



## Linking functional brain synchronization to underlying neurotransmission

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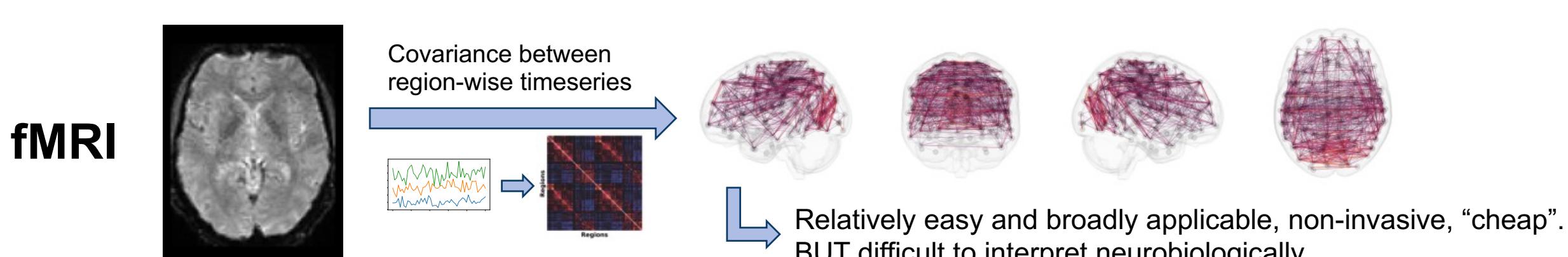
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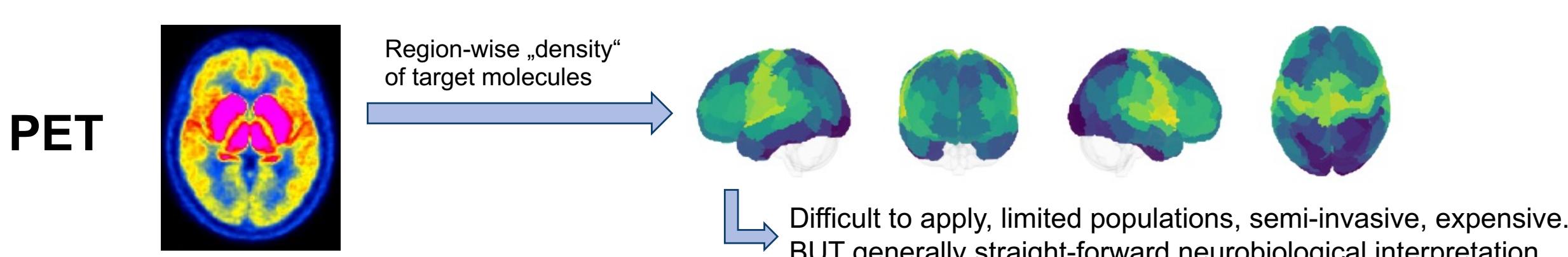
### Rationale

