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Review

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Prefrontal cortical circuits in social behaviors: an overview

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Abstract: Social behaviors are fundamental and intricate functions in both humans and animals, governed by the interplay of social cognition and emotions. A noteworthy feature of several neuropsychiatric disorders, including autism spectrum disorder (ASD) and schizophrenia (SCZ), is a pronounced deficit in social functioning. Despite a burgeoning body of research on social behaviors, the precise neural circuit mechanisms underpinning these phenomena remain to be elucidated. In this paper, we review the pivotal role of the prefrontal cortex (PFC) in modulating social behaviors, as well as its functional alteration in social disorders in ASD or SCZ. We posit that PFC dysfunction may represent a critical hub in the pathogenesis of psychiatric disorders characterized by shared social deficits. Furthermore, we delve into the intricate connectivity of the medial PFC (mPFC) with other cortical areas and subcortical brain regions in rodents, which exerts a profound influence on social behaviors. Notably, a substantial body of evidence underscores the role of *N*-methyl-D-aspartate receptors (NMDARs) and the proper functioning of parvalbumin-positive interneurons within the mPFC for social regulation. Our overarching goal is to furnish a comprehensive understanding of these intricate circuits and thereby contribute to the enhancement of both research endeavors and clinical practices concerning social behavior deficits.

Key words: Prefrontal cortex (PFC); Social behavior; Autism spectrum disorder (ASD); Schizophrenia (SCZ); Parvalbumin-positive interneuron; *N*-Methyl-D-aspartate receptor (NMDAR)

1 Introduction

Generally, social behaviors can be defined as any form of communication and interaction between two conspecifics. These behaviors are indispensable and complex in many species and essential for survival and reproduction (Ebstein et al., 2010; McGraw and Young, 2010). However, when exhibited at inappropriate time, places, or intensity, social behaviors can have detrimental effects on both individuals and the social group as a whole. Impairments in social functioning are prominent features of several neuropsychiatric disorders, including autism spectrum disorder (ASD) and schizophrenia (SCZ) (Chen and Hong, 2018).

The prefrontal cortex (PFC) and its extensive bidirectional connections, forming a top-down modulatory system for social behaviors, are components of the intricate and vast neural networks related to social behaviors (Anastasiades and Carter, 2021; Klune et al., 2021). Throughout the evolution of mammals, the prefrontal region has expanded in size relative to the rest of the cortex, reaching its largest volume in the human brain. Present-day neuroscientists have increasingly turned to research involving mice to gain insights into the underlying mechanisms taking place in the PFC for social behaviors. Studies in both humans and

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animals have underscored the central role of the frontal brain regions in cognition (Carlén, 2017).

Despite the rapid advancements in molecular, cellular, and genetic methodologies, alongside the implementation of cutting-edge imaging technologies, the precise neural circuit mechanisms responsible for social behaviors remain elusive. In this paper, we aim to provide a concise review of the role of PFC in mediating a wide range of social behaviors in ASD/SCZ patients and animal models.

2 Prefrontal cortex and social regulation in humans

2.1 Structure and function of the PFC

The PFC plays an indispensable role in higher brain functions, including cognition, motivation, reward, and emotion. It also governs goal-directed behaviors, social behaviors, and moral judgement (Forbes and Grafman, 2010; Buschman and Miller, 2014; Hanganu-Opatz et al., 2023). In humans, the PFC can be divided into distinct regions, including dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC), dorsomedial PFC (dmPFC), ventromedial PFC (vmPFC), and orbitofrontal cortex (OFC) (Forbes and Grafman, 2010). While the medial PFC (mPFC) regions are specifically associated with social behaviors, the lateral regions, including the dlPFC and vlPFC, may become active during social tasks while they are generally regarded as "domain general" (Amodio and Frith, 2006; Mitchell et al., 2006). Other brain regions commonly recruited by social behaviors in humans include the anterior cingulate cortex (ACC), nucleus accumbens (NAc), amygdala, hippocampus (HPC), superior temporal sulcus, and temporal parietal junction (Gangopadhyay et al., 2021; Chen et al., 2023). Regions of the PFC exhibit dense interconnections. Significant glutamatergic projections emanate from the PFC to the ACC, thalamus, ventral tegmental area (VTA), HPC, and NAc. Furthermore, glutamatergic neurons arise from the HPC and innervate the hypothalamus (HT), VTA, NAc, and PFC, and from the amygdala to HT, ACC, and NAc (Sarawagi et al., 2021). From birth to early adulthood, PFC cells and circuits undergo physiological changes, altering their strength of connectivity with distant brain regions. The extended maturation of the PFC likely enables the emergence of complex behaviors but may render them more susceptible to disruptions (Kolb et al., 2012; Klune et al., 2021).

