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Age and Gender Effects on Intrinsic Connectivity in Autism Using Functional Integration and Segregation

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ABSTRACT

BACKGROUND: The objective of this study was to examine intrinsic whole-brain functional connectivity in autism spectrum disorder (ASD) using the framework of functional segregation and integration. Emphasis was given to potential gender and developmental effects as well as identification of specific networks that may contribute to the global results.

METHODS: We leveraged an open data resource (N = 1587) of resting-state functional magnetic resonance imaging data in the Autism Brain Imaging Data Exchange (ABIDE) initiative, combining data from more than 2100 unique cross-sectional datasets in ABIDE I and ABIDE II collected at different sites. Modularity and global efficiency were utilized to assess functional segregation and integration, respectively. A meta-analytic approach for handling site differences was used. The effects of age, gender, and diagnostic category on segregation and integration were assessed using linear regression.

RESULTS: Modularity decreased nonlinearly in the ASD group with age, as evidenced by an increase and then decrease over development. Global efficiency had an opposite relationship with age by first decreasing and then increasing in the ASD group. Both modularity and global efficiency remained largely stable in the typically developing control group during development, representing a significantly different effect than seen in the ASD group. Age effects on modularity were localized to the somatosensory network. Finally, a marginally significant interaction between age, gender, and diagnostic category was found for modularity.

CONCLUSIONS: Our results support prior work that suggested a quadratic effect of age on brain development in ASD, while providing new insights about the specific characteristics of developmental and gender effects on intrinsic connectivity in ASD.

Keywords: ABIDE, Age, Autism, Functional connectivity, Functional integration, Gender

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The dysconnectivity hypothesis of autism spectrum disorder (ASD) posits that the heterogeneous symptom presentation of social communicative deficits and restricted and repetitive behaviors and interests (1) reflects a neural systems disorder characterized by altered brain connectivity (2,3). In support of this model, there is a confluence of evidence that ASD is characterized by alterations in the functional organization of the brain, in particular, decreased connectivity between mesocorticolimbic, frontal, and posterior-temporal cortical systems that play key roles in processing social-affective information (4) as well as local overconnectivity and long-distance underconnectivity (5). Task-based functional magnetic resonance imaging studies have found altered connectivity in ASD during language comprehension (6), cognitive control (7), mentalizing (8), social processing (9), working memory (10), and visuospatial processing (11). Studies using functional connectivity of intrinsic networks during rest have found evidence in support of within-network underconnectivity, such as decreased frontal-posterior default network connectivity (12,13), decreased default mode network connectivity (14,15), and reduced functional connectivity within and between resting-state networks incorporating social brain regions, including the insula and amygdala within the default mode and salience networks, respectively, in ASD (16).

The precise nature of intrinsic brain connectivity in ASD remains difficult to characterize, owing, at least in part, to the wide variety of analytic methods used in the more than 70 published studies on this topic (17,18). The methods used have included seed-based studies (13), graph-theoretical approaches (19), self-organizing maps (20), independent component analysis (21), examination of intrinsic connectivity networks (22), and regional homogeneity approaches (23). Another obstacle has been the wide age range of participants in studies of intrinsic brain connectivity in ASD. To address this obstacle, there have been attempts to place the nature of intrinsic brain connectivity in ASD within a developmental framework (24). In this regard, there appears to be some degree of convergence that intrinsic brain connectivity in

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adolescents and adults with ASD is generally relatively reduced, whereas in younger children with ASD, it is generally increased, a pattern that appears to be consistent using regional homogeneity (25), wavelet correlation (26), and independent component analysis (27) approaches.

An additional obstacle to a fuller understanding of intrinsic brain connectivity differences in ASD is the underexplored potential influence of gender effects. This is particularly relevant given that a recent meta-analysis suggests that the male-to-female ratio in ASD is close to 3:1 (28) and that gender is recognized as a potential major source of heterogeneity in ASD neurobiology (29). Many smaller neuroimaging studies of ASD have excluded female subjects altogether or have covaried the effects of gender when female subjects are included. One exception is a recent study that used the first Autism Brain Imaging Data Exchange (ABIDE) dataset to examine gender differences with respect to intrinsic connectivity of the posterior superior temporal sulcus, a region with strong connections with brain regions that code for social information, and the posterior cingulate cortex, a core region of the default network (30). The investigators found gender effects wherein female individuals with ASD had high connectivity patterns that resembled patterns observed in typically developing male individuals, whereas connectivity in male individuals with ASD resembled the low connectivity patterns in typically developing female individuals. These preliminary findings suggest that gender exerts moderating effects on patterns of intrinsic connectivity in ASD.