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



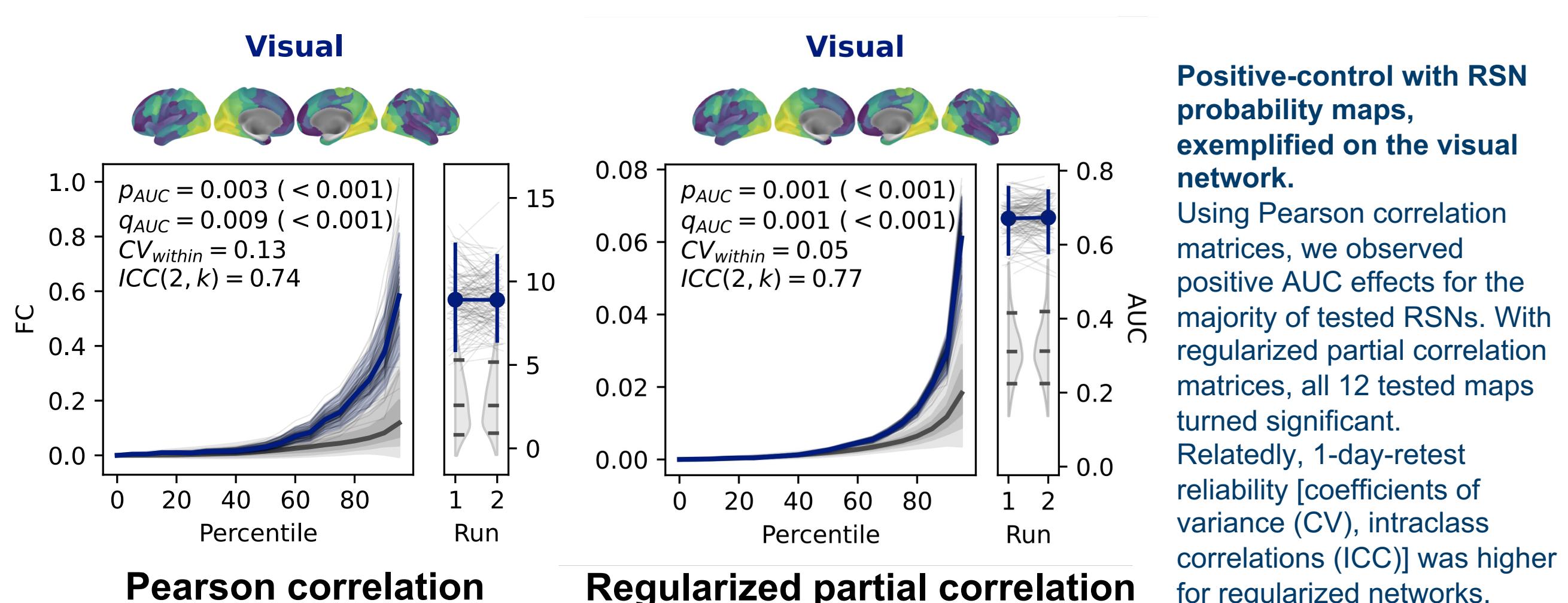
- Changes in FC related to physiology, age, behavior, and psychopathology are well documented<sup>1</sup>. However, investigating the (patho-)neurobiology underlying these changes remains challenging.

- 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.



Positive-control with RSN probability maps, exemplified on the visual network.  
Using Pearson correlation matrices, we observed positive AUC effects for the majority of tested RSNs. With regularized partial correlation matrices, all 12 tested maps turned significant. Relatedly, 1-day-retest reliability (coefficients of variance (CV), intraclass correlations (ICC)) was higher for regularized networks.

