

# ALTERED INTRINSIC ANTERIOR INSULAR CONNECTIVITY UNDERLYING SOCIAL IMPROVEMENTS IN YOUNGER CHILDREN WITH AUTISM SPECTRUM DISORDERS

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Target audience:

Neuroimaging researchers; ASD researchers.

Purpose:

To investigate the altered functional connectivity underlying social improvements using resting-state functional MRI in younger children with autism spectrum disorders (ASD).

Methods:

The current study is a pre-post within-subject design with ASD children. Written informed consent was obtained from all parents as approved by the Henan Provincial People's Hospital Subcommittee on Human Studies and conducted in accordance with the Declaration of Helsinki. To investigate how the intrinsic functional connectivity in ASD children (10 ASD children, aged 4 – 6 years old) changed as behavioral training reduced the severity of social impairment, we choose the right anterior insular (AI) as the seed region (Figure 1A) to perform a seed-based whole-brain connectivity analysis. Regions that show significantly altered connectivity using paired-t test ( $P < 0.05$ , AlphaSim corrected) are considered for the next step. Furthermore, we explored the relationship between the regional altered connectivity and the social improvements assessed by social response scores (SRS).

Results:

The paired t-test showed that the SRS scores are significantly reduced in ASD children post-training compared to the scores pre-training, which suggested significantly improved social ability in ASD children (SRS scores (raw): pre-training:  $116.7 \pm 18.33$  (mean  $\pm$  SD); post-training:  $98.8 \pm 24.11$  (mean  $\pm$  SD);  $t(9) = 3.73$ ,  $p = 0.002$ ). Compared with the connectivity before training, ASD children after training show significantly decreased right anterior insular cortex connectivity with the prefrontal cortex (PFC). Meanwhile, the connectivity with the occipital-temporal cortex significantly increases in ASD children after training ( $P < 0.05$ , AlphaSim corrected) (Figure 1B). Moreover, social response scores (SRS) is positively correlated with the altered connectivity of the right dorsolateral prefrontal cortex (DLPFC) ( $t(9) = 6.94$ ,  $p < 0.001$ , peak MNI coordinates: 30 46 28) and occipital-temporal cortex ( $t(9) = 11.83$ ,  $p < 0.001$ , peak MNI coordinates: 50 -58 14) (Figure 2).

Discussion:

In the current study, we measure right anterior insular (AI) whole-brain connectivity to assess the altered intrinsic functional connectivity in ASD younger children. The right anterior insular has bidirectional neural connections with the amygdala, anterior cingulate cortex, orbitofrontal cortex and superior temporal cortex<sup>1</sup>. And the right anterior insular is a core region of salience network (SN), which plays a causal role in coordinating networks<sup>2</sup>. Our results of the reduced functional connectivity between the right AI and PFC with social improvements, and the positive relationship between the altered connectivity and social improvements fit well with the theoretical accounts of greater connectivity in children with ASD<sup>3,4</sup>. Moreover, as the DLPFC is a core site for the central executive network (CEN) which is often activated in cognitively demanding tasks, and the SN plays a critical and causal role in activating the CEN during cognitive tasks<sup>2</sup>, the aberrant connectivity between the AI and DLPFC may also reflect abnormal interactions between networks in ASD. Meanwhile, with social improvements, the increased connectivity between the right AI and posterior brain areas including the temporal cortex, occipital regions and fusiform gyrus compared with functional connectivity pre-training in ASD children suggests the complementary role of lower-order perception information processing in the development of ASD<sup>5</sup>.

Conclusions:

ASD are characterized as neurodevelopmental disconnections between brain regions. The alterations in some of these regions are correlated with the progression of ASD. A reduction of intrinsic functional connectivity in prefrontal cortex with reduced social severity in ASD children in our study indicates that the functional connectivity with PFC in ASD children may be over-connected and behavioral training may induce PFC connectivity remediation. Meanwhile, an increased connectivity between right anterior insular with occipital-temporal region also suggests that the occipital-temporal cortex may play a compensatory role in ASD.

References:

1. Craig, A., How do you feel—now? the anterior insula and human awareness. *Nature Reviews Neuroscience*, 2009. **10**(1).
2. Sridharan, D., D.J. Levitin, and V. Menon. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the national academy of sciences*, 2008. **105**(34): p. 12569-12574.
3. Di Martino, A., et al., Aberrant striatal functional connectivity in children with autism. *Biological psychiatry*, 2011. **69**(9): p. 847-856.
4. Rudie, J.D. and M. Dapretto, Convergent evidence of brain overconnectivity in children with autism? *Cell reports*, 2013. **5**(3): p. 565-566.
5. Simmons, D.R., et al., Vision in autism spectrum disorders. *Vision research*, 2009. **49**(22): p. 2705-2739.
6. Kelly, C., et al., A convergent functional architecture of the insula emerges across imaging modalities. *Neuroimage*, 2012. **61**(4): p. 1129-1142.

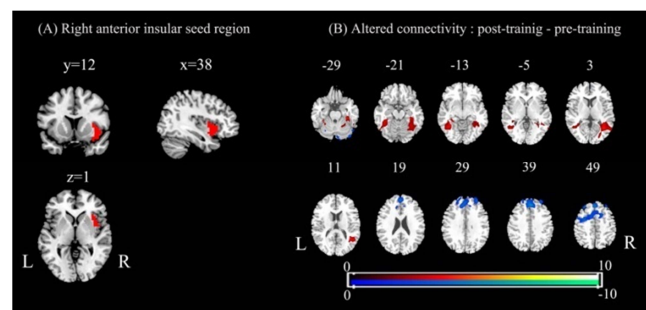
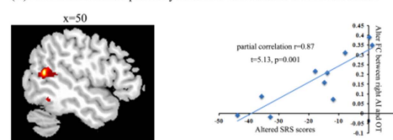


Figure 1. Right anterior insular cortex functional connectivity. (A) The right AI, derived as described in Kelly et al, 2012<sup>6</sup>, used as seed region and displayed on the 1mm MNI152 T1 standard brain. (B) Direct pre-post within subject paired-t test corrected for multiple comparisons using AlphaSim thresholded at  $p < 0.05$ . Post-training relative to pre-training showed stronger functional connectivity in bilateral fusiform gyrus, right temporal-occipital region, and less connectivity in dorsal anterior cingulate cortex, prefrontal cortex and supplementary motor cortex.

(A) Altered SRS score is positively correlated with altered FC in the OT cortex



(B) Altered SRS score is positively correlated with altered FC in DLPFC

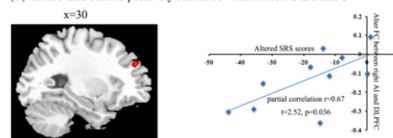


Figure 2. Multiple regression analysis of the altered connection maps and the altered SRS with age and SRS pre-training as covariates in the clusters that showed significantly group difference. Altered SRS score is positively correlated with altered functional connectivity in the occipital-temporal (OT) cortex,  $t(9) = 11.83$ ,  $p < 0.001$ , peak MNI coordinates: 50 -58 14 (A) and dorsolateral prefrontal cortex (DLPFC),  $t(9) = 6.94$ ,  $p < 0.001$ , peak MNI coordinates: 30 46 28 (B). The threshold was set at  $p = .05$  with a minimum cluster size of 50 voxels.