Studies in humans have highlighted the central role of the frontal brain regions in cognition. Higher-order cognitive abilities encompass attention, salience detection, working memory, strategy shifting, and inhibitory control, all of which facilitate adaptation to varying conditions (Diamond, 2013; Buschman and Miller, 2014). These abilities necessitate the coordination of cellular ensembles that balance the stability and flexibility of neural representations. During baseline activity, prefrontal neurons lack the functional coordination of activity; however, when task-related demands arise, the temporal coordination of activity dynamically binds prefrontal neurons into functional units through oscillations and polychrony (Hanganu-Opatz et al., 2023). This synchronization influences communication between neuronal groups and ensures that presynaptic activation patterns reach postsynaptic neurons in a temporally coordinated manner. Oscillatory phase locking is primarily driven by bottom-up-directed gamma band activity (30–90 Hz) (Fries, 2015). In each oscillatory cycle, representing a transition between an averaged depolarized state and a hyperpolarized state, neurons have a temporal window to synchronize their firing, establishing connections (Buzsáki and Draguhn, 2004). Oscillations are hypothesized to create a temporal scaffold for intra- and inter-brain area communication (Buzsáki and Llinás, 2017). The gamma rhythm primarily arises from the synchronized fast inhibition of excitatory neurons by parvalbumin (PV)-expressing interneurons, demonstrating its role as a resonant property in local networks (Cardin et al., 2009; Sohal et al., 2009). It has been suggested that local gamma oscillations mirror the transient activation of PFC neuronal assemblies (Fujisawa et al., 2008). The gamma rhythm usually occurs along with the theta rhythm (4–12 Hz). The synchronization of theta rhythm between the PFC and HPC can influence various cognitive states, including memory integration and sequential working memory (Backus et al., 2016; Su et al., 2024). To this end, research has illuminated the vital role of oscillatory synchrony, particularly gamma and theta rhythms, in facilitating communication within the PFC and among various brain areas, which underscores their significance in orchestrating complex behaviors, including social interactions.

2.2 Cognitive and emotional processing in social regulation

Social behavior deficits represent a fundamental dimension of many psychiatric disorders, such as the neurodevelopmental disorders, ASD and SCZ. In social decision-making contexts, individuals frequently need to recognize other individuals, infer their intentions and emotions, and weigh the values of both social and non-social outcomes before choosing an action. To a significant extent, these aspects of social information processing rely on the PFC, specifically the mPFC (Kietzman and Gourley, 2023). Consequently, social cognition and emotion play critical roles in social regulation.

Social cognition encompasses a wide array of mental operations used for identifying and interpreting social signals, as well as the utilization of these signals to flexibly guide appropriate social behaviors in changing environments (Millan and Bales, 2013). Social cognition has three major facets: social motivation, self and other knowledge, and group dynamics. Research using both humans and translational animal models has demonstrated that these aspects of social cognition relate to psychiatric disorders. Social motivation can be described as biasing the individual to preferentially orient to the social world (social orienting), to seek and take pleasure in social interactions (social reward), and to strive to foster and maintain social bonds (social maintaining). The social motivation theory of autism suggests that a lack of early social interest may contribute to subsequent social cognitive deficits that manifest themselves later in development (Chevallier et al., 2012). Thus, social motivation can be seen as a developmental and evolutionary foundation for other social behaviors. Self and other knowledge forms the core of social cognition and encompasses concepts explored in basic processes like facial recognition, action perception, and empathy, as well as more sophisticated social behaviors such as cooperation and intergroup interaction (Catmur et al., 2016). Living in groups is common in mammalian societies, and dominance hierarchy is a fundamental organizing mechanism based on repeated social competitions. The result of social competition is influenced by personality traits under the regulation of high cortical functions (Zhou et al., 2018). Among the high cortical regions, the mPFC has been specifically associated with social dominance (Wang et al., 2011; Zhang et al., 2022; Fan et al., 2023). Hence, social cognition encompasses a wide range of mental processes crucial for our understanding of social interactions. These facets of social cognition not only have been linked to psychiatric disorders in humans and animal models but also offer insights into the fundamental building blocks of social behaviors.