### 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>.

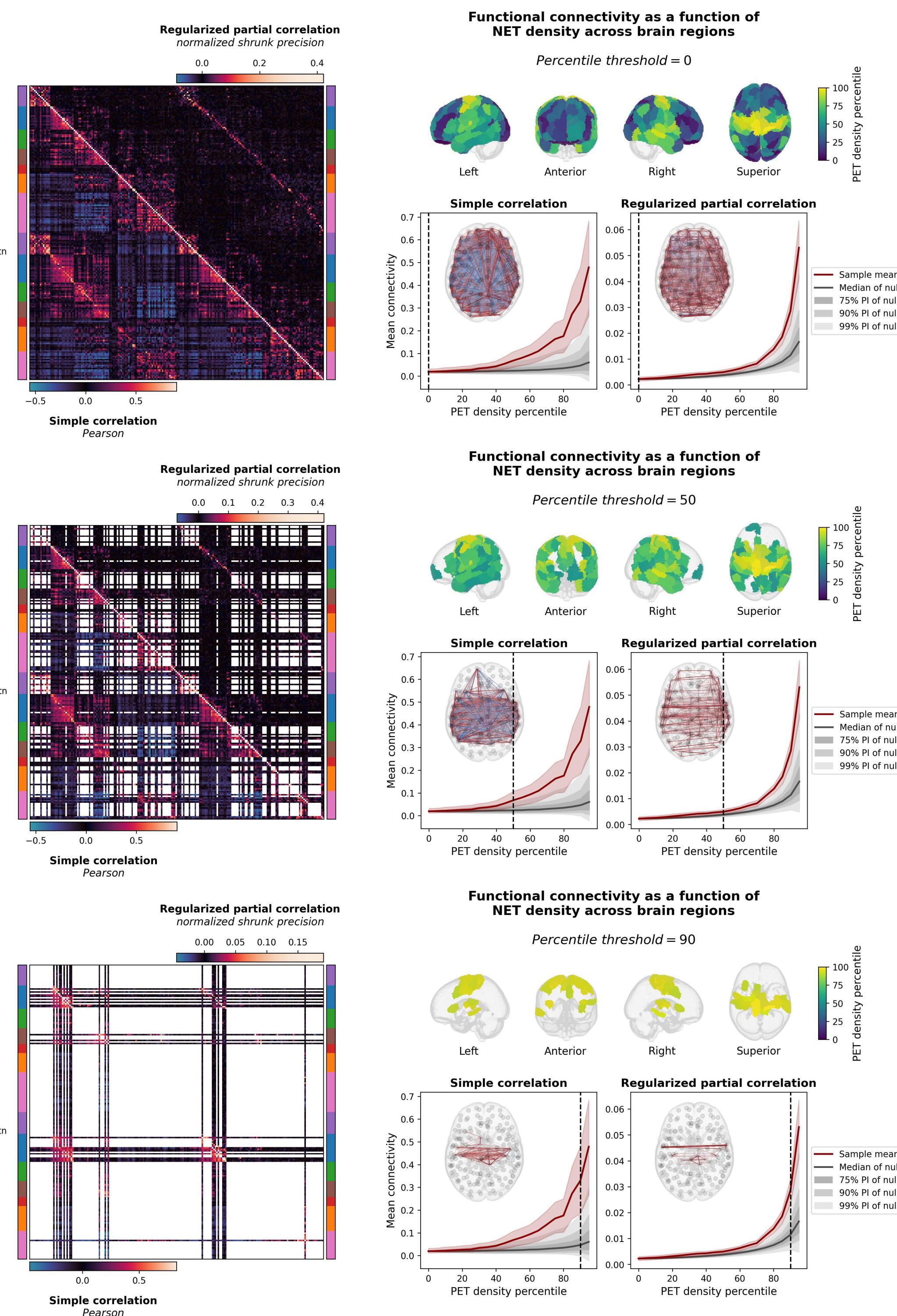
- We expect the average interregional FC to increase with higher receptor/transporter density in these regions.

