Increased frontal irregularity of resting state fMRI in children with autism spectrum disorders

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PURPOSE: Two approaches to understanding the etiology of neurodevelopmental disorders such as Autism Spectrum Disorders (ASD) involve network level functional connectivity (FC) and the dynamics of local neuronal signaling. The former approach has revealed increased local FC and reduced long-range FC in children with ASD, leading to the "developmental disconnection model." The latter approach has found high frequency EEG oscillations and higher levels of epilepsy in children with ASD. Together these two approaches have led to the hypothesis that atypical excitatory-inhibitory neural signaling may lead to impaired long-range association pathways[1]. However, simultaneously reconciling local temporal dynamics with network scale spatial connectivity remains a difficult task. Resting-state functional MRI (rs-fMRI) provides a compromise of excellent spatial resolution and good temporal resolution. We employ a recently introduced measure of rs-fMRI signal dynamics, wavelet-based regularity analysis[2], to simultaneously investigate the intrinsic irregularity of the local signal and FC using a seed-based correlation analysis in a cohort of children with ASD and matched typically developing (TD) children.

METHODS: Rs-fMRI scans were obtained from 15 children with ASD (13.8 yrs, 15 male, IQ=103) and 15 TD children (13.1 yrs, 13 male, IQ=106), with the following parameters: TR⌈TE=3000⌋22ms, 26 slices, matrix: 64x64, voxel=3.44x3.44x5mm, 120 volumes. *Preprocessing:* Volumes were spatially aligned and 12 motion parameters (motion plus derivatives) as well as white matter and cerebrospinal fluid time series were regressed from voxel intensities. *Wavelet-based Regularity Analysis:* The regularity with which rs-fMRI signal patterns recur was measured with Sample Entropy[3] at three temporal scales obtained via a band-pass filter using the stationary wavelet transform (WaveLab850 toolbox[4]). The noise level is estimated from the highest frequency subband and used as an intrinsic distance threshold with which to gauge pattern similarity. Patterns were constructed from time-delayed points to account for the serial correlations present in rs-fMRI data. Patterns of length m(+1)=1(2) were used. Two sample t-tests were performed voxel-wise at each scale and a cross-scale p-value was obtained using Fisher's method. *Seed-based Functional Connectivity:* Ten ROIs were obtained from regions showing significant cross-scale difference in wavelet-based regularity analysis. Seed signals were obtained from the average signal within each ROI and correlated with each voxel within a whole-brain mask. Two sample t-tests were performed for each ROI separately. All measures were normalized to MNI space prior to group comparisons.

RESULTS: Greater intrinsic rs-fMRI signal irregularity ($p<0.001$, cluster corrected for $p<0.05$) is observed extensively across the prefrontal cortex of the ASD group with bilateral effects occurring in both caudal and rostral regions of the middle frontal gyrus (Figure 1a). Reduced FC to these regions of irregular activity is observed across several posterior areas, including the temporal lobe, in the ASD group, with six ROIs showing bilateral effects. Contrariwise, anterior areas of the brain, including areas of the basal ganglia, and regions in the cerebellum exhibit an increased FC with these irregular activity regions in the ASD group (Figure 1b). Unlike the bilateral effects observed in the posterior areas, these increases exhibit a more random distribution with only two ROIs showing bilateral effects. Differences in FC are significant to $p<0.01$ (voxel and cluster).

DISCUSSION: We report a clear association between FC and the intrinsic signal dynamics in individuals with autism. Increased irregularity of rs-fMRI in frontal regions matches reported hyper-excitability and reduced inhibitory neurotransmitter in these brain regions. A systematic decrease in correlations between these "noisy" seeds and posterior regions of the brain in the ASD group, as well as a disorganized distribution of increased local correlations with frontal regions is consistent with the "neurodevelopmental disconnection model" of ASD. This suggests that regions exhibiting noisier fluctuations are significantly decoupled from posterior regions of the brain in individuals with ASD.

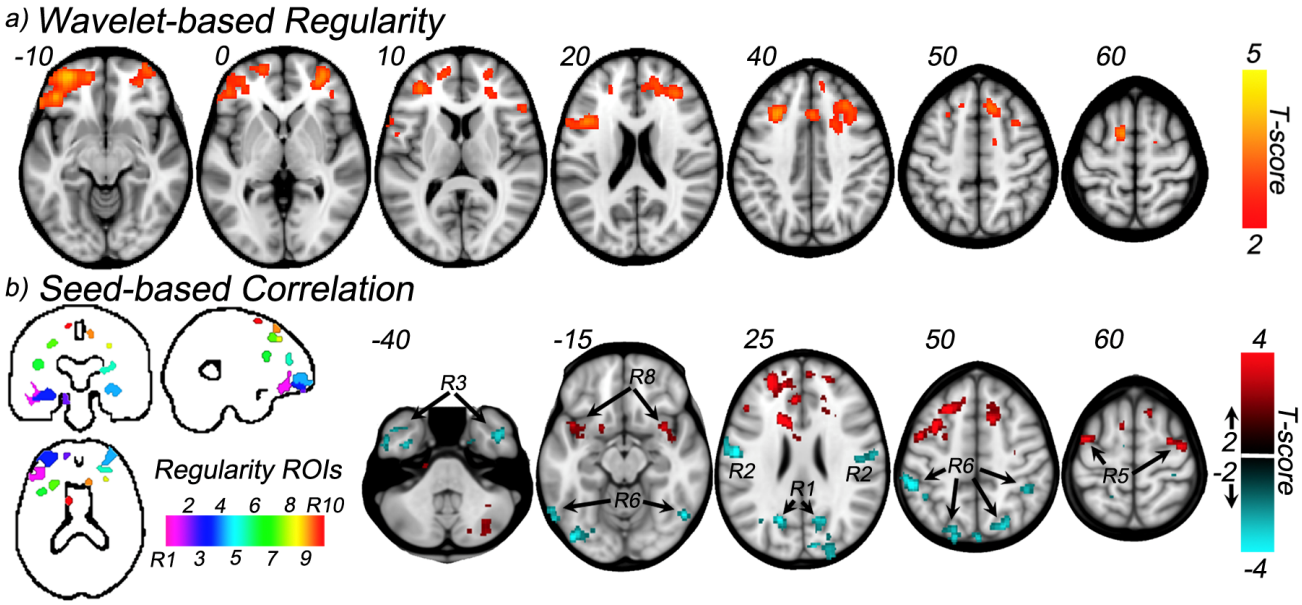

Figure 1. Frontal dynamics related to whole-brain functional connectivity in ASD. (a) Two sample t-tests of wavelet-based regularity results ($p<0.001$ corrected for $p<0.05$). (b) Composite map of two sample t-test for seed-based correlation analysis for ten seed regions (left) identified from (a) ($p<0.001$, cluster corrected for $p<0.01$).

REFERENCES: [1] Rubenstain JL *et al.*, Genes, Brain and Behavior, 2 (2003); [2] Smith RX *et al.*, ISMRM:No4135 (2014); [3] Richman J *et al.,* Am. J. Physiol. Heart Circ. Physiol., 278 (2000); [4] Buckheit J *et al.* www.stat.stanford.edu:80/wavelab/ (2005)