

Disrupted structural covariance networks of cholinergic interconnections in schizophrenia

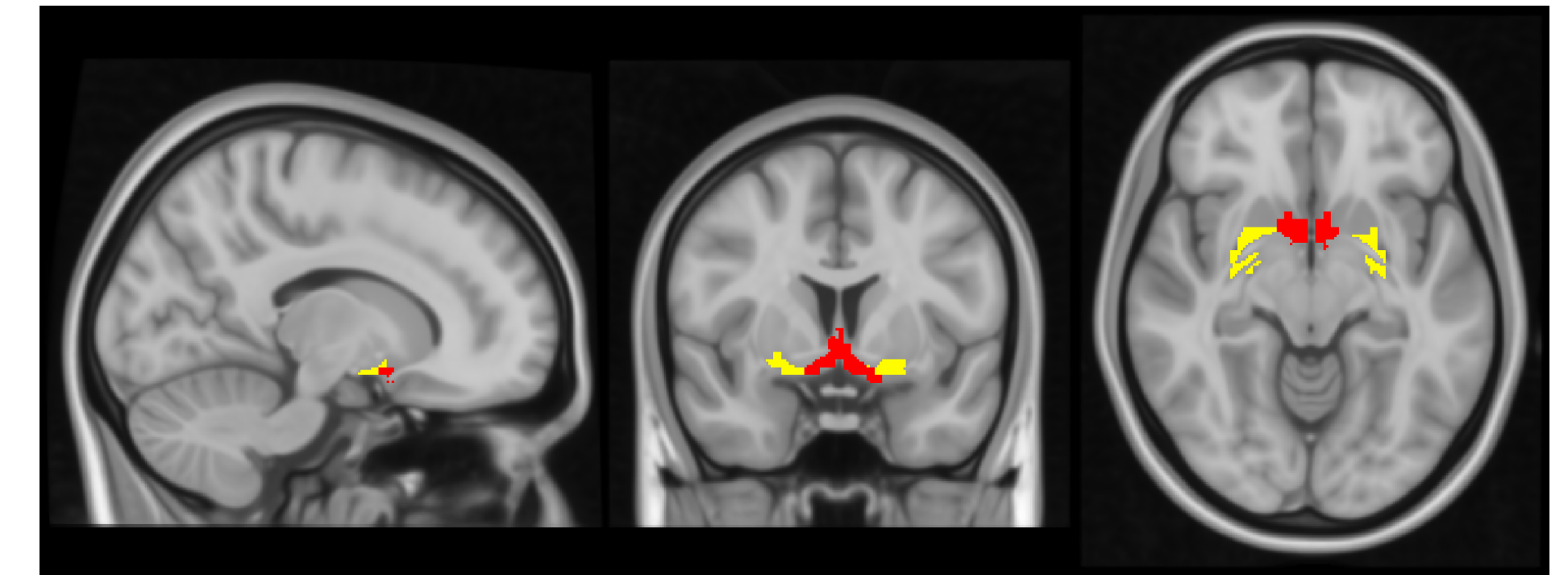
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Introduction

- **cholinergic basal forebrain nuclei (BFCN)** → cognitive functions (Eickhoff et al. 2022)
- BFCN follow a distinct topographical organization (Ballinger et al. 2016; Fritz et al. 2019)
anterior part (red) → hippocampus, amygdala, and entorhinal cortex
posterior part (yellow) → insula, thalamus, neocortex
- BFCN volumes are altered in schizophrenia (Avram et al. 2021)

