Atypical intrinsic functional connectivity of FFA is associated with social communication deficit in ASD

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INTRODUCTION

Background:

- Individuals with autism spectrum disorder (ASD) have difficulty in social interaction including deficits in gaze processing, face identification and recognition of face expression.
- Atypical activation patterns[1] to facial stimuli have been observed in individuals with ASD in the fusiform face area (FFA), part of the core system mediating face perception[2].

Objective:

- To examine intrinsic functional connectivity (iFC)* of the face processing network in children and adolescents with ASD using rFFA as seed region.
- To correlate iFC patterns with social communication deficits in individuals with ASD.

*iFC assesses the synchronicity of spontaneous low-frequency signal fluctuations between brain areas.

METHODS

Participants:

	ASD (n = 40)	TD (n = 42)	
Gender (M/F)	34/6	33/9	
Handedness (R/L)	33/7	36/6	
	M ± SD (range)	*M* ± SD (range)	*p* value
Age (years)	13.55±2.7 (7.4-17.7)	13.36±2.6 (8.1-17.6)	0.76
RMSD	0.06 ±0.03 (0.01-0.1)	0.06±0.03 (0.01-0.13)	0.84
Verbal IQ*	103.5±19.4 (70-147)	107.9±9.1 (87-127)	0.19
Non-verbal IQ*	106.5±18.1 (53-140)	105.1±11.2 (85-129)	0.69
Full-scale IQ*	105.1±17.8 (66-141)	107.1±9.4 (66-126)	0.53
ADOS2			
Social Affective	10.8 ± 4.2 (5-20)	n/a	--
Repetitive Behavior	3.3 ± 2.5 (0-12)	n/a	--
Severity	7.5 ± 2.1 (3-10)	n/a	--
Total	13.8 ± 4.4 (5-24)	n/a	--
SRS¥, Total	81.5±8.6 (58-94)	41.8±4.5 (35-50)	<0.000

* Wechsler Abbreviated Scale of Intelligence ¥ Social Responsiveness Scale

Data Acquisition:

- GE 3T MR750 scanner with an 8-channel head coil:
  - T1 weighted IR-SPGR anatomical sequence: 1mm^3 resolution.
  - 6:10min resting-state (eyes open), T2* weighted EPI sequence: 180 whole-brain volumes, TR = 2000ms; TE = 30ms; 3.4mm^3 isotropic resolution.

Data Processing and Analyses:

- Preprocessing: slice-time-, motion-, and field-map-correction; co-registration to T1 and normalization (to MNI) with FNIRT; spatial smoothing to a FWHM of 6mm; .008<*f*<.08Hz bandpass filter; 6 motion parameters, signal from WM and ventricles, and their first temporal derivatives as regressors; censoring time points with head motion >0.5mm.
- Seed (6mm-radius spheres), masked with a gray matter mask, was placed in right FFA (using coordinates reported in a task-activation study in adolescents[3]).
- Average BOLD time series extracted from rFFA seed were correlated with the time courses of all voxels in the brain; resulting statistical maps (Fisher r-to-z transformed) were entered into 1- and 2-sample t-tests to examine within- and between-group FC effects. Results were restricted to voxels with <20% nongray partial volume.

RESULTS

Within-group analysis:

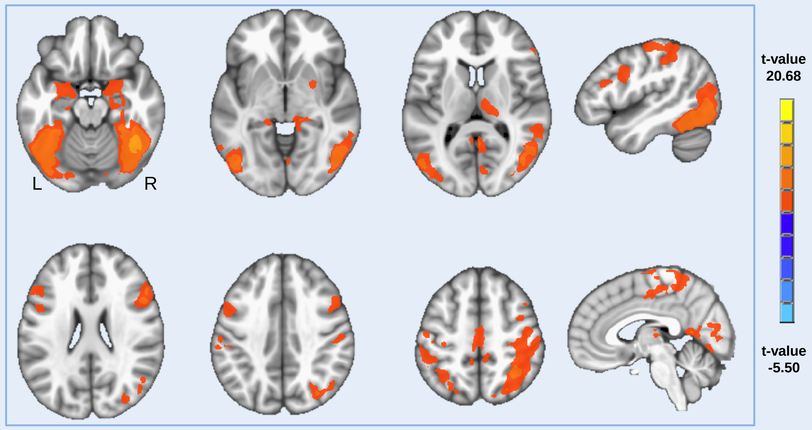

Figure 1. Resting-state iFC of the rFFA in ASD group spans the key face processing regions, including bilateral occipital-temporal visual regions, postcentral gyrus, limbic regions and more; TD group exhibited similar within-group connectivity patterns

