Commentary

Biological Psychiatry

Autism as a Disorder of Altered Global Functional and Structural Connectivity

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For a long time, autism spectrum disorder (ASD) played only a minor role in clinical adult psychiatry and psychotherapy. This situation recently changed, particularly when high functioning variants of ASD were recognized as an underlying basic disorder or personality structure on which secondary forms of psychiatric reactions, such as in depression, anxiety, or personality disorders, arise (1). From a clinical perspective, it is important to recognize the autistic pattern for a more comprehensive understanding of the psychodynamics of the psychopathology. For example, a secondary conflict-induced depressive syndrome can be explained by the conflict-inducing rigidity, stereotypies, or interpersonal communication difficulties of the patient as a sequela to the autistic structure (1).

The psychobiological and social consequences of autistic features are now considered to be independent from the cause of autism. However, patients with autism as well as physicians and scientists want to understand the causes of this developmental disorder. Etiologically, it is well recognized that autism does not represent a single disease entity. Rather, autism is an umbrella term for etiologically heterogeneous diseases with different neurobiological causes (2). In this context, the distinction between secondary and primary forms of autism has recently been suggested to reintroduce elements of causal thinking into the purely descriptive classification of ASD in DSM-5 and ICD-11. Secondary autism is represented by clear-cut monogenetic or oligogenetic syndromic variants or recognized acquired causes, such as valproate exposure in utero, whereas in primary autism, no such causes can be discovered (3). Still, primary autism runs in families, and therefore a complex familial genetic pattern is assumed in which $\geq$100 genes interacting with environmental factors represent the heritability of autism (2,4).

However, despite different neurobiological causes, secondary and primary forms of autism must have some commonality because the typical psychopathologic features of autism (problems in social perception, social cognition, and communication; rigidity and the need for routines and stereotypies; and perceptual abnormalities, such as the propensity for sensory overflow, special interests, and gifts) do cluster. This empirical observation is obvious to every clinician familiar with ASD and supports the notion that there might be a common final pathophysiologic pathway to the different causes of autism.

It has been suggested that the brain's functional or structural connectivity pattern might represent such a common final pathway or neurobiological pathogenetic correlate of the autistic phenotype where different ASD etiologies converge (3,5,6). Following this line of thought, the nonautistic or holistic endophenotype is characterized by intensive long-distance cerebral communication as expressed by increased functional or structural connectivity of separated brain regions and circuits. This connectivity leads to a high degree of synchronization of global cerebral information processing. In contrast, the autistic pattern of information processing is characterized by a reduced long-distance communication (5) and enhanced "local network connectivity" (Figure 1) (7). In this model, enhanced local network connectivity is not a mandatory pattern in all ASD variants. However, the increased likelihood for local neuronal networks to develop idiosyncratic functional features might be a function of the reduced "holistic control" of the global pattern of information processing (3), and it might explain the increased prevalence of special capacities or phenomena, such as synesthesia, in ASD.

This hypothesis of specifically altered neuronal network connectivity has also been linked to the idea of an excitation-inhibition dysbalance and the increased prevalence of epilepsy and electroencephalography pathologies in autism (2,3). The enhanced excitation-inhibition dysbalance or subclinical epileptiform discharges represent one of the different possible causes that stimulate the restructuring of the global neuronal network into the autistic pattern of connectivity (3). In this theory, pathologic excitatory discharges that gain access to the global network through long-distance connections are counteracted by the global network in a homeostatic move to maintain functional equilibrium. Dampening or terminating affected long-distance connections might induce the same autistic pattern of information processing caused by the interplay of several hundred genes in primary autism (Figure 1). This pathogenetic theory of autism, as a correlate of a specific functional/structural connectivity pattern, is able to integrate secondary forms of autism in the context of epilepsy, which are categorical in nature, as well as dimensional variants as represented by primary familial autism.

In this issue of *Biological Psychiatry*, Nebel *et al.* (8) present intriguing evidence in support of such etiopathogenetic models of autism. They start with the observation that impairments in visuomotor integration, which are thought to be related to the brain's wiring, are well-documented phenomena in autism. Based on the above-illustrated model, they hypothesize that long-range visuomotor functional connectivity would be reduced in children with ASD compared with their typically developing peers. To test this hypothesis, the authors investigated 50 children 8–12 years old with autism and compared them with 50 typically developing 8- to 12-year-old children by acquiring resting-state functional magnetic resonance imaging data in all subjects. Behavioral and psychometric data included social deficit severity, imitation capacities, and

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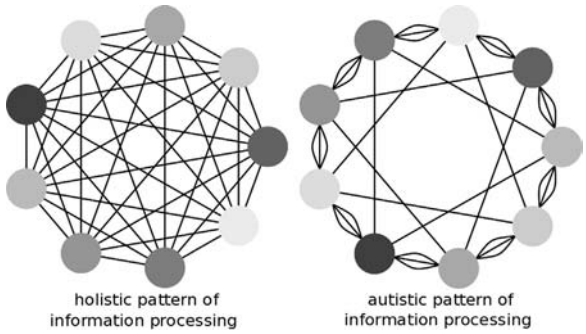

Figure 1. Illustration of autism as an altered functional/structural pattern of network connectivity. The nonautistic or holistic mode of information processing (neurotypical control subjects) is characterized by the intensive cross-talk of distant neuronal modules and circuits. In autism, there is less long-distance communication.

gesture performance scores. The main finding was an increased intrinsic asynchrony between higher order visual information processing and motor area activity in children with ASD. The authors were able to replicate this primary finding in an independent sample from the Autism Brain Imaging Data Exchange. The finding of unimpaired early visual information processing with abnormal signals in higher level vision correlates with similar neurophysiologic and psychophysical findings in adults with high functioning primary ASD (9). Psychometrically, Nebel *et al.* (8) show that the severity of visuomotor activity desynchronization was associated with more severe autistic traits and inversely linked to better imitation capacities. They interpret their findings as a correlate of reduced global neuronal network integration.

These findings support the model of a specifically altered global neuronal network architecture in autism as outlined here and in Figure 1. In this framework, the autistic mode of information processing can be understood as an extreme variant of a dimensional trait, which is probably caused by a very large number of genes with small effect sizes. This is the likely constellation of primary familial autism or the broader autism phenotype. Such an "autistic connectivity pattern" can also be induced by a single gene or a few genes with large effect sizes (syndromal autism) or other causes such as epilepsy, encephalitis, or valproate exposure in utero (secondary autism). Other recent research supports the theory that a combination of categorical and dimensional factors has to be considered to explain the complex causality of autism (10) and that not only functional—as in the study by Nebel *et al.* (8)—but also structural connectivity is a key factor in such pathogenetic models of autism (6).

In conclusion, Nebel *et al.* (8) present solid evidence that the autistic syndrome is linked to desynchronized processes of long-distance or global cerebral information processing. The data support a model of autism in which the final pathogenetic pathway is represented by a less centralized or harmonized pattern of global neuronal information processing, leaving local networks and circuits the cybernetic "freedom" to develop idiosyncratic properties. This pathogenetic theory is heuristically strong in that it can explain how different causal pathways of secondary (monogenetic, oligogenetic, acquired) or primary (polygenetic familial) autism can lead to a similar clinical picture. By including dimensional and categorical features, such a model might prove useful in explaining the neurobiological nature of autism in different patient subgroups.

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Article Information

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