

The Triple Network Model, Insight, and Large-Scale Brain Organization in Autism

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Autism is characterized by significant heterogeneity in the degree of social and emotion impairments. Addressing sources of variability in the expression of clinical symptoms, behavioral phenotypes, and their underlying neural bases is now a growing focus of research into the neurobiology of autism. In this issue of *Biological Psychiatry*, two studies investigate heterogeneity in autism from different viewpoints. Both studies are based on intrinsic brain connectivity analysis of resting-state functional magnetic resonance imaging (fMRI). The study by Hogeveen *et al.* (1) uses the triple network model of psychopathology (2) as a framework for characterizing sources of variability in internalizing symptoms in children and adolescents with autism and for determining brain signatures that index lack of insight into their own psychopathology. The second study by Dickie *et al.* (3) investigates heterogeneity in brain organization arising from anatomical and spatial variation in functional networks.

The triple network model of psychopathology posits that aberrant functional organization of the salience network (SN), frontoparietal network (FPN), and default mode network (DMN) and their dynamic cross-network interactions underlie a wide range of psychopathologies, including autism (2,4). The SN integrates sensory, emotional, and cognitive information and acts as an interface between the DMN and the FPN to integrate and balance internal mental processes with external stimulus-driven cognitive and affective processes (2). Dysfunction in frontoparietal-opercular neurocognitive networks have been reported (4), and the DMN's role in social dysfunction is now increasingly clear (5), but their relation to internalizing symptoms in autism has not been directly investigated.

Internalizing symptoms, including anxiety, phobias, somatization, and excessive worry, are prominent in autism spectrum disorders and can exacerbate primary autism symptom severity (6). Drawing on the triple network model, Hogeveen *et al.* (1) examine cross-network interactions between the SN, FPN, and DMN and their relation to internalizing symptoms in autism and, more importantly, to lack of accurate self-appraisal, which is operationalized as the difference between self- and parent-reported internalizing symptoms.

The main new finding of Hogeveen *et al.* (1) is that lack of accurate self-appraisal was correlated with dysfunction in interactions between the SN and DMN, and in particular with hyperconnectivity between the insula node of the SN and the retrosplenial cortex node of the DMN. However, internalizing symptoms were not directly related to dysfunction in insula-retrosplenial cortex circuitry. Rather, using path analysis, the

authors report that the relation between internalizing symptoms and SN-DMN dysfunction was mediated by reduced insight in individuals with autism.

The study highlights a novel use of mismatch between self and parent rating to investigate internalizing symptoms. Hogeveen *et al.*'s approach (1) has a particular strength and a potential weakness. On one hand, the ratings are based on standardized checklists that are routinely used in developmental and clinical studies—this is a strength. On the other hand, the joint use of parent-rated internalizing symptoms and “lack of insight” measures in the mediation model is problematic given that the latter are derived from parent-rated internalizing measures—that is, the predictor and mediator are not strictly independent measurements. Nevertheless, the finding that hyperconnectivity between the insular cortex and retrosplenial cortex may contribute to lack of insight into one's psychopathology is important in its own right because it suggests a viable target for interventions to improve awareness of one's symptoms. An important question for future research is whether dysfunction in SN-DMN circuitry and discrepancies between self-described and observed internalizing behaviors can be used to probe an individual's lack of insight into psychopathology in other psychiatric disorders where similar aberrations exist, such as bipolar disorder and schizophrenia.

The manner in which aberrations in SN-DMN circuitry contribute to internalizing symptoms, such as anxiety, emotion awareness, and emotion regulation, also remains to be investigated. A surprising aspect of the Hogeveen *et al.* study (1) relates to the retrosplenial cortex as the locus of SN-DMN dysfunction rather than ventromedial prefrontal cortex regions implicated in anxiety and mood disorders. Further work is needed to disentangle social and nonsocial factors that contribute to internalizing symptoms, including social anxiety, generalized anxiety, and phobias, as they are thought to engage different brain systems. The role of other nodes of the SN (e.g., the posterior insula), DMN (the ventromedial prefrontal cortex), and FPN (e.g., the dorsolateral prefrontal cortex) as well as subcortical systems, including the amygdala, will be crucial to investigate.

