



## Linking functional brain synchronization to underlying neurotransmission

Leon D. Lotter<sup>1,2,3</sup>, Daouia Larabi<sup>1,2</sup>, Kaustubh Patil<sup>1,2</sup>, Simon Eickhoff<sup>1,2</sup>, & Juergen Dukart<sup>1,2</sup>

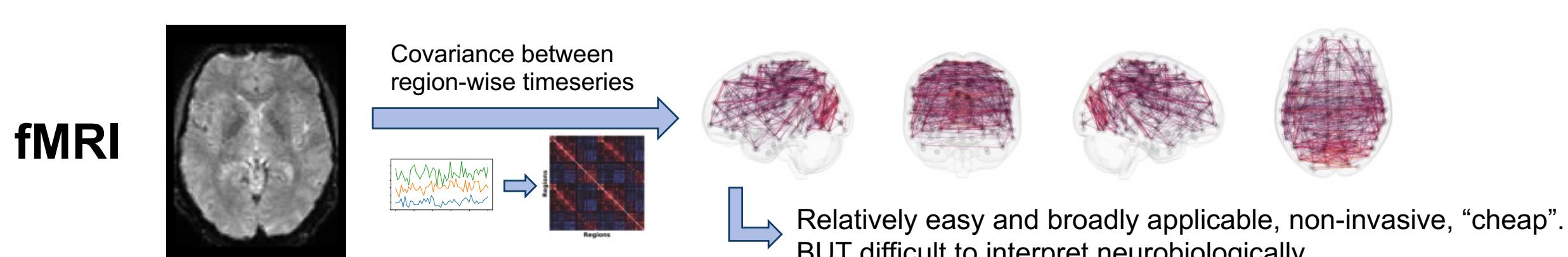
<sup>1</sup>Institute of Systems Neuroscience, Heinrich Heine University Düsseldorf; Düsseldorf, Germany

<sup>2</sup>Institute of Neuroscience and Medicine (INM-7: Brain and Behaviour), Research Centre Jülich; Jülich, Germany

<sup>3</sup>Max Planck School of Cognition; Leipzig, Germany

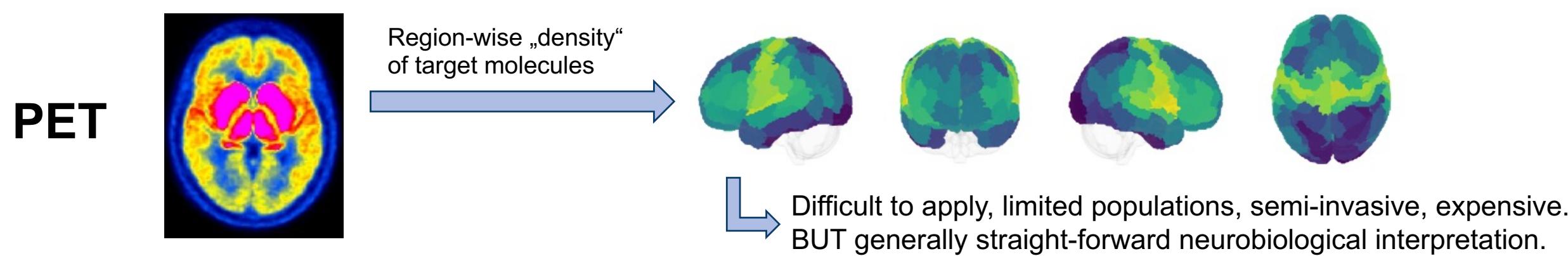
### Rationale

- Functional connectivity (FC) derived from resting-state fMRI is a commonly used measure of interregional brain synchronization.



