Title: Increased Resting-State Whole-Brain Connectedness in Youth with Down Syndrome

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Introduction: Recent work on resting state functional connectivity (rsFC) in young adults with Down syndrome (DS) has revealed conflicting results. For example, some studies have demonstrated increased connectivity between brain networks (e.g., Anderson et al., 2013) while other studies have demonstrated a mix of increased and decreased functional connectivity (e.g., Pujol et al., 2015; Vega et al., 2015). No studies to date have examined whole-brain rsFC at the voxel level using fMRI in youth with DS. Thus, the proposed research sought to fill this gap in the literature.

Methods: A sample of 19 children and adolescents with DS (M age = 16.5; range = 6-23; 13 Female) and 33 typically developing (TD) children (M age =17.5; range = 6-24; 18 Female), matched on chronological age and sex, completed a 5-minute and 15-second eyes-open resting-state scan [BOLD EPI: 44 slices per volume aligned to AC-PC axis; TR=2500 ms; voxel size = 3.438 x 3.438 x 2.8 mm^3]. Scans were preprocessed using AFNI (Cox, 1996) and the ANATICOR denoising approach (Jo et al., 2010; Gotts et al., 2012). Whole-brain connectedness (average Pearson correlation of each voxel with the rest of the brain) was calculated for each scan and compared between DS and TD groups using voxelwise 2-sample t-tests, with results thresholded voxelwise at $p<.0005$ and corrected by cluster-size with random permutation testing. Head motion during the scans was estimated using AFNI's @1dDiffMag (comparable to mean Framewise Displacement) and covaried from the t-test results using AFNI's 3dttest++.

Results: Whole-brain connectedness was significantly higher in youth with DS compared to TD controls in widespread regions throughout the brain bilaterally, particularly in ventral temporal cortex, dorsolateral prefrontal and frontopolar cortex, ventromedial prefrontal cortex, anterior cingulate cortex, as well as subcortical structures such as the thalamus and putamen. To further check that group differences were not due to motion, post-hoc analyses examined rsFC in a subset of motion-matched participants (13 DS and 19 TD) with no qualitative change in results. Results were also found to replicate across independent halves of the data.

Discussion: These results suggest that baseline network organization is disrupted in youth with DS such that disparate networks are overly connected with less selective network connections, suggesting a potential target for clinical interventions.

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