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 and TD.
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 as follows:
1. Timecourses were extracted from 10mm spheres using MINI literature identified coordinates literature as nodes in the default mode network (DMN/DMN), dorsal attention network (DAN/DAN), frontoparietal 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).

Table 1. Significant Group Differences in Correlations Across Networks

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>HCA ASD Sedated &lt; HCA ASD Awake</th>
<th>Awake HCA ASD &gt; Awake TD</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3 &amp; F2</td>
<td>.001</td>
<td>F3 &amp; F2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>F4 &amp; F3</td>
<td>&lt; .001</td>
<td>F2 &amp; F6</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

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

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 ASD 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 cing 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.

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

Fig 1 - Factor Solutions

Awake HCA & TD

Sedated LCA & DD

HCA sedated & awake

Fig 2 – SAL connectivity

Awake HCA & TD
F3. SAL in HCA ASD + TD (group average) vs. F3. SAL in HCA ASD - TD (group average)

Sedated LCA & DD
F4. SAL in LCA ASD + TD (group average) vs. F4. SAL in LCA ASD - TD (group average)

Fig 3 – DAN connectivity

Awake HCA ASD > Awake TD

F5. DAN in HCA ASD + TD (group average) vs. F5. DAN in HCA ASD - TD (group average)

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