

Clusters of seed-based voxel-wise functional connectivity predict local glutamate in pregenual anterior cingulate cortex

L.N. Martens^{1,2}, N. B. Kroemer², V. Teckentrup², L. Colic^{3,4}, M. Li^{2,3,4}, M. Walter^{1,2,3,4}

1. Max Planck Institute for Biological Cybernetics, Tübingen, Germany 2. Department of Psychiatry and Psychotherapy, University Tübingen, Tübingen, Germany 3. Clinical Affective Neuroimaging Laboratory, Magdeburg, Germany 4. Leibniz Institute for Neurobiology, Magdeburg, Germany

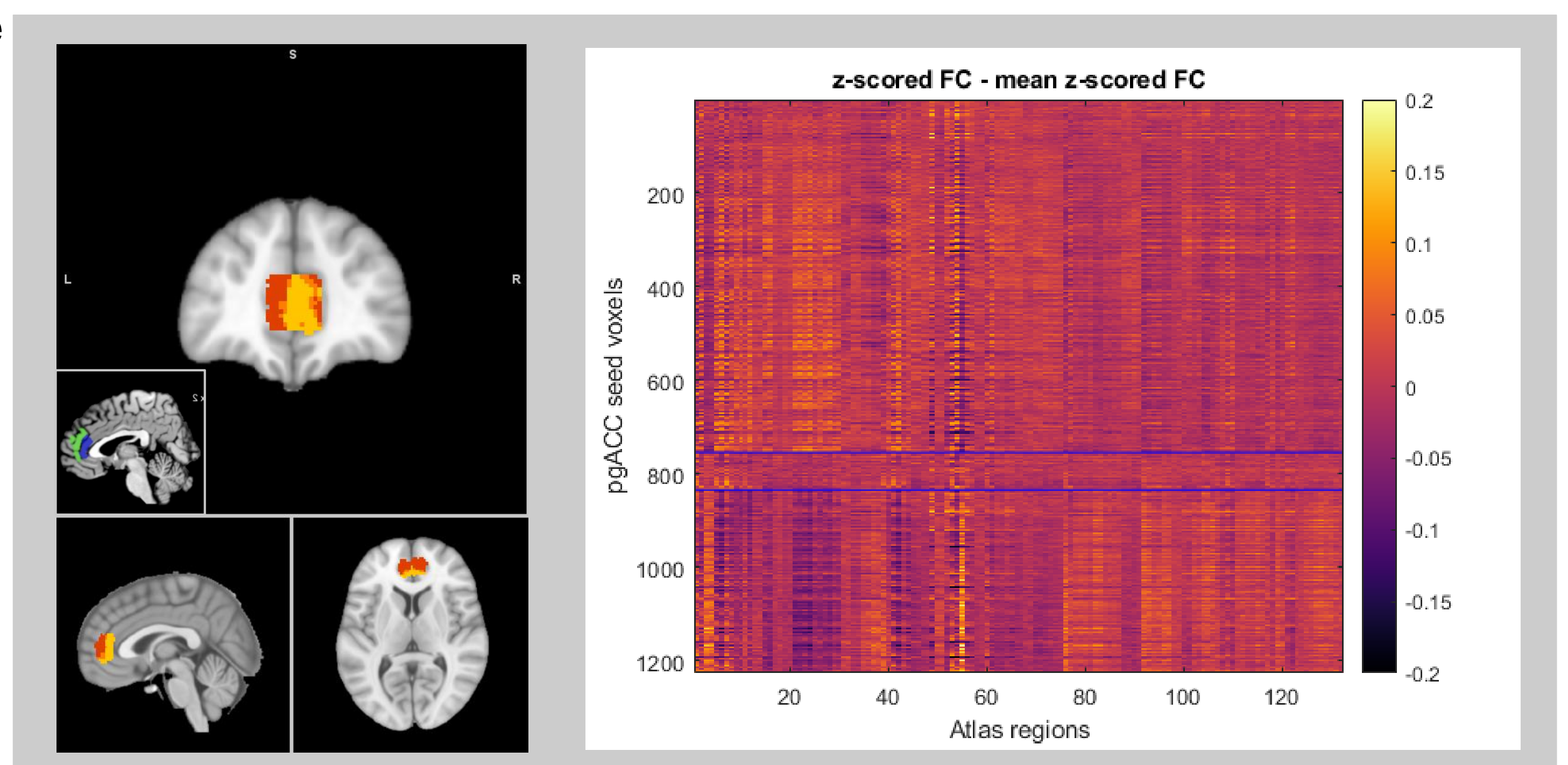
Introduction

- Magnetic resonance spectroscopy (MRS) measurements of excitatory neurotransmission may provide valuable insights into underlying neurobiology of altered functional connectivity (FC) in psychiatric disorders
- Local measures of glutamate (Glu) are often reported to moderate resting-state FC^{1,2,3}
- Inherently low signal-to-noise ratio (SNR) of conventional single-voxel MRS necessitates voxel sizes far exceeding those of functional magnetic resonance imaging (fMRI)
