Review

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The Default Mode Network in Autism

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ABSTRACT

Autism spectrum disorder (ASD) is characterized by deficits in social communication and interaction. Since its discovery as a major functional brain system, the default mode network (DMN) has been implicated in a number of psychiatric disorders, including ASD. We review converging multimodal evidence for DMN dysfunction in the context of specific components of social cognitive dysfunction in ASD—self-referential processing, which is the ability to process social information relative to oneself; and theory of mind or mentalizing, which is the ability to infer the mental states, such as beliefs, intentions, and emotions, of others. We show that altered functional and structural organization of the DMN and its atypical developmental trajectory are prominent neurobiological features of ASD. We integrate findings on atypical cytoarchitectonic organization and imbalance in excitatory-inhibitory circuits, which alter local and global brain signaling, to scrutinize putative mechanisms underlying DMN dysfunction in ASD. Our synthesis of the extant literature suggests that aberrancies in key nodes of the DMN and their dynamic functional interactions contribute to atypical integration of information about the self in relation to "other" as well as to impairments in the ability to flexibly attend to socially relevant stimuli. We conclude by highlighting open questions for future research.

Keywords: Autism, Default mode network, Mentalizing, Self-referential processing, Social, Theory of mind

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AUTISM SPECTRUM DISORDER, SOCIAL DEFICITS, AND DEFAULT MODE NETWORK

Autism, derived from the Greek word "auto" meaning "self," describes a lack of interest in social interactions with the "other." The term autism was first used by Eugen Bleuler to describe adolescents and adults with schizophrenia (1), and it became the cornerstone for Leo Kanner's characterization of infants and young children who showed a lack of interest in communicating with others and appeared to be "lost in their own narrow worlds" (2). Although these early descriptions have been influential in describing the cluster of social impairments now known to characterize autism spectrum disorder (ASD), it has become increasingly evident that self-related cognitive processing is also atypical in affected individuals (3). Understanding of "self" in the context of "other" is integral to successful social interactions (4), and it is theorized that individuals with ASD struggle with reciprocal social interaction largely owing to difficulties in both self-referential cognitive processing and inferring the mental states of others (5). Perhaps it is not surprising then that the default mode network (DMN), a core brain system for processing information about the self and other (6,7), has emerged as a key system underlying social dysfunction in ASD (3,6–9).

Despite the unique functional properties of the DMN and its links to the ASD phenotype (10), few attempts have been made to synthesize the extant multimodal literature and provide a unified framework of DMN dysfunction in ASD. We review converging evidence from multiple scales of brain organization that DMN dysfunction is a significant component of social impairments in ASD. We first describe the functional architecture of the DMN, focusing on aspects of social function that are known to be affected in ASD. These include self-referential processing, which is the ability to process social information relative to oneself, and mentalizing or theory of mind, which is the ability to infer the mental states, such as beliefs, intentions, and emotions, of others. We provide evidence for aberrant function of the DMN in ASD as it relates to deficits in these domains of social cognition. We then review functional, structural, cytoarchitectural, and neurophysiological evidence for neuronal disorganization in key nodes of the DMN in ASD. Our synthesis of the extant literature suggests that an altered developmental trajectory of structural and functional organization of the DMN is a prominent neurobiological feature of ASD. We discuss putative neuronal mechanisms underlying DMN dysfunction and highlight questions for future research.

FUNCTIONAL NEUROANATOMY OF DMN AND ITS ROLE IN SOCIAL COGNITION

Over the past 3 decades, a number of influential studies have consistently demonstrated that a strongly intrinsically interconnected network of brain structures (11,12), including the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex (mPFC), temporoparietal junction (TPJ), and hippocampus (13,14) (Figure 1), is attenuated during a wide range of cognitive tasks (13,15). In parallel, several investigations have also uncovered that these structures, collectively named the default mode network, are significantly engaged during tasks involving social cognitive mental processes that are evaluative (16,17), including self-referential and autobiographical processing (13,15,16,18) and mentalizing and theory of mind

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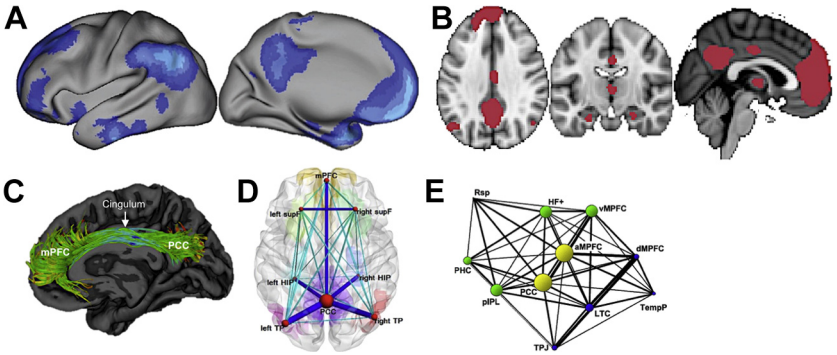

