

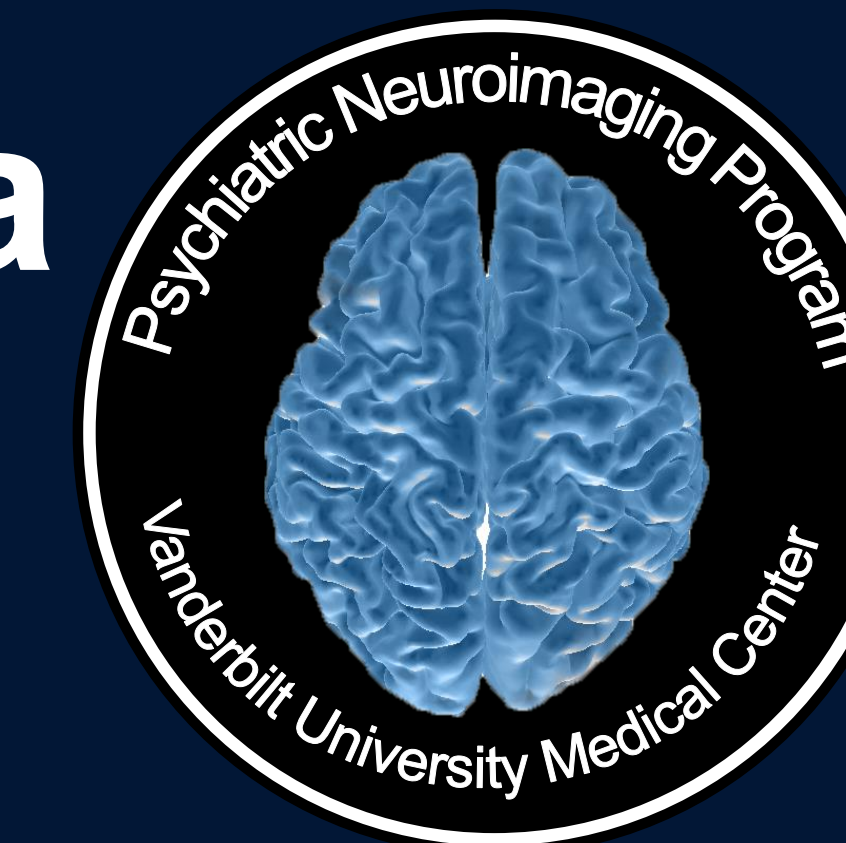


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Characterizing insula functional connectivity in schizophrenia

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Background

- The structure of the insula is abnormal in schizophrenia^{1,2,3}
- The insula is a heterogeneous structure comprised of separate sub-regions with distinct functions and connectivity profiles, including⁵:
 - Dorsal anterior- cognitive
 - Ventral anterior- affective
 - Posterior- sensorimotor
- Functional connectivity of the insula is altered in schizophrenia⁶; however, few studies have taken into account sub-regions, and associations with specific clinical symptoms have not been thoroughly characterized.
- We hypothesized: **schizophrenia patients would show altered functional connectivity in all insula sub-regions** and tested brain-behavior relationships in schizophrenia:
 - Hypo-connectivity of dorsal anterior insula → worse cognition**
 - Altered connectivity of ventral anterior insula → negative symptom severity**
 - Hyper-connectivity of posterior insula → positive symptom severity**

Methods

	HEALTHY CONTROLS N=196	SCHIZOPHRENIA N=191	STATISTIC
AGE	28.83 (10.33)	27.90 (10.22)	t(385)=.89, p=.373
GENDER (M/F)*	120/76	136/55	X ² =4.30, p=.038
RACE	139/46/11	131/54/6	X ² =7.40, p=.116
(WHITE/AA/OTHER)			
PERSONAL EDUCATION*	15.23 (2.12)	13.37 (2.20)	t(365)=8.25, p<.001
PARENTAL EDUCATION	14.42 (2.35)	14.74 (2.75)	t(342)=-1.19, p=.235
PANSS POSITIVE	--	17.46 (7.89)	--
PANSS NEGATIVE	--	15.68 (6.99)	--
PANSS GENERAL	--	31.33 (8.29)	--
CPZ-EQUIVALENT	--	420.33 (242.39)	--

