

Dissociating neurotransmitter signals underlying human functional brain synchronization



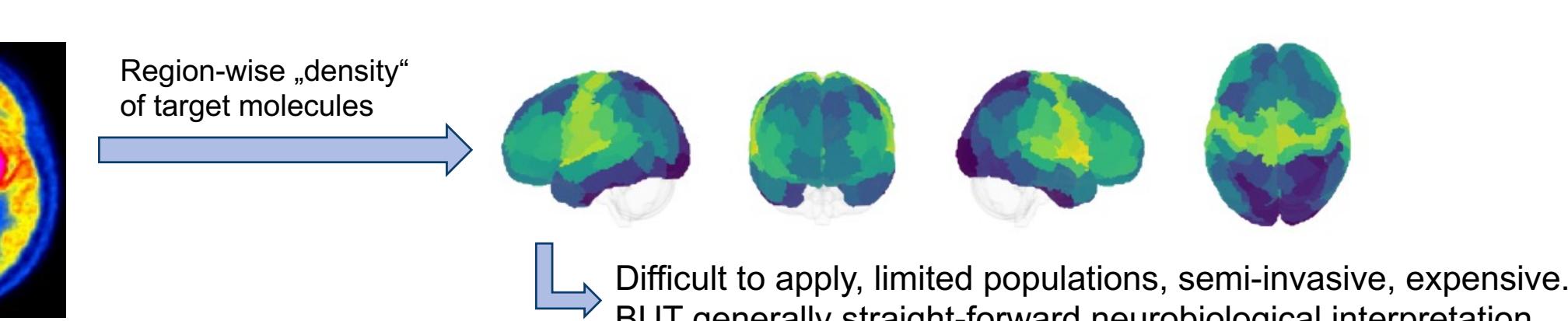
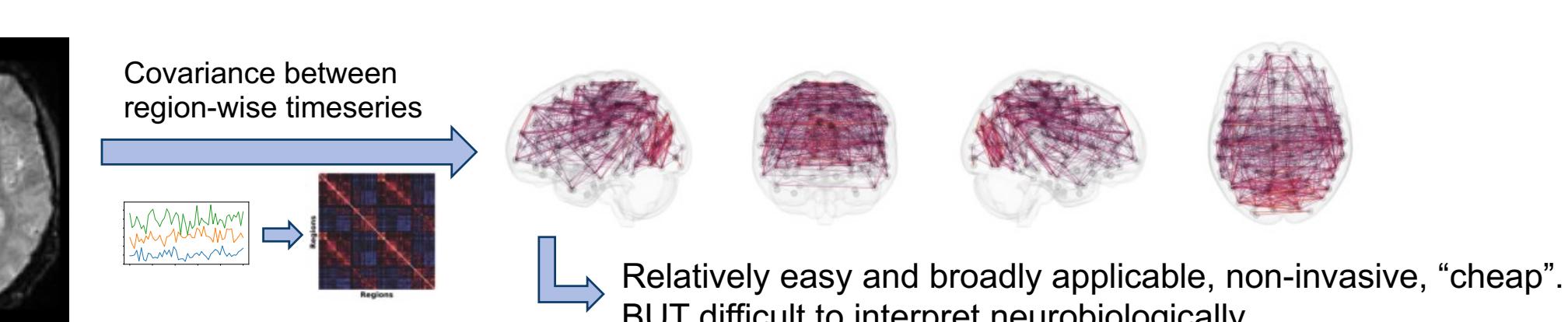
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Leading institutes:

