Dynamic systems imaging in adolescents with ASD of lower and higher cognitive ability

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Introduction

Abnormal connectivity is a key component of the neural basis of ASD. Current evidence suggests that both under- and over-connectivity may be characteristic of the autism phenotype. Less is known about dynamic changes in the timing of network configurations in ASD and the integrity of large-scale physiologic systems in individuals with ASD of lower cognitive ability (LCA) or non-ASD developmental delay (DD).

Objectives

1. **Characterize and compare network dynamics** and standard connectivity in LCA and higher cognitive ability (HCA) adolescents with ASD.
2. **Investigate the impact of light sedation** on network dynamics and the limitations/potential of this methodology.
3. **Investigate the relationship** between network dynamics and autism severity.

Methods

Three, 6.5 minute resting state fMRI scans were collected on 13-15 year olds. A subset of participants were scanned under propofol sedation. Participants scanned while alert were instructed to close their eyes, relax and let their minds wander.

Group contrasts (matched on age and IQ):

1. Awake HCA ASD (n=6) vs typically developing (TD) (n=6).
2. Sedated LCA ASD (n=5) vs sedated DD (n=5).
3. Awake HCA (n=5) vs sedated HCA (n=5).

Preprocessing in FSL and AFNI included: motion correction, despiking and smoothing (3mm). Single point motion regressors were identified and entered into the GLM model in FSL Feat.

fMRI Analysis

Using a network kernel modeling approach[1] as follows:

1. Timecourses were extracted from 10mm spheres using MNI literature identified coordinates literature as nodes in the default mode network (DMN+/DMN-), dorsal attention network (DAN+/DAN-), fronto-parietal task control network (FPTC+/FPTC-), and salience network (SAL+/SAL-).
2. In each contrast, timecourses were submitted to an exploratory factor analysis in a structural equation modeling framework to identify identical factors (network kernels) across groups (Fig. 1).
3. A time-varying factor score was identified for each factor, and used as a regressor in a voxelwise general linear model (GLM) in FSL (Fig 2,3).
4. We computed the partial correlations between all factor pairs and compared them across groups (Table 1).

Fig 1. Factor solutions obtained for each contrast. The size of each node represents its weight/importance within the identified factor. The color of each node corresponds to the literature-identified network from which MNI coordinates were extracted.
(inset) – scatter plot showing the relation between the correlation of F4 & F7 and symptom severity in awake HCA ASD.

Results

Correlation analyses showed predominantly higher correlations in HCA compared to TD in networks involved in attention and introspection (Table 1). Further, the correlation between the DAN and FPTC is correlated with ADOS symptom severity (Fig 1.), r(4)=.87, *p*=.02, and is higher in all HCA participants than controls. Though no group differences in correlations were observed between LCA and DD factors, GLM analysis revealed higher connectivity with SAL in the left nucleus accumbens, left anterior insula and right temporal gyrus and lower connectivity in crus V & VI in LCA ASD (Fig 2). Compared to TD, HCA ASD showed increased connectivity with SAL in the orbital frontal cortex and the right temporal gyrus and decreased connectivity in the right lateral occipital cortex. GLM analysis showed higher DAN connectivity with the precuneus and the middle frontal gyrus in HCA ASD compared to TD (Fig 3). Sedation effects were observed in both factor correlations and functional connectivity. The contrast between awake and sedated individuals with ASD showed higher correlations between attention and DMN factors in awake subjects, suggesting that these two networks may be less differentiated in awake ASD subjects. Additionally, lower correlations between SAL and DAN factors in awake ASD (relative to sedated ASD) were observed.

Table 1. Significant Group Differences in Correlations Across Networks

Factors	p-value	Factors	p-value
HCA ASD Sedated < HCA ASD Awake		Awake HCA ASD > Awake TD	
F3 & F2	.001	F1 & F2	< .001
F4 & F3	< .001	F2 & F6	< .001
HCA ASD Sedated > HCA ASD Awake		F3 & F6	.002
F5 & F2	< .001	F4 & F7	< .001
F6 & F2	.001	F6 & F7	< .001
F7 & F4	.002		
F6 & F5	.002		

* No significant differences in correlations in LCA ASD and DD groups.