- This leads to crude measurements of local neurometabolism
- **Hypothesis:**
decomposing the pregenual anterior cingulate (pgACC) functional connectome using hierarchical clustering provides incremental information on the neurotransmitters governing its function

Methods

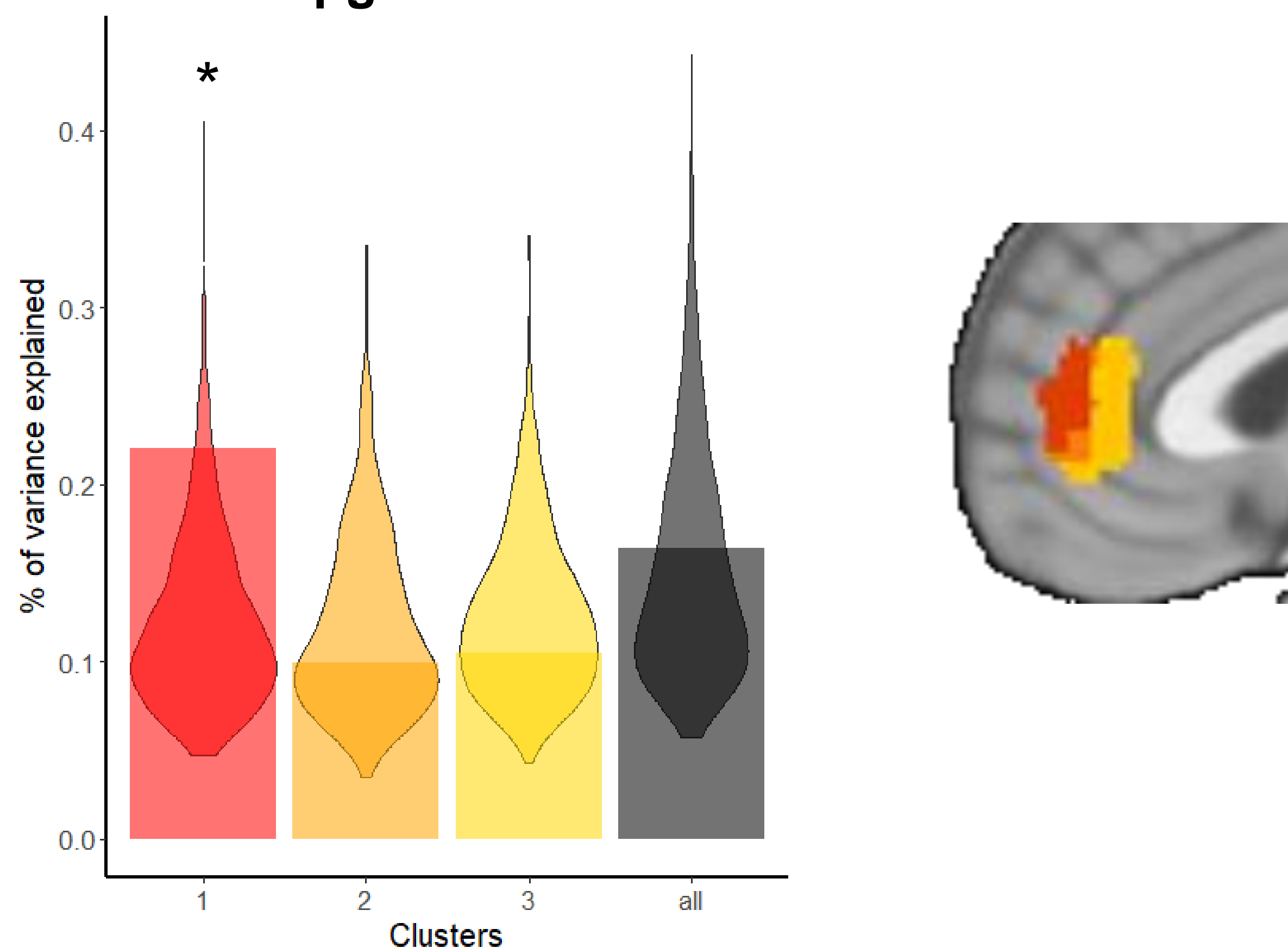
- 89 healthy subjects underwent structural, resting-state (TR/TE: 2800/22 ms, FA = 80°, 62 slices, number of volumes = 270, voxel size 2 mm isotropic) and MRS (STEAM, TE/TM/TR = 20/10/3000 ms, voxel-size 20 x 15 x 10 mm³) measurements at 7 Tesla.
- fMRI: preprocessed using default CONN pipeline⁴, then denoised in Matlab
- MRS: fitted with LCModel⁵, expressed as ratio to total Creatine (tCr)
- Seed voxels: only those fMRI voxels in composite MRS mask
- FC with CONN atlas nodes
- Hierarchical clustering of pgACC seed-voxels (3 clusters)
- **Prediction of Glu/tCr and GABA/tCr from cluster FC to atlas regions: partial-least-squares regression (PLSR) and Elastic Net (EN)**

