Links between thalamocortical and cerebrocerebellar intrinsic functional connectivity in autism

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Introduction

- Previous studies on autism spectrum disorders (ASD) have indicated atypical functional connectivity between cerebral cortex and deep structures such as the thalamus and cerebellum.[1, 2, 3]
- These studies report mixed patterns of over- and underconnectivity for thalamocortical [1,3] (TC) and cerebro-cerebellar [2] (CC) connectivity in ASD; however, they suggest similar domain-specific patterns of stronger iFC for sensori-motor (SM) and weaker iFC for supramodal (SU) connections.
- The present study tested whether differential effects for SM and SU domains might be linked between TC and CC iFC.

Methods

Data Acquisition

- Data were acquired on a 3T GE MR750 scanner with an 8-channel head coil.
- 42 ASD and 43 typically developing (TD) participants ages 7-17 years, completed a 6:10 minute eyes-open resting state scan (185 whole-brain volumes; TR: 2000ms; TE: 30ms; slice thickness: 3.4mm).
- Subjects were matched (at group-wise level) on parameters such as motion, age, verbal IQ, and nonverbal IQ.

Group	RMSD	Age	Verbal IQ	Nonverbal IQ
ASD	0.08 (.06)	13.83 (2.79)	104.35 (17.71)	105.5 (15.46)
	p = 0.75	p = 0.56	p = 0.54	p = 0.87
TD	0.07 (.05)	13.5 (2.67)	106.2 (13.5)	106.02 (14.56)

Table 1: Mean(SD) demographic information. P values from 2-tail between group t-tests

Data Preprocessing

- Data were preprocessed and analyzed using AFNI.
- Pipeline consisted of field map, slice-time, and motion correction; .01Hz < *f* < .1Hz temporal bandpass filtering; normalization to MNI space; nuisance regression including 6 rigid-body motion parameters and time series from trimmed ventricles and white matter. Time points exceeding 0.5mm displacement, along with 4 subsequent timepoints were censored.

Regions of Interest

- All ROIs were derived from atlases available in FSL Toolbox. Thalamic and cerebellar masks came from the Harvard-Oxford atlas. Cortical ROI masks (36 for each hemisphere) were derived to cover the entire cortex and obtained using both Jülich-Histological & Harvard-Oxford atlases.
- Available ROIs from the Jülich Histological atlas, which is based on cytoarchitectonic probability, were complemented by ROIs from the Harvard-Oxford atlas, for complete coverage of cerebral cortex.
- After extraction from atlases, masks were binarized and multiplied by a grey matter mask to exclude white matter. Fslmaths was used to control for overlap between ROIs, as well as to segregate Harvard-Oxford atlases into right and left segments. Particluarly large ROIs (>2000 voxels) were further segregated into subdivisions.

Intrinsic Functional Connectivity

- In a first-pass analysis, average time series from each ROI were correlated with time series from ipsilateral thalamus (TC) and contralateral cerebellum (CC).
- Raw correlations (described immediately above) were then converted into z-scores via Fisher transform.
- Subsequently, left and right z-scores were averaged together, making a total of 36 CC and 36 TC indices. Figure 2 shows the correlations between each of these averaged Z-scores.

Results

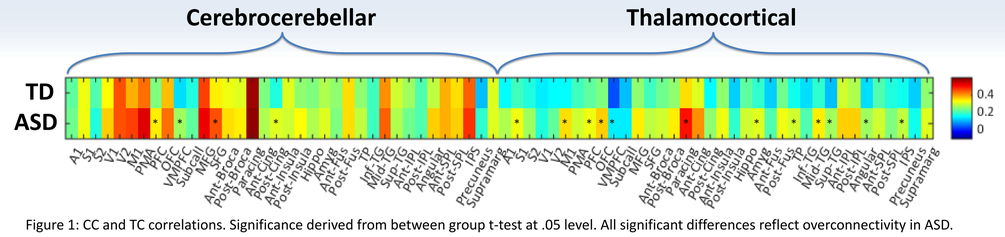

Figure 1: CC and TC correlations. Significance derived from between group t-test at .05 level. All significant differences reflect overconnectivity in ASD.