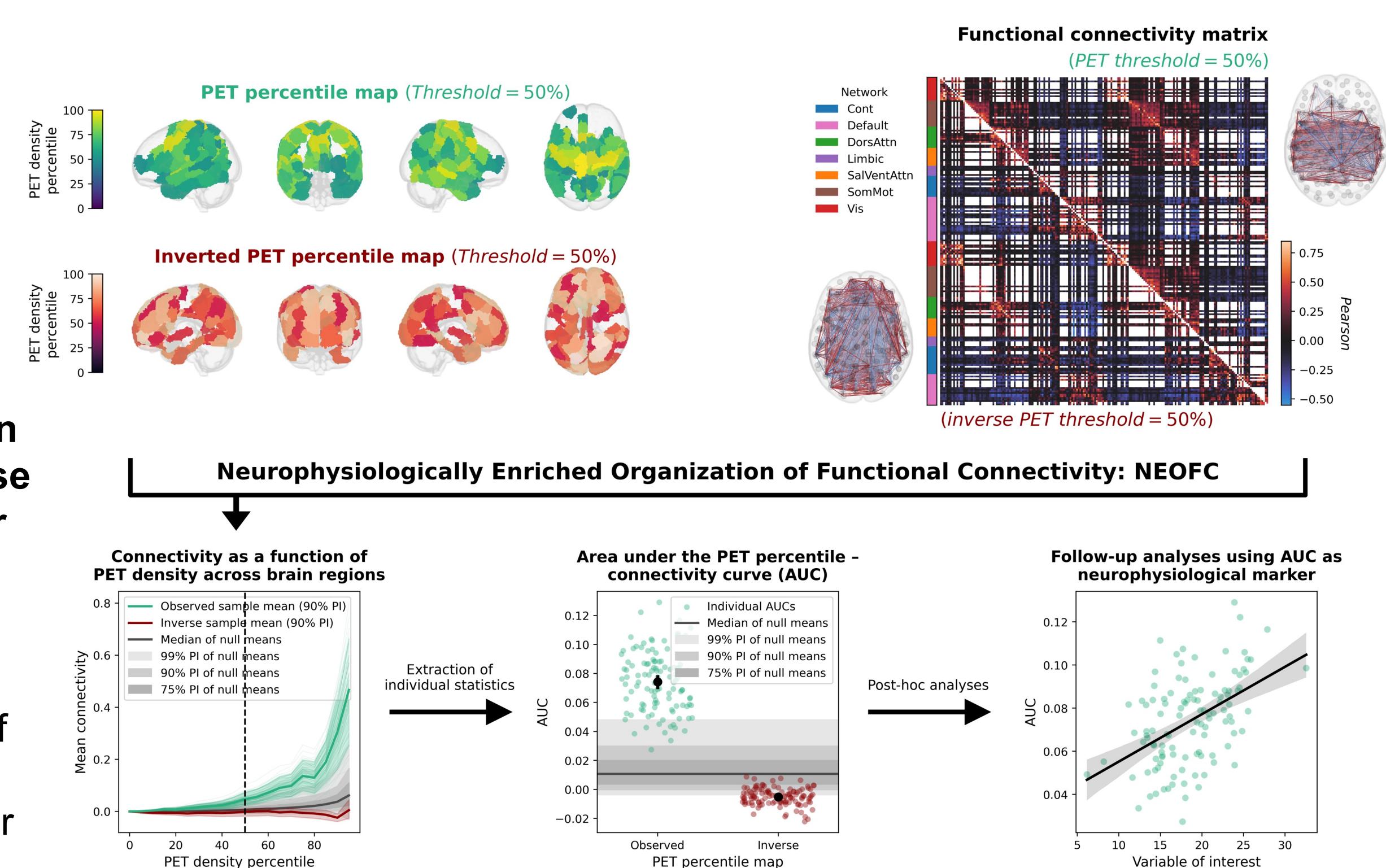
Rationale

- Functional connectivity (FC) derived from resting-state fMRI is a commonly used measure of interregional brain synchronization.
- PET
- We developed an integrative framework (see right side) to quantify associations between individual FC and underlying neurotransmission^{2,3}.