Clinical Assessment:

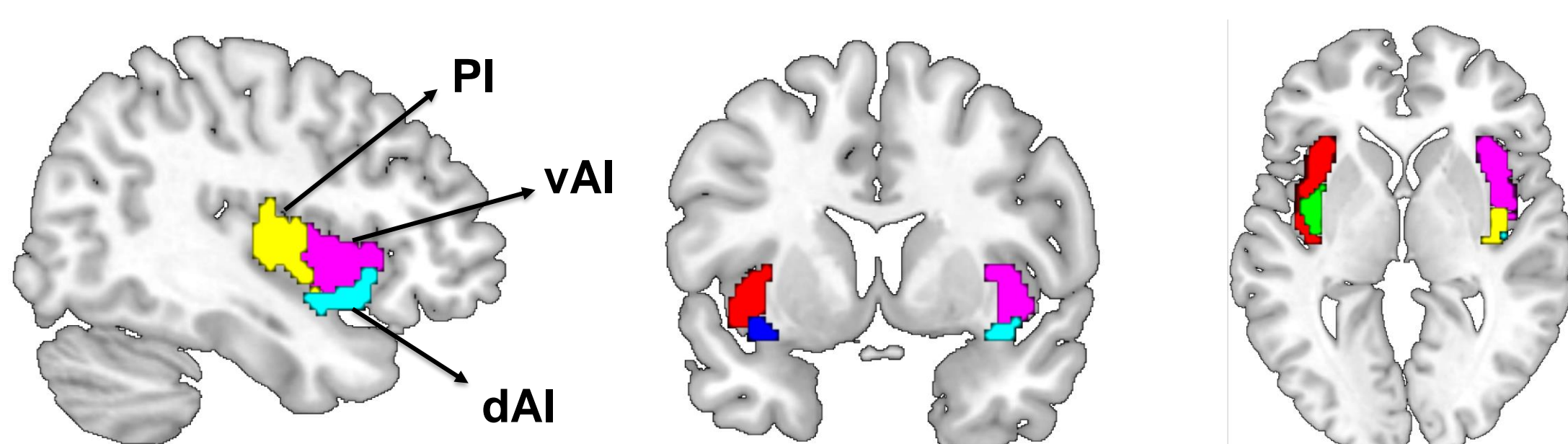
Cognitive Ability: Screen for Cognitive Impairment in Psychiatry (SCIP)

Negative Symptoms: Positive and Negative Syndrome Scale (PANSS)

