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Commentary

Connectivity in Context: Emphasizing Neurodevelopment in Autism Spectrum Disorder

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Convergent evidence from genetics, neuropathology, and functional neuroimaging implicates aberrant cortical connectivity in the pathogenesis of neurodevelopmental disorders, such as autism spectrum disorder (ASD). Chromosomal variants associated with ASD include genes that are critical for synaptic structure and function, leading to a hypothesis that ASD results from a failure to establish necessary cortical connections, particularly in brain regions critical for social cognition and language (1). Although brain connectivity has become a central concept in autism research, its operationalization varies widely among studies. Defined broadly, connectivity refers to associations between brain components that can range in scale from individual neurons to large brain regions spanning multiple neuroanatomic structures (2).

Connectivity may be categorized as structural, functional, or effective. Structural, or anatomic, connectivity refers to physical links between nodes of a network (e.g., white matter tracts measured by diffusion tensor imaging). Functional connectivity reflects the statistical dependence of nodes on one another (e.g., temporal covariation in hemodynamic activity in separate regions measured by functional magnetic resonance imaging). Effective connectivity corresponds to the presumed causal influence of one node on another within prespecified, theoretically derived networks (e.g., predictive value of electrophysiologic brain activity in one region on activity in disparate regions, analyzed with structural equation modeling) (3). Connectivity patterns in the brain can be represented mathematically as networks, with various measures that quantify the strength and efficiency of connections among nodes. Because the brain is a dynamic system, connections at the micro (cellular) and macro (cortical regions) levels change over time through intrinsic and extrinsic influences, with functional and effective connectivity being more temporally sensitive than structural connectivity to these fluctuations.

Despite limitations in spatial resolution, electrophysiology (through electroencephalography and magnetoencephalography) provides an ideal method for the investigation of functional connectivity. As a direct measure of postsynaptic brain activity, electrophysiology has several orders of magnitude greater temporal resolution than functional magnetic resonance imaging, allowing it to resolve neurophysiologic oscillations and dynamics and to provide information about timing required for analysis of effective connectivity.

Kitzbichler et al. (4) apply a sophisticated methodologic approach to address the challenges inherent in functional connectivity research in ASD. To achieve temporal and spatial resolution, they use the structural information provided by magnetic resonance imaging to inform the sources of temporally sensitive magnetoencephalography recordings of brain networks at rest, effectively measuring brain activity with respect to space and time. By generating connectivity matrices for each subject in five distinct frequency bands and applying tools from mathematical models for network analysis (graph theory), the authors characterize differences in connectivity across cortical regions as a function of diagnostic grouping (ASD vs. typically developing [TD] control subjects) and individual differences (chronologic age, autism symptoms). To the authors' credit, and in contrast to much prior work, they present a complex picture of connectivity in the brains of individuals with ASD that is not characterized by simple overconnectivity or underconnectivity. Group differences were evident primarily in high-frequency oscillations, with the ASD group demonstrating networks in the gamma band that were more efficient, integrated, and widely distributed than in the TD group; network density (the average number of connections from each node in the network) in these high-frequency bands was also associated with level of symptoms in core features of ASD. A developmental trend of frontal networks increasing in density with age was observed only in the TD group, suggesting atypical maturation of connectivity networks in individuals with ASD.

Although these developmental findings are constrained by a small sample size and broad age range, Kitzbichler et al. highlight a key issue in the theoretical conceptualization of brain development in individuals with ASD—the role of generically impaired systemic connectivity versus dysfunction in functionally specific brain systems. Connectivity studies, including the study by Kitzbichler et al., tend to implicate domain-general brain dysfunction in ASD. In these models, the clinical phenotype emerges from limitations in the functional capacity of a disconnected brain. For example, deficient cortical connectivity may preclude the complex neural computations required for experiential learning or effective interpersonal interaction, leading to the disruptions in social and communicative behavior that are the hallmarks of ASD (5). In contrast, domain-specific social accounts of the neuropathology of ASD implicate dysfunction specific to brain regions and networks subserving social communication. These accounts posit that the core impairments of ASD result from dysfunction in designated brain systems that evolved to process information pertaining to conspecifics (6). These social functions and associated brain regions include face perception (fusiform gyrus), biological motion perception (superior temporal sulcus), the action-perception system (inferior frontal gyrus), perception of emotional states and emotional experience (amygdala), and social reward (orbitofrontal cortex) (7).

Current evidence indicates dysfunction in these functionally specific brain systems and larger scale networks, raising important questions about developmental primacy. ASD is a

neurodevelopmental disorder with symptoms emergent in the first years of life; the patterns of regional and systemic brain activity observed in children with ASD likely represent the interplay of innate neural anomalies and their developmental sequelae. As illustrated in Figure 1, the presumptive neural state in individuals with ASD (Figure 1C) is characterized by dysfunction (displayed in red dashed lines) in localized activation in regions essential for social function and connectivity among disparate regions. However, the developmental precursors of this state are unknown. As shown in Figure 1A, innate structural or functional deficiencies in connectivity may exist early in development and preclude appropriate development of brain regions subserving social and communicative abilities (e.g., domain-general accounts). Conversely, as illustrated in Figure 1B, early dysfunction in one or more nodes of the network underpinning social behavior could emerge first (e.g., domain-specific accounts), preventing establishment of typical functional and structural functional connectivity (8).
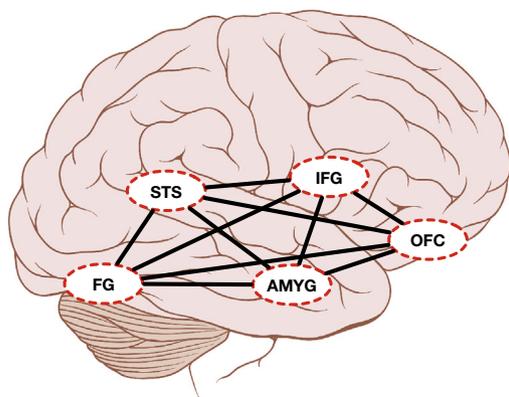
Prospective studies of infants at high risk for developing ASD have not yet resolved this debate, providing evidence for both possibilities (9,10). Given the appropriateness of electrophysiologic recording methods for infants, the application of the techniques of Kitzbichler *et al.* in larger, longitudinal samples of infant cohorts offers unique promise to address this question about neurodevelopment in ASD.