Hierarchical clustering results (insert: Palomero-Gallagher et al.⁶)

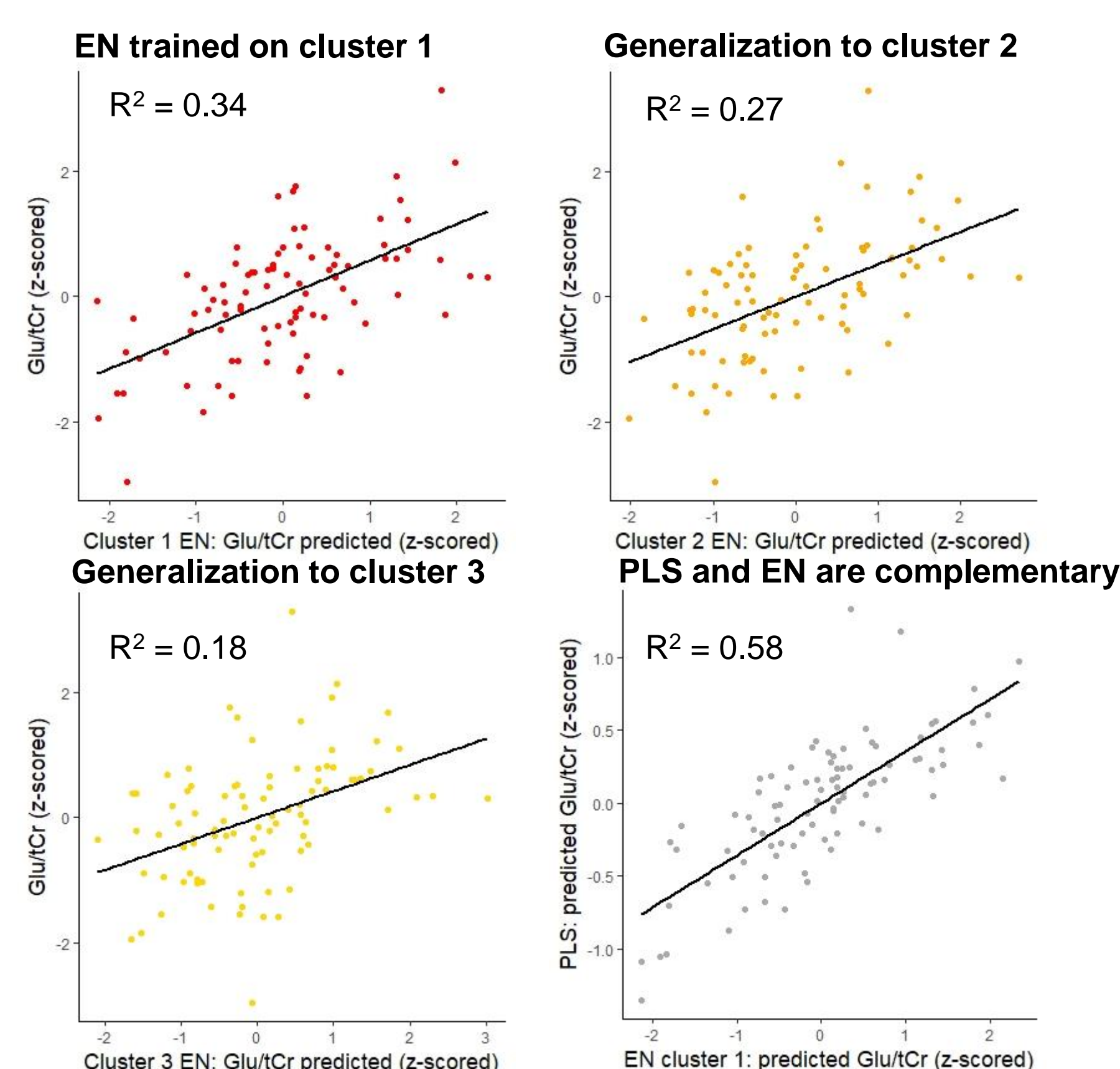