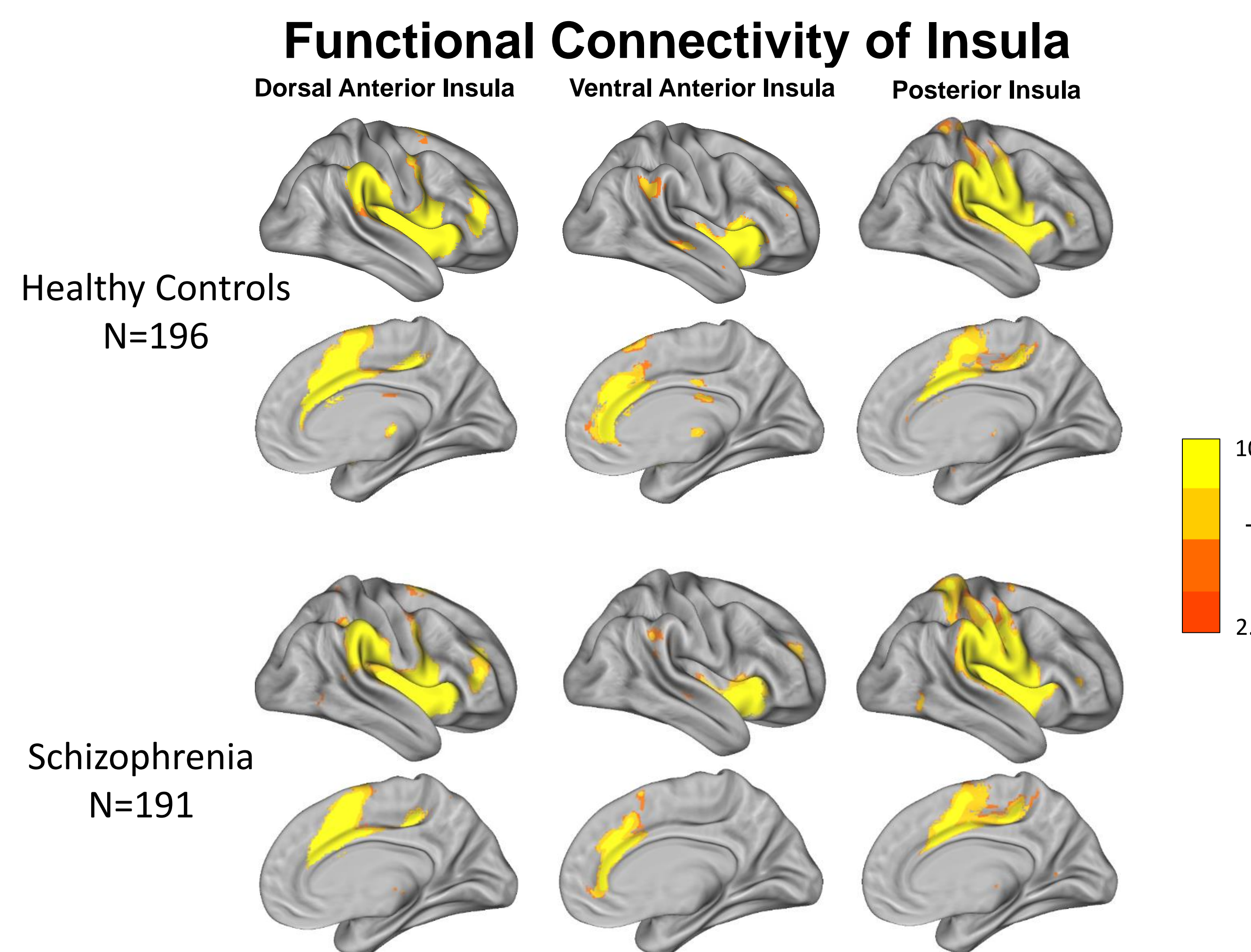
Positive Symptoms: Positive and Negative Syndrome Scale (PANSS)

Functional Connectivity: Whole Brain functional connectivity of *a priori* insula sub-divisions quantified during 7-10 minute resting-state fMRI scan. All results thresholded at whole-brain cluster-level corrected p<.05 for voxel-wise p=.001 (uncorrected).

Insula Sub-Region Seeds Used for Functional Connectivity Analysis

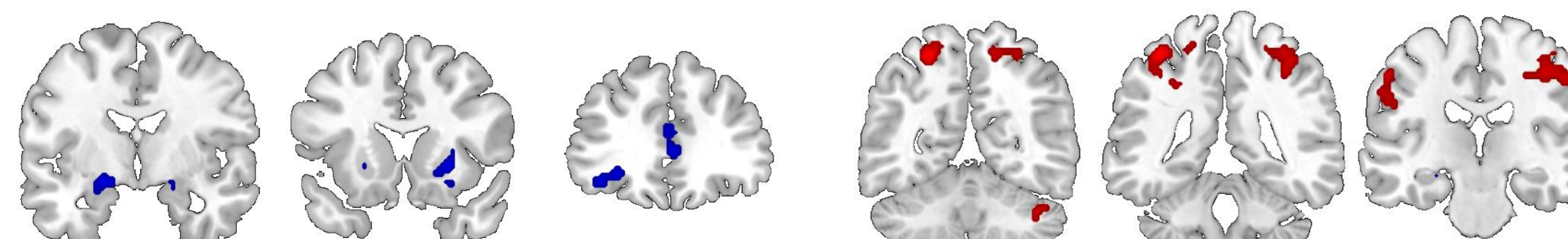


Results



Group Differences in Insula Connectivity

Dorsal Anterior Insula



- Healthy Controls > Schizophrenia**
- Bilateral Substantia Innominata
 - Dorsal Anterior Cingulate Cortex (dACC)
 - Orbitofrontal Cortex (OFC)