- 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.

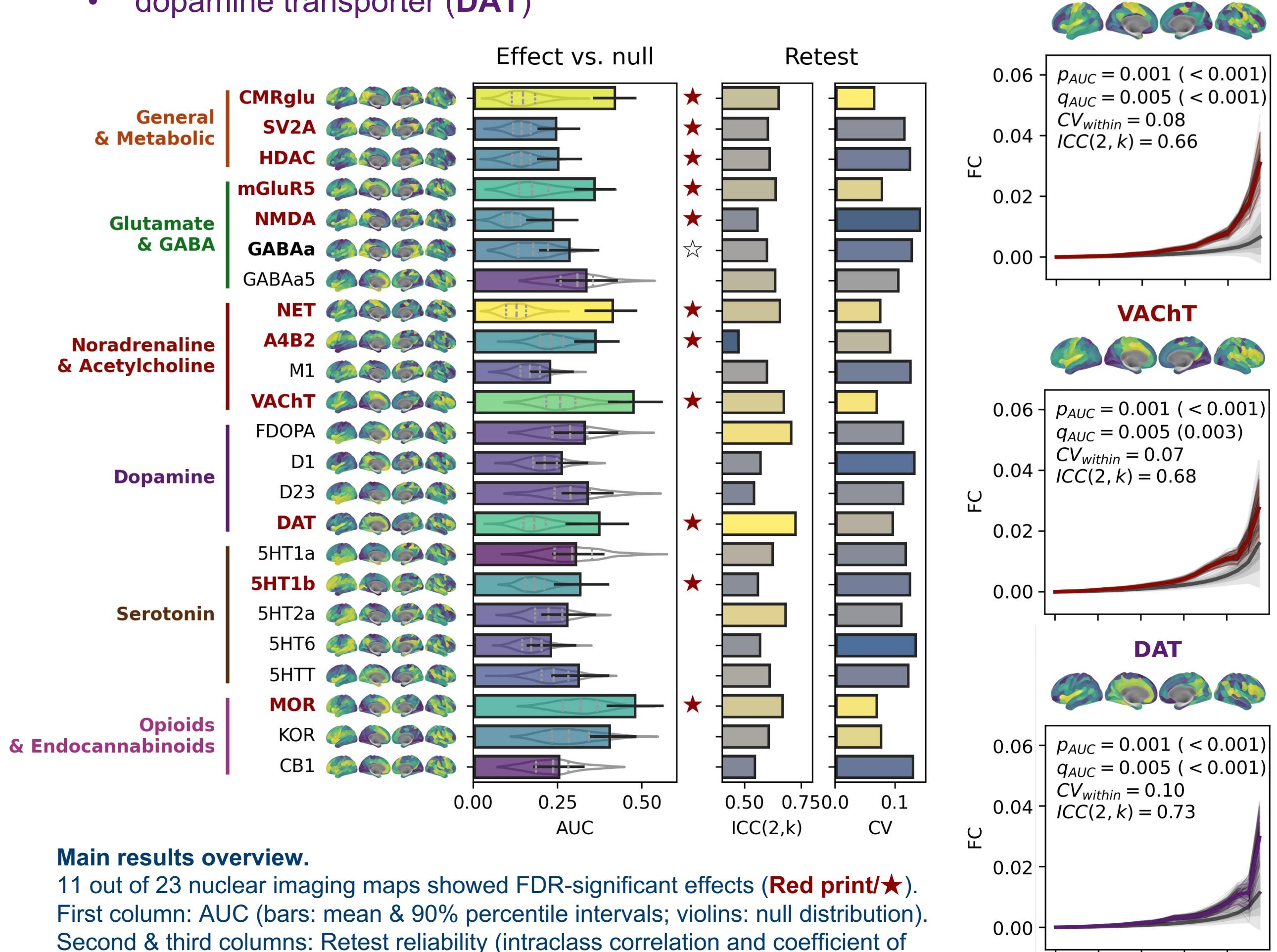
- Statistical significance is determined using a spatial permutation framework.

