

# Molecular imaging-informed biomarkers link functional brain synchronization to underlying neurotransmission

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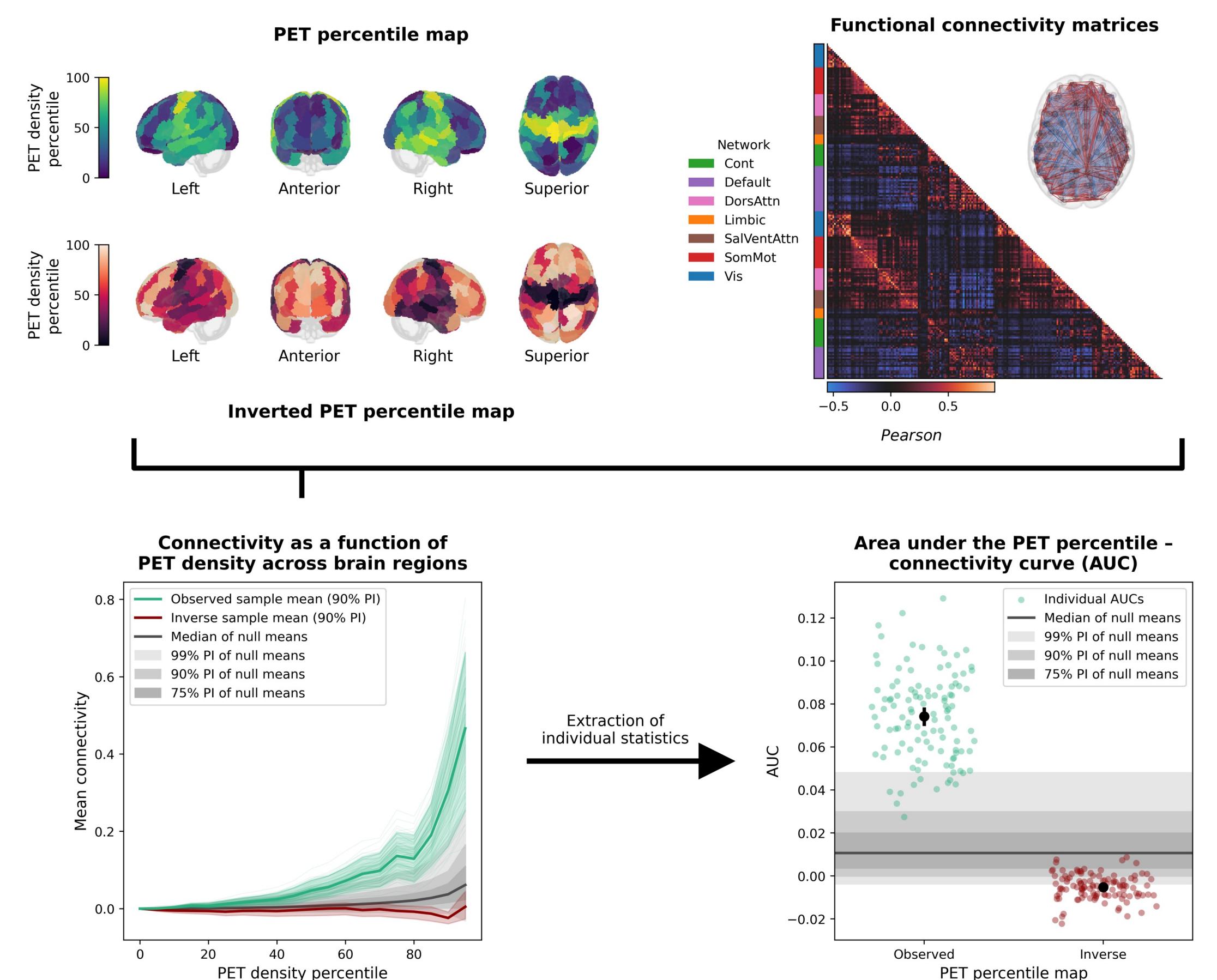


## Rationale

- Functional connectivity (FC) derived from resting-state fMRI is a commonly used measure of interregional brain synchronization.
- fMRI**: Covariance between region-wise timeseries → Relatively easy and broadly applicable, non-invasive, "cheap". BUT difficult to interpret neurobiologically.
- 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 offers more direct insight into biological mechanisms, albeit at a considerably higher cost and with practical constraints.
- PET**: Region-wise "density" of target molecules → Difficult to apply, limited populations, semi-invasive, expensive. BUT generally straight-forward neurobiological interpretation.
- We developed an integrative framework (see right side) to quantify associations between individual FC and underlying neurotransmission<sup>2,3</sup>.

