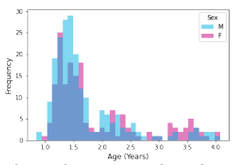
Multivariate clustering and validation for parcellating the prefrontal cortex in a large sample of rhesus macaques

UC DAVIS
UNIVERSITY OF CALIFORNIA

Carly M Drzewiecki, Jonathan A Oler, Rasmus M Birn, Alexander J Shackman, Andrew L Alexander, Ned H Kalin, Andrew S Fox

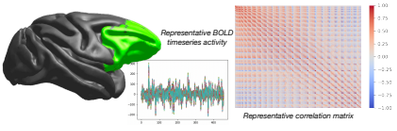
Introduction & Data Acquisition

- The **prefrontal cortex (PFC) is a functionally heterogeneous brain region made up of architectonically distinct subregions**, which are defined differentially based on various factors (e.g. cytoarchitecture, anatomical connectivity, task-related activation, etc.)
- Cortical subdivisions make up larger cortico-cortical networks, which have been identified in the PFC of humans and nonhuman primates and are implicated in emotional behaviors
- Here we use a large same of rhesus macaques to explore **a data-driven approach to parcellating the primate PFC based on intrinsic functional connectivity**
- Data from 378 young rhesus macaques housed and scanned at the University of Wisconsin - Madison were used for this study (0.95 yrs - 4.4 yrs, mean age 1.89; 208 males).



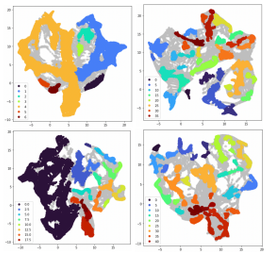
- Resting state fMRI scans were collected under anesthesia using a General Electric Signa 3T scanner (GE Medical Systems) equipped with a standard 16 cm quadrature extremity coil
- **Subjects underwent behavioral testing to assess phenotypic anxious temperament (AT). Metabolism data was collected via PET scan**, results have been previously reported (Fox et al., 2015)

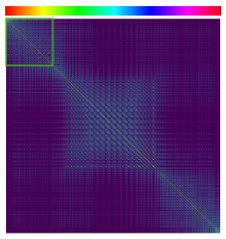
Multivariate Clustering Pipeline

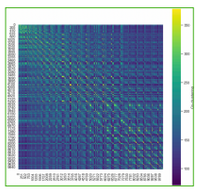


1. Resting state timeseries extracted from PFC (45,914 voxels total) and correlated to identify functional connectivity patterns

2. Within-subjects timeseries clustering using UMAP dimensionality reduction + HDBSCAN (4 representative subjects shown)





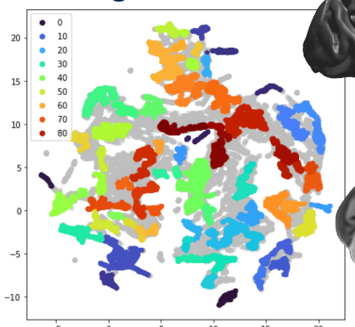


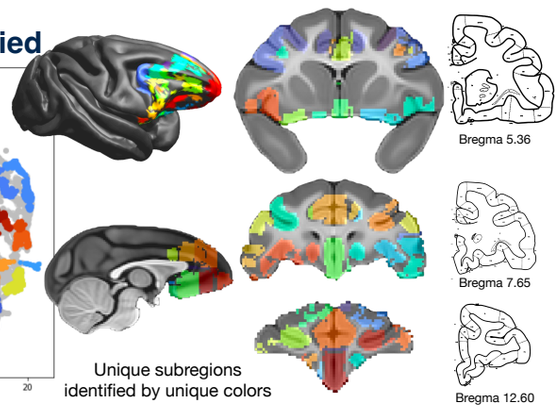
3. The co-clustering matrix captures how often voxels are grouped into the same cluster across multiple subjects.