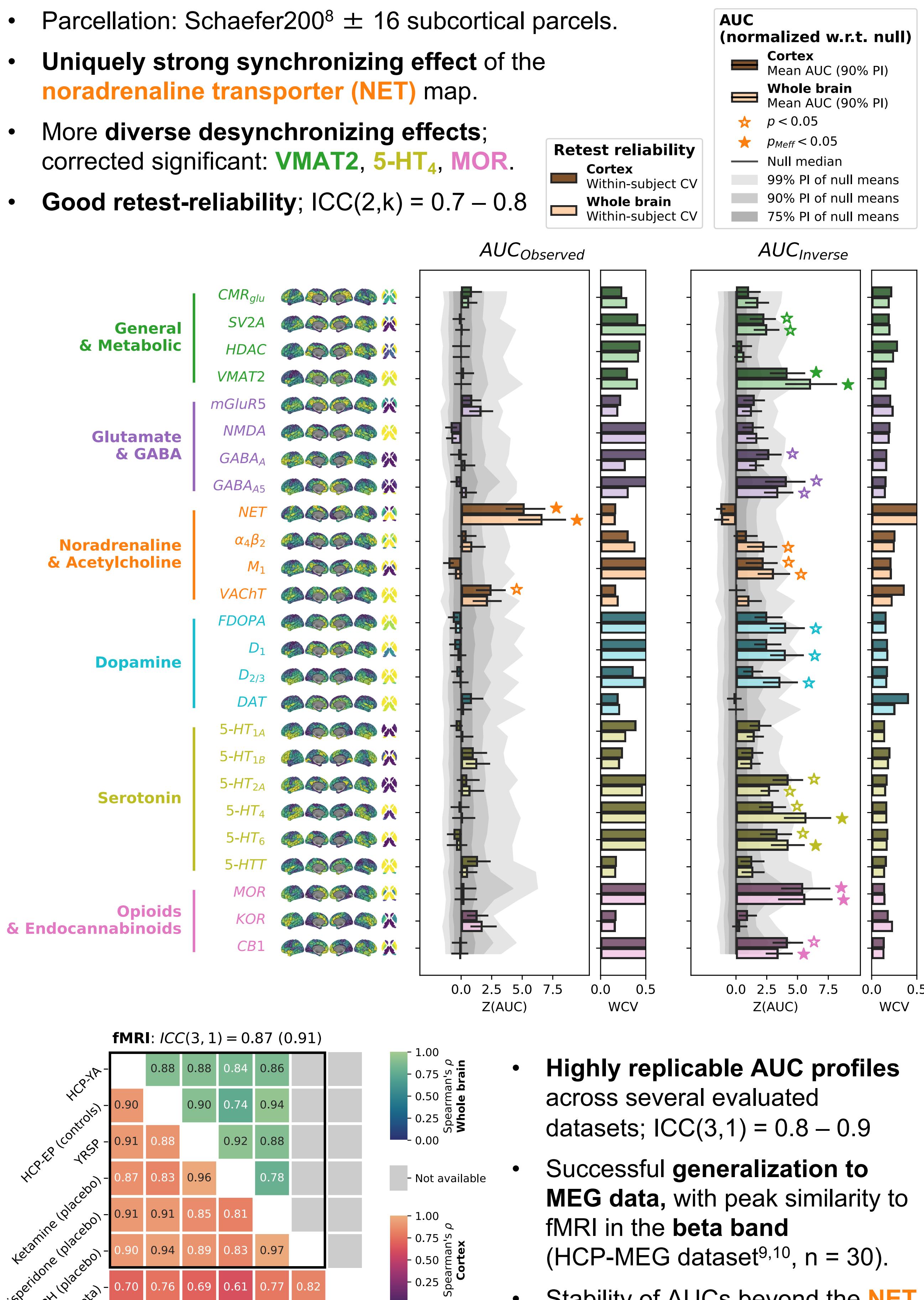
Methodological Framework

- A region-to-region FC matrix is systematically thresholded based on densities of 25 nuclear imaging maps^{4,5}.
- If FC patterns were positively associated with a certain PET map, the average FC between regions should increase with higher receptor or transporter density in the same regions.
- Analysis of the inverse of each PET map tests if FC is highest in the absence of a receptor or transporter.
- The area under the curve (AUC) is evaluated as a subject-level association index.
- Spatial null models^{4,6} are used for significance testing.