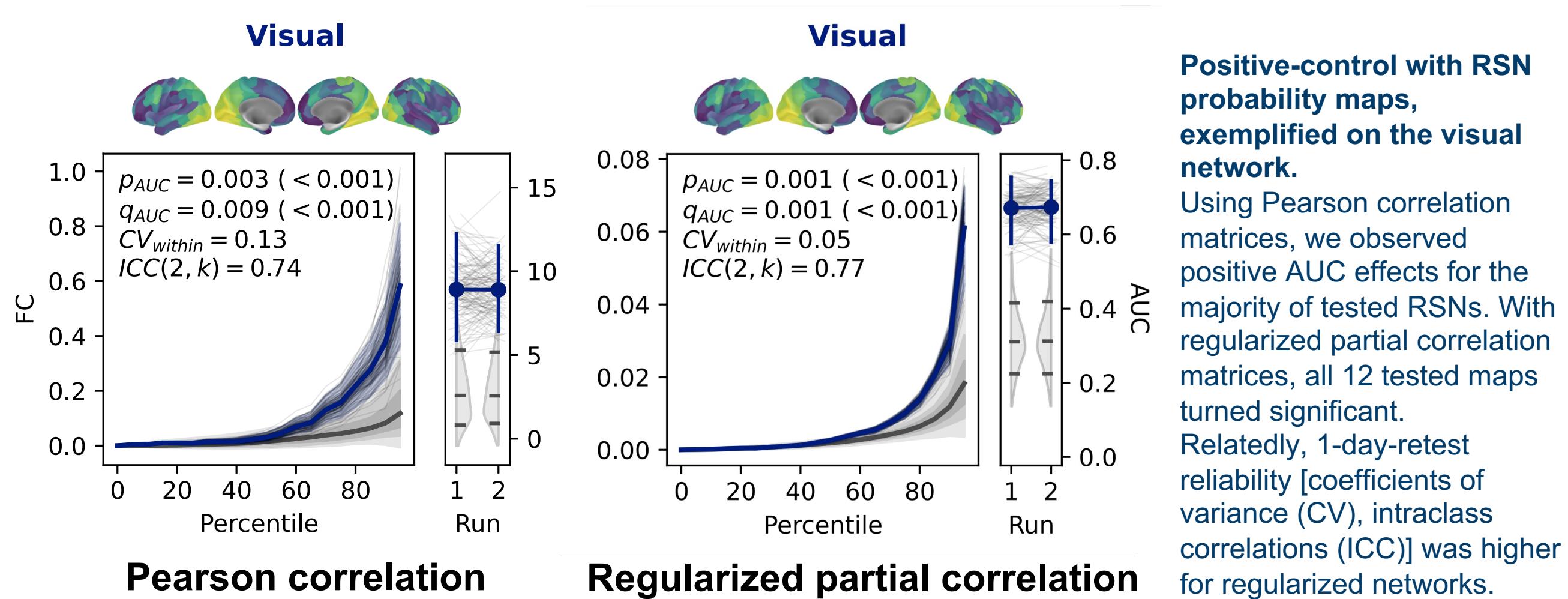
- Changes in FC related to physiology, age, behavior, and psychopathology are well documented<sup>1</sup>. However, investigating the (patho-)neurobiology underlying these changes remains challenging.

- In contrast, nuclear imaging provides a more direct window into biological mechanisms, but at considerably higher cost.



- We developed an approach (see right side) to link functional brain synchronization to underlying neurotransmission<sup>2,3</sup>.

- Resting-state network (RSN) maps<sup>4,5</sup>, instead of nuclear imaging maps, were used as a positive-control, confirming the hypothesized effects.



### Approach

- We study interregional FC as a function of neurotransmitter receptor/transporter density in corresponding brain regions.

- A region-to-region FC matrix is systematically thresholded based on densities of 23 normative nuclear imaging maps<sup>6,7</sup>.

- We expect the average interregional FC to increase with higher receptor/transporter density in these regions.

