**OPINION**

# What to make of contradictions in connectivity findings?

BY **GREG BOUSTEAD**

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In his **Viewpoint last month** for SFARI.org, **Vinod Menon**wrestled with the apparent conflict between findings over the past few years suggesting that **both too little and too much brain connectivity** may contribute to autism.

Menon highlighted his new work showing a surprisingly high level of overconnectivity in the brains of children with autism. This raises an intriguing question about how relatively strong or weak connectivity might lead to information-processing problems in the disorder.

We asked four other researchers who study brain signaling for their perspectives on this **apparent connectivity conundrum** as part of our new discussion series, **Cross Talk**.

What do you think? Share your reactions and follow-up questions in the comments section below.

*Editor's note: For an in-depth discussion of the types of mechanisms that can alter brain connectivity — including specific genetic mutations, environmental factors and disrupted circuits — check out the Viewpoint **inspired by this discussion** from **John Rubenstein** and **Vikaas Sohal**.*

## *A swinging pendulum*

### Damien Fair

*Assistant Professor of Behavioral Neuroscience and Psychiatry, Oregon Health & Science*

*University*

***Different lenses:*** "For years, the push-pull of these two seemingly opposing phenomena (under- and overconnectivity in autism) has been well documented in the literature. What is interesting in current times is that studies using the same magnetic resonance imaging (MRI) measurements, on the same datasets, are capable of showing seemingly opposing findings in this regard[1, 2]. This highlights the complexity of the question and, equally important, the lens from which we view it.

"The scale of inquiry (from neuronal junctions, or **synapses**, to brain networks), measurement types (such as structural or functional connectivity) and analysis approach (such as **graph theory**) can all lead to apparently discrepant findings. Thus, as Menon explained, the question of whether children with autism have over- or underconnected brains has limited utility without considerable context."

***Multiple mechanisms:*** "Another aspect worth considering is the vast heterogeneity in autism spectrum disorders.However, as we and many others have noted, there is considerable evidence suggesting that the DSM [the *Diagnostic and Statistical Manual of Mental Disorders]* reflects the end result of multiple unique, independent mechanistic pathways within a disorder[3].

"The mechanistic heterogeneity that potentially underlies the existing classification scheme might be limiting our ability to clarify etiology. It will be important in future work to account for the 'multiple-mechanisms' hypothesis when considering connectional topology of complex mental disorders such as autism."

# *Too much noise*

## John Rubenstein

*Nina Ireland Distinguished Professor in Child Psychiatry, University of California, San Francisco*

***Complex conversation:*** "Hyperconnectivity might result in impaired information processing by increasing the background noise or overall circuit output, in much the same way that increasing the

number of people having separate conversations in a room might drown out a more complex conversation between a subset of those individuals."

***Primitive circuits?*** "Autism undoubtedly results from a constellation of diverse mechanisms. Nonetheless, compensatory mechanisms may lead to common features, which may include a propensity for increased connectivity of certain circuits (perhaps developmentally more primitive), and reduced connectivity of later-forming circuits."

***Altered development:*** "We are at the very beginning of understanding the cellular and molecular processes that could create circuit dysfunctions. Altered development of the brain's wiring is the most obvious mechanism."

## *Are we looking at cause or effect?*

### Tal Kenet

*Instructor in Neurology, Massachusetts General Hospital*

***Defining resting state:*** "Intrinsic connectivity, often referred to as 'resting-state' connectivity, measures synchronization between different brain regions in the absence of any particular task. Menon focuses on this type of connectivity in his Viewpoint article. But what does such connectivity really reflect? Resting state is a nebulous concept. While connected networks during resting state generally seem remarkably robust across different typical controls, there is evidence that **they are more variable in autism**. Could it be because the resting state itself is inherently different in individuals with autism? In other words, are we looking at cause or effect?"

***Sensory focus:*** "Individuals with autism, during resting state, may tend to reflect on sensations and input, rather than, say, on the movie they saw or the book they read, or their argument with their parents earlier that day. These are the kinds of places the mind normally wanders in typical individuals. But if individuals with autism really are focusing on sensations, it would not be a surprise that their salience network [which integrates information from the external world, such as sensory input, with their internal mental states] seems overconnected relative to controls, who are

focusing on more self-reflecting thoughts. This would also explain the correlations with behavioral scores."

***Validating metrics:*** "On the flip side, if they were explicitly directed to think about a recent social interaction during 'resting state,' would the results change? These findings are exciting, but without a clearer understanding of what resting state really is in autism relative to controls, it may be difficult to interpret the findings.

"The findings are in children, who are relatively poor reporters of their thoughts during the experiment. The call to investigate these metrics at different developmental stages is absolutely appropriate. It may be worthwhile to begin with adults, who could be better reporters of what resting state is like for them."

## *A surprising notion — and it might just be right*

### Jon Brock

*Research Fellow, Macquarie University, Sydney, Australia*

***A counterintuitive hypothesis:*** "Intuitively, the idea that the brain in autism is underconnected makes sense for many of the disorder's symptoms. But as Menon notes, there are an increasing number of studies finding the opposite — overconnectivity or, as Menon calls it, 'hyperconnectivity.' Much of the new data comes from children. Menon's argument seems to be that at some stage early in development, the autistic brain is hyperconnected, but later in development it becomes underconnected. This is an interesting idea — and it may be right."

***Mixed methods:*** "However, I think we first need to make sure that we're comparing like with like. I'm certainly not a functional MRI (fMRI) expert, but I wonder how much of the discrepancy between studies can be attributed to **different approaches in data analysis**. An interesting experiment would be for different research groups to analyze the exact same fMRI datasets independently and see whether they converge on the same conclusions."

***Developmental cycles:*** "We also need to look earlier in development. In a 2002 paper, my colleagues and I hypothesized that autism might be caused by disruption to the early development of brain connectivity[4]. We were inspired in part by a series of elegant electroencephalography (EEG) studies by Robert Thatcher [a former neuroimaging special expert at the National Institute of Neurological Disorders and Stroke][5].

"Thatcher found that in typically developing children, there are cycles of increasing and decreasing synchronization between electrodes at the front and back of the brain. This, he argued, is consistent with the idea that development involves a back-and-forth process of producing lots of synapses (leading to increased synchronization) and then pruning them, leaving only the connections that have been well used. Our idea was that this process might be disrupted in autism."

***Answer may be under our noses:*** "In light of Menon and colleagues' findings — and recent advances in EEG analysis[6] — perhaps now is a good time to revisit that idea. In fact, the relevant data may already be out there, collected as part of the various EEG studies of **baby siblings of children with autism**."

***Cross Talk*** *is a periodic discussion series that invites a diversity of reactions from the research community to new findings and hot topics in the field. Suggest future discussion topics here.*

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