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Journal
Cell Reports, 5(3)

ISSN
2639-1856

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Publication Date
2013-11-01

DOI
10.1016/j.celrep.2013.10.043

Peer reviewed

HHS Public Access

Author manuscript

Cell Rep. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Cell Rep. 2013 November 14; 5(3): 565–566. doi:10.1016/j.celrep.2013.10.043.

Convergent Evidence of Brain Overconnectivity in Children with Autism?

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Abstract

In this issue of *Cell Reports*, Keown et al. and Supekar et al. report widespread increases in brain connectivity in children with autism. These studies challenge the widely established theory of underconnectivity in autism, suggesting a more complicated picture of brain connectivity alterations.

In this issue of *Cell Reports*, two articles (Keown et al., 2013; Supekar et al., 2013) describe the results of advanced neuroimaging methods used to analyze intrinsic functional brain connectivity in children with autism spectrum disorder (ASD). Although the approaches are quite different, both groups used robust methods to provide a more comprehensive understanding of functional brain organization in ASD. They report that both long- and short-range intrinsic connectivity was increased across multiple brain networks in young children with ASD and that increased connectivity was associated with more severe social deficits. These studies stand in contrast to multiple prior reports of underconnectivity in ASD, suggesting that disrupted brain connectivity in ASD may be dependent on altered age-related trajectories. Critically, the extent to which aberrant patterns of brain connectivity may cause ASD symptomatology instead of resulting from it remains to be determined.

Early studies of brain connectivity in ASD linked widespread underconnectivity to higher-level cognitive deficits observed in autism (e.g., Just et al., 2004). However, these initial reports examined functional connectivity during cognitive tasks. More recent work has used resting-state functional connectivity MRI (rs-fcMRI) to map spontaneous low-frequency fluctuations within cognitive networks that are independent of task performance (and related confounds). These studies have mostly focused on specific networks (i.e., the default mode network) and have generally found reduced long-range connectivity in ASD (see Vissers et al., 2012, for review). Relatively few studies have implemented advanced whole-brain methods for analyzing functional connectivity in ASD (Anderson et al., 2011; Rudie et al., 2013; Di Martino et al., 2013). Importantly, closer methodological scrutiny is now required, given the recent controversy regarding the effects of motion confounds, whereby not

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appropriately correcting for head motion can lead to both spurious increases in local connectivity and reductions in long-range connectivity (i.e., Power et al., 2012). Thus, it is important to note that both studies previewed here used advanced motion-correction techniques and addressed other major methodological concerns (i.e., global signal regression).

In Keown et al. (2013), the authors focused on local connectivity in adolescents with ASD. Several groups have hypothesized that enhanced local circuit connectivity may provide an explanation for the preservation or enhancement of certain cognitive functions in ASD, such as visual or auditory discrimination (e.g., Geschwind and Levitt, 2007). However, few studies have comprehensively addressed whole-brain local connectivity in ASD. By using methods developed from graph theory, Keown et al. (2013) used rs-fcMRI to compute whole-brain maps of local connectivity. They compared these maps between youths with and without ASD (mean age = 13.8 years) and reported an anterior-posterior gradient of local under- to overconnectivity in ASD. Specifically, occipitotemporal regions showed diffuse overconnectivity in ASD, which was more pronounced in individuals with more severe social deficits, whereas reduced local connectivity was found in frontal regions and was more pronounced in ASD adolescents with less severe social impairments.

In Supekar et al. (2013), the authors used a systematic whole-brain connectivity approach to analyze intrinsic brain connectivity in younger children with ASD (mean age = 10.1 years). By implementing several parcellation schemes and rigorous motion correction techniques, they reported that connectivity was diffusely increased in ASD both within and between different brain networks. This was observed regardless of physical distance, such that both short- and long-range connections were stronger in ASD. Furthermore, they reported that the amount of overconnectivity was associated with increasing levels of social deficits in ASD and replicated both main findings in two additional samples. Interestingly, they also reported that increased connectivity was related to abnormally high amplitudes of low-frequency fluctuations, which they hypothesized to be related to an imbalance of excitation to the inhibition in the brains of children with ASD.

These new findings are not entirely consistent with other recent whole-brain connectivity studies in ASD, although there appears to be more agreement with regards to the findings of Keown et al. (2013). The most relevant data come from a study reporting the establishment of the Autism Brain Imaging Data Exchange (ABIDE), a database which include rs-fcMRI data collected in ASD and neurotypical individuals at 20 different sites (including data from both studies previewed here) (Di Martino et al., 2013). Here, the authors performed several whole-brain connectivity analyses in a sample of over 700 subjects, including analyses of regional homogeneity as a measure of local connectivity. Remarkably, they also found an anterior-posterior gradient of under- to overconnectivity in ASD, similar to what was observed by Keown et al. (2013). Thus, consistent reports of local connectivity alterations in ASD lend support to the hypothesis that increased local connectivity in occipitotemporal regions may be related to islets of superior functioning in sensory systems, whereas reduced local connectivity in frontal regions may relate to disrupted social behavior.

As far as more global connectivity analyses, the findings of Supekar et al. (2013) appear to directly contradict those of Di Martino et al. (2013), who reported widespread reductions in connectivity across multiple systems (except for increased connectivity between primary sensory and subcortical regions). Two other previous studies (Anderson et al., 2011; Rudie et al., 2013) using whole-brain approaches to characterize intrinsic connectivity in ASD also reported widespread reductions in connectivity at both short and long distances. However, a major difference of Supekar et al. (2013) is that the study focused on younger children with ASD (mean age = 10.1) whereas the median age was 14.7 in Di Martino et al. (2013) and the mean ages in Rudie et al. (2013) and Anderson et al. (2011) were 13.5 and 22.7, respectively. This suggests the possibility that early overconnectivity in ASD may give way to underconnectivity across time, particularly at the onset of puberty. However, an rs-fcMRI study of toddlers with ASD found reduced inter-hemispheric connectivity at this very young age (Dinstein et al., 2011); therefore, connectivity alterations may follow an even more complicated developmental timetable. Additionally, it is important to consider methodological differences (e.g., spiral versus echo planar acquisition and wavelet transformation versus band-pass filter), given that they could have large downstream effects on connectivity data.

Altogether, the new studies by Keown et al. (2013) and Supekar et al. (2013) add considerable weight to the hyperconnectivity side of the current hypo- versus hyperconnectivity debate in ASD while also painting a more complicated story wherein age may play a critical role. It is clear that more studies are needed with younger and longitudinal cohorts in order to obtain a clearer picture of the entire developmental trajectory of altered connectivity in ASD. Lastly, given the heterogeneity of samples and methods used across studies, these new findings highlight the importance of large-scale collaborative efforts such as ABIDE, given that data sharing across multiple sites should help disentangle the impact of several key variables on brain connectivity in typical and atypical development. Continued efforts using advanced analytical approaches, as demonstrated by the studies previewed here, are necessary in order to reach the ultimate goal of using neuroimaging as a clinical biomarker to guide the diagnosis and treatment of complex neuropsychiatric disorders (Fox and Greicius, 2010).

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