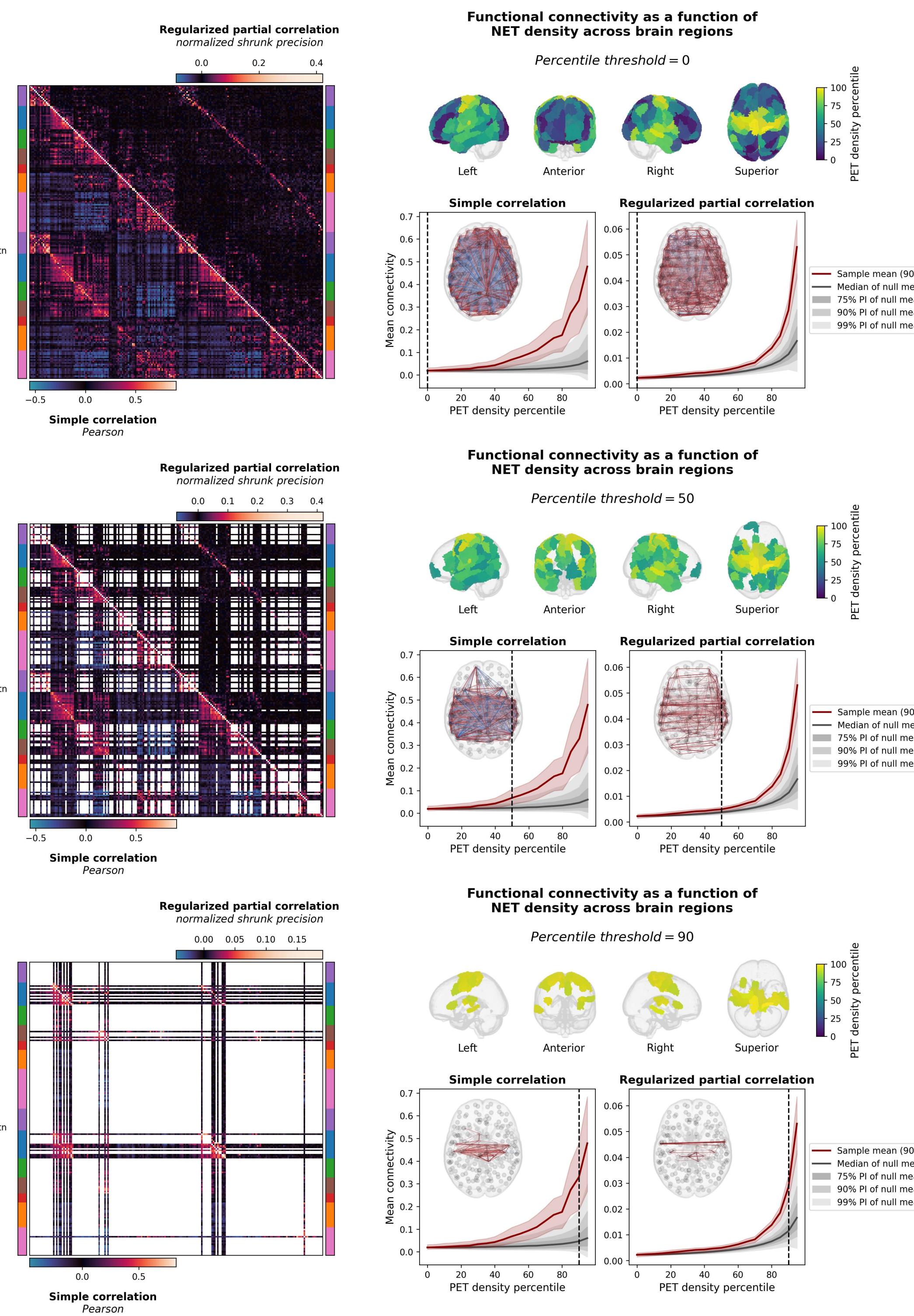
- Two FC estimation methods are tested: Pearson vs. regularized partial correlation ("shrunken covariance")

- The area under the curve (AUC) is evaluated as an index of a system's contribution to brain synchronization.

- Statistical significance is determined using a spatial permutation framework.