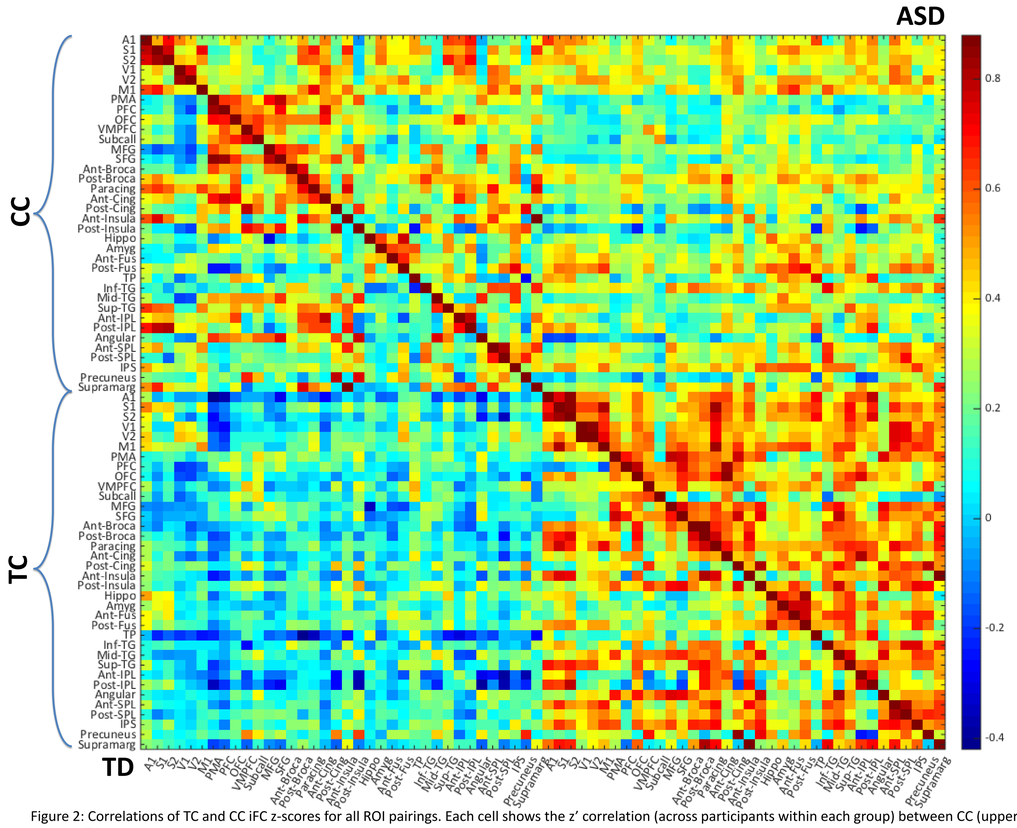

Figure 2: Correlations of TC and CC iFC z-scores for all ROI pairings. Each cell shows the z' correlation (across participants within each group) between CC (upper rows) or TC (lower rows) for two ROIs (as listed on x and y axes).

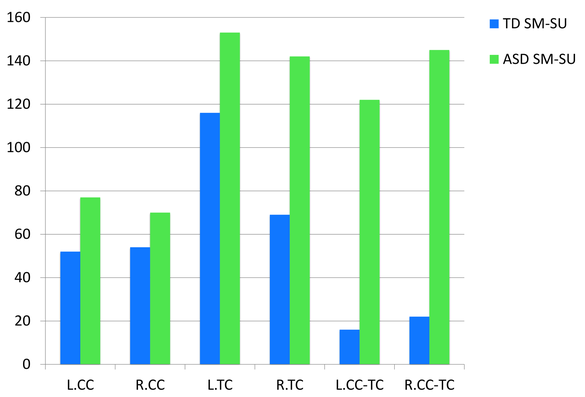

Table 2: Number of significant inter-domain (i.e. sensorimotor to supramodal) correlations within each group, separate by hemispheres. ASD group shows singificantly more inter-domain correlations that TD (p<.05).

