A Functional Connectivity-Based Evaluation of Competing Models of Sex Differentiation and Autism

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Background: Accumulating evidence suggests that mechanisms regulating normative sex differences may be affected in autism spectrum disorder (ASD) (Lai et al., 2015). Two models have emerged: 1) the ‘extreme male brain theory’ (EMB) (Baron-Cohen 2002) suggesting that autism is related to masculinization, regardless of sex, and 2) the gender incoherence theory (GI) suggesting that females with ASD are masculinized, whereas males with ASD are feminized (Bejerot et al., 2012). To systemically examine these two models we investigated whether regions of atypical connectivity in ASD overlapped with regions showing normative sex differences.

Methods: We used data from two large previous R-fMRI studies: one showing normative sex differences (males=471; females=357; age=8-85 years; Yan et al., 2013), the other revealing atypical connectivity in males with ASD (neurotypical controls (NT)=403; ASD=360; age range=6-58 years; Di Martino et al., 2014). We examined five R-fMRI measures that have been shown to be affected in ASD (Di Martino et al., 2014) and to have distinct patterns by sex (Yan et al., 2013). These included degree centrality, fractional amplitude of low frequency fluctuations, regional homogeneity, voxel-mirrored homotopic connectivity and posterior cingulate seed-based correlation. Spatial overlap analyses were performed by conjunction analyses of the statistical maps from the above studies. Four pairs of contrasts were examined: ASD>NT & M>F (EMB 1); NT>ASD & F>M (EMB 2); ASD>NT & F>M (GI 1); NT>ASD & M>F (GI 2). To test for significance of overlaps, we computed the null distribution of random overlap via Monte Carlo simulations (5000 iterations) for voxel-level thresholds ranging from p=0.0001 to p=0.05 (Lai et al., 2013). To address confounds related to differing demographics and preprocessing pipelines, sub-samples of the original datasets were reanalyzed as above using the Configurable Pipeline For The Analysis of Connectomes.

Results: Across all R-fMRI measures, there were consistent and non-random overlaps above the 99th percentile of the null distribution between regions showing normative sex differences and those showing ASD-NT differences. Regions consistent with the EMB model were mainly in the default network (DN) bilaterally. In contrast, regions consistent with the GI model mostly encompassed left somatomotor, ventral attention and posterior auditory systems. Results were confirmed in the secondary sub-samples.

Conclusions: Here, we provide evidence for both EMB and GI models, both of which vary as a function of the neural system involved. Notably, aspects previously reported in ASD such as hypoconnectivity in the DN and posterior language regions may be regulated by atypical sexual differentiation in males with ASD. Future work is warranted to identify the underlying biological mechanisms linking sexual differentiation and ASD.