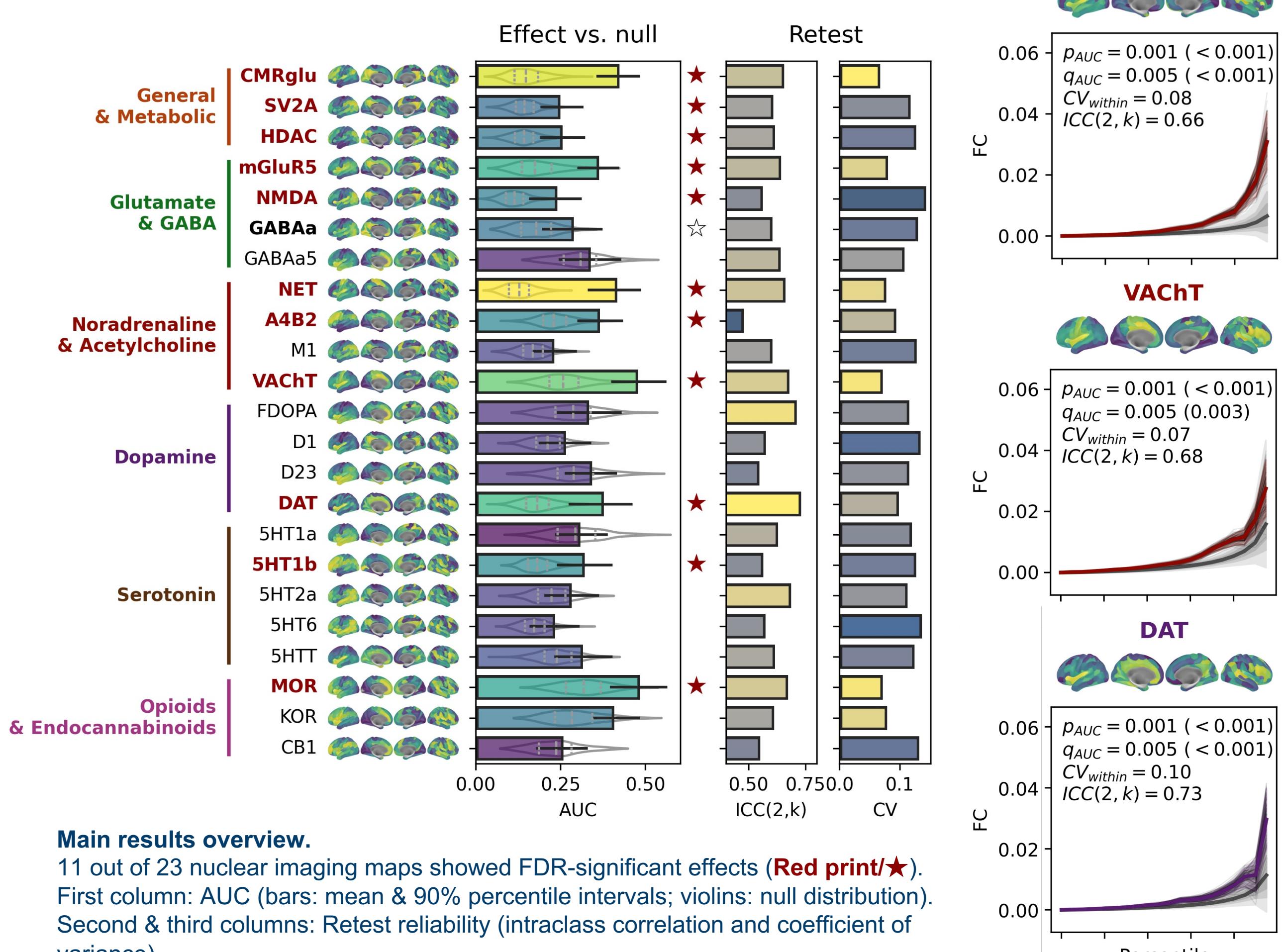
Overview of the analysis approach, exemplified on a noradrenaline transporter (NET) map. Three figures visualize the percentile-wise thresholding (percentiles 0, 50, and 90).

