VIEWPOINT

More or less connected in autism, compared to what?

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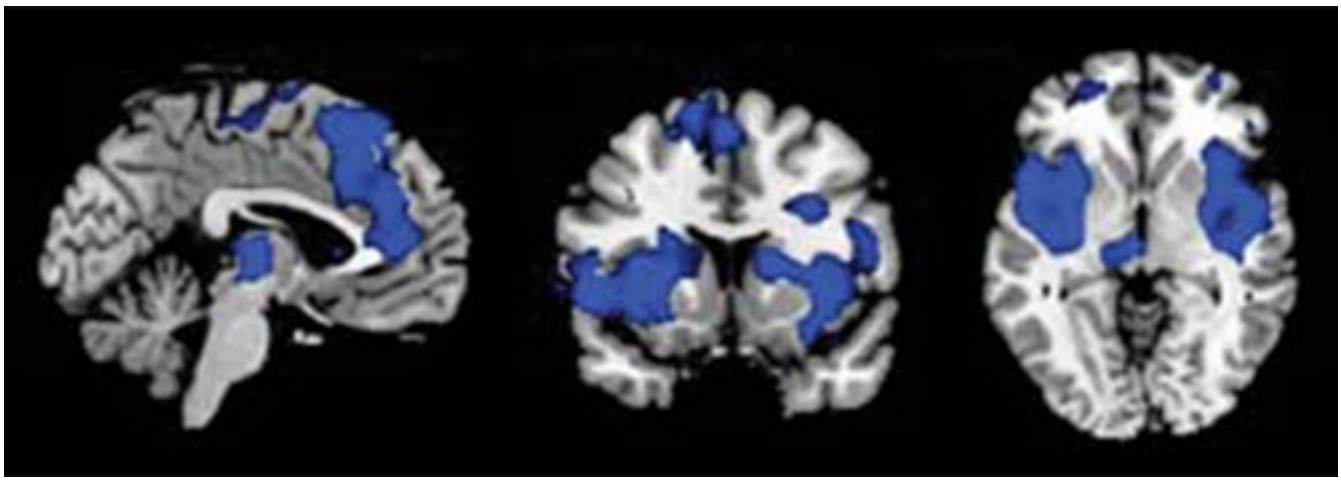

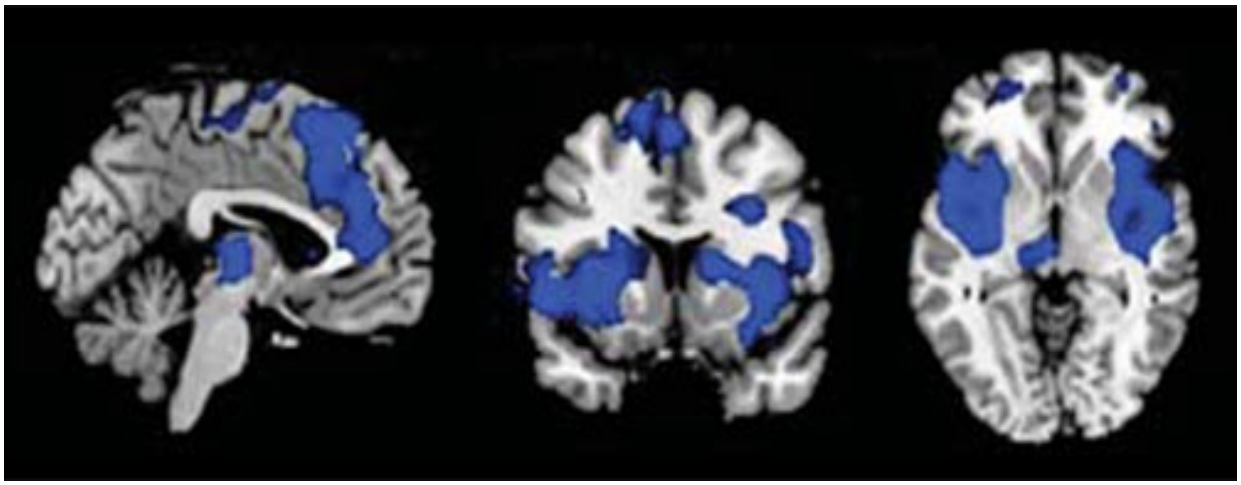

Emotional response: Children with autism show hyperconnectivity in the brain's salience network, which integrates external stimuli with internal mental states, such as emotion.

Many researchers have posited that underconnectivity, meaning weak connections between brain regions, is a hallmark of brain organization in autism. But emerging findings in children with autism are painting a decidedly more complex picture, showing both hyperconnectivity and underconnectivity in different regions and circuits throughout the brain.