Emotion regulation involves processes that affect both the experience and expression of emotions, which plays a crucial role in facilitating successful social interactions and overall functioning (McRae and Gross, 2020). Effective emotion regulation is correlated with an enhanced capacity to engage in socially appropriate emotions and behaviors, contributing to adaptive social interactions and social competence (Eisenberg et al., 1995, 2000). Conversely, disruptions in effective emotion regulation strategies may arise from negative social experiences, leading to difficulties in social behaviors and negative social encounters (Eisenberg et al., 1999; Geckeler et al., 2022). These intricate processes of emotion regulation play pivotal roles in shaping the quality of social interactions and overall social functioning.

Taken together, the PFC, with its intricate network of regions and dynamic neural activity patterns, serves as the cornerstone of higher brain functions, influencing cognition, emotions, social behaviors, and more. At the same time, addressing social behavior deficits in psychiatric disorders like ASD and SCZ necessitates a comprehensive exploration of the interconnected dimensions of social cognition and emotion regulation. These conditions often involve complex processes of social information processing that heavily rely on the PFC, particularly the mPFC.

3 Prefrontal dysfunction in autism and schizophrenia

3.1 Brain imaging as evidence for impaired PFC networks in ASD

Numerous researchers have underscored the pivotal role of the PFC in the manifestation of various ASD symptoms. For instance, functional magnetic resonance imaging (fMRI) studies have revealed that dysfunctional networks within the frontal lobes may affect social cognition, repetitive behavior, executive

function, and verbal communication—functions primarily controlled by the frontal lobe (Baron-Cohen et al., 1999; Carper and Courchesne, 2000, 2005; Ohnishi et al., 2000; Luna et al., 2002; Herbert et al., 2003; Chandana et al., 2005; Rafiee et al., 2022). Moreover, individuals with ASD have been observed to exhibit diminished serotonergic synthesis in the frontal lobes, alongside concomitant abnormalities in global brain serotonin production (Chugani et al., 1999; Chandana et al., 2005). Serotonin, similar to the brain-derived neurotrophic factor (BDNF), plays a critical role in modulating axonal arborization. Dysregulation of serotonin synthesis has been linked to abnormalities in frontal lobe connectivity (Kumar et al., 2010).

Disorders of neural connectivity, which explain a substantial portion of ASD variance, enable the integration of cognitive theories (e.g., central coherence) with a comprehensive understanding of ASD behaviors at the neuroanatomical, neurophysiological, and neuropsychological levels (Hughes, 2007, 2008). Impaired integration in ASD may arise from functional dysconnectivity among brain systems. Existing data suggest both cortico-subcortical and inter-/intra-hemispheric hyperconnectivity or hypoconnectivity (Vissers et al., 2012; Uddin et al., 2013; Kleinhans et al., 2016; Martínez et al., 2020). The function of frontal streams, as presented in the following section, has been validated through postmortem studies conducted on individuals with ASD. An important finding was the observation of brain overgrowth postpartum early in life, particularly of the PFC, which correlated with significantly larger head circumferences in children under three years of age (Courchesne et al., 2003; Sacco et al., 2015). Subcortical brain regions involved in sensory processing including the cerebellum and thalamus, both of which project to the PFC, exhibit anatomical differences in comparison to neurotypical individuals (Hazlett et al., 2005; Courchesne et al., 2011a, 2011b). The underconnectivity observed between frontal-thalamic areas has been associated with the severity of symptoms in individuals with ASD (Martínez-Sanchis, 2014; Rane et al., 2015). Moreover, there are strong connections between the PFC and the cerebellum, and abnormalities in both regions have been linked to symptom severity (Carper and Courchesne, 2000; Kumar et al., 2010).

3.2 Brain imaging as evidence for impaired PFC networks in SCZ

Numerous reports have underscored the significant similarities between the cognitive deficits observed in patients with frontal lesions and those encountered in SCZ (Müller et al., 2002). Furthermore, functional imaging studies have shed light on altered PFC activation during cognitive testing in SCZ patients, supporting the hypothesis that disruptions in PFC activity cause deficits in working memory and other cognitive functions (Weinberger and Berman, 1996; Karlsgodt et al., 2009). In fact, SCZ patients exhibit reduced blood flow in the PFC during task performance, along with diminished functional connectivity between the PFC and other brain regions while engaged in cognitive tasks (Goldman-Rakic and Selemon, 1997; Fornito et al., 2009).