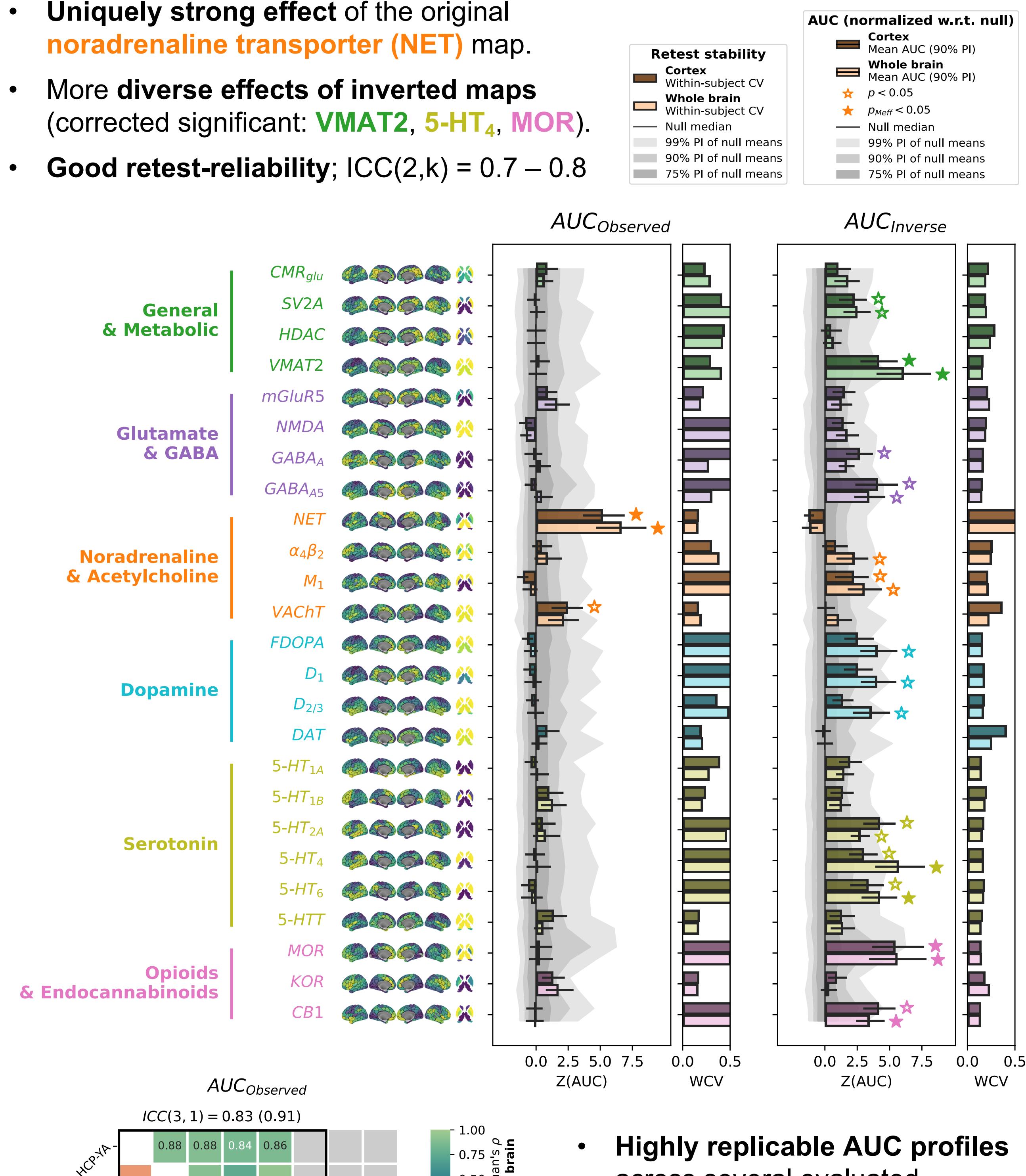
## Methodological Framework

- A region-to-region FC matrix is systematically thresholded based on densities of 25 nuclear imaging maps<sup>4,5</sup>.
- 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<sup>4,6</sup> are used for significance testing.