The purpose of this study was to evaluate the joint developmental and gender effects on intrinsic connectivity using measures that assess functional segregation and integration. We used data from ABIDE, which contains brain imaging data collected from laboratories around the world. The ABIDE initiative now includes two large-scale collections: ABIDE I was compiled from 17 sites, containing 1112 datasets from 539 individuals with ASD and 573 typically developing control (TDC) individuals (age range 7–64 years and median age 14.7 years across groups) (31), and ABIDE II was compiled from 19 sites, containing 1114 datasets from 521 individuals with ASD and 593 TDC individuals (age range 5–64 years) (32). Together, the combined ABIDE I and ABIDE II datasets provide 2226 unique cross-sectional datasets allowing researchers to address unprecedented questions owing to the sample size afforded by these unique data repositories.

Our analytic approach applied the framework of functional segregation and integration to examine both gender and age differences in whole-brain intrinsic connectivity in participants selected from the ABIDE I and II datasets. Additionally, we probed these results to localize specific functional networks that contributed to any findings obtained at the whole-brain level. We used the meta-analytic approach of inverse variance weighted effect size estimates (33) to control for site difference for all analyses. Based on developmental models of intrinsic connectivity reviewed earlier, we expected to find a quadratic relationship between whole-brain segregation and integration and age in the ASD sample, relative to a linear pattern in the TDC sample (34). Finally, although we expected to find whole-brain differences in functional segregation and integration in ASD, we hypothesized that these differences would be pronounced in the somatosensory network (35–37) and/or the salience network (38–41). Based on previous work using the ABIDE I dataset on gender differences in ASD functional connectivity (30), we examine both main effects and interactions with age of gender on segregation and integration.

METHODS AND MATERIALS

Participants

Data from ABIDE I and II were used in this study. Anatomical and resting-state scans were acquired from 1060 individuals with ASD and 1166 TDC individuals. Each site confirmed ASD diagnosis through clinical judgment and/or standard diagnostic instruments (Autism Diagnostic Observation Schedule and/or Autism Diagnostic Interview–Revised). Full-scale IQ was collected using a variety of instruments, and the measure was then set to a standard scale among sites. For site-specific details on both diagnostic criteria and IQ, see http://fcon_1000.projects.nitrc.org/indi/abide/.

Site Exclusion Criteria

Both ABIDE I and II datasets were collected from a variety of sites, using a variety of different scanner protocols. A number of sites were excluded from the current analysis for the following criteria: 1) no female subjects were collected (nine sites), 2) no TDC individuals were collected (one site), and 3) the data at the site failed visual quality control (two sites). Demographic and motion data for each site are presented in Supplemental Tables S1 and S2, respectively.

Preprocessing

Preprocessing was performed using FSL version 5.0 (FMRIB Software Library; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (42) as follows. Anatomical and functional scans were converted to left anterior superior alignment. Slice time correction was performed on each scan using FSL slicetimer. Rigid body motion correction was performed using FSL MCFLIRT; using the estimated motion parameters, 24-parameter regression was used to additionally correct for motion. Skull stripping was then performed using information from the T1 anatomical scans. The skull stripped functional images were then normalized to each participant's T1 scans using FSL FLIRT, the T1 scans were normalized to the Montreal Neurological Institute 152 2-mm standard image, and the functional scans were normalized to the Montreal Neurological Institute 152 space by combining those transformations. White matter and gray matter masks were generated by FSL FAST and regressed out from the functional signals. Finally, bandpass filtering was performed with the bounds 0.08 to 0.001 Hz. The preprocessed voxel-level time series were parcellated into the Power functional atlas (43), using 10-mm spheres centered around the provided coordinates. This atlas contains 264 functional regions of interest (ROIs) divided into 14 functional networks as follows: sensory/somatomotor hand, sensory/somatomotor mouth, cingulo-opercular task control, auditory, default mode, memory retrieval, ventral attention, visual, frontoparietal task control, salience, subcortical, cerebellar, dorsal attention, and undetermined. The 28 ROIs classified as being part of undetermined networks were omitted from subsequent analysis, and the final count of ROIs was 236.