- Schizophrenia > Healthy Controls**
- Superior Parietal Lobe
 - Somatosensory Cortex
 - Cerebellum (Ventral Attention Network)
 - Visual Cortex

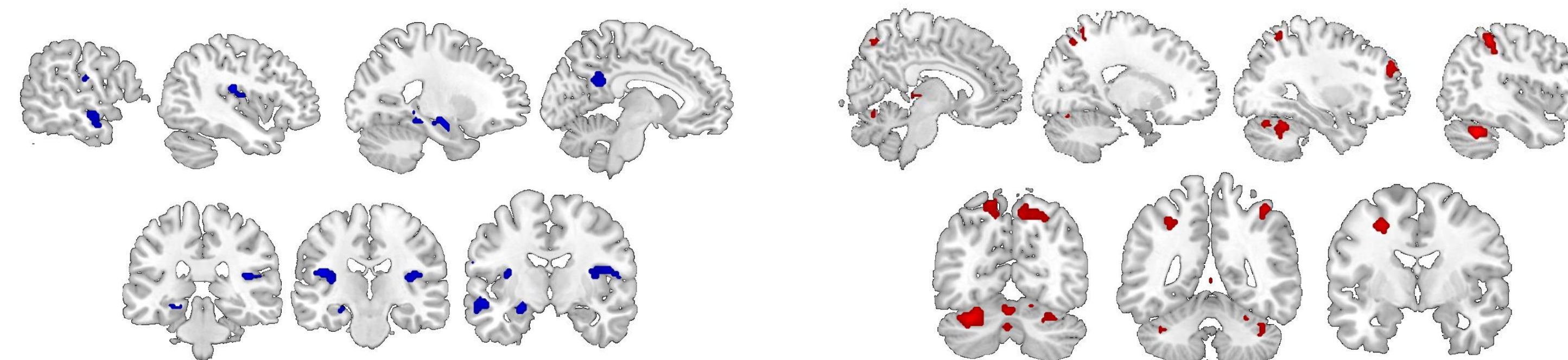
Ventral Anterior Insula



- Healthy Controls > Schizophrenia**
- Dorsal Anterior Cingulate Cortex (dACC)

- Schizophrenia > Healthy Controls**
- Cerebellum (Default Mode Network)
 - Precuneus

