

Effects of Participant Functioning Level on Brain Functional Connectivity in Autism

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Understanding how brain functional connectivity (FC) is altered in individuals with autism spectrum disorder (ASD) is critical for uncovering its etiology, parsing heterogeneity, and tailoring treatments for this increasingly prevalent neurodevelopmental disorder. Currently, one of the most popular neuroimaging approaches for investigating FC in ASD is resting-state functional magnetic resonance imaging (fMRI), in which fMRI data are acquired in the absence of task performance. The acquisition of fMRI data, however, is particularly challenging in clinical pediatric populations owing to the requirements to remain still and to cooperate with instructions in a confined environment. Even in studies of individuals with relatively high IQ, success rates for fMRI data collection can be as low as 50% (1). Consequently, almost everything that is currently known about brain FC in ASD comes from studies of individuals with average or above-average IQ (e.g., high-functioning autism). Clinically, however, it is lower-functioning individuals who experience the most significant impairments. This bias toward studying high-functioning autism leaves a large gap in our understanding with respect to FC in lower-functioning autism, which constitutes nearly one third of all individuals on the autism spectrum.

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Reiter *et al.* (2) present results combining their own data and capitalizing on the Autism Brain Imaging Data Exchange-II to compare children and adolescents 6 to 15 years of age with ASD with low and high IQ (≤ 85 and ≥ 115 , respectively). They arrived at a respectable sample of 22 participants in each of four groups (lower IQ autism [L-ASD], higher IQ autism [H-ASD], average IQ typically developing [TD], and higher IQ TD) and conducted whole-brain FC analyses using several seed regions of interest that have long been implicated in the autism neuroimaging literature: the medial prefrontal cortex (mPFC) and posterior cingulate cortex of the default mode network, the bilateral amygdala, the anterior insula, and the posterior superior temporal sulcus. An elegant design with four group comparisons allowed for examination of whether atypical FC is simply more pronounced in L-ASD compared with H-ASD or rather is distinct in terms of FC patterns.

Significant differences in FC were observed between L-ASD and H-ASD groups, such that L-ASD showed underconnectivity between the mPFC and the posterior cingulate cortex as well as between the posterior superior temporal sulcus and the pericalcarine cortex. Comparing L-ASD and average IQ TD subjects revealed overconnectivity of the mPFC with the precalcarine cortex in the clinical group. Higher IQ TD versus H-ASD subject comparisons revealed

underconnectivity of the posterior cingulate cortex in the clinical group. H-ASD versus average IQ TD comparisons revealed overconnectivity of the mPFC in the clinical group. Taken together, these findings suggest distinctive patterns of atypical FC in L-ASD subjects. Reiter *et al.* (2) summarize these altered FC patterns by positing that they may be indexing reduced network integration (lower FC between nodes of the same network) in L-ASD and reduced network segregation (higher FC between networks) in H-ASD. This work points to the need for careful consideration of functioning level in future studies of brain functional network abnormalities in ASD and provides a welcome first step toward addressing a critical gap in the current literature.

A surprising outcome from the analysis conducted by Reiter *et al.* (2) was the finding of no significant group differences in FC for the amygdala seeds examined. In a recent study of frontoamygdala FC in an Autism Brain Imaging Data Exchange-II sample of patients 7 to 25 years of age, individuals with ASD of average IQ were shown to exhibit weaker FC between the right basolateral amygdala and the rostral anterior cingulate cortex compared with TD individuals (3). This is in line with other work demonstrating underconnectivity of the amygdala in children with ASD (4). While it is puzzling that the current analysis did not replicate these commonly observed effects, the null findings with respect to amygdala FC in the current study point to the possibility that atypical amygdala circuitry in autism may not be a broadly generalizable finding.

The finding of generally reduced network segregation in H-ASD is in line with another recent longitudinal study of high-functioning youth demonstrating that TD individuals exhibit increased negative FC between the default mode network and the central executive network with age, unlike those with ASD (5). Although Reiter *et al.* (2) observe no age effects in their analysis of 6- to 15-year-olds, they acknowledge that their cross-sectional design does not rule out the possibility of altered developmental trajectories of FC across the lifespan in ASD.

We recently observed that clinical heterogeneity and methodological standardization are critical issues to address before progress can be made toward the identification of robust and reliable brain-based biomarkers of autism (6). The findings presented by Reiter *et al.* (2) suggest that in addition to the sources of heterogeneity in the ASD FC literature that have already been identified, including methodological choices (7) and developmental stage of participants (8), participant functioning level must also be seriously considered.

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As Reiter *et al.* (2) have demonstrated, it is no longer a tenable assumption that discoveries regarding brain FC in high-functioning ASD can necessarily be generalized to individuals of differing functioning levels. This leads us to the difficult problem of how to collect sufficiently large samples of neuroimaging data from individuals with lower-functioning ASD to arrive at robust and reproducible findings. One possible future direction is the use of more naturalistic paradigms, such as movie-watching in the MRI. While one must consider the relative advantages and disadvantages of the use of fMRI data acquired during movie-watching for the analysis of brain FC (9), in theory this approach can facilitate data acquisition from younger individuals and lower-functioning individuals who are unable to comply with the instructions typically used in resting-state fMRI data collection.

Only one other study to date has attempted non-sedated MRI data collection from lower-functioning (in this case low verbal and cognitive performance [LVCP], IQ \leq 79) children 7 to 17 years of age with autism using movie-watching paradigms. Gabrielsen *et al.* (10) implemented extensive preparation and support procedures, including video modeling and live modeling as well as individualized anxiety reduction techniques before MRI data collection. They found evidence of decreased within-network connectivity in LVCP children compared with higher functioning children with ASD in the default, salience, auditory, and frontoparietal networks. They also found increased between-network connectivity for default dorsal attention and default frontoparietal networks in LVCP children with ASD compared with neurotypical children. However, Gabrielsen *et al.* (10) do not find evidence for qualitatively different FC patterns between higher- and lower-functioning children with ASD in their analyses. Rather they suggest that the “signature” of abnormal connectivity in autism is preserved but is worse in the LVCP group, suggesting that this signature is more pronounced with decreased cognitive and language performance levels (10). Nevertheless, both research groups agree that stratification of samples by general functional levels will be critical for moving the field of autism neuroimaging forward. Taken together, the studies by Reiter *et al.* (2) and Gabrielsen *et al.* (10) demonstrate that MRI data collection and investigation of brain FC in children with lower-functioning ASD will continue to provide novel insight into this heterogeneous neurodevelopmental disorder.

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Article Information

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