This picture has thrown into sharp relief the challenges facing our understanding of brain connectivity in autism. At the same time, they open new possibilities for a deeper understanding of the neurobiological origins of the disorder.

New studies are using intrinsic functional connectivity — which measures how synchronized two or more brain areas are — to investigate typical and atypical development of functional brain networks in children[1]. These studies are revealing that in the brains of children with autism there is a surprisingly high level of hyperconnectivity, a finding that was not anticipated based on previous studies in adults.

Based on measurements taken when the brain is ‘at rest’ — while study participants are awake but not performing any task — five major brain networks are functionally hyperconnected in children with autism[2]. The salience network, which integrates information about external stimuli, such as sights or sounds, with internal mental states, such as emotion, is the most heavily hyperconnected network in autism.

Strong links:

Using data from the open-source **Autism Brain Imaging Data Exchange** (ABIDE) database[3], we have also found evidence for hyperconnectivity at the whole-brain level in more than 100 children with autism, between the ages of 7 and 12 years. Across three different research sites and magnetic resonance imaging (MRI) scanners, more regions show hyperconnectivity rather than underconnectivity in autism brains compared with controls. Remarkably, the degree of global brain hyperconnectivity also predicts the severity of social symptoms in childhood autism.

Crucially, hyperconnectivity in the salience network is associated with **repetitive behaviors** and restricted interests[2], and hyperconnectivity in the default mode network is associated with social deficits[4].

Hyperconnectivity is not uniform across brain regions in children with autism, however — some circuits have weaker connections than in controls. Notably, links between brain regions that

respond to the human voice and those that process reward are weakly connected in children with autism. What's more, the weaker these connections are, the worse the children's language and communication deficits[5].

Thus, hyperconnectivity and underconnectivity coexist in childhood autism, are behaviorally and clinically meaningful, and help explain distinct clinical features of the disorder.

These findings highlight the need to reassess our current thinking about underconnectivity as an organizing principle in the autism brain, and underscore the need to reconsider aberrations in brain connectivity from a developmental perspective[6]. In particular, they point to a critical need for further research on how brain connectivity changes with age — not just in individuals with autism, but also in the comparison group of typically developing individuals.

These 'controls' are themselves undergoing significant maturational changes in brain connectivity during childhood and adolescence[7]. The developmental profile of hyperconnectivity and underconnectivity in autism from infancy to adulthood has yet to be charted. Progress in this direction will lead to a more comprehensive understanding of the neurobiology of autism[2].

Model connections:

It will also be important to link findings of connectivity in humans toanimal models of autism. We need to link hyperconnectivity and underconnectivity in autism to the underlying physiology of local neuronal circuits and their interconnectedness with other brain areas[1].

Remarkably, intrinsic hyperconnectivity in childhood autism is consistent with findings in animal models of autism, which have generally reported hyperconnectivity in local neuronal circuits[2]. Two findings published this year may help us link local circuit aberrations seen in animal models to the large-scale hyperconnectivity observed in children with autism.

First, in our own studies of children, we have found evidence for abnormal high-amplitude oscillations in local functional MRI signals,likely arising from hyperconnectivity and hyperexcitability in local neuronal circuits[8]. Crucially, the amplitude of these oscillations is positively correlated with hyperconnectivity between distant brain regions in children with autism[3].

Second, a magnetic resonance spectroscopy study found an imbalance in the ratio of neurotransmitter signals that excite (glutamate) versus those that inhibit (GABAergic) brain activity. Within the posterior cingulate cortex, this imbalance correlates with greater large-scale connectivity within the default mode network[9]. This finding is noteworthy because the posterior cingulate cortex — a key node of the default mode network and a major hub in the brain — is structurally aberrant[10]. Postmortem studies have shown that this region has irregularly distributed neurons[11] and has fewer receptors for gamma-aminobutyric acid (GABA) in individuals with autism than in controls[12].

Although preliminary, these findings suggest that the relative balance of excitation and inhibition in local circuits may play a key role in altering brain connectivity, contributing to both hyperconnectivity and underconnectivity in autism.

This discussion brings to the fore an unaddressed challenge in the field: How do hyperconnectivity and underconnectivity within specific brain circuits each affect information processing in autism? One possibility is that that there is an optimal range of connectivity required for information processing. Outside of this range, the ability of local circuits to influence processing in a distal brain region may be limited.

The degree to which this manifests as reduced or enhanced modulation of connectivity in specific brain circuits may influence how the brain processes sensory, cognitive, affective and social information in individuals with autism.

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