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Review

Disrupted cortical connectivity theory as an explanatory model for autism spectrum disorders

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Abstract

Recent findings of neurological functioning in autism spectrum disorder (ASD) point to altered brain connectivity as a key feature of its pathophysiology. The cortical underconnectivity theory of ASD (Just et al., 2004) provides an integrated framework for addressing these new findings. This theory suggests that weaker functional connections among brain areas in those with ASD hamper their ability to accomplish complex cognitive and social tasks successfully. We will discuss this theory, but will modify the term underconnectivity to 'disrupted cortical connectivity' to capture patterns of both under- and over-connectivity in the brain. In this paper, we will review the existing literature on ASD to marshal supporting evidence for hypotheses formulated on the disrupted cortical connectivity theory. These hypotheses are: 1) underconnectivity in ASD is manifested mainly in long-distance cortical as well as subcortical connections rather than in short-distance cortical connections; 2) underconnectivity in ASD is manifested only in complex cognitive and social functions and not in low-level sensory and perceptual tasks; 3) functional underconnectivity in ASD may be the result of underlying anatomical abnormalities, such as problems in the integrity of white matter; 4) the ASD brain adapts to underconnectivity through compensatory strategies such as overconnectivity mainly in frontal and in posterior brain areas. This may be manifested as deficits in tasks that require frontal–parietal integration. While overconnectivity can be tested by examining the cortical minicolumn organization, long-distance underconnectivity can be tested by cognitively demanding tasks; and 5) functional underconnectivity in brain areas in ASD will be seen not only during complex tasks but also during task-free resting states. We will also discuss some empirical predictions that can be tested in future studies, such as: 1) how disrupted connectivity relates to cognitive impairments in skills such as Theory-of-Mind, cognitive flexibility, and information processing; and 2) how connection abnormalities relate to, and may determine, behavioral symptoms hallmarked by the triad of Impairments in ASD. Furthermore, we will relate the disrupted cortical connectivity model to existing cognitive and neural models of ASD.
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Keywords: Functional connectivity; Autism; fMRI; Theory-of-Mind; Cognitive flexibility; Processing speed; Triad of impairments

Abbreviations: ASD, Autism Spectrum Disorder; fMRI, functional Magnetic Resonance Imaging; ToM, Theory-of-Mind; DTI, Diffusion Tensor Imaging; PET, Positron Emission Tomography; FA, Fractional Anisotropy; ACC, Anterior Cingulate Cortex; PCC, Posterior Cingulate Cortex; EEG, Electroencephalogram; MEG, Magnetoencephalogram; MPFC, Medial Prefrontal Cortex; DLPFC, Dorsolateral Prefrontal Cortex; GABA, Gamma Aminobutyric Acid; TPJ, Temporoparietal Junction; STS, Superior Temporal Sulcus.

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1. Background

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in social interaction, language and communication, and restricted interests and repetitive stereotyped behaviors [1]. The Center for Disease Control (CDC) estimates the prevalence of ASD to be 1 in 110 children, affecting all racial, ethnic, and socioeconomic groups equally, with 4–5 times greater prevalence in boys than in girls [2]. Individuals with ASD often display challenging problem behaviors, such as self-injury, aggression, tantrums, stereotypies (repetitive, purposeless movements or utterances), anxiety, sleep disturbances, problems with feeding, and non-compliance with directions [3]. They may also display odd, repetitive behaviors, such as hand flapping, tip-toe walking, body rocking, echolalia (automatic repetition of others' speech), or spinning objects [4,5]. It is estimated that around 15% of individuals diagnosed with ASD will become reasonably self-sufficient by adulthood, while another 15–20% will function well with sporadic support [6]. ASD is often co-morbid with other disorders, such as attention deficit hyperactivity disorder (ADHD) and seizures, and 50–75% of individuals with ASD also have an intellectual disability [7,8]. The autism spectrum refers to several disorders including classic autism, high-functioning autism, Asperger Syndrome, Rett Syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). While all of these disorders share similar developmental characteristics, the discussion in this paper will mostly focus on classic autism, high-functioning autism, and Asperger Syndrome.

Autism was first described by Leo Kanner in 1943, in a case description of 11 children who demonstrated a lack of social engagement, absence of language, and a strong need for sameness [9]. By 1978, the criteria for ASD were refined to include the triad of impairments currently used today: 1) impairments in social interaction, 2) impaired communication, and 3) restricted and repetitive behaviors and interests [10,11]. ASD is currently diagnosed based on this behavioral phenotype according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) [12], with patients meeting criteria by demonstrating symptoms in all three areas by the age of 3 years. The most commonly used tools for diagnosis are the Autism Diagnostic Observation Schedule-Generic (ADOS-G) [13] and the Autism Diagnostic Interview-Revised (ADI-R) [14]. While the behavioral manifestation of ASD spans social, communicative, and cognitive domains, making it quite an intriguing disorder, such breadth of symptoms has made it difficult to discover a unifying causal explanation.

Although it has been established that ASD is a disorder with genetic and neurobiological origin, the quest for a single gene or a focal brain area to explain its origin has been elusive. Instead, genetic research has pointed to hundreds of genes with links to ASD [15], and neurobiological investigations have implicated several brain areas as abnormal in ASD [16]. As the quest for causal explanations of ASD continues, designing effective and early interventions to improve the lives of affected individuals is equally or more important. Empirical evidence suggests that children with ASD who enter programs at younger ages make greater gains than those who enter programs at older ages [17,18]. At present, behavioral therapy is used to improve functioning and independent living skills, and language interventions are implemented to improve communication. On the pharmacological front, psychotropic medications and other drugs are often prescribed to those with ASD to reduce anxiety and aggression toward the self or others. While these medications may reduce negative behaviors, they do not treat the core symptoms of ASD. The difficulties that people with ASD experience are usually manifested in interpersonal interactions and complex cognition. The triad of impairments that defines ASD is a good starting point for studying behavioral differences, tracing autism back to its causes, and finding appropriate solutions.

Social impairment is the hallmark of ASD and may include issues with social referencing, difficulty initiating and responding to social cues, difficulty initiating and maintaining eye contact, failing to engage in joint attention, or displaying inappropriate emotional reactions [19–23]. As a result of their difficulties with social interactions, children with ASD are often rejected by peers, have difficulty achieving success in school, and may develop other mental health problems [24,25]. While social difficulties in ASD are striking, such difficulties are also intertwined with problems in language and communication. It is estimated that about 20–50% of children with ASD may not develop functional speech [26,27]. Of those who do, some children with ASD will develop speech late in childhood [28]. For individuals who have reasonably good language, the problem lies in using language in social communication or in dealing with the pragmatic aspects of language [27,29,30]. A relatively under-researched component of the triad of impairments in ASD is the one involving repetitive and restricted behaviors and interests. Persons with ASD may have restricted, narrow interests, form odd object attachments (such as with a household broom instead of a teddy bear), or have an unusual preoccupation with objects (e.g., repeatedly spinning the wheel of a toy car) [31]. They may also display