In addition to emphasizing the importance of studying neuropathology in a developmental context, the work of Kitzbichler *et al.* raises numerous considerations germane to most studies of resting brain connectivity in ASD, particularly involving task design and participant characteristics. Kitzbichler *et al.* assessed resting activity during a prolonged visual fixation to an immobile crosshair, a common approach to the study of baseline brain activity. The viability of this method relies on the presupposition that clinical and typical groups approach this task in a similar fashion. Many factors, such as sensory sensitivities, attentiveness, mood, level of

A. Domain-general disconnectivity

C. ASD state dysfunction
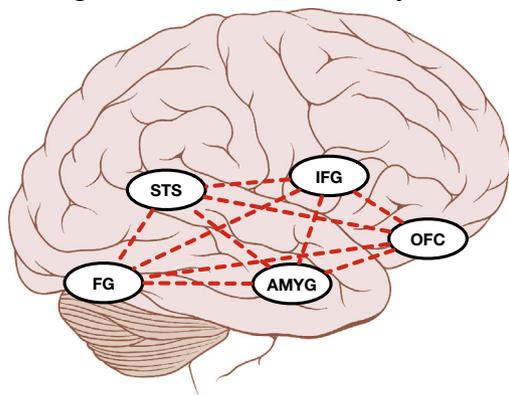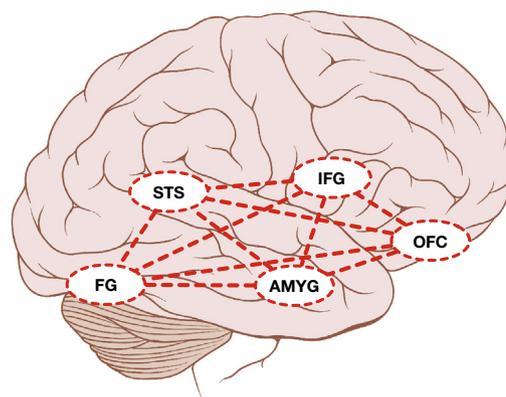
B. Domain-specific regional dysfunction

Figure 1. **(A,B)** Potential developmental precursors for autism spectrum disorder (ASD). **(A)** Domain–general developmental account in which generic, potentially brain-wide (only connections among social nodes are depicted for parsimony) deficiencies in connectivity preclude typical specialization of individual regions supporting social and communicative function. **(B)** Domain-specific account in which initial insult to functionally specific brain regions subserving social communication prevents normative development of interregional connectivity. **(C)** Recognized patterns of dysfunction (dotted red lines) in individuals with ASD, reflecting widespread anomalies in disconnectivity (lines connecting regions) and atypical activity in specific regions subserving social and communicative abilities (specified nodes). AMYG, amygdala; FG, fusiform gyrus; IFG, inferior frontal gyrus; OFC, orbitofrontal cortex; STS, superior temporal sulcus.

comprehension, and the presence of experimenters in the room, can introduce elements that may differentially affect individuals with ASD and TD control subjects. In this study, the investigators focused on chronologic age and autism symptoms (based on scores from a standardized diagnostic measure) as relevant factors. Although the group differences in IQ did not reach statistical significance, the ASD group included individuals in the impaired-to-borderline range of cognitive ability, leading to the possibility that differences in cognition may have contributed to observed differences in connectivity. This IQ difference becomes an especially relevant consideration given that observed increases in frontal network activity may reflect increased cognitive effort reflective of group differences in attention (i.e., increased difficulty of maintaining a prolonged fixation) or comprehension (e.g., increased effort to understand test demands). Given the exclusively male sample in this study, it will be important to investigate in future work generalizability to girls with ASD, a severely understudied group.

Finally, these sophisticated network methods could facilitate, with larger samples and richer clinical characterization of individuals, meaningful advances in diagnostic stratification, leading to the definition of biologically based subgroups within the autism spectrum. Such subgroups could directly inform intervention targets, and connectivity metrics could be tracked as quantitative measures of treatment response. For instance, weighted graph density might identify a subgroup of children with reduced connectivity in the gamma band in frontal cortex who are more responsive to behavioral interventions that target cognitive domains modulated by prefrontal cortex. The integration of these refined connectivity measures with genetics and behavioral data could help realize the ultimate goal of personalized, evidence-based care for children with ASD.

In conclusion, Kitzbichler *et al.* apply state-of-the-art imaging technologies and sophisticated analytic approaches to highlight the complexity of atypical patterns of connectivity in ASD. This work draws attention to the central nature of brain maturation in the study of neurodevelopmental disorders and highlights the challenges inherent in studying complex patterns of brain activity in heterogeneous samples. This study offers a launching point for next-generation connectivity research in ASD.

Article Information

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