Results

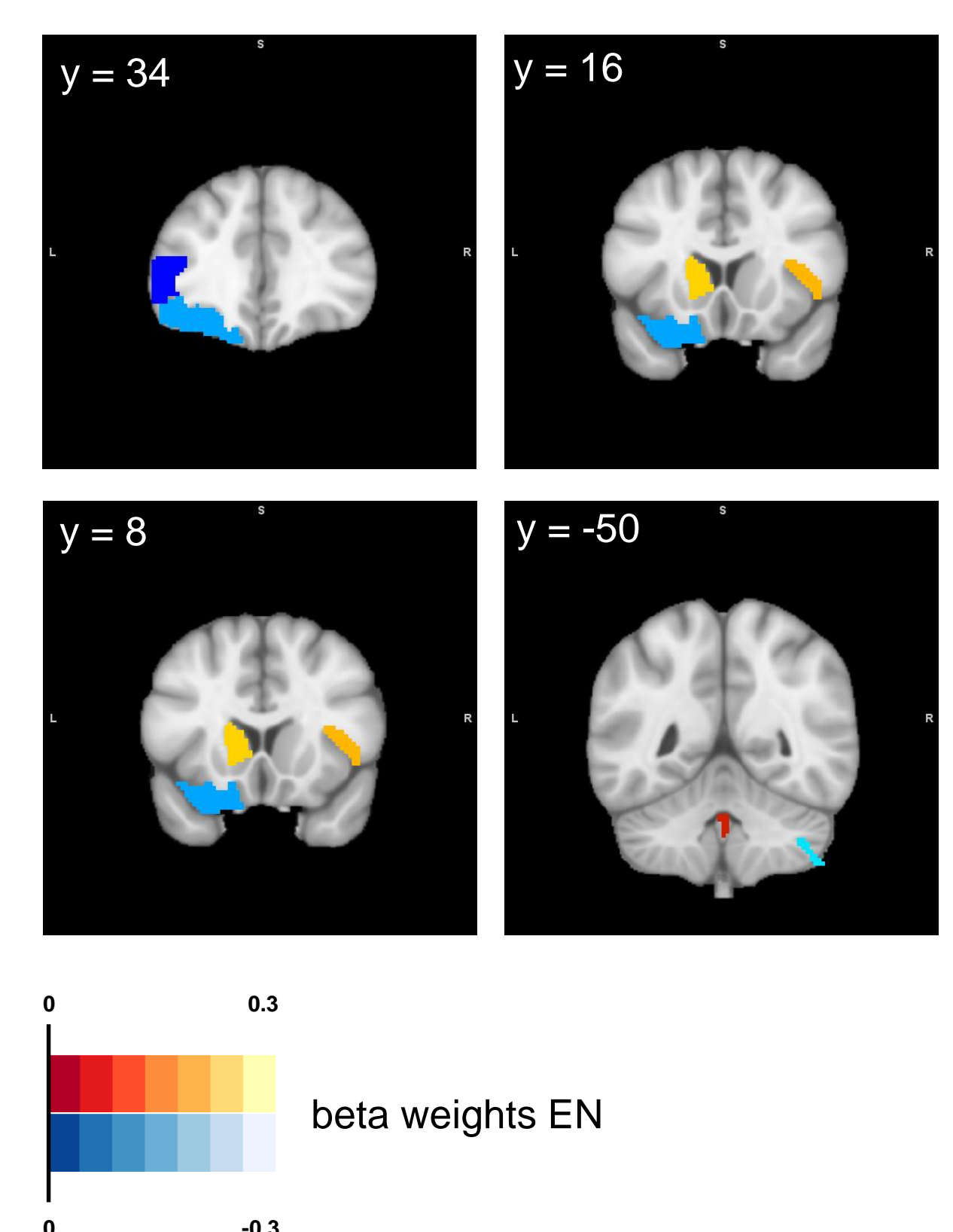
PLSR for Glu/tCr, trained on FC matrix for each pgACC cluster