The study by Dickie *et al.* (3) takes a different approach to examining heterogeneity in autism and examines spatial heterogeneity of brain network organization in autism and how brain networks might get spatially tuned with age. The past 10 years of neuroimaging research have advanced our understanding of atypical functional brain organization in autism, but findings have been based on a set of interacting brain areas

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(nodes), the anatomical locations of which are assumed to be identical across participants and groups. But what if they are not, despite our best attempts at nonlinear spatial registration of brain images? Anatomical variability of network nodes and their equivalence among individuals is a topic of great interest as functional circuits underlying key aspects of cognition may differ across individuals and at different stages of development. This is particularly true for developmental disorders such as autism in which brain anatomy, functional organization, and developmental trajectory may differ significantly from neurotypical individuals.

To address the challenge of brain network variability at the node level, Dickie *et al.* (3) propose a personalized intrinsic network topography (PINT) algorithm and apply it to resting-state functional magnetic resonance imaging data from the open-source ABIDE consortium (7). ABIDE has significantly advanced the study of autism with resting-state functional magnetic resonance imaging and phenotypic data from more than 2000 individuals. ABIDE data have facilitated key discoveries regarding brain organization in autism, but no study has directly examined anatomic variability in network organization. Rather, most previous studies have assumed strict correspondence between network node across participants and sites.

The PINT algorithm was applied to 80 template nodes from the DMN and the ventral attention, frontoparietal, dorsal attention, sensory motor, and visual networks identified by Yeo *et al.* (8). PINT works as follows: for each participant, the algorithm iteratively shifts the locations of each network node to a nearby cortical location (within 6 mm), or “personalized” node, that maximizes the partial correlation of the node with other nodes from its network. The approach is a generalization of a method to improve transcranial magnetic stimulation targeting the dorsolateral prefrontal cortex in a participant-specific manner based on correlations with the subgenual cingulate cortex (9). For each network and participant, the shift in individual node locations from their initial template node locations is used as an index of spatial variability in network organization. Note that PINT does not shift nodes across networks, only their anatomical location within each network, and yields an average increase of 52% in within network connectivity, from about 0.34 to 0.52, and a decrease in between-network connectivity of 20% from 0.15 to 0.12.

The main finding of the study is that individuals with autism showed greater spatial shifts in cortical resting-state networks than age-matched control participants. Interestingly, an age by group interaction was observed with intrinsic network location variability decreasing linearly from 8 to 30 years of age in control participants, but not in individuals with autism. This finding suggests weaker reorganization and fine tuning of network architecture with age in autism compared to control subjects.

Dickie *et al.*'s findings (3) add to growing evidence of unique heterogeneity of cortical organization in autism. The specific question of equivalence of network nodes across individual participants is important, and an optimal solution to this problem may have broad implications for the study of developmental psychopathologies. PINT and other related approaches may lead to better characterization of individual

networks, more reliable subtyping and symptom prediction, and more precise identification of anatomical targets for intervention and circuit manipulation. However, caution is needed in the use of PINT-like algorithms because exactly what is gained in terms of insights into the neurobiology of autism spectrum disorder symptoms is still unclear. For example, it is not clear whether PINT-derived network metrics are better predictors of clinical symptoms than standard template-based approaches. PINT might in fact reduce variability in network properties, making it less sensitive to detecting group differences and addressing the clinical relations it set out to study in the first place. Further studies that directly compare findings with and without shifts in network node layout are needed to address this question. Whether the observed variation stems from genetic variability, as the authors suggest, or more mundane methodological issues, such as errors in anatomical-functional registration, remains unclear. Finally, future studies will need to include crucial subcortical nodes, including the amygdala and striatum, whose connectivity is known to be impaired in autism.

Overall, the two studies add to our growing knowledge of heterogeneity in autism. Both studies use intrinsic functional connectivity to probe heterogeneity—one in terms of lack of an individuals' insight into their own symptoms, a clinical feature that has not been investigated in developmental psychopathology before, and the other in terms of heterogeneity in brain network organization. They both provide new and complementary tools for investigating aberrancies in the functional architecture of the developing brain and their relation to psychopathology (10).

Acknowledgments and Disclosures

This work was supported by National Institute of Mental Health Grant No. MH084164 and by a Nichols Professorship.

The author reports no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Jun 14, 2018; accepted Jun 19, 2018.

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