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Commentary

The Influence of Brain State on Functional Connectivity in Autism

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While it is almost universally agreed amongst autism researchers that the disorder involves atypical development of brain connectivity, several open questions remain with regard to the precise nature of these atypicalities. A limitation of the current neuroimaging literature is a focus on adulthood autism, with recent work beginning to examine late childhood and adolescence (Uddin et al., 2013). In this issue of *EBioMedicine*, Buckley and colleagues contribute to this emerging literature by analyzing EEG data collected from a large sample of young children (age 2–6) with autism spectrum disorder (ASD), developmental delay without autism (DD), and typical development (TYP) (Buckley et al., 2015).

Previous studies of functional connectivity in autism have examined either task-related or resting-state connectivity, with mixed findings of over- and under-compared with neurotypical populations (see Just et al., 2012; Muller et al., 2011 for reviews). Very few have examined differential brain connectivity as a function of brain state, with the exception of some recent functional MRI work examining task-rest differentiation in autism (Barttfeld et al., 2012; Uddin et al., 2014; You et al., 2013). The current study by Buckley and colleagues took the unique approach of examining functional brain connectivity using EEG spectral power, coherence, phase lag, Pearson and partial correlations. As EEG data can more easily be collected from young children, this allowed the researchers to examine a very young and low functioning sample compared with studies reporting data acquired using MRI, which is much more susceptible to motion artifact and requires more patient compliance. The authors were further able to examine functional connectivity differences in autism as a function of brain state, as they collected data during the awake, slow wave sleep (SWS), and rapid eye movement sleep (REM) states. A final innovation was the use of machine learning to classify children with autism based on correlation networks derived from computation of correlations between electrode pairs.

Univariate between-group comparisons revealed increased coherence in ASD relative to TYP, mostly during SWS and concentrated in the frontal–parietal electrode pairs. No differences in coherence were seen between ASD and TYP during the awake state. Multivariate analyses using support vector machines revealed that children with ASD could be accurately separated from both the TYP and DD groups using both Pearson and partial correlations.

As high EEG coherence values are taken as a measure of strong connectivity between the brain regions that produce the signals, the current findings are in line with recent fMRI work suggesting that the brains of young children with ASD exhibit more instances of over-connectivity than under-connectivity (Nomi and Uddin, 2015; Supekar et al., 2013). A novel and interesting finding of the current study is that SWS was the brain state in which the most striking group differences were observed. This has important implications for the resting-state fMRI literature, which has historically collected data in either the eyes-open or eyes-closed condition with roughly equal frequency. The current results highlight the importance of carefully monitoring sleep states in studies attempting to characterize group differences in functional connectivity that are clinically relevant.

Children with autism and other neurodevelopmental disorders benefit most from early interventions. Thus, the development and validation of brain-based biomarkers to aid in objective diagnosis can facilitate this clinical aim. Increasingly, neuroscience has shifted from a focus on identifying neural correlates of clinical conditions to using metrics derived from brain imaging to predict diagnostic category. The current study adds to a growing body of work suggesting that sensitive and specific biomarkers for autism may be on the horizon. While previous classification studies focused primarily on adults with autism (Ecker et al., 2010), the current results report data from an age range closer to the typical time point of diagnosis by expert clinicians. The ultimate goal would be to develop robust brain-based classifiers that can eventually be used to assist clinicians in making the earliest and most accurate diagnoses.

The key questions that the field still grapples with include the following: 1) What is the nature of brain connectivity alteration in autism, and how does it manifest across the lifespan? 2) Are some indices of brain function (e.g., EEG coherence, fMRI functional connectivity) more robust and reproducible, and thus more suitable for biomarker discovery? 3) How is connectivity altered in specific states (e.g., sleep, active task) and what are the implications of these state-specific changes for behavior and cognition in autism? The current study provides a nice example of how investigation of younger children, and careful

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consideration of brain state, can provide a more nuanced characterization of brain connectivity abnormalities in ASD.

Disclosure

The author declared no conflicts of interest.

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