The rising importance of the periphery for regulating centrally mediated social behaviors.

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Deficits in social behaviors, including delayed onset and decreased intensity in play, and classification by peers as less socially desirable are observed in children diagnosed with autism spectrum disorders, early-onset schizophrenia, attention deficit hyperactivity disorder, and generalized anxiety disorder [1-5], social withdrawal is observed in people diagnosed with major depression [6] and persons diagnosed with personality disorder display abnormalities in social cognition [7]. Despite the neurobiological underpinnings of these disorders and the central mediation of social behaviors, several recent studies suggest that some of the deficits in social behaviors that are observed in animal models of psychiatric illness may begin outside of the brain and involve altered communication between peripheral and central systems.

Disruption of Mecp2, an X-linked methyl-CpG-binding protein, is found in patients with Rett syndrome, an autism spectrum disorder and other neurodevelopmental disorders [8,9]. Disruptions of Mecp2 have generated several mouse models of neurodevelopmental disorders that recapitulate several aspects of these diseases, including the social deficits [10]. Recently, mice with a Mecp2 deletion targeted specifically to somatosensory neurons were generated to produce a sensitivity to touch as evidenced by a startle response to a puff of air on their backs and an inability to distinguish between rough and smooth textures [11]. Surprisingly, these mice are classified as more anxious due to their increased preference for staying close to the walls in an open field and remaining in the walled sides of an elevated platform rather than venturing into the open area or wall-less sides to explore and exhibit decreased sociability by demonstrating equal preference for a social stimulus and an object (control mice will exhibit a preference for the social stimulus) [11]. The authors postulate that the heightened sensitivity to touch experienced by these mice inundates them, resulting in anxiety and deficits in mechano-sensory processing [11].

In a step towards identifying a potential mechanism by which the peripheral immune system can influence brain function and therefore social behavior, interferon-\(\lambda\), a soluble factor secreted from T cells which cannot themselves enter the brain parenchyma, can increase inhibitory neuronal signaling in the prefrontal cortex, thus producing changes in preference for a social versus a non-social stimulus [12]. There is also mechanistic data to support that social stressors, such as social defeat, create an inflammatory environment in the brain through activation of microglia (the resident immune cells of the brain) resulting in increased trafficking of peripheral monocytes into the brain via the blood-brain barrier to produce anxiety-like behaviors, including social avoidance [13]. This mechanism is of particular interest because it demonstrates the cycle of social dysfunction, in which a social stressor produces subsequent social avoidance [14].

These studies demonstrating how peripheral systems can alter centrally mediated social behaviors are complemented by a recent study suggesting that social interactions throughout the lifespan of chimpanzees plays a larger role in influencing the composition of the gut microbiome than acquisition of gut bacteria transferred by the mother to her offspring [15]. The gut microbiome influences immunity, which can impact immune regulation of the central nervous system, but can also directly mediate brain development and function [16].

The current focus has been on basal levels of sociability indicated by preferences for a social over a non-social stimulus. The use of more complex behavioral paradigms that require sensory perception of another individual, interpretation of the context and the ability to respond adequately to that stimulus, such as juvenile play behavior and pro-social/helping behaviors will help to determine specific aspects of social behavior that are affected and to identify whether peripheral mechanisms might be implicated in the types of social deficits that are observed in patients with psychiatric illness.

References
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