Posterior Insula

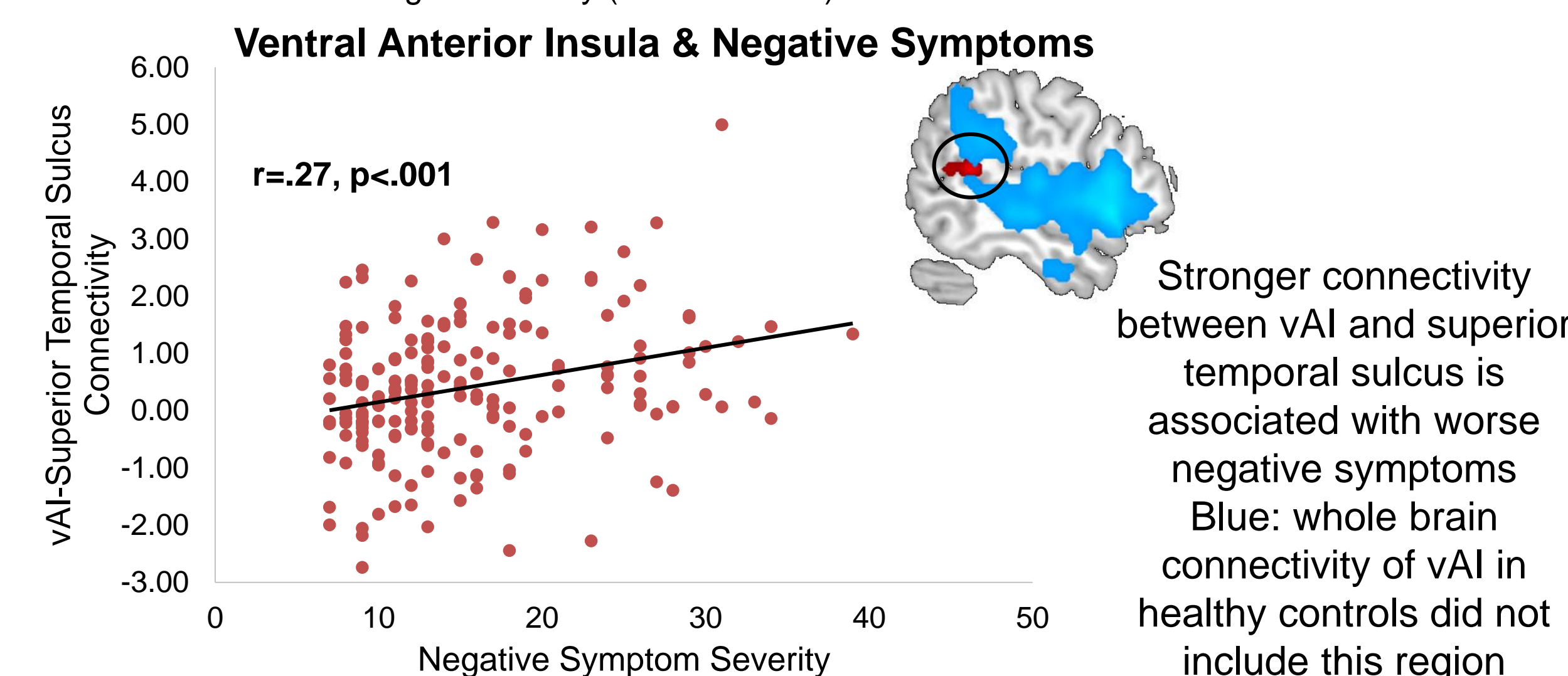
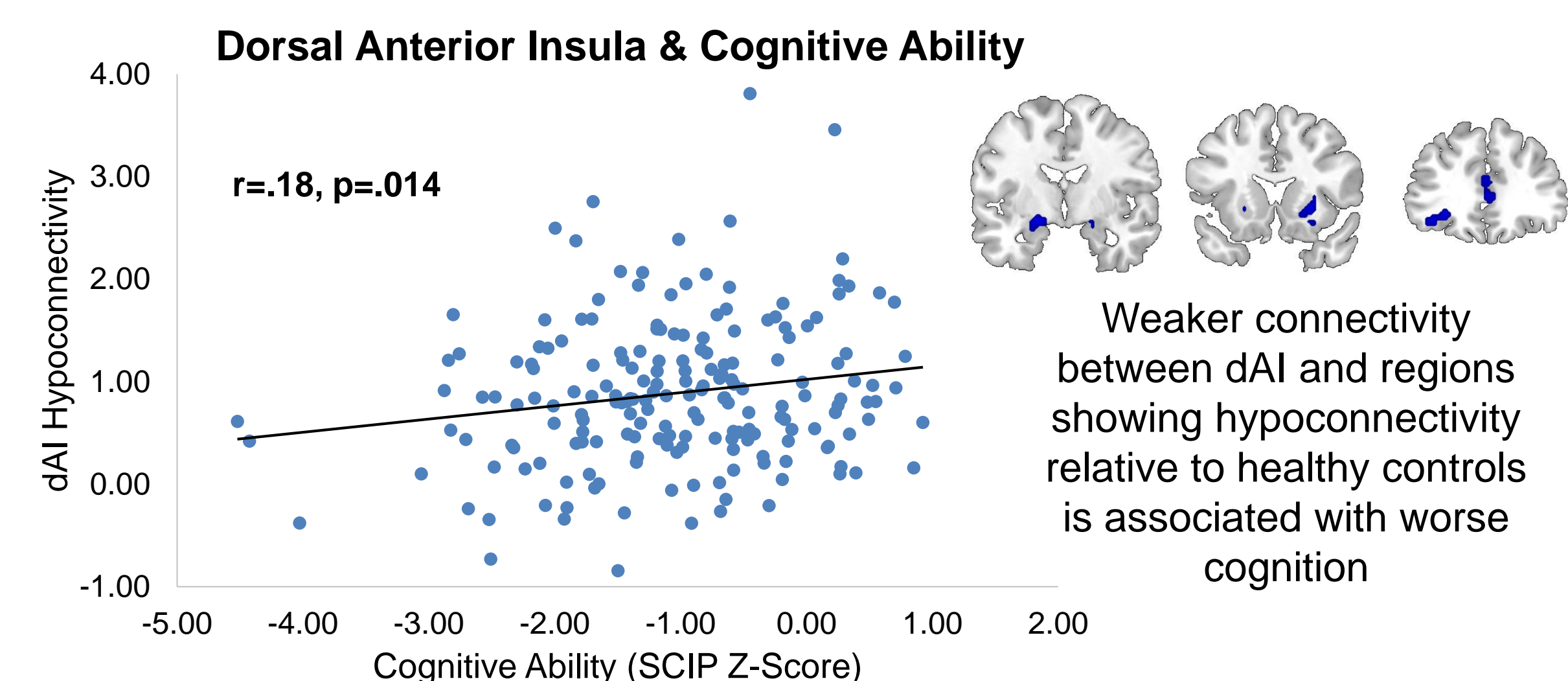