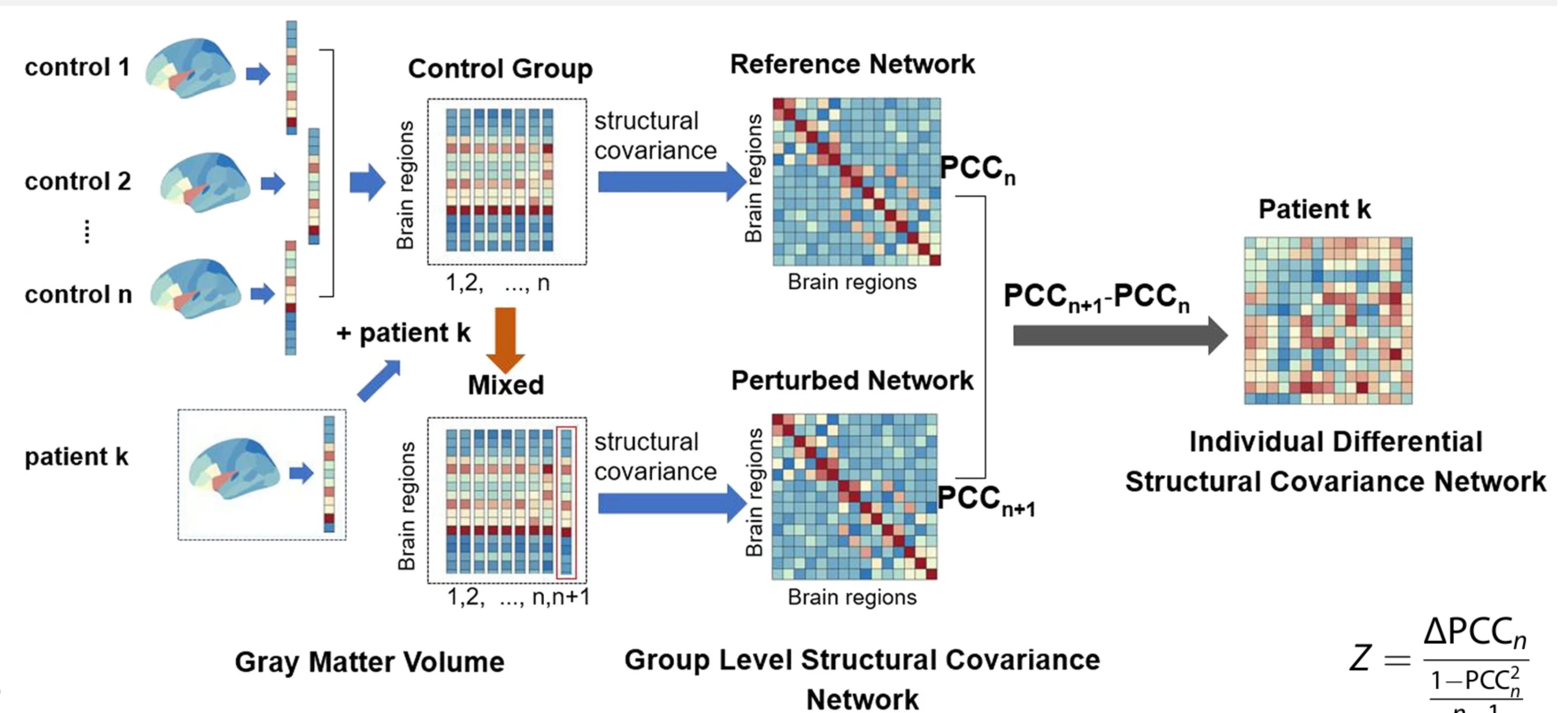


Hypothesis

Structural covariance between the BFCN and their cortical and subcortical projecting regions is disrupted in patients with schizophrenia

Methods

- 98 patients with schizophrenia, 97 healthy controls
- fsl anat of T1w from two sites (Munich, COBRE)
- NeuroHarmonize (Pomponio et al. 2020)
- cytoarchitectonical BFCN atlas
- subject-specific difference in structural covariance between two ROIs to the control network (Liu et al. 2021)
- Z-score of ΔPCC_n was calculated → p-value from Z-score (fdr) in each patients network: identify edges that were significantly different from the control network
→ Top34 edges (in terms of # of patients with significant change)
- Subtyping using k-means clustering → 2 clusters (silhouette analysis)