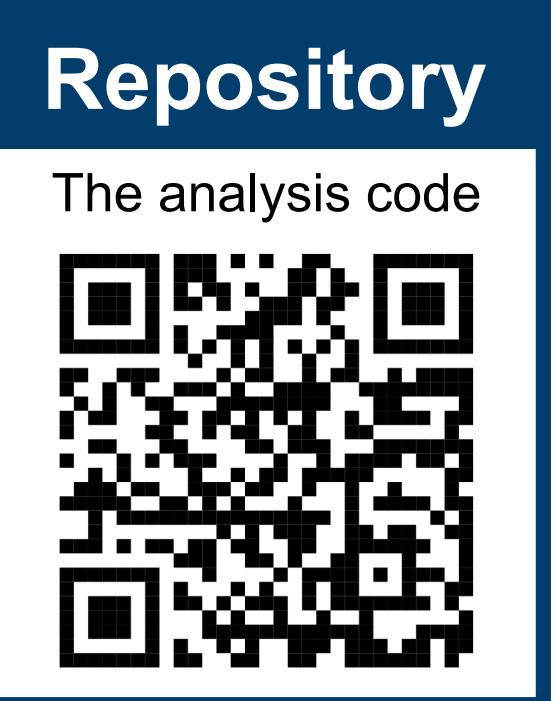
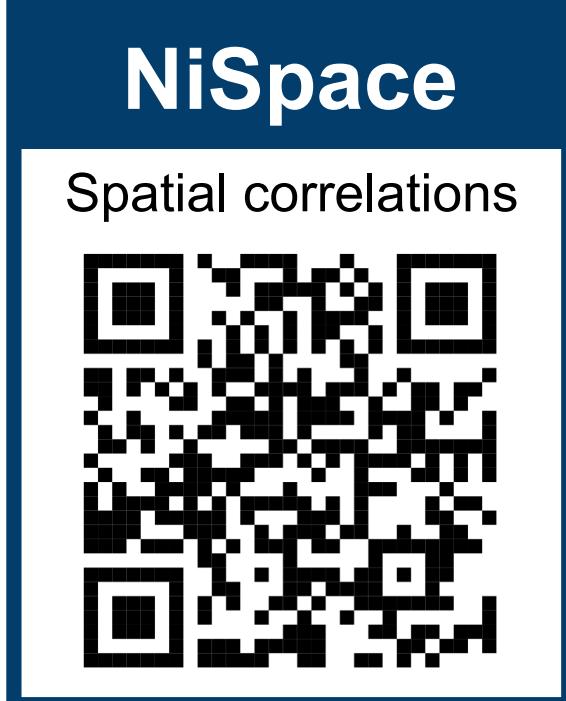
Discovery, Retest-reliability, & Replicability

- Sample: Human Connectome Project (HCP-YA)⁷; n = 132, 29 ± 3.6 years.
- Parcellation: Schaefer200⁸ ± 16 subcortical parcels.
- Uniquely strong synchronizing effect of the noradrenaline transporter (NET) map.
- More diverse desynchronizing effects; corrected significant: VMAT2, 5-HT₄, MOR.
- Good retest-reliability; ICC(2,k) = 0.7 – 0.8