Fig 1 - Factor Solutions

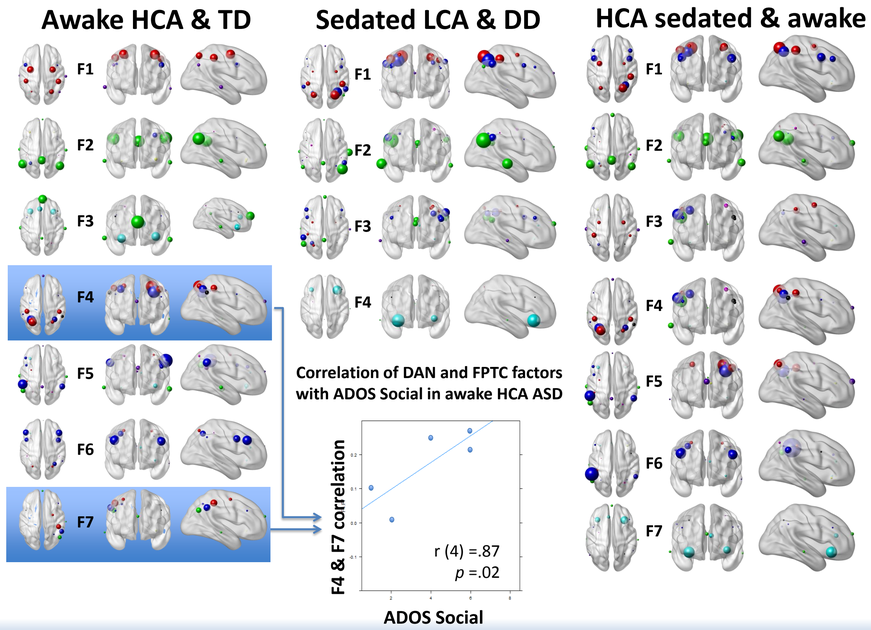

Fig 2 – SAL connectivity

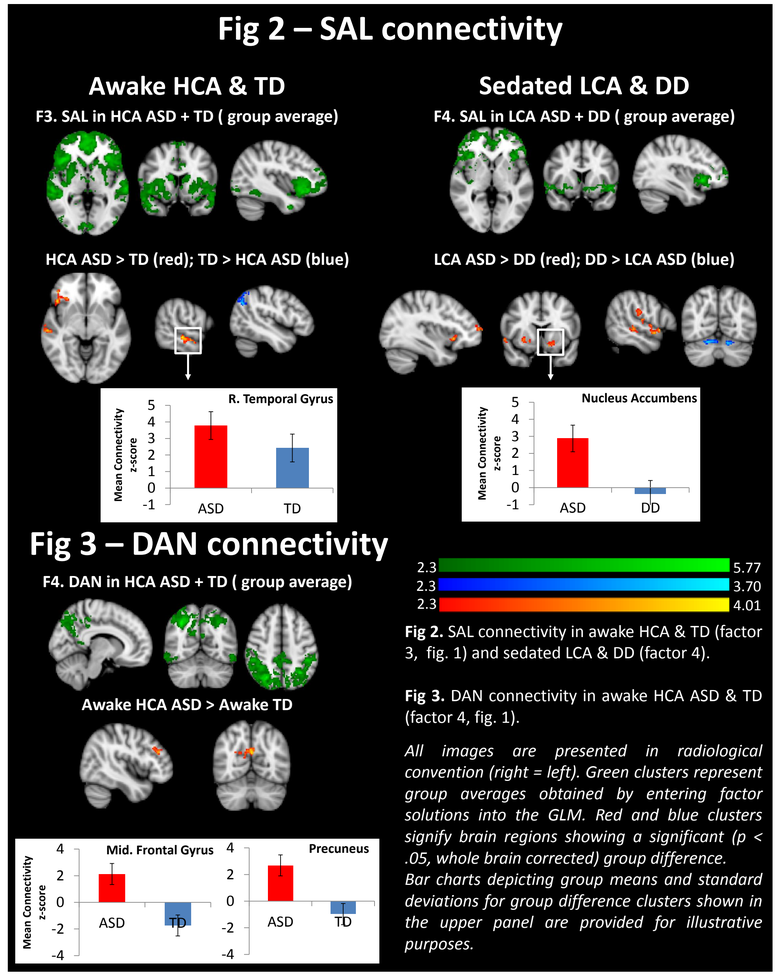

Fig 3 – DAN connectivity

Fig 2. SAL connectivity in awake HCA & TD (factor 3, fig. 1) and sedated LCA & DD (factor 4).

Fig 3. DAN connectivity in awake HCA ASD & TD (factor 4, fig. 1).

All images are presented in radiological convention (right = left). Green clusters represent group averages obtained by entering factor solutions into the GLM. Red and blue clusters signify brain regions showing a significant (p < .05, whole brain corrected) group difference.
Bar charts depicting group means and standard deviations for group difference clusters shown in the upper panel are provided for illustrative purposes.

Conclusions

Large-scale brain system alterations are observable in individuals with ASD with both higher and lower cognitive abilities. Network kernel analysis is highly sensitive to diagnostic status and individual differences in autism severity. However, it may be less sensitive for identifying abnormal network dynamics when participants are scanned under sedation, because sedation itself appears to lower differentiation of networks and reduce network expression.

References

1. Madhyastha T., Askren M.K., Zhang J. et al., Group comparison of spatiotemporal dynamics of intrinsic networks in Parkinson disease. *Brain*, (in press).

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***Supported by Autism Speaks 3628;* NICHD/NICHD 5P50HD055782**

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