A crucial source of excitatory input to the PFC originates from the thalamus, notably the mediodorsal nucleus. A reduction in correlated activity between the thalamus and the PFC during cognitive assessments could be a potential factor contributing to cognitive deficits (Mitelman et al., 2005; Woodward et al., 2012; Giraldo-Chica et al., 2018). Similarly, assessments of resting-state functional connectivity have indicated reduced thalamo-prefrontal connectivity in various stages of SCZ, including in adolescents with early-onset SCZ, young individuals at clinical high risk, and adults in the initial phases of the disorder (Anticevic et al., 2015; Cho et al., 2016; Woodward and Heckers, 2016; Huang et al., 2021; Zhang et al., 2021). Notably, the reduction in thalamo-prefrontal connectivity among high-risk individuals becomes the most pronounced in those who are subsequently diagnosed with the disorder (Anticevic et al., 2015). These findings intriguingly suggest that thalamo-PFC dysconnectivity during adolescence might contribute to the developmental etiology of SCZ (Anticevic et al., 2015; Woodward and Heckers, 2016).

SCZ is associated with both atypical PFC development during embryonic stages and impaired PFC maturation in later adolescence, influenced by environmental stressors. Due to this unique aspect, SCZ can be characterized by two critical susceptibility periods (Selemon and Zecevic, 2015). The disruption of cortical synaptic pruning has been proposed as a key factor in the etiology of SCZ, given that its symptoms typically manifest themselves in late adolescence,

which coincides with the developmental period when PFC connectivity matures (Feinberg, 1990; Lewis, 1997). Gray matter loss, reflecting cortical maturation, tends to occur later in higher-order association cortices such as the prefrontal and temporal cortices compared with lower-order somatosensory and visual cortices, indicating a delayed maturation of these cortical regions (Gogtay et al., 2004). Cortical gray matter loss is more pronounced in individuals at clinical high risk for SCZ who later develop the disorder, in contrast to others (Cannon et al., 2015; Chung et al., 2017). These observations suggest that alterations in prefrontal maturation may play a role in the etiology of the disorder.

Findings from postmortem studies have consistently revealed changes in elements of GABAergic neurotransmission within the PFC of individuals with SCZ. The effectiveness of GABAergic neurotransmission correlates with the availability of γ-aminobutyric acid (GABA) in the synapse. In SCZ, both messenger RNA (mRNA) and protein levels of 67 kDa glutamic acid decarboxylase (GAD67), the primary enzyme responsible for cortical GABA synthesis, are diminished in the PFC (Vawter et al., 2002; Woo et al., 2008; Curley et al., 2011; Kimoto et al., 2014). This aligns with the notion that the availability of presynaptic GABA is diminished in this disorder. Additionally, the numbers of PV^+ (Beasley and Reynolds, 1997; Beasley et al., 2002; Hashimoto et al., 2003), cholecystokinin-positive (CCK^+) (Hashimoto et al., 2008; Fung et al., 2010), and somatostatin-positive (SST^+) (Hashimoto et al., 2008; Morris et al., 2008; Fung et al., 2010) interneurons are decreased in the PFC of individuals with SCZ. Interestingly, GABA concentration has been found to predict the gamma oscillatory frequency (Edden et al., 2009). There is substantial evidence supporting *N*-methyl-D-aspartate receptor (NMDAR) hypofunction in SCZ, as the administration of NMDAR antagonists, such as MK-801 or phencyclidine, could induce SCZ-like symptoms in human subjects. Consequently, it is postulated that the NMDAR hypofunction in SCZ primarily affects cortical GABAergic interneurons (Nakazawa et al., 2017).

In brief, mounting evidence regarding PFC impairment in both ASD and SCZ patients highlights the critical role of this brain region in the manifestation of symptoms in these disorders. Brain imaging studies have unveiled disrupted PFC and PFC network functionality, enhancing our understanding of the cognitive deficits and behavioral challenges seen in these conditions. Additionally, insights from studies examining neural connectivity and neurotransmission further emphasize the significance of the PFC in the pathophysiology of ASD and SCZ. Understanding these neural underpinnings is crucial for developing targeted interventions and treatments to improve the lives of individuals affected by these disorders.