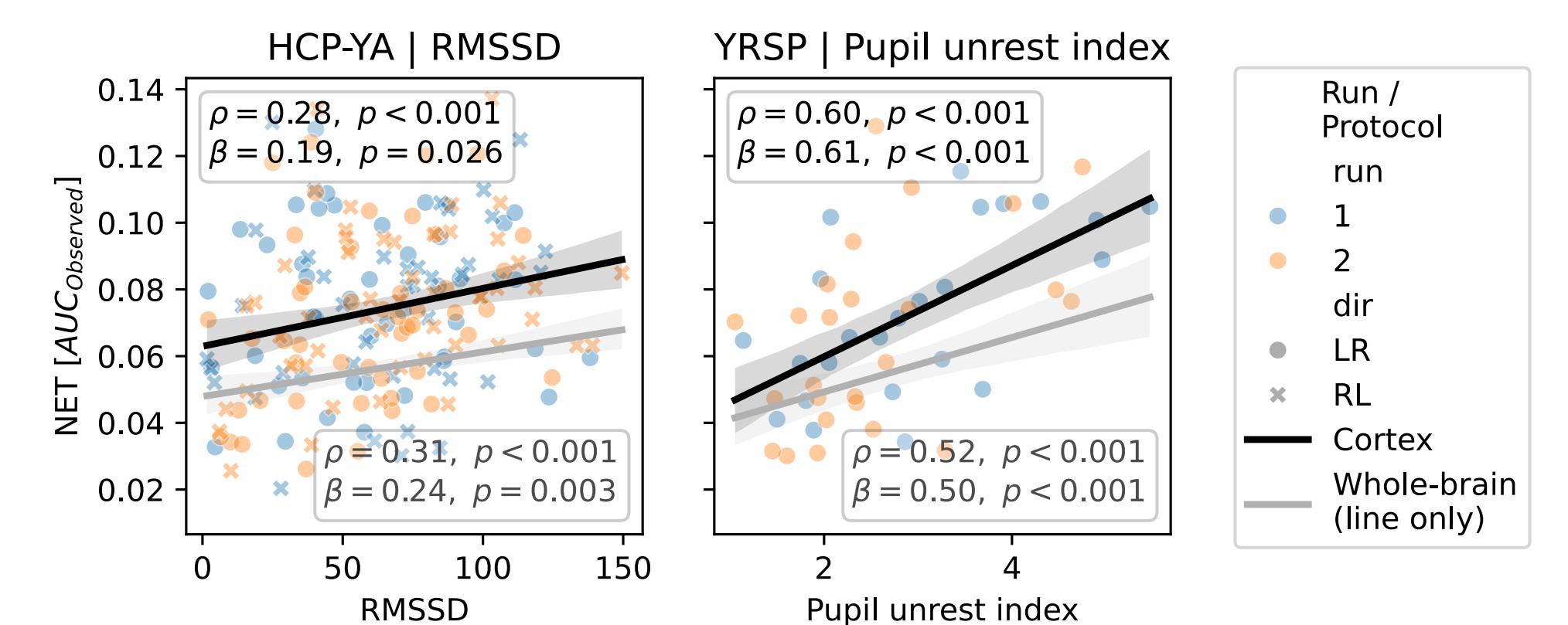
- Highly replicable AUC profiles across several evaluated datasets; ICC(3,1) = 0.8 – 0.9
- Successful generalization to MEG data, with peak similarity to fMRI in the beta band (HCP-MEG dataset^{9,10}, n = 30).
- Stability of AUCs beyond the NET finding and p value meta-analysis suggest relevant sub-threshold effects.

