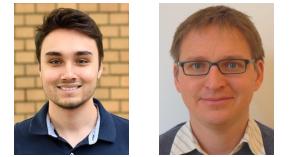
Classifiers	Features								
	FC (6)	FC (21)	FC (55)	St. DCM	Sp. DCM	rDCM (6)	rDCM (21)	rDCM (55)	
Ada	0.52	0.49	0.56	0.49	0.47	0.55	0.54	0.56	
DTC	0.49	0.49	0.52	0.50	0.51	0.51	0.53	0.52	
GBC	0.51	0.50	0.57	0.49	0.45	0.60*	0.60*	0.64*	
GNB	0.53	0.54	0.54	0.50	0.49	0.61*	0.61*	0.63*	
kNN	0.52	0.54	0.51	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

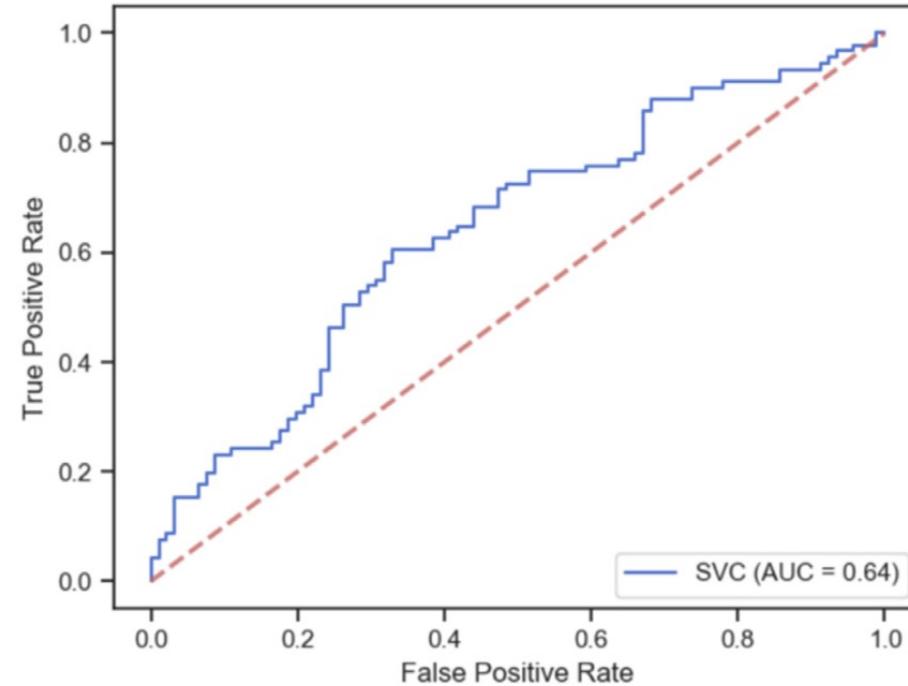


# PREDICTING FUTURE DEPRESSIVE SYMPTOMS (TRAINING SET)

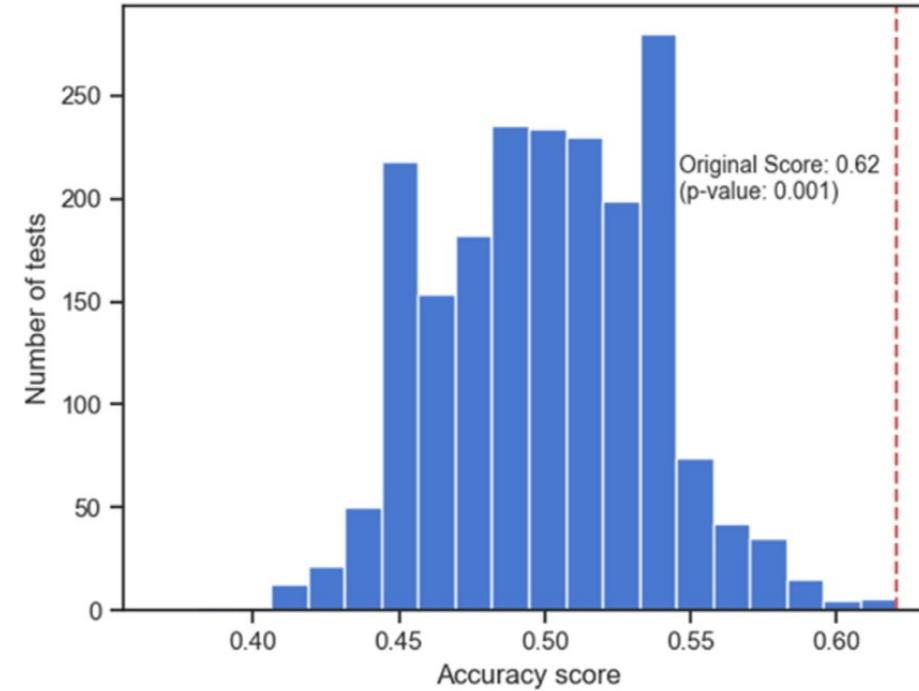




# PREDICTING FUTURE DEPRESSIVE SYMPTOMS (**TEST SET**)

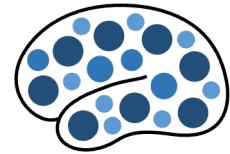


ROC curve of rDCM (55ICs) with sigmoid SVM run on test data.



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

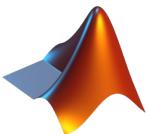
# SOFTWARE



## TAPAS

Translational Algorithms for Psychiatry-Advancing Science (TAPAS) toolbox  
<https://www.tnu.ethz.ch/de/software/tapas>

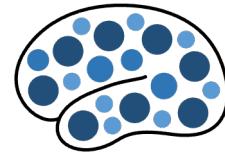
rDCM (Matlab version)



rDCM (Julia version)



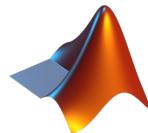
# SOFTWARE



## TAPAS

Translational Algorithms for Psychiatry-Advancing Science (TAPAS) toolbox  
<https://www.tnu.ethz.ch/de/software/tapas>

### rDCM (Matlab version)



### rDCM (Julia version)



More about  
the package  
in poster  
session on  
Friday  
(poster #15)

# 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:** Python

**Materials:** GitHub

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*

*Translational Neuromodeling Unit (TNU)*

*University of Zurich & ETH Zurich*

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

Email: [ikertesz@biomed.ee.ethz.ch](mailto:ikertesz@biomed.ee.ethz.ch)

Phone: +41 44 634 91 12

## 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, Heinze 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, Heinze 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