4 Prefrontal mechanisms of social deficits in rodents

4.1 Measuring social behaviors in rodents

A multitude of studies have demonstrated that rodents exhibit behaviors closely aligned with ethological aspects of social processing demands. These behaviors encompass sociability, social memory/recognition, and dominance, offering conceptual parallelism with human social categories (Moy et al., 2004; Bariselli et al., 2018; Zhou et al., 2018). Given their inherent social nature, mice serve as invaluable research models, facilitating the exploration of aberrant social behaviors associated with ASD and SCZ.

In order to assess sociability in mice, behavioral paradigms like social preference tests have often been employed. These tests assess the amount of time spent in proximity to an unfamiliar mouse compared with an empty side within a three-chamber apparatus. Typically, the novel social stimulus is confined to a compartment that allows sniffing and interaction but prevents physical contact (Moy et al., 2004). Alternatively, sociability can be evaluated by measuring the time spent engaged in unconstrained interactions.

In order to quantify social recognition in mice, researchers can measure the time spent with novel versus familiar conspecifics in a three-chamber apparatus (Moy et al., 2004). Typically, wild-type mice exhibit a preference for social novelty by spending more time with the novel conspecifics. Other paradigms for measuring social recognition take advantage of mice's natural tendency to habituate to familiar conspecifics while showing greater interest in exploring a novel mouse. A reduction in sniffing time during repeated trials indicates recognition of the familiar mouse. After repeated presentations, a novel mouse is introduced, and an increased investigation of the novel

mouse reflects a preference for social novelty (Bariselli et al., 2018).

Dominance hierarchy serves as a fundamental organizing mechanism in most animal societies. Once established, the hierarchical rank remains relatively stable and reduces intense conflicts among group members. To assess the dominance tendencies of mice, the tube test was developed, in which one mouse, termed as "loser," is compelled to back out of a narrow tube by another mouse, referred to as "winner" (Wang et al., 2011; Zhang et al., 2022). A simpler method is to observe the behaviors of animals within their home cages or to monitor aggressive interactions, which typically occur when a group is placed into a new cage (Shemesh et al., 2013).

Play behavior can be observed in various animals, including rodents. In rats, most play behaviors are social, encompassing play fighting, where individuals compete for an advantage (Palagi et al., 2016; Pellis et al., 2023). Play fighting activity peaks during the juvenile period, with juveniles exhibiting a strong motivation to engage peers in such interactions (Varlinskaya et al., 1999). Consequently, social play interactions serve as a primary source of social experience during this developmental stage. It is important to note, however, that play fighting does not specifically train particular motor actions; instead, it enhances a skill set applicable in various social and non-social contexts. Depriving juvenile rats of typical peer-to-peer play experiences results in adults displaying socio-cognitive deficiencies, which correlate with physiological and anatomical alterations in neurons, notably in the PFC, especially the mPFC (Pellis et al., 2023).

Over the last decade, there has been a surge of investigations focused on how mPFC circuits and pathways modulate social behaviors. While the hypothalamus and other subcortical circuits play a central role in generating social behaviors, the mPFC is uniquely equipped to integrate pertinent information such as social rank, memories, and contextual factors to modulate these behaviors. In the subsequent sections, we review the available evidence indicating that activity within the rodent mPFC can lead to alterations in social behaviors.

4.2 Involvement of the mPFC in social deficits in rodents

The mPFC of rodents consists of the ACC, the prelimbic cortex (PL), and the infralimbic cortex (IL), each of them with unique connectivity and functional properties. Multiple lines of evidence indicate the significance of neural activity originating from the mPFC in shaping social behaviors in rodents. Although the medial aspect of the secondary motor cortex (M2) is sometimes considered to be a part of the rodent mPFC, we do not include it in this review (Barthas and Kwan, 2017).

