ABSTRACT

Resting-State Functional Connectivity in Youth with Gender Dysphoria

by

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Current developmental models of gender identity and gender dysphoria (GD) lack sex-specific profiles of brain function, or neuroendophenotypes, that differentiate between typically-developing and cross-gender identified youth, as postulated by models like the unified theory of the origins of sex differences (Arnold, 2009) and the neurobiological theory of the origins of transsexuality (Swaab & Garcia-Falgueras, 2009). Previously, investigators have used brain imaging modalities such as Resting-State functional Magnetic Resonance Imaging (R-fMRI) to demonstrate differences in resting-state functional connectivity (RSFC) between typically-developing male and female youth, and between typically-developing and clinically-diagnosed youth. In the present pilot study, I used R-fMRI to investigate differences in RSFC between typically-developing and cross-gender identified male and female youth, with the hypothesis that GD-diagnosed subgroups would demonstrate connectivity patterns in between those of the typically-developing males and females. Eleven youth diagnosed with gender dysphoria (four males, ages 9 to 20 years; 7 females, ages 12 to 20 years) were matched on age and assigned gender with 11 typically-developing youth. All participants completed written informed consent to undergo the IRB-approved research procedures. R-fMRI were collected while the participants

were lying down and resting, with their eyes closed. Primary analyses focused on 14 brain regions selected because they showed sex differences most frequently or reliably in previous studies of R-fMRI in typically-developing youth. Statistical analysis used a 2 x 2 mixed effects analysis (assigned female versus assigned male x typically-developing versus GD-diagnosed), with-individual level connectivity maps as the dependent variable. Results showed that significant interaction effects of functional connectivity patterns were associated with 6 of the 14 selected brain regions. GD-diagnosed assigned females exhibited connectivity patterns similar to those of typically-developing males associated with the right medial superior frontal gyrus, right supplementary motor area, left lingual gyrus, right lingual gyrus, left middle frontal gyrus, left medial superior frontal gyrus, left cuneus, right thalamus, left dorsolateral superior frontal gyrus, and left inferior frontal gyrus, triangular part. GD-diagnosed assigned males exhibited functional connectivity patterns similar to typically-developing females associated with the right medial superior frontal gyrus and right supplementary motor area; in between those of typically-developing females and males associated with left lingual gyrus, right lingual gyrus, left middle frontal gyrus, left medial superior frontal gyrus, right medial superior frontal gyrus, left dorsolateral superior frontal gyrus, and left inferior frontal gyrus, triangular part; and similar to typically-developing males associated with the right lingual gyrus and left middle frontal gyrus. The right precuneus, hypothesized to show robust findings, did not reveal any effects. In the current study, GD-diagnosed assigned males tended toward demasculinized effects (quantitative interactions showing differences of magnitude), whereas GD-diagnosed assigned females tended toward masculinized effects (qualitative interactions showing differences in direction of correlation). The current findings support the view that brain development associated with gender dysphoria proceeds along separate but overlapping sex-related regions for GD-diagnosed

assigned females and males and provide further evidence of greater cross-gender brain differentiation in assigned females at an earlier age than in assigned males (possibly due to earlier onset of puberty in females). These data suggest that any future use of patterns of brain function for diagnosing gender dysphoria may require separate criteria (e.g., different sets of brain regions) for assigned males and assigned females but will require replication on larger samples.

Keywords: gender dysphoria, gender identity, cross-gender identification, sexual differentiation, youth, adolescent, resting-state fMRI, functional connectivity, seed-based connectivity analysis, neuroendophenotype