4. Apply UMAP + HDBSCAN to the co-clustering matrix for group-level

Multivariate clustering results

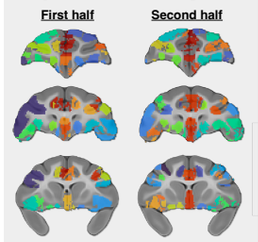
88 unique PFC subregions identified





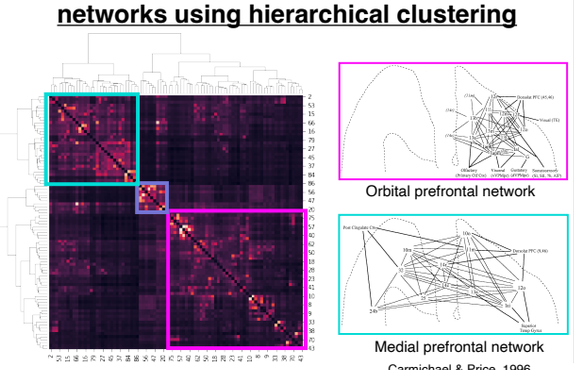
Unique subregions identified by unique colors

Split half analysis



Split-half analysis demonstrates ~89% correspondence at the group level (dice coefficient)

Replication of anatomical cortico-cortico networks using hierarchical clustering

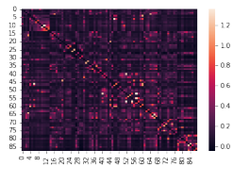


Orbital prefrontal network

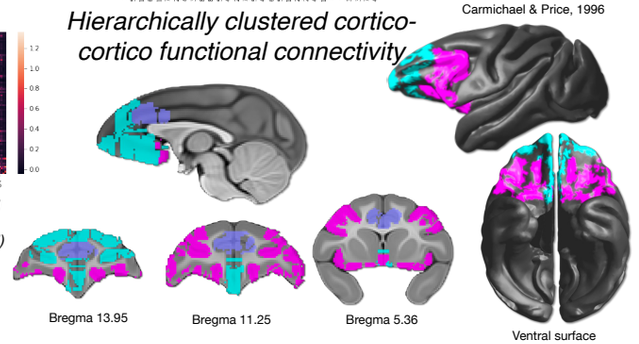
Medial prefrontal network

Carmichael & Price, 1996

Hierarchically clustered cortico-cortico functional connectivity



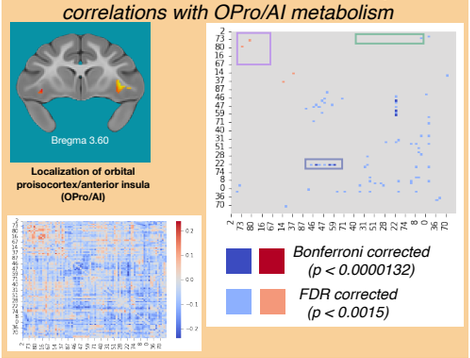
Cortico-cortico functional connectivity, averaged across subjects (z-scored)



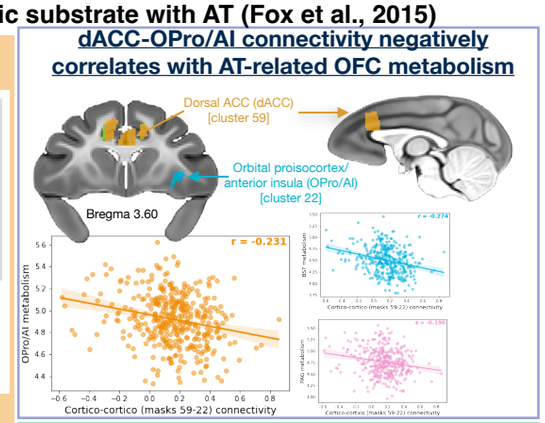
Cortico-cortico connectivity and anxiety

Cortico-cortico functional connectivity as a predictor of AT-related brain metabolism sharing a genetic substrate with AT (Fox et al., 2015)