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



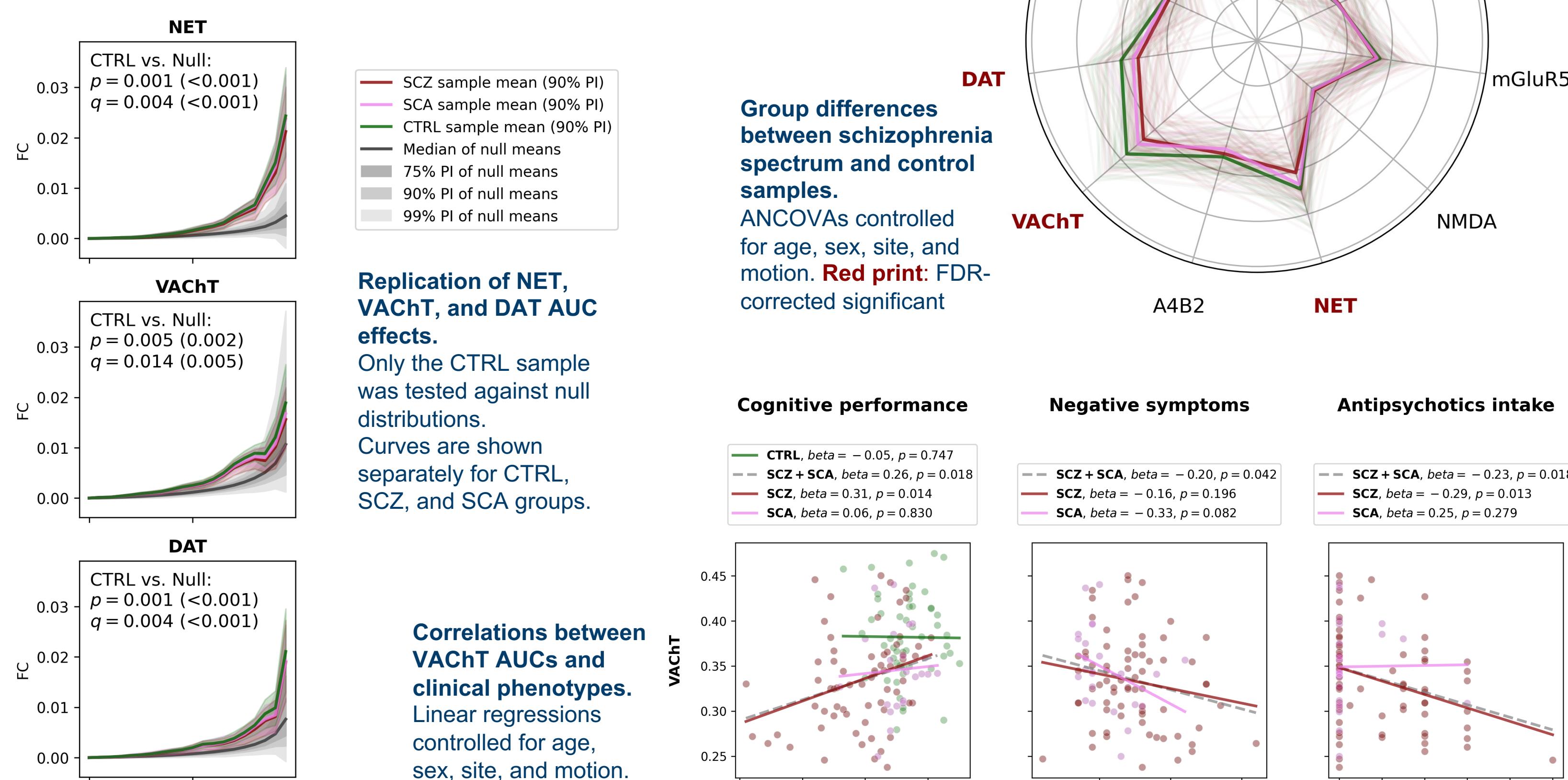
### Results: Discovery

- 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

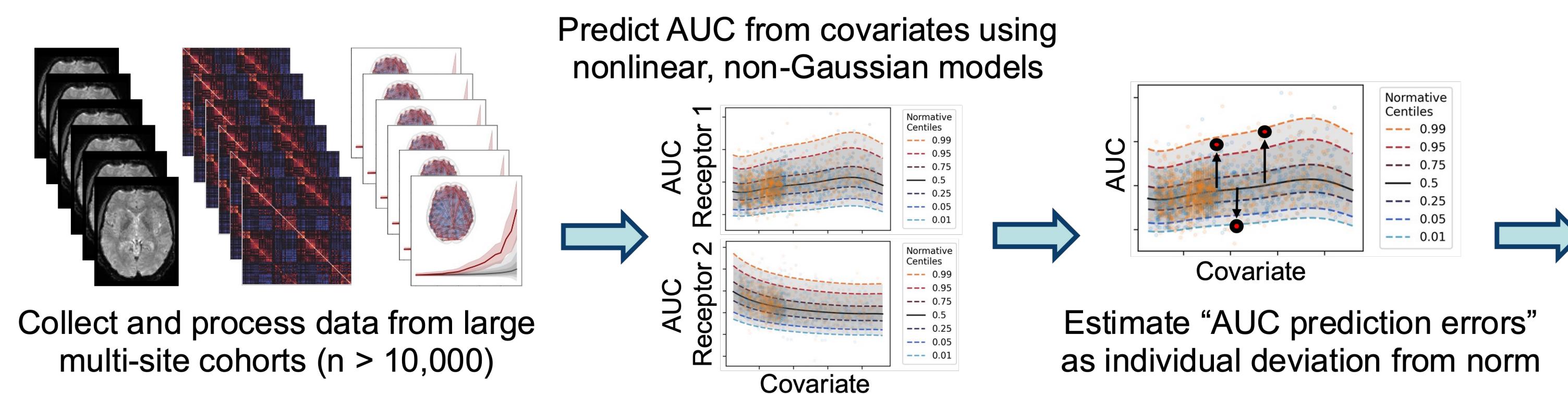
- Sample: Early Psychosis Human Connectome Project<sup>9</sup>, n = 96 with schizophrenia spectrum diagnoses (non-affective: SCZ, affective: SCA), n = 55 controls (CTRL).
- All effects observed in the discovery sample replicated in the CTRL cohort.
- Of the FDR-significant AUC estimates (see left side), 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



Adjust model to unseen cohort and generate individual deviation profiles



PDF