### Approach



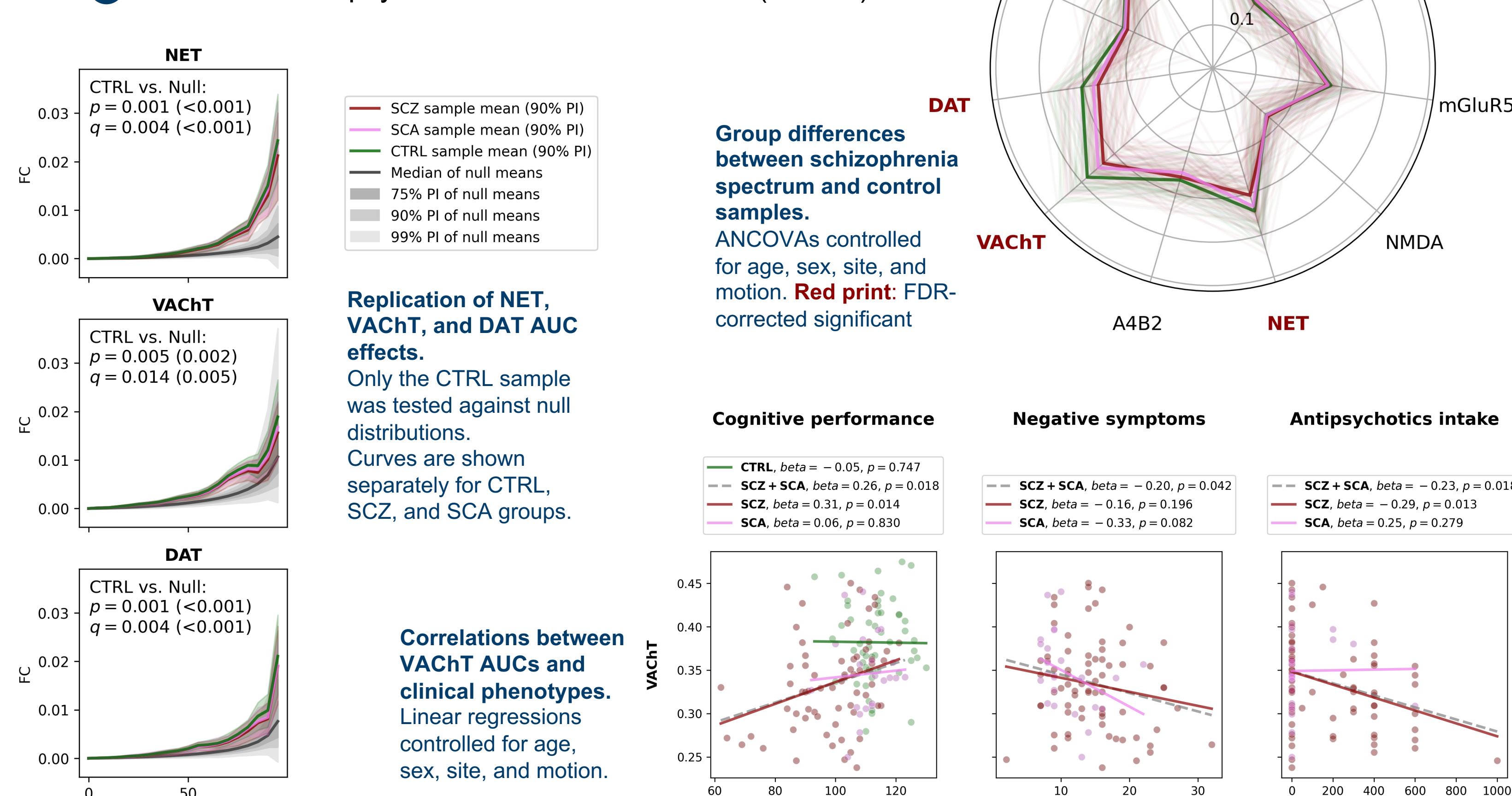
### Results: Discovery

- Sample: Young Adult Human Connectome Project<sup>8</sup>, n = 143, 20 – 35 years.
- Focus on regularized partial correlation connectomes, which were more sensitive and reliable as compared to Pearson connectomes (see above).
- Strongest significant effects (FDR-corrected) for:
  - noradrenaline transporter (NET) and vesicular acetylcholine transporter (VACHT)
  - glucose uptake (CMRglu)
  - glutamate receptors (mGluR5, NMDA)
  - dopamine transporter (DAT)



### Results: Application

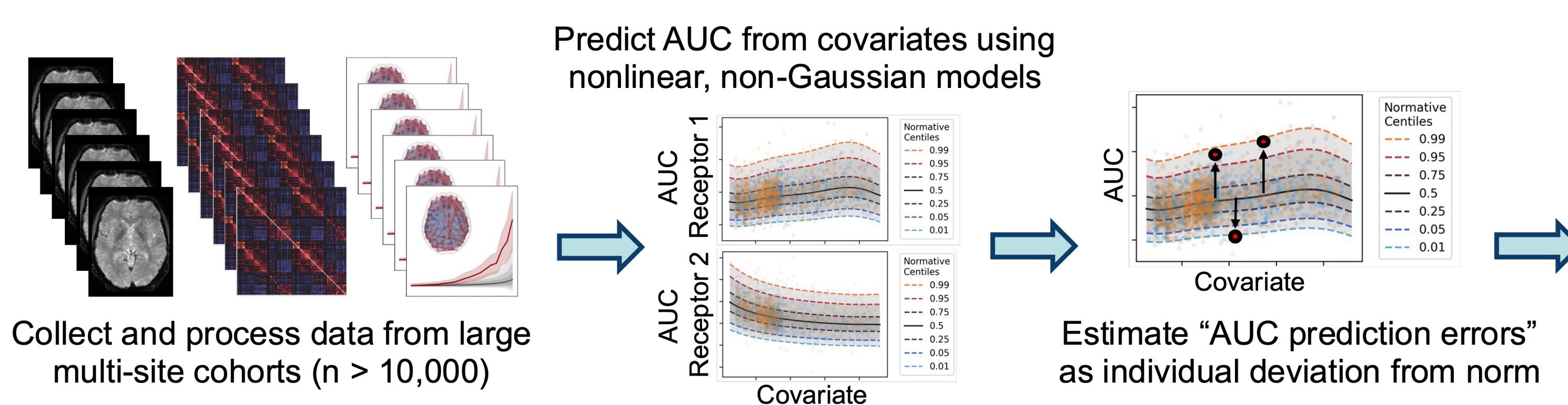
- Sample: Early Psychosis Human Connectome Project<sup>9</sup>, n = 96 with schizophrenia spectrum diagnoses (non-affective: SCZ, affective: SCA), n = 55 controls (CTRL).
- All effects observed in the discovery sample replicated in the CTRL cohort.
- Of the FDR-significant AUC estimates (see left side), 3 were reduced in SCZ/SCA vs. CTRL:
  - VACHT & NET (FDR-corrected)
  - DAT (FDR-corrected)
- VACHT AUCs, showing the strongest group differences, correlated
  - + with cognitive performance in SCZ+SCA (uncorr.)
  - with negative symptoms in SCZ+SCA (uncorr.)
  - with current antipsychotics intake in SCZ+SCA (uncorr.)



### Conclusions and Outlook

- We developed an effective approach to evaluate potential mechanisms supporting functional brain synchronization.
- We provide first indications of its clinical relevance.
- Outlook: A normative modelling framework for straight-forward application

### A normative modelling framework to generate individual receptor deviation profiles for unseen subjects



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