Between-group comparison:

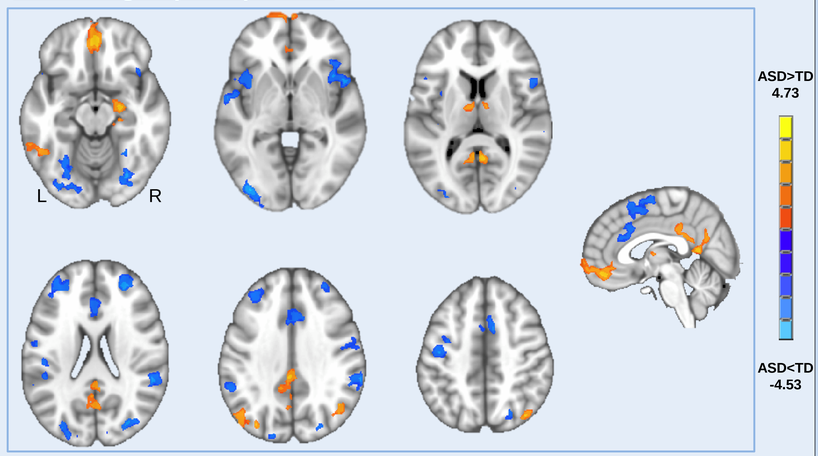

Figure 2. Between-group differences (ASD v. TD) in iFC

- Direct group comparisons (*p*<.05 corr.) revealed a mixed pattern of over- and underconnectivity in ASD:
  - ASD group showed widespread underconnectivity (ASD < TD) of the rFFA throughout cortex, including the middle frontal gyrus, bilateral Insula, SMA, and other regions.
  - Overconnected clusters (ASD > TD) mostly fell outside the canonical face processing network, including cortical (mid orbital gyrus, PCC, bilateral angular gyrus, left inferior temporal gyrus) and subcortical regions (right hippocampus and thalamus).

RESULTS (Cont.)

Behavioral correlation:

- Canonical and univariate correlation analyses were performed to probe the relationship between the over- and underconnectivity effects with clinical symptoms as measured by SRS Total scores.

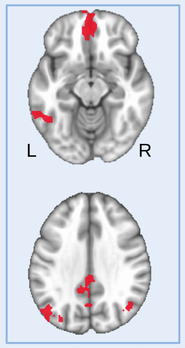

Figure 3: All cortical overconnectivity clusters

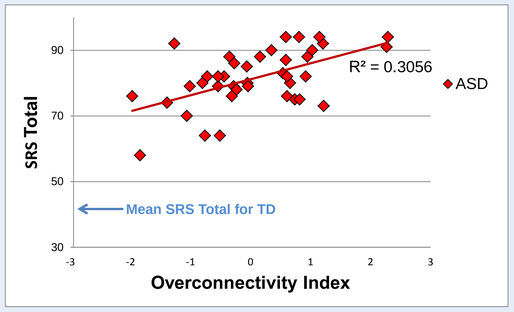

Figure 4: Significant correlation between the overconnectivity index captured by the overconnectivity index and SRS Total.

- Canonical correlation analysis on the cerebral overconnectivity clusters yielded one statistically significant canonical variate pair (R_c = 0.55, Wilk's λ = 0.02).
- The correlations between the cerebral overconnectivity clusters and the canonical variate (CV) suggest that the CV represents an **overconnectivity index** (the degree of the ASD>TD iFC effect) in ASD.
- Correlation analysis revealed a significant positive correlation between CV scores and SRS Total (*r* = 0.55, *p* < 0.001) in ASD group.
  - Those with greater social impairment had more excessive connectivity outside of face processing network (**Fig 3**).
- There were no behavioral correlations for underconnectivity clusters.

SUMMARY and CONCLUSIONS

- Whole-brain iFC analysis with rFFA as seed revealed a mixed pattern of both over- and underconnectivity in ASD.
- Increased connectivity was found between rFFA and regions outside of the canonical face processing network, suggesting that the face network is not well segregated from other brain networks in children and adolescents with ASD, consistent with the hypothesis of reduced network sculpting in ASD[4,5].
- The robust positive correlation between the strength of overconnectivity and ASD social symptom severity suggests that social impairment in individuals with ASD may be linked to inefficient face processing circuitry.

References:

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