Figure 1. Functional and structural architecture of the default mode network (DMN) identified using multiple imaging modalities and methods. **(A)** Architecture of the DMN, identified as regions of "task-induced deactivation" in the seminal meta-analysis by Shulman *et al.* (135). Data derived from nine studies using $[^{15}O]H_2O$ positron emission tomography and reproduced as a surface rendering, as in Buckner *et al.* (136). **(B)** DMN topology is readily identifiable using resting-state functional magnetic resonance imaging data and use of an independent component analysis. **(C)** Core midline DMN nodes, the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), are structurally connected via a major white matter pathway, the cingulum bundle. Fibers reconstructed using diffusion tensor imaging tractography. **(D)** The strength of structural connections among DMN nodes can be quantified using diffusion imaging. Edge thickness and node size represent connection strength and node degree, respectively. PCC is the most strongly connected node within the DMN. **(E)** Spring graph illustrates the differing functional connectivity weights between DMN nodes, such that more strongly connected nodes are closer together in space, and these midline hubs are embedded centrally within the network. aMPFC, anteromedial prefrontal cortex; dMPFC, dorsomedial prefrontal cortex; HF+, hippocampal formation; HIP, hippocampus; LTC, lateral temporal cortex; pIPL, posterior inferior parietal lobule; PHC, parrahippocampal cortex; Rsp, retrosplenial cortex; supF, superior frontal gyrus; TempP, temporal pole; TP, temporal pole; TPJ, temporoparietal junction; vMPFC, ventromedial prefrontal cortex. [**A,** Adapted with permission from Buckner *et al.* (13); **B,** adapted with permission from Shirer *et al.* (137); **C,** adapted with permission from van den Heuvel *et al.* (138); **D,** adapted with permission from Tao *et al.* (139); **E,** adapted with permission from Andrews-Hanna *et al.* (140).]

(13,17). Beyond socially relevant functions, the DMN is also associated with mind wandering and initiation of spontaneous thought processes (13) and subjective value judgments (19), but how these functions contribute to social cognition is not known. Given its central importance to the phenomenology of ASD, we focus on processes that are more directly relevant to social function. Analysis of the extant literature in neurotypical individuals reveals considerable overlap between core DMN nodes and brain regions involved in social cognition (6,17,20–22), most notably the PCC, mPFC, and TPJ (Figure 2). We next summarize some of the known functional roles of these three brain regions as relevant for the present review.

As one of the most highly connected regions in the brain (23), with a high baseline metabolic rate (14), the PCC is considered to be a core functional "hub." The PCC, which is situated between the marginal ramus of the cingulate sulcus and the parieto-occipital sulcus, has been implicated in both self-relevant and other-relevant processing, including tasks requiring autobiographical memory and imagining oneself in the future (20), and evaluating and processing mental states of others (16,24,25). The mPFC encompasses a collection of strongly interconnected, contiguous regions in the prefrontal cortex, including the medial superior frontal, orbital, and frontopolar cortices, and anterior portions of the cingulate cortex. The mPFC is associated with monitoring of both one's own mental states and the mental states of others (16,17), which are thought to engage the ventral and dorsal subregions, respectively (13,26). The TPJ is situated between the inferior parietal cortex and posterior superior temporal cortex, with prominent overlap with the angular gyrus node of the DMN (27). The TPJ preferentially encodes other-relevant information, including the mental states and beliefs of others. For example, transcranial magnetic stimulation to the right TPJ has been shown to disrupt a participant's ability to attribute intentions to others (28) and the ability to distinguish other-relevant from self-relevant information (29). The TPJ has also been linked with predicting behaviors of others during social interactions (30). Thus, the PCC, dorsal and ventral mPFC, and TPJ, core DMN nodes, play distinct and interacting roles in monitoring of both the psychological state of self and evaluation of others.

TASK-BASED FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES OF ATYPICAL DMN FUNCTION

A prominent cognitive deficit of ASD is impairment in the ability to decode the mental states of self and others, and DMN dysfunction may be a critical neural signature of these deficits (31–33). The majority of task-based functional magnetic resonance imaging (fMRI) studies of ASD have been conducted with adults, or mixed groups of adolescents and adults, with ASD relative to age-matched neurotypical individuals. Task-related fMRI studies also focus primarily on activation in specific nodes of the social brain, including the DMN regions described above.

Studies of self-referential processing, requiring self-related versus other-related judgments, demonstrate reduced activation in the PCC (34) and mPFC (33). One study comparing the neural response in the ventral mPFC to self-related versus other-related judgments, showed preferential activation of this region for self-related judgments in neurotypical control adults, but not in adults with ASD (33). Analysis of multivariate voxel patterns further suggests that in adults with ASD, these midline structures and the PCC in particular are insensitive to semantic processing of words that connote social interactions. Moreover, machine learning algorithms classified individuals as autistic or control with 97% accuracy from their fMRI neurocognitive markers in these regions (35). Together, results suggest that the PCC and mPFC exhibit aberrant patterns of self-representation in ASD.

Theory of mind and mentalizing tasks typically involve viewing images, animation, or stories and test participants' understanding of others' intentions or mental states. Overall, these studies report decreased recruitment of the TPJ and dorsal mPFC in adults with ASD (36–41). However, other studies report decreases only in relation to sexual dimorphism in ASD, with one study showing that male, but not female,

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