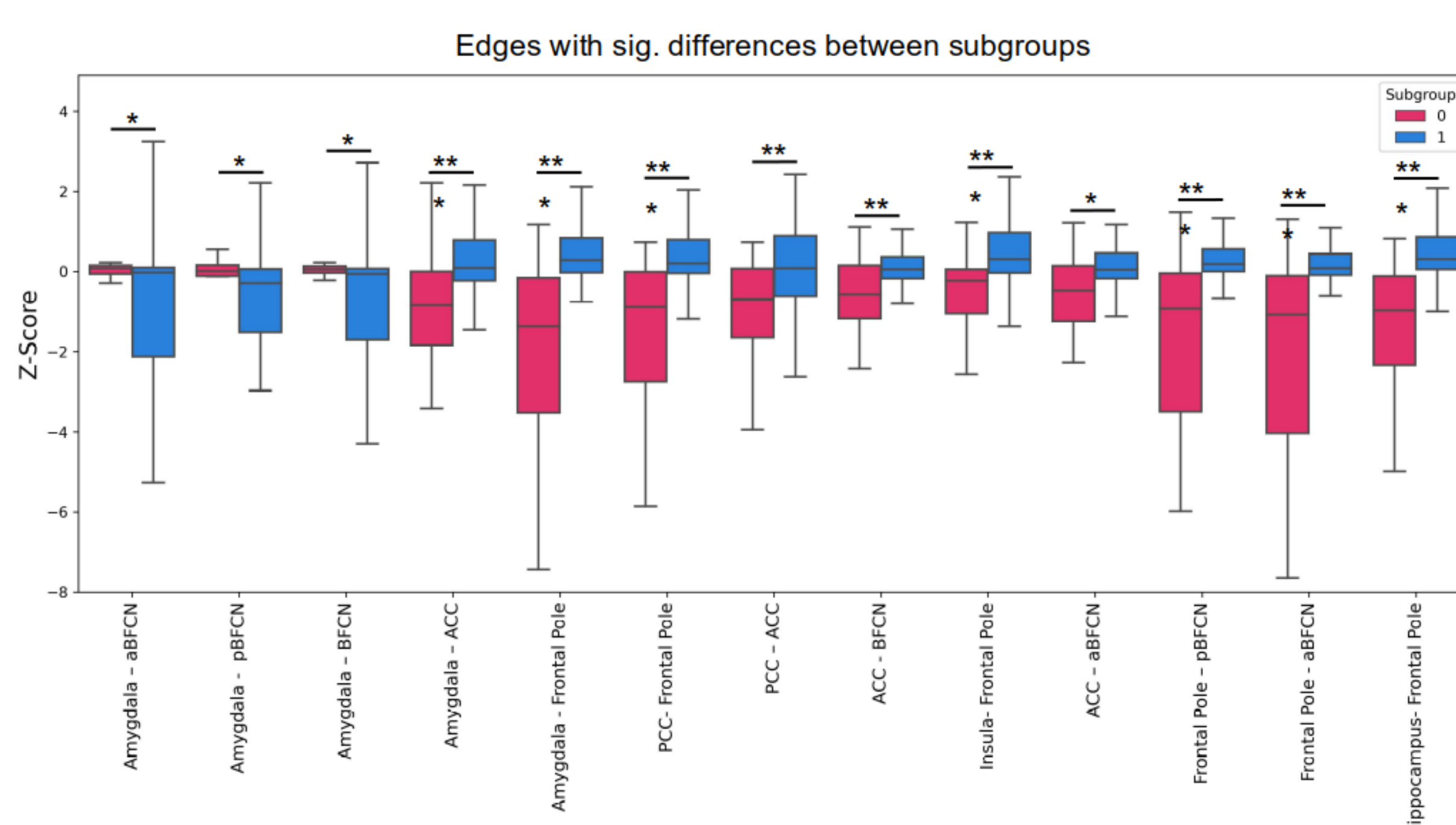


$$Z = \frac{\Delta PCC_n}{1 - \frac{PCC_n^2}{n-1}}$$

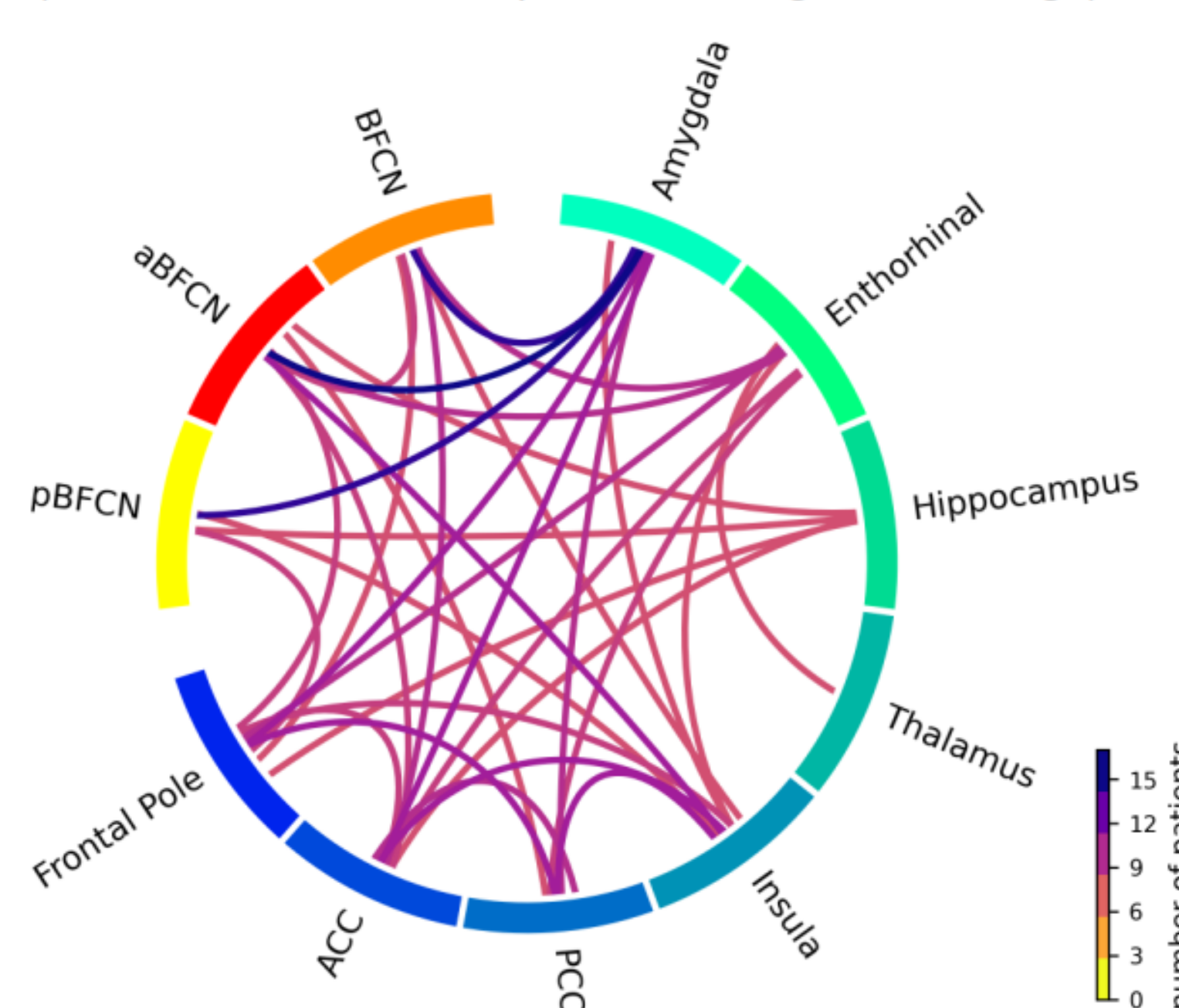
Liu et al. 2021

Results

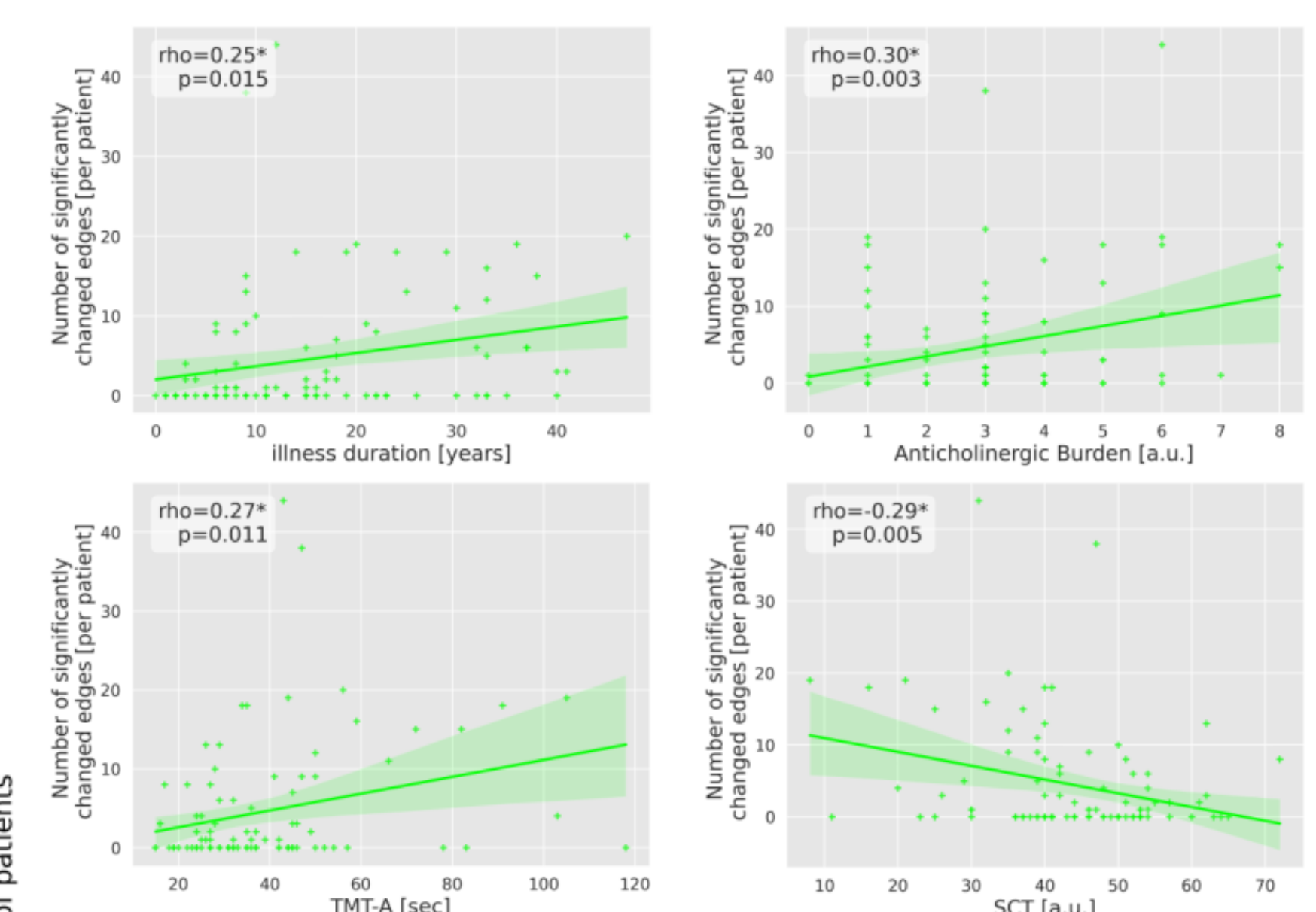
- **high heterogeneity** in IDSCN
- 55 covariance edges out of 121 were changed in at least 2 patients
- **Top34 edges** (6 - 17 patients with significant change in this edge)
- Number of changed edges correlates with illness duration, anticholinergic burden of medication, and cognitive impairments