Elastic net results are congruent with PLSR



EN: Non-zero ROIs cluster 1



Identical analyses for GABA/tCr yielded no significant results.

Conclusion

- A pgACC MRS voxel can be parcellated into functionally distinct clusters that differentially predict local Glutamate.
- Prediction of Glu using the best performing cluster (corresponding to p32⁶) is partially driven by connectivity between pgACC and subcortical regions.
- **Take-home: capitalize on higher spatial resolution of fMRI to get more fine-grained insight into local neurometabolism (e.g. in psychiatric disorders)**

References

1. Duncan, N. W., Wiebking, C., Tiet, B., Marjańska, M., Hayes, D. J., Lyttleton, O., ... Northoff, G. (2013). Glutamate Concentration in the Medial Prefrontal Cortex Predicts Resting-State Cortical-Subcortical Connectivity in Humans. *PLoS ONE*, 8(4). <https://doi.org/10.1371/journal.pone.0060312>
2. Horn, D. I., Yu, C., Steiner, J., Buchmann, J., Kaufmann, J., Osoba, A., ... Walter, M. (2010). Glutamatergic and resting-state functional connectivity correlates of severity in major depression - the role of pregenual anterior cingulate cortex and anterior insula. *Frontiers in Systems Neuroscience*, 4(July), 1-10. <https://doi.org/10.3389/fnys.2010.00033>
3. Kapogiannis, D., Reiter, D. A., Willette, A. A., & Mattson, M. P. (2013). Posteromedial cortex glutamate and GABA predict intrinsic functional connectivity of the default mode network. *NeuroImage*, 64(1), 112-119. <https://doi.org/10.1016/j.neuroimage.2012.09.029>
4. Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connectivity*, 2(3), 125-141. <https://doi.org/10.1089/brain.2012.0073>
5. Provencher, S. W. (2001). Automatic quantitation of localized in vivo 1 H spectra with LCModel. 260-264. <https://doi.org/10.1002/nbm.698>
6. Palomero-Gallagher, N., Hoffstaedter, F., Mohlberg, H., Eickhoff, S. B., Amunts, K., & Zilles, K. (2018). Human Pregenual Anterior Cingulate Cortex: Structural, Functional, and Connective Heterogeneity. *Cerebral Cortex*. <https://doi.org/10.1093/cercor/bhy124>