## Discovery, Retest-reliability, & Replicability

- Sample: Human Connectome Project (HCP-YA)<sup>7</sup>; n = 132, 29 ± 3.6 years.
- Parcellation: Schaefer200<sup>8</sup> with and without 16 subcortical parcels.
- Uniquely strong effect of the original noradrenaline transporter (NET) map.
- More diverse effects of inverted maps (corrected significant: VMAT2, 5-HT<sub>4</sub>, 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 replication in MEG data, with peak similarity to fMRI in beta band (HCP-MEG dataset<sup>9,10</sup>, n = 30).
- Stability of "observed" AUCs beyond the NET finding suggests relevant sub-threshold effects.

## Resources

### Poster

This poster as a PDF



### NiSpace

Spatial correlations



### Toolbox

Apply the framework



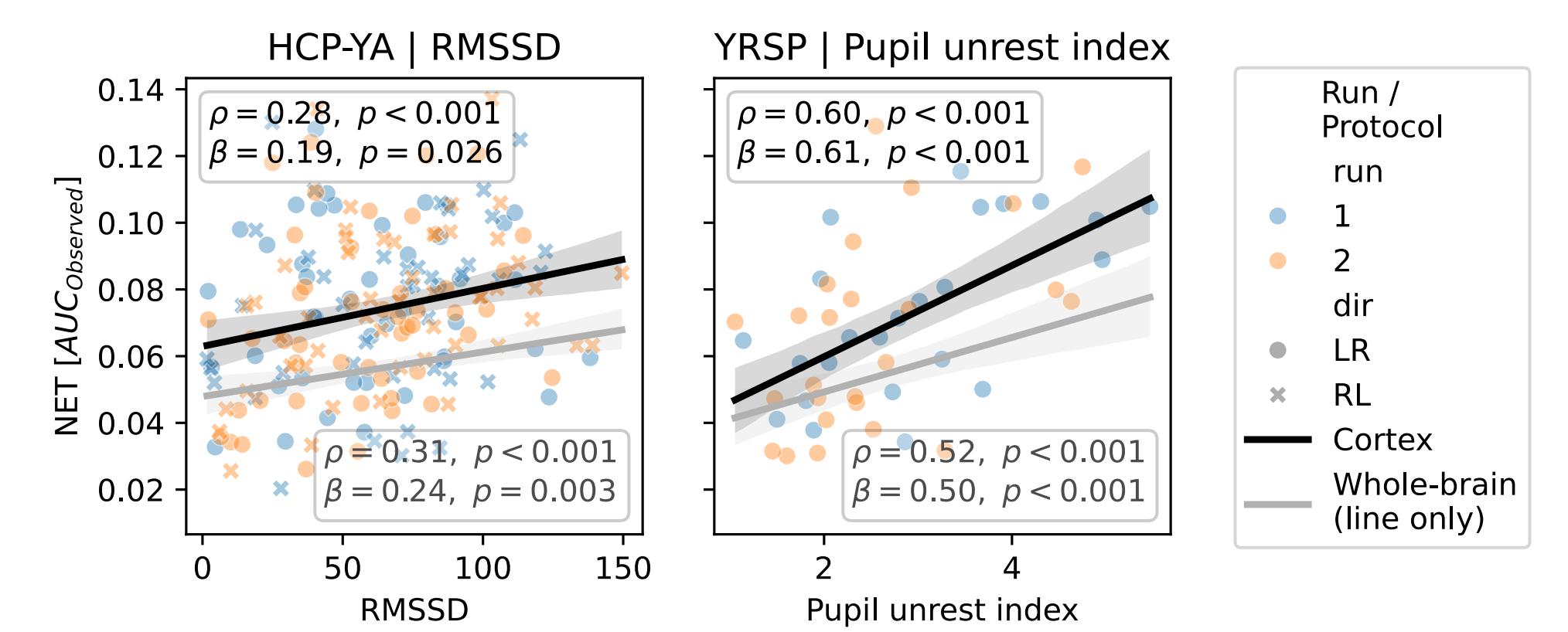
### Repository

The analysis code



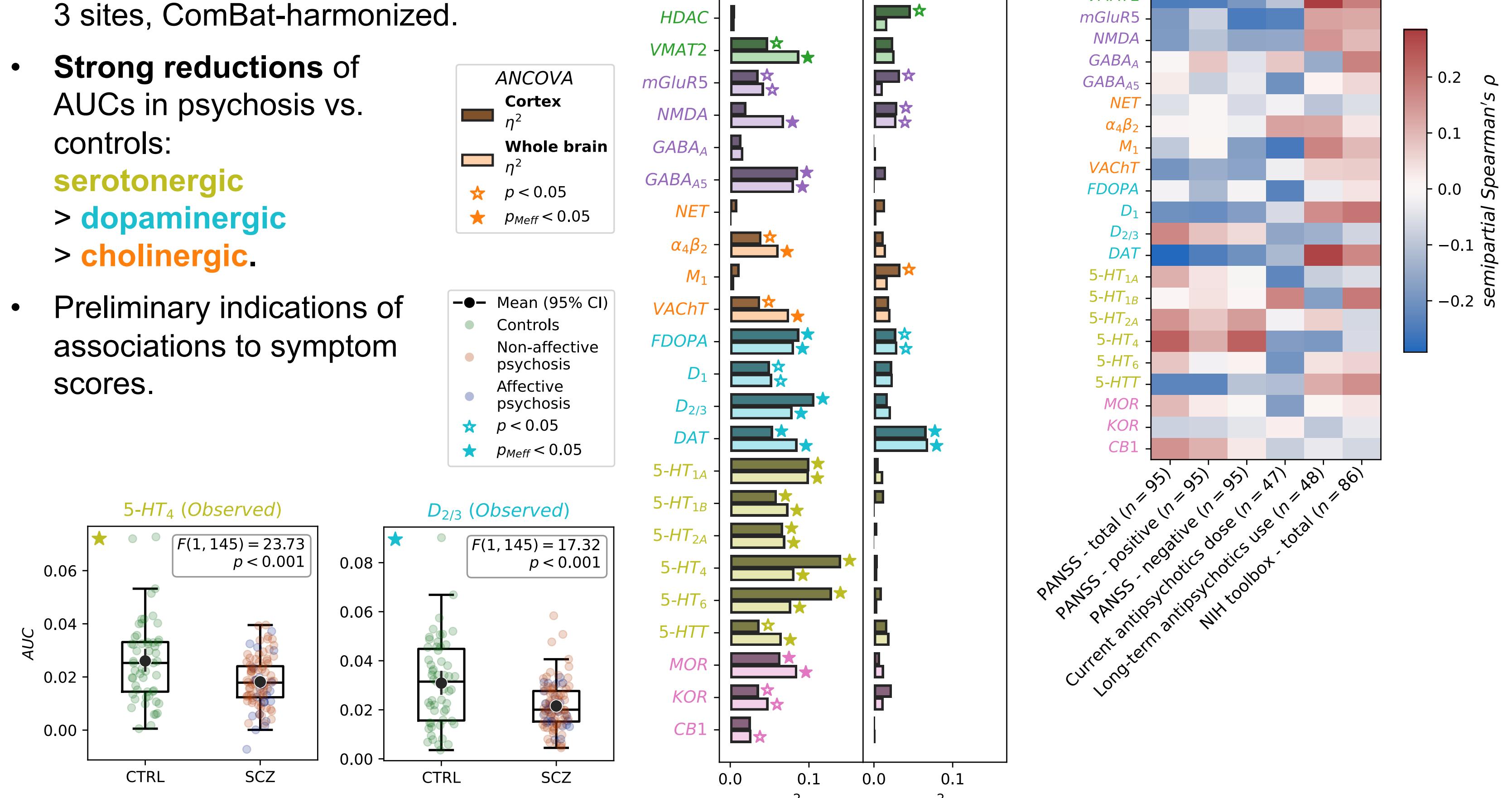
## Application | NET as a marker of general central autonomic regulation

- Sample: HCP-YA (n = 81) and Yale Resting-State fMRI/Pupilometry (YRSP) study<sup>11</sup> (n = 26).
- Strong 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 Project<sup>12</sup>; n = 96 with schizophrenia spectrum diagnoses (SCZ), n = 55 controls (CTRL); 3 sites, ComBat-harmonized.
- Strong reductions of AUCs in psychosis vs. controls: serotonergic > dopaminergic > cholinergic.
- Preliminary indications of associations to symptom scores.



## Conclusions & Outlook

- We developed an effective framework to evaluate the biology of functional brain synchronization.
- The derived markers are robust and replicable, show external validity, and biologically sensible physiological and clinical associations.
- Further data (not shown) suggest sensitivity to pharmacological interventions and developmental trajectories with plateau phases from ~30 years.
- Focus on resting-state may emphasize auto-regulatory mechanisms, potentially causing the dominant NET effect.
- Future analysis of task-related connectomes could reveal more fine-grained associations.
- Left side: Confirmation by meta-analytic task connectomes generated from ~14,000 studies<sup>13</sup>.