4.2.1 Altered synaptic transmission in the mPFC

Studies involving rodents have shown that dysfunction in the PFC reduces social interest (Murray et al., 2015), impairs social memory (Rudebeck et al., 2007), hinders the processing of social hierarchy information, and lowers social rank (Wang et al., 2014). Research has also delved into synaptic transmission in mouse models with genetic modification derived from risk genes for ASD and SCZ, and revealed general synaptic dysfunctions in the cortex and in some cases, specifically in the PFC. These studies have involved the abnormal expression of various molecules, including methyl-CpG-binding protein 2 (MeCP2) (Sceniak et al., 2016), β2-subunit nicotinic receptor (Avale et al., 2011), insulin receptor substrate protein, 53 kDa (IRSp53) (Chung et al., 2015), SH3 and multiple ankyrin repeat domains protein 3 (Shank3) (Duffney et al., 2015; Lee et al., 2015), and neuroligin 3 (NL3) (Cao et al., 2018), which have all been linked to altered synaptic transmission in the mPFC and abnormal social behavior.

Excitation/inhibition imbalance and synaptic dysfunction have been identified as common pathophysiological features in various mouse models of ASD and SCZ. For instance, the conditional knockout of neuroligin 2 (NL2) in the adult mPFC induced significant reductions in synaptic inhibition and caused parallel impairments in anxiety, fear memory, and social interaction behaviors (Liang et al., 2015). Also, NMDAR hypofunction and dysfunction of PV^+ interneurons have been observed in NL3-deficient mice, and the micro-infusion of NMDAR co-agonist D-cycloserine (DCS) into the mPFC rescued the social deficits in these mice (Cao et al., 2022). Similar findings have been reported in other mouse models. For example, a 16p11.2 deletion mouse model exhibited NMDAR hypofunction in PFC pyramidal neurons and cognitive and social impairments, which could be rescued by the chemogenetic activation of PFC pyramidal neurons

(Wang et al., 2018). Moreover, treatment with NMDAR antagonists such as dizocilpine (MK-801) or phencyclidine could induce SCZ-like symptoms in rodents. These symptoms encompassed hyperlocomotion, indicative of positive symptoms, as well as deficits in social behavior observed during a social interaction test and increased immobility in a forced swimming test, serving as indices of negative symptoms (Kehrer et al., 2008; Nakazawa et al., 2017; Kruse and Bustillo, 2022). This strongly supports the NMDAR hypofunction hypothesis of SCZ. Overall, the above findings suggest the importance of normal synaptic function in the mPFC, particularly the role of NMDAR, and provide valuable insights into potential therapeutic approaches targeting specific molecular and synaptic mechanisms, such as NMDARs, for the development of more effective treatments for ASD and SCZ.

Excitation/inhibition imbalance within the mouse mPFC has been linked to profound social deficits (Yizhar et al., 2011). Studies of mouse models lacking contactin-associated protein-like 2 (*CNTNAP2*) gene, implicated in autism, have demonstrated that modulating excitation/inhibition in the mPFC through neuron type-selective, real-time, reversible optogenetic manipulations can acutely rescue deficits in social behavior and hyperactivity (Selimbeyoglu et al., 2017). Moreover, a 16p11.2 duplication mouse model exhibited deficient GABAergic synaptic transmission and elevated excitability in PFC pyramidal neurons, as well as social and cognitive deficits. These deficits could be restored by the expression of neuronal PAS domain-containing protein 4 (Npas4), a key regulator of GABA synapses, in PFC (Rein et al., 2021). In line with this finding, it has been commonly observed that cortical inhibition and/or PV^+ interneuron number decreased in mouse models with social impairments (Han et al., 2012; Filice et al., 2016; Cao et al., 2018, 2022). These results indicate that maintaining normal synaptic transmission and proper inhibition within the mPFC neuronal network is essential for normal social behaviors.

4.2.2 Neuronal oscillations in the mPFC during social interactions

The neural activity of principal neurons in the mPFC is crucial for the social behavior of rodents. Studies have shown that certain mPFC principal neurons increase their activity during social interactions in mice (Lee et al., 2016; Brumback et al., 2018). Calcium activity recordings in mPFC principal neurons have identified distinct and dynamic ON and OFF neural ensembles that encode social exploration and linked dysfunctions in the activity of these ensembles to abnormal social exploration (Liang et al., 2018). Furthermore, the transient excitation of excitatory neurons in the mPFC through optogenetic manipulation led to reduced sociability (Yizhar et al., 2011) but improved social competition (Zhang et al., 2022).