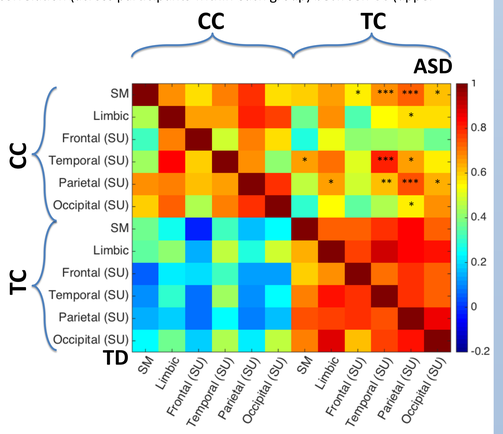

Figure 3: Z' correlations averaged within sensorimotor, limbic, and several supramodal domains. Significance derived from between group Z-test (* p < .05; ** p < .01; *** p < .005).

Results (cont.)

Structure Matrix	
TC Temporal SU	0.486
TC Frontal SU	0.386
TC Limbic SU	0.367
TC Parietal SU	0.362
TC SM	0.33
CC Limbic	0.3
CC Frontal SU	0.285
TC Occipital SU	0.189
CC Occipital SU	0.168
CC Parietal SU	0.083
CC SM	0.061
CC Temporal SU	0.03

Table 3: Structure matrix for correlations of connectivities with DFA derived linear discriminant function (LDF). LDF represents moderate effect size (.333) and correctly selects group membership at 78.8% (p < .002).

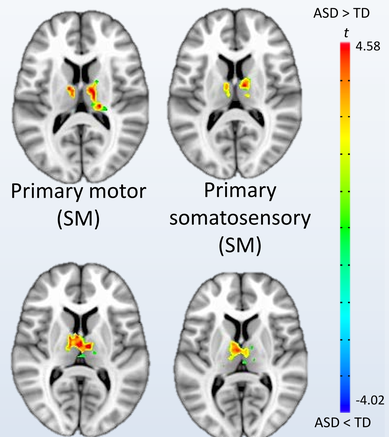

Figure 4: Between-group differences on cortical seed-based TC and CC connectivity analyses.

Conclusions

- Findings suggest that atypical TC and CC connectivity in ASD is not governed by a single principle of increased sensorimotor vs. reduced supramodal iFC.
- In general, ASD brains show an increase in inter-network (thalamocortical with cerebrocerebellar) correlations
- This effect was found both within-domain (e.g., temporal SU and parietal SU) and between domains (e.g. SM to temporal and parietal SU)
- These findings suggest an overall reduced differentiation
  (i) between cerebral cortical regions with respect to their thalamocortical and cerebrocerebellar connectivity, and
  (ii) between thalamic and cerebellar circuits themselves.
- This indicates that the previous evidence of reduced network differentiation or segregation in cerebral cortex[4,5] also applies to 'deep' connectivity with thalamus and cerebellum.
- Findings from an exploratory discriminant function analysis suggest that thalamocortical connectivities generally discriminate more robustly between ASD and TD groups than cerebrocerebellar connectivities.

References

1. Nair A, Treiber JM, Shukla DK, Shih P, Müller R-A. (2013). Impaired thalamocortical connectivitin autism spectrum disorder: a study of functional and anatomical connectivity. *Brain* 136, 1942-1955.
2. Khan AJ, Nair A, Keow CL, Dako M, Lincoln A, Müller R-A (2015). Cerebro-cerebellar resting state functional connectivity in children with autism spectrum disorder. *Biological Psychiatry* 78, 625-634.
3. Nair A, Carper RA, Abbott AE, Chen CP, Solders S, Nakutin S, Datko M, Fishman I, Müller R-A (2015). Regional specificity of aberrant thalamocortical connectivity in autism. *Human Brain* Mapping. E-pub.
4. Rudie JD, Shehzad Z, Hernandez LM, Colich NL, Bookheimer SY, Iacoboni M, Dapretto M (2012): Reduced functional integration and segregation of distributed neural systems underlying social and emotional information processing in autism spectrum disorders. *Cereb Cortex* 22, 1025-1037.
5. Shih P, Keehn B, Oram JK, Leyden KM, Keown CL, Müller R-A (2011): Functional differentiation of posterior superior temporal sulcus in autism: A functional connectivity magnetic resonance imaging study. *Biol Psychiatry* 70, 270-277.

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