Resources



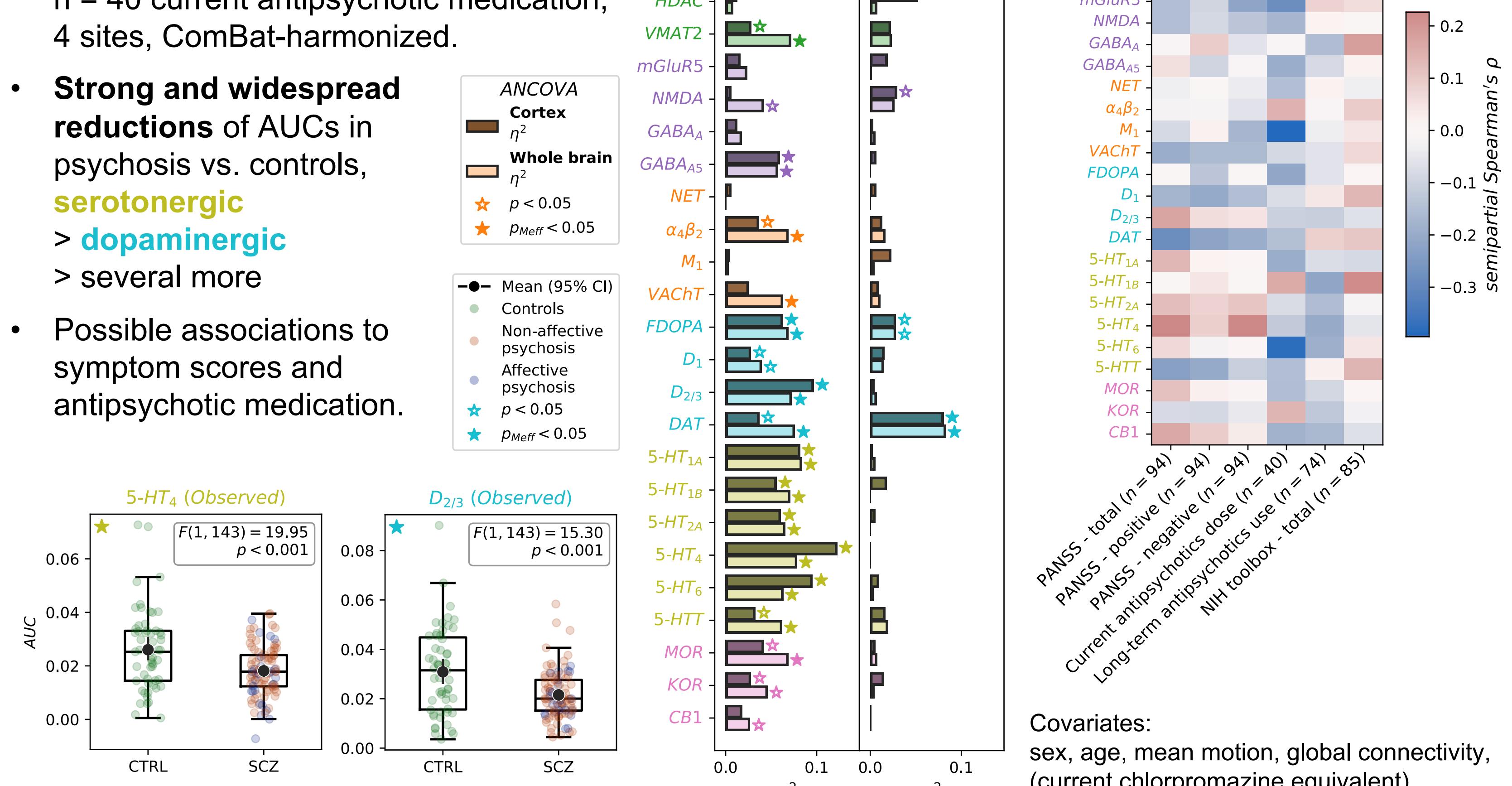
Application | NET as a marker of central autonomic regulation

- Sample: HCP-YA (n = 81) and Yale Resting-State fMRI/Pupilometry (YRSP) study¹¹ (n = 26).
- Associations of NET AUCs with resting heart rate variability (left) and pupil unrest (right).
- Suggests lower NET AUC is associated to stronger arousal.



Application | Dominant serotonergic and dopaminergic alterations in psychosis

- Sample: Early Psychosis Human Connectome Project¹²; n = 96 with schizophrenia spectrum diagnoses (SCZ), n = 55 controls (CTRL); n = 40 current antipsychotic medication; 4 sites, ComBat-harmonized.
- Strong and widespread reductions of AUCs in psychosis vs. controls, serotonergic > dopaminergic > several more
- Possible associations to symptom scores and antipsychotic medication.



Conclusions & Outlook

- We introduce an effective framework to evaluate the biology of functional brain synchronization.
- The derived markers are robust and replicable, show external validity, and biologically plausible physiological and clinical associations.
- Further data (not shown) suggest sensitivity to pharmacological challenges and developmental trajectories with plateau phases from ~30 years.
- Focus on resting-state may emphasize auto-regulatory mechanisms, potentially causing the dominant NET effect.
- Extension to task-related connectomes could increase sensitivity to specific transmitter systems.
- Left side: First evidence from meta-analytic task connectomes generated from ~14,000 studies¹³.