In addition, neural oscillations in the low gamma frequency range (30–50 Hz) have been found to be disturbed in ASD and SCZ (Gandal et al., 2012; David et al., 2016). Optogenetic studies have revealed that activating PV^+ interneurons is both necessary and adequate for inducing gamma oscillations in the cortex, thereby influencing cortical information processing (Cardin et al., 2009; Sohal et al., 2009). Modulating these oscillations, especially through patterned optogenetic stimulation (40 Hz nested at 8 Hz) of mPFC PV^+ interneurons, has been shown to rescue social deficits in an NL3-deficient mouse model of autism (Cao et al., 2018). Interestingly, the excitation of vasoactive intestinal polypeptide-positive interneurons or the inhibition of PV^+ interneurons induced winning, and vice versa (Zhang et al., 2022). The optogenetic synchronization of either PV^+ interneurons or somatostatin-positive interneurons at a low gamma frequency improved sociability in wild-type mice (Liu et al., 2020). These findings underscore the close correlation between social interaction and elevated gamma rhythms in the prefrontal local field potentials, controlled by PV^+ interneurons. As a result, targeted interventions aimed at restoring neuronal oscillations hold great promise for future therapeutic strategies in neurodevelopmental and neuropsychiatric disorders.

4.2.3 Distinct mPFC circuits involved in social behaviors

The mPFC receives a variety of long-range inputs and sends diverse outputs to many other brain regions, connected via local circuits involving different excitatory and inhibitory neurons and communicating with each other based on specific wiring rules.

Cell type-specific optogenetic and chemogenetic manipulations, behavioral testing, and electrophysiological recordings have been used to investigate the functional coupling of the mPFC with subcortical systems in social behavior. Studies have shown that

projection neurons of the basolateral amygdala (BLA) in the IL are preferentially activated in response to a social cue as compared with BLA-projecting neurons in the PL, and the chemogenetic activation of PL-BLA or the inhibition of IL-BLA circuits impairs social behavior (Huang et al., 2020). Moreover, the activation of BLA input to the mPFC leads to an increase in anxiety-like behavior and a decrease in sociability (Felix-Ortiz et al., 2016). Interestingly, PL-to-NAc stimulation decreases the preference for a social target (Murugan et al., 2017). The ventral HPC (vHPC) has been implicated in social memory, and the inhibition of direct projections from vHPC to mPFC impaired social memory expression (Okuyama et al., 2016; Sun et al., 2020). In addition, the firing rates of VTA dopamine neurons projecting to the mPFC were dramatically decreased in a mouse model of repeated social defeat-induced depression. The activation of VTA projections to the NAc or the inhibition of VTA projections to the mPFC induces susceptibility to social defeat stress (Liu et al., 2018). The mPFC is also involved in processing the affective state of others through non-verbal communication. Utilizing in vivo single-cell microendoscopic Ca^{2+} imaging, researchers have demonstrated that increased synchronous activity of mPFC somatostatin-positive interneurons, which guides the inhibition of pyramidal neurons, has been associated with the discrimination of affective states (Scheggia et al., 2020). Interestingly, prior social experience incentivizes later instrumental choices such as food, and the social incentivization of future choices requires the PL (Kietzman et al., 2022).

Moreover, serotonergic neurons in the dorsal raphe nucleus (DRN) play a role in social behavior modulation through their interaction with the mPFC. The manipulation of synaptic inputs from the mPFC to the DRN influences social avoidance behaviors (Michelsen et al., 2008; Challis et al., 2013; Challis and Berton, 2015). The oxytocinergic system, originating from the hypothalamus and acting through SST^+ interneurons expressing oxytocin receptors (OXTRs) in the mPFC, also has an important function in regulating sociosexual behaviors in female mice but anxiety-related behaviors in male mice (Donaldson and Young, 2008; Nakajima et al., 2014; Li et al., 2016). Furthermore, OXTRs are also expressed on glutamatergic neurons in the mPFC, and the optogenetic stimulation of axons in the BLA arising from OXTR-expressing neurons in the PFC eliminates the ability to distinguish novel conspecifics from familiar ones (Tan et al., 2019). Thus, this section provides a comprehensive overview of the intricate neural circuits and systems that regulate social behaviors, emphasizing the central role of the mPFC and its interactions with various brain regions and neurotransmitter systems. The mPFC receives inputs from the vHPC, BLA, and VTA, and it sends outputs to the NAc, BLA, VTA, and DRN, all of which are implicated in social memory, sociability, social defeat, or anxiety. The modulation of PFC circuits by monoaminergic systems profoundly affects PFC-mediated social behaviors.