Top34 edges
(in terms of the number of patients with significant change)



Associations of number of changed edges with clinical scores



- 2 patient **subgroups** based on their altered covariance (Z-scores) with different directions of altered covariance compared with controls
- Z-Scores of 13 edges differed significantly between subgroups
- Covariance edges in one subgroup were associated with changes in **BFCN/amygdala** interconnections
- **Cognitive performance** (phonemic fluency) was significantly reduced in BFCN/amygdala subgroup ($F_{1,66}=5.95$, $p=0.02$)

References

Avram, Mihai, Michel J. Grothe, Lena Meinhold, Claudia Leucht, Stefan Borgwardt, Felix Brandl, and Christian Sorg. 2021. "Lower Cholinergic Basal Forebrain Volumes Link with Cognitive Difficulties in Schizophrenia." *Neuropsychopharmacology* 46 (13): 2320–29.
Ballinger, Elizabeth C., Mala Ananth, David A. Talmage, and Lorna W. Role. 2016. "Basal Forebrain Cholinergic Circuits and Signaling in Cognition and Cognitive Decline." *Neuron* 91 (6): 1199–1218.
Eickhoff, Sofia, Leon Franzen, Alexandra Korda, Helena Rogg, Valerie-Noelle Trulley, Stefan Borgwardt, and Mihai Avram. 2022. "The Basal Forebrain Cholinergic Nuclei and Their Relevance to Schizophrenia and Other Psychotic Disorders." *Frontiers in Psychiatry* 13 (July).
Fritz, Hans Christian J., Nicola Ray, Martin Dyrb, Christian Sorg, Stefan Teipel, and Michel J. Grothe. 2019. "The Corticopit Organization of the Human Basal Forebrain as Revealed by Regionally Selective Functional Connectivity Profiles." *Human Brain Mapping* 40 (3): 868–78.
Liu, Zhaowen, Lena Palaniyappan, Xinran Wu, Kai Zhang, Jiangnan Du, Qi Zhao, Chao Xie, et al. 2021. "Resolving Heterogeneity in Schizophrenia through a Novel Systems Approach to Brain Structure: Individualized Structural Covariance Network Analysis." *Molecular Psychiatry* 26 (12): 7719–31.
Pomponio, Raymond, Guray Erus, Mohamad Habes, Jimit Doshi, Dhivya Srinivasan, Elizabeth Mamourian, Vishnu Bashyam, et al. 2020. "Harmonization of Large MRI Datasets for the Analysis of Brain Imaging Patterns throughout the Lifespan." *NeuroImage* 208 (March).