- Healthy Controls > Schizophrenia**
- Superior Temporal Gyrus
 - Hippocampus
 - Posterior Cingulate Cortex
 - Somatosensory Cortex
 - Posterior Insula

- Schizophrenia > Healthy Controls**
- Prefrontal Cortex
 - Frontal Eye Fields
 - Cerebellum (Ventral Attention Network)
 - Precuneus
 - Superior Parietal Cortex

Results

Brain-Behavior Relationships



Conclusions

- All sub-regions of the insula are altered in schizophrenia
- Consistent with a recent report on increased diversity of insula connectivity in schizophrenia⁶
 - PI hyperconnected to regions typically connected to dAI, involved in control of attention
 - dAI hyperconnected to regions typically connected to PI, involved in somatosensory processing
- Hypoconnectivity of dAI → worse cognitive ability
- Hyperconnectivity of vAI– superior temporal sulcus → worse negative symptoms
- Insula connectivity is clearly abnormal in schizophrenia, across all sub-regions, with most widespread alterations in PI. There is some specificity of sub-region connectivity alterations with clinical characteristics, but task-based studies may reveal these relationships more strongly.

References

- Shepherd, A. M., Laurens, K. R., Matheson, S. L., Carr, V. J., & Green, M. J. (2012). Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. *Neuroscience & Biobehavioral Reviews*, 36(4), 1342-1356.
- Spalthoff, R., Gaser, C., & Nenadić, I. (2018). Altered gyrification in schizophrenia and its relation to other morphometric markers. *Schizophrenia research*, 202, 195-202.
- Palaniyappan, L., Marques, T. R., Taylor, H., Handley, R., Mondelli, V., Bonaccorso, S., ... & David, A. S. (2013). Cortical folding defects as markers of poor treatment response in first-episode psychosis. *JAMA psychiatry*, 70(10), 1031-1040.
- Craig, A. D., & Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nature reviews neuroscience*, 10(1), 53-62.
- Uddin, L. Q., Kinnison, J., Pessoa, L., & Anderson, M. L. (2014). Beyond the tripartite cognition–emotion–interception model of the human insular cortex. *Journal of cognitive neuroscience*, 26(1), 16-27.
- Tian, Y., Zalesky, A., Bousman, C., Everall, I., & Pantelis, C. (2019). Insula Functional Connectivity in Schizophrenia: Subregions, Gradients, and Symptoms. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 4(4), 399-408.
- Deen, B., Pitskel, N. B., & Pelphrey, K. A. (2010). Three systems of insular functional connectivity identified with cluster analysis. *Cerebral cortex*, 21(7), 1498-1506.