In conclusion, the rodent studies summarized in this section strongly support the notion that PFC neurons and their interconnected neural circuits play a central role in the regulation of social behaviors. Within the microcircuits of the mPFC, NMDARs and PV^+ interneurons have merged as critical components that potentially serve as pivotal elements in the regulation of social behaviors.

5 Perspectives

The PFC remains a central focus of inquiry in the field of neuroscience, with the potential to unveil deep insights into the complexities of social behaviors. Deciphering the pivotal role of the PFC in governing social behaviors not only enriches our comprehension of fundamental brain mechanisms but also carries profound implications for addressing social deficits witnessed in psychiatric disorders such as ASD and SCZ.

Future research endeavors are predicted to illuminate the dynamic interplay within the PFC and its impact on our social interactions. There is a necessity for continued exploration into the neural circuitry of the PFC, with the objective of unraveling how this region choreographs a multitude of processes integral to social cognition and emotion regulation. Furthermore, it is essential to approach the neural mechanisms of social activities by considering social networks as a cohesive entity, including the PFC. In rodents, the unique input and output from diverse subregions, layers, and cell types within the PFC govern various facets of social behaviors. For example, neurons in layer 2/3 IL that express the neuropeptide corticotropin-releasing

hormone (CRH) respond to social interactions with familiar over novel mice and release CRH into the rostral lateral septum (rLS) to suppress social interactions with familiar mice through lateral septum (LS) disinhibition (de León Reyes et al., 2023). The mPFC cells that project to the lateral hypothalamus promote dominance behavior during reward competition (Padilla-Coreano et al., 2022). Decreased PV^+ interneuron excitability in the mPFC is a causative factor of social novelty deficits (Cao et al., 2018). Hence, forthcoming research should focus on meticulously categorizing PFC cells according to their precise spatial localization, physical connections, and protein markers. Subsequently, examining the regulatory impact of these smaller cell groupings on social behaviors is imperative. A more comprehensive investigation into the intricate microcirculatory networks within the PFC is also warranted; a deeper understanding of PFC circuits will not only expand our knowledge of social behaviors but also provide new treatment strategies for social disorders.

In the preceding discussion, we emphasized the significance of gamma oscillations in the mPFC concerning social behavior and suggested that targeted interventions aimed at restoring neuronal oscillations might be a promising route for addressing the social disorders of ASD and SCZ. There are three potential approaches for implementing oscillation interventions. The first method involves directly enhancing the weakened oscillations in social behavior through physical interventions. Optogenetics is commonly used in animal studies, but the introduction of exogeneous genes into the brain hinders its application in humans. Currently, electrode stimulation based on information decoding (Li et al., 2023) provides a more physiological and precise approach, potentially adaptable for translation in patients if the concern about invasive surgery can be addressed. Additionally, non-invasive neuromodulations such as transcranial direct current stimulation or transcranial magnetic stimulation can be evaluated in clinical trials, with observations on whether social behavior and gamma oscillation are improved in subjects. The second method comprises pharmacological intervention, utilizing specific drugs that target PV^+ interneurons to regulate their excitability, thereby impacting gamma oscillation. For instance, potential options include drugs targeting voltage-gated sodium channel Nav1.1 (Ogiwara et al., 2007) and voltage-gated potassium channel Kv3.1 (Kaczmarek and Zhang, 2017), specifically expressed on PV^+ interneurons. Moreover, it is noteworthy that the excitability of PV^+ interneurons can also be modulated by NMDARs (Cao et al., 2022), although this modulation is not exclusive to PV interneurons. The third method entails neuron transplantation. Studies have shown that transplanting Nav1.1-enhanced interneurons can increase gamma oscillation and enhance cognition in a mouse model of Alzheimer's disease (Martinez-Losa et al., 2018). As research progresses, this approach could potentially prove effective in human patients. In summary, the exploration of the above various approaches underscores the potential for targeted interventions in manipulating gamma oscillations, opening up promising avenues for addressing disorders with social disfunction, such as ASD and SCZ. Continued research in these areas may pave the way for novel therapeutic strategies in the realm of neurobiological interventions for social behavior-related conditions.

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Author contributions

Jianhong LUO determined the topic of the article, proposed the program, and was responsible for the supervision and manuscript revision. Wei CAO and Huiyi LI were responsible for reference searching and manuscript writing. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

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