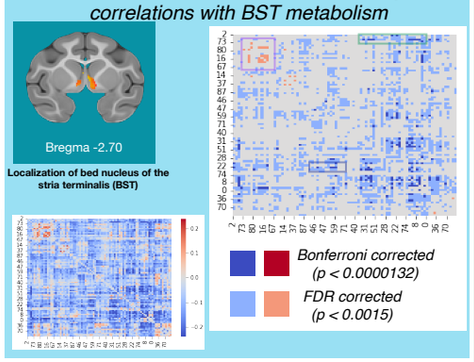
Cortico-cortico functional connectivity correlations with OPro/AI metabolism



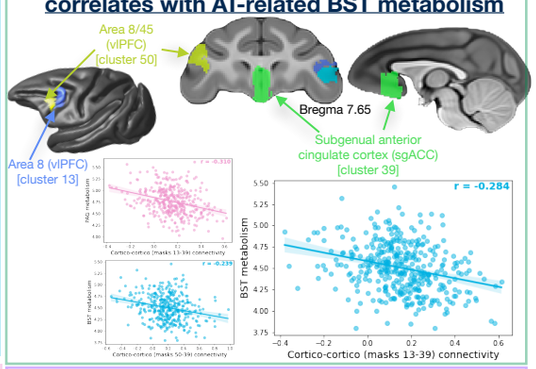
dACC-OPro/AI connectivity negatively correlates with AT-related OFC metabolism



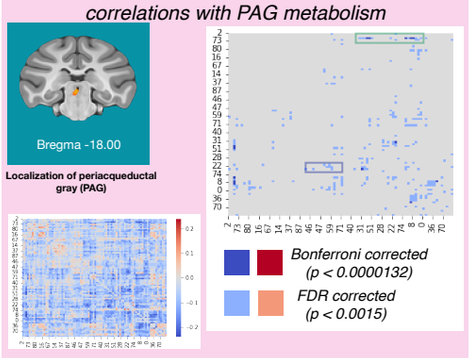
Cortico-cortico functional connectivity correlations with BST metabolism



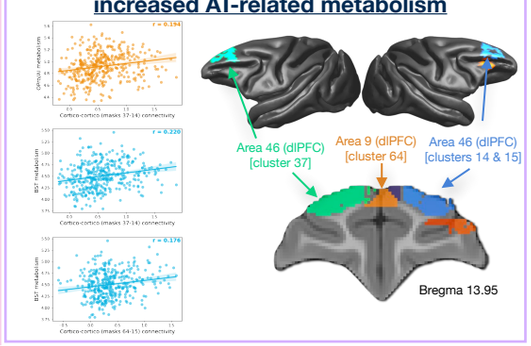
Area 8/45-sgACC connectivity negatively correlates with AT-related BST metabolism



Cortico-cortico functional connectivity correlations with PAG metabolism

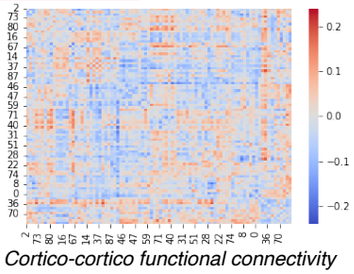


Intra-dlPFC connectivity correlates with increased AT-related metabolism



Conclusions & Future Directions

- Our multivariate clustering pipeline identified 88 distinct PFC subregions at the group level, based on intrinsic functional connectivity patterns
- This novel clustering approach enables the creation of cortical masks for efficient extraction and correlation of BOLD activity
- Analysis uncovered multiple cortico-cortico connectivity patterns linked to AT-related brain metabolism
- Future work will focus on using these connectivity patterns to predict AT-relevant behaviors and explore sex-specific connectivity differences associated with AT



Cortico-cortico functional connectivity as a predictor of AT

Acknowledgements: We thank the California & Wisconsin National Primate Research Centers, the staff of the Harlow Center for Biological Psychology at UW-Madison and Steve Shelton in particular. This work was supported by grants P50-MH100031, P51-OD011106, R01-MH046729, R01-MH081884, R01-MH107444, R21-DA040717