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EXPERT REVIEW

Mechanisms of synaptic transmission dysregulation in the prefrontal cortex: pathophysiological implications

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Abstract

The prefrontal cortex (PFC) serves as the chief executive officer of the brain, controlling the highest level cognitive and emotional processes. Its local circuits among glutamatergic principal neurons and GABAergic interneurons, as well as its long-range connections with other brain regions, have been functionally linked to specific behaviors, ranging from working memory to reward seeking. The efficacy of synaptic signaling in the PFC network is profundedly influenced by monoaminergic inputs via the activation of dopamine, adrenergic, or serotonin receptors. Stress hormones and neuropeptides also exert complex effects on the synaptic structure and function of PFC neurons. Dysregulation of PFC synaptic transmission is strongly linked to social deficits, affective disturbance, and memory loss in brain disorders, including autism, schizophrenia, depression, and Alzheimer's disease. Critical neural circuits, biological pathways, and molecular players that go awry in these mental illnesses have been revealed by integrated electrophysiological, optogenetic, biochemical, and transcriptomic studies of PFC. Novel epigenetic mechanism-based strategies are proposed as potential avenues of therapeutic intervention for PFC-involved diseases. This review provides an overview of PFC network organization and synaptic modulation, as well as the mechanisms linking PFC dysfunction to the pathophysiology of neurodevelopmental, neuropsychiatric, and neurodegenerative diseases. Insights from the preclinical studies offer the potential for discovering new medical treatments for human patients with these brain disorders.

The prefrontal cortex (PFC) is the central hub for high-level executive functions critically involved in mental health and diseases. In this review, we will provide an overview on how synaptic transmission in PFC is regulated in normal and pathological conditions. We will first summarize PFC functional organization by describing the local and long-range neuronal circuits and the behavioral correlates to these top-down and bottom-up synaptic connections. Next, we will summarize PFC modulation by describing the influence of monoaminergic systems, stress hormones, and neuropeptides on the synaptic structure and function of PFC neurons. Finally, we will summarize the PFC synaptic dysregulation in a variety of brain disorders and potential treatment strategies. Because of the broad scope of this review, only selective neuronal circuits, signaling molecules, and disease mechanisms are included. Interested readers are encouraged to find more comprehensive details on specific aspects of the topic in the original papers and review articles cited here.

PFC organization and function

PFC network organization and functional implications

PFC is the cortical region located at the anterior part of the frontal lobe. PFC of humans is delineated into two functionally, morphologically, and evolutionarily different regions: ventromedial PFC and lateral PFC. PFC is the last portion of the brain to fully develop. In monkey PFC neurons, the rapid phase of synaptogenesis reaches the plateau at 2-months old and maintains the consistently high synaptic density from early adolescence through puberty (2 months to 3 years), the formative time when learning experiences are most intense [1].

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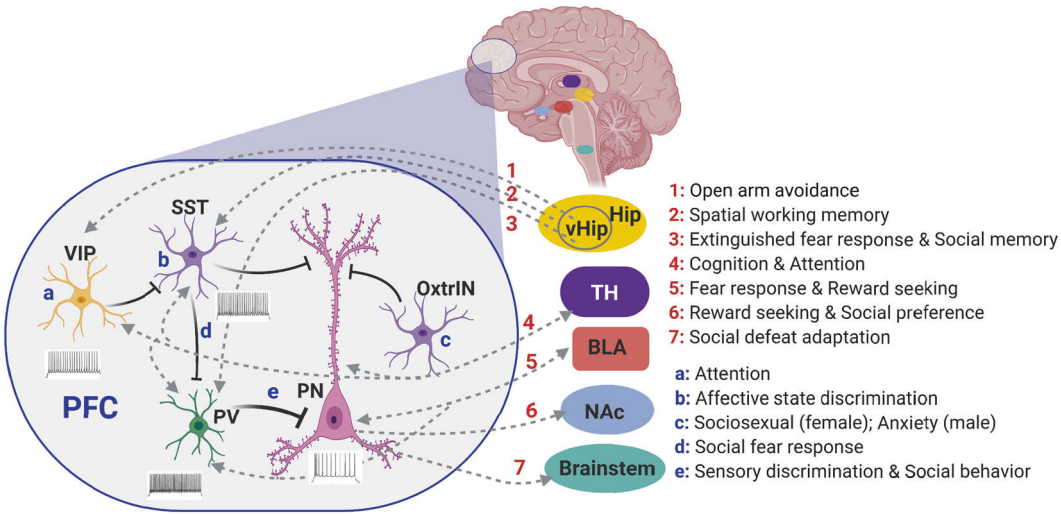

Fig. 1 Plot of PFC organization highlