Atypical Network Integration and Differentiation in Autism: An ICA Study Using Resting State fcMRI

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INTRODUCTION

Background:

- Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by sociocommunicative impairments, and repetitive and restricted behaviors and interests.
- Converging evidence suggests that the developmental abnormalities in ASD may be due to atypical brain network connectivity.
- In typical development, functional brain networks show both increasing within-network integration and between-network differentiation with age, corresponding to the growing cortical and functional specialization of neural networks across development.
- Recent findings suggest that aberrant connectivity in ASD might be due to reduced connectivity within neurotypical networks and increased connectivity with extraneous regions that are not typically part of the network of interest.[1,2]

Objective:

- To evaluate network integration and differentiation in children and adolescents with ASD, as compared to age-matched typically developing (TD) controls, across a large number of intrinsic networks, utilizing independent component analysis (ICA) applied to resting state fMRI data.

METHODS

Participants:

- Children and adolescents with ASD and TD controls, ages 7-17 years:

	ASD† (n = 40)	TD§ (n = 40)	
Gender (M/F)	34/6	32/8	
Handedness (R/L)	33/7	32/8	
	M ± SD (range)	*M* ± SD (range)	*p*-value
Age (years)	14.0 ± 2.6 (7.2-17.8)	13.4 ± 2.8 (8.0-17.6)	0.34
RMSD (1mm)	0.06 ± 0.03 (0.02-0.15)	0.05 ± 0.03 (0.02-0.12)	0.18
Verbal IQ*	104.6 ± 18.4 (70-147)	109.2 ± 10.3 (87-132)	0.18
Non-verbal IQ*	106.7 ± 17.2 (53-140)	108.1 ± 12.3 (87-133)	0.67
Full-scale IQ*	106.7 ± 16.3 (66-141)	108.9 ± 10.7 (88-137)	0.48
ADOS			
Social Interaction	8.3 ± 2.9 (3-14)	n/a	
Communication	3.8 ± 1.9 (0-9)	n/a	
Repetitive Behavior	2.0 ± 1.3 (0-4)	n/a	
ADI-R			
Social Interaction	18.4 ± 5.6 (6-28)	n/a	
Communication	13.7 ± 5.5 (2-24)	n/a	

* IQ assessed with Wechsler Abbreviated Scale of Intelligence (WASI-II).

† Diagnoses established using Autism Diagnostic Observation Schedule (ADOS[3]), Autism Diagnostic Interview-Revised (ADI-R[4]), and clinical judgment according to DSM-IV criteria.[5]

§ TD participants had no family history of ASD, no personal history of neurologic or psychiatric conditions.

MRI Data Acquisition:

- GE 3T MR750 scanner with an 8-channel head coil:
  - T1 weighted SPGR anatomical sequence: 1mm^3 resolution.
  - 6:10min resting state (eyes open) EPI sequence: 185 whole-brain volumes, TR = 2000ms; TE = 30ms; 3.4mm^3 isotropic resolution.

MRI Data Processing and ICA 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 10mm; .008<f<.08Hz bandpass filter; 16 nuisance regressors: 6 motion parameters, WM and CSF signal, and their respective derivatives (no censoring).
- *Independent Component Analysis (ICA):*
  - ICA was performed on a low-motion subset of 30 ASD and 30 TD participants from publicly available ABIDE dataset[6] (matched to the local dataset on age, motion, and IQ), using MELODIC in FSL.
  - The dual regression (DR) algorithm implemented in MELODIC was applied to estimate subject-specific spatial maps corresponding to the group-level template ICs (or functional networks) derived from the ABIDE data.
- *Network integration (NI)* was assessed with IC *Z*-scores (average *Z*-scores across all IC voxels), reflecting the *within-network connectivity strength* for each participant. Group NIs were compared with 2 sample t-tests (AFNI *3dttest++* controlling for motion).
- *Network differentiation (ND)* was assessed by correlating the time courses associated with each IC with each other, reflecting the *between-network* pairwise connections.

RESULTS

I. Within-Network Connectivity / Network Integration

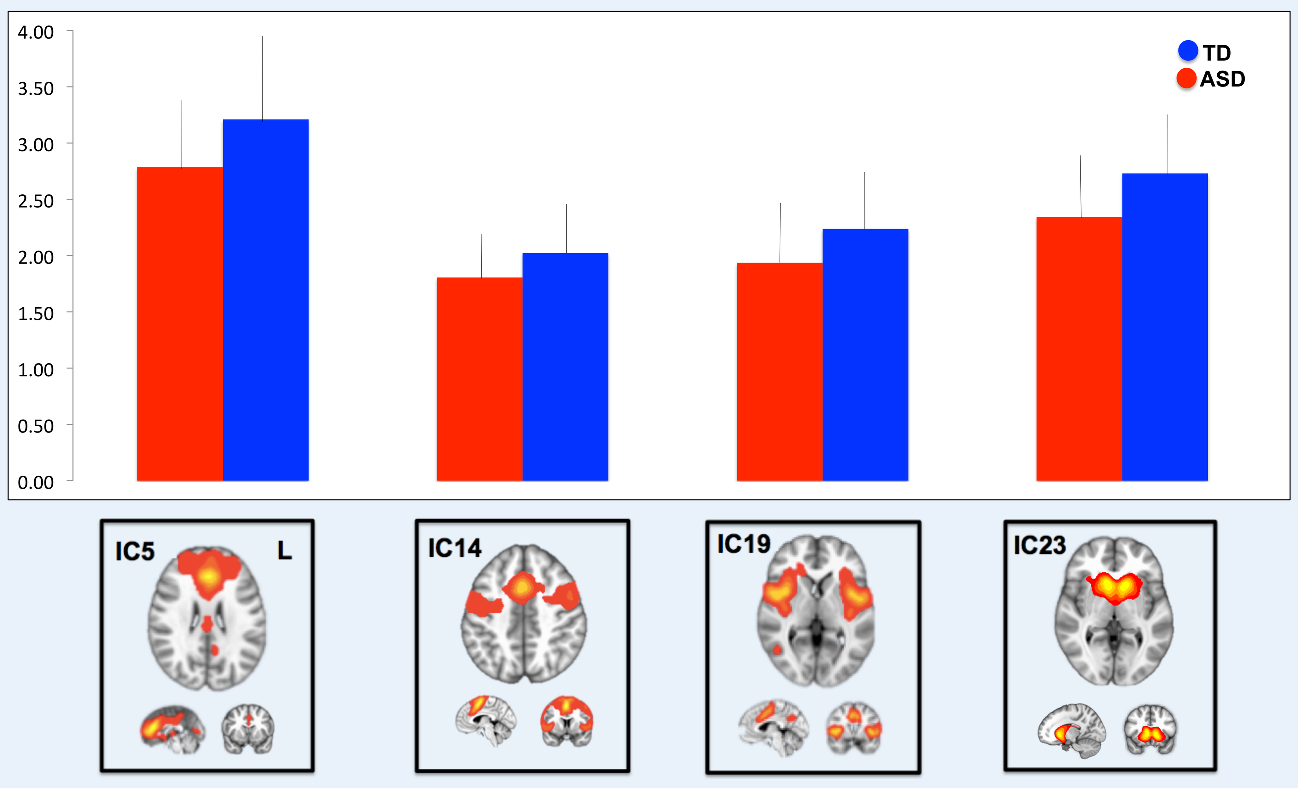


Figure 1. Of the 30 ICs of interest (representing functional networks), four showed significant group differences in within-network connectivity, after controlling for motion (all ASD < TD). No TD > ASD effects were observed in any of the networks examined. Three most informative orthogonal slices for each IC are displayed in standard MNI space. ***IC5*** represents an executive control network including medial prefrontal cortex and the anterior cingulate cortex. ***IC14*** represents a motor network including motor cortex, basal ganglia, and cerebellum. ***IC19*** represents a salience sub-network including the insula cortex and the anterior cingulate cortex. ***IC23*** consists primarily of the basal ganglia. Error bars denote 1 SD.

Links between Network Integration and Behavior:

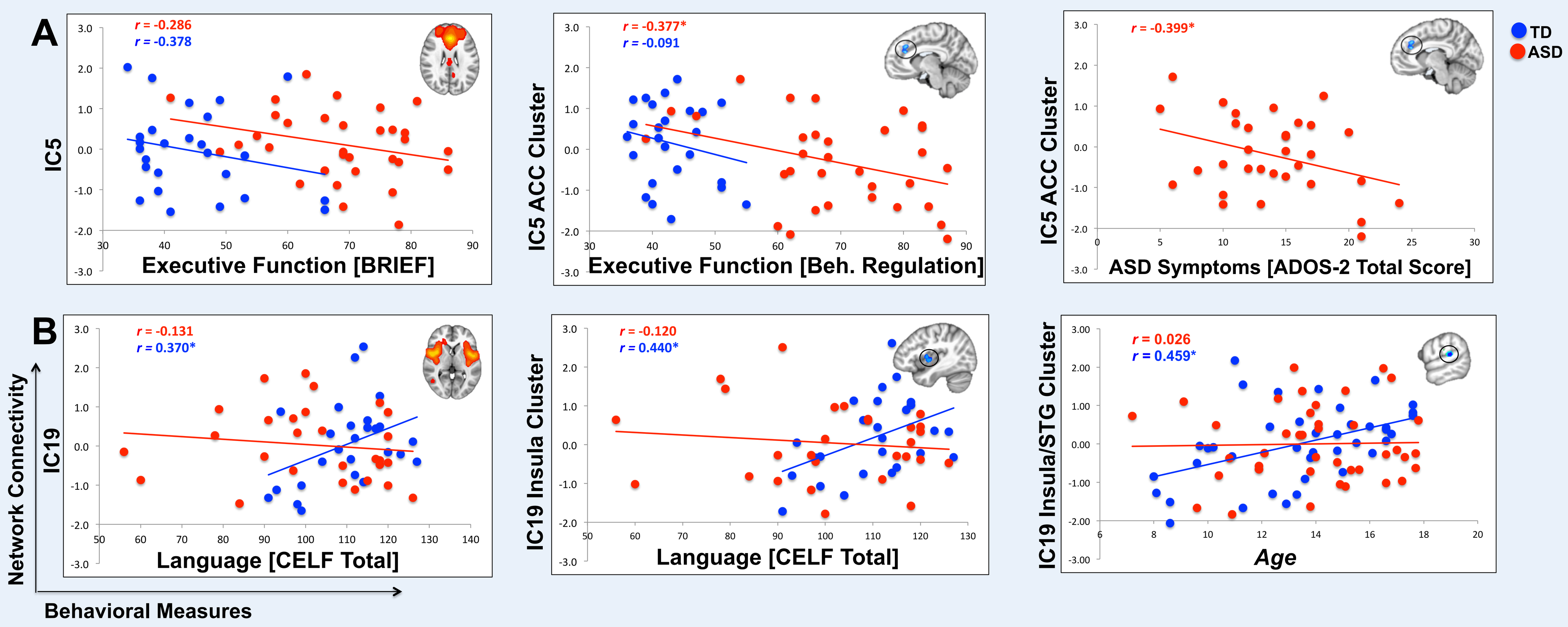
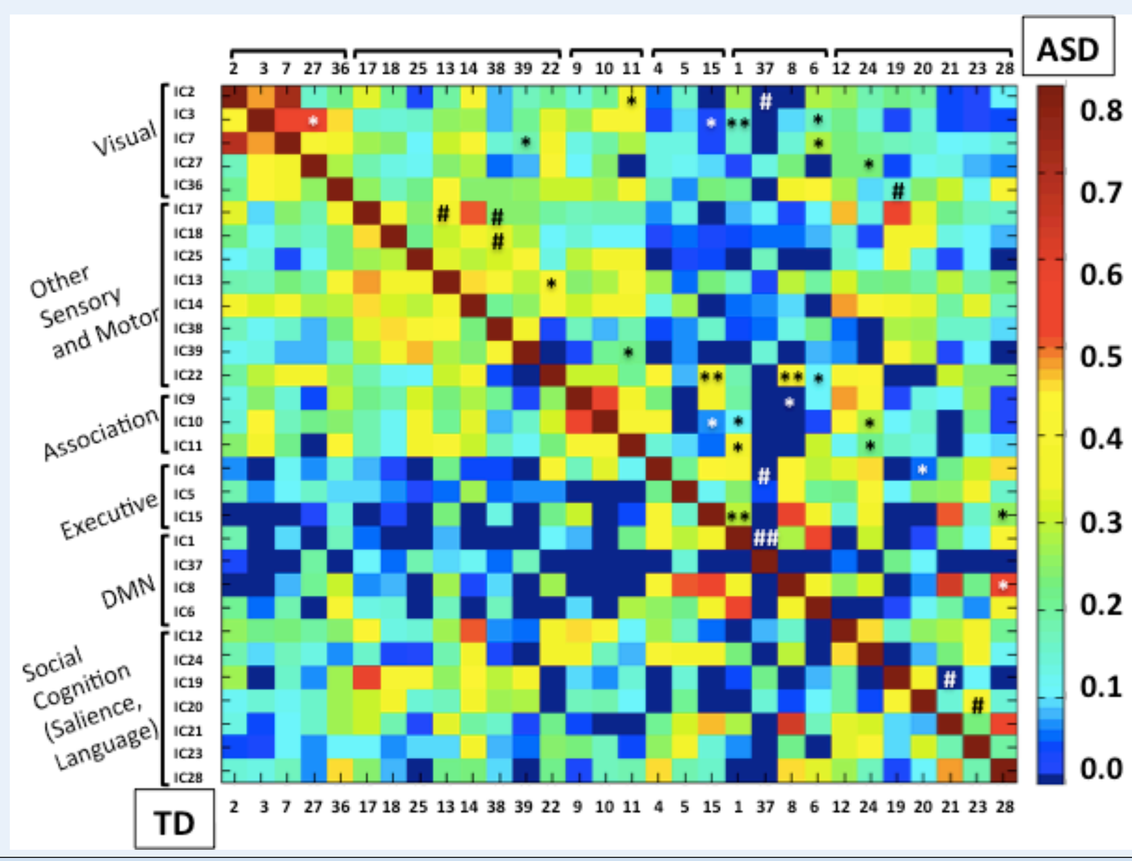


Figure 2. Relationships between diagnostic/behavioral measures and network integration (after partialling out effect of motion [RMSD] on connectivity values). **A.** Executive Control network (IC5) was linked to an executive functioning measure (BRIEF), in both groups, with *weaker integration associated with more impaired executive function* (greater scores on BRIEF signify impairment). Correlations between the ACC cluster accounting for the significant ASD < TD effect and executive functioning (BRIEF – BRI) and ASD symptoms (ADOS-2 scores) in ASD point to links between *greater ASD symptoms* and *weaker executive control network integration*. **B.** Greater integration of the insula / ACC network (IC19) was linked to better language skills (CELF Total score) in the TD group, but showed no such relationship (a negative trend) in the ASD group, suggesting atypical role of this network network in language in ASD. An insula/STG cluster accounting for the ASD < TD effect was correlated with age in the TD group, suggesting that this network continues maturing in typical development across adolescence, the effect not seen in ASD. Asterisks (*) indicate *p* < 0.05.

II. Between-Network Connectivity / Network Differentiation

Figure 3. Pairwise network correlation matrix, with ASD between-network correlations summarized in the upper triangle and TD – in the lower triangle. Both axes represent the 30 networks of interest (ICs), organized by domains; pixel color and color bar represent the magnitude of correlation coefficient.
* indicate network pairs with significantly greater connections in ASD (* and ** indicate *p* < 0.05 and *p* < 0.01, respectively), while # denote network pairs with significantly weaker connections in ASD (# and # # indicate *p* < 0.05 and *p* < 0.01, respectively). Colors of * and # (white and black) are not meaningful and are used for better display contrast.
Overall, 31 network pairs showed significant differences between groups. Of those, 23 network pairs showed greater between-network connectivity in ASD (* and **), e.g., overconnectivity between visual and executive networks, executive control and fronto-parietal attention networks, among others. Notably, a subcomponent of the DMN network (IC37) was disproportionally de-coupled (showed weaker connectivity in ASD, relative to the TD group) from other networks, including visual and executive control networks.



SUMMARY and CONCLUSIONS

- Out of the 50 ICs derived from ICA, 30 were non-artifactual networks of interest. Network integration and differentiation analyses were run on all 30 components, along with correlations with behavioral and diagnostic measures.
- In ASD, network integration, or within-network connectivity, was significantly *weaker* in 4 (out of 30) functional networks (executive control, motor, salience subnetwork and basal ganglia networks). No within-network overconnectivity (ASD>TD) effects were observed.
  - Weaker network integration of the executive control network (IC5) observed in ASD was associated with executive function impairments and greater ASD symptoms.
  - Greater integration of the salience subnetwork consisting of the insula and ACC (IC19) was associated with better language scores in the TD group. This relationship was not observed in ASD, in the face of significantly lower connectivity in this network. Correlation with age observed in TD in this network suggests that this neural system continues maturing throughout adolescence in typical development, but such developmental trajectory was absent in ASD.
- Network differentiation analyses revealed primarily greater between-network connectivity in ASD, suggesting reduced segregation between functional networks in children and adolescents with ASD.
- Overall, we observed a pattern of underconnectivity within, but overconnectivity between functional networks, suggesting that many brain networks are less integrated and less functionally segregated from each other in children and adolescents with ASD. This pattern is in contrast with typical development and reflects aberrant network maturation,[1,2] whereby excessive out-of-network functional connections strengthen secondary to inefficiency of the primary neural circuits.

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This study was supported by NIH R01-MH081023 (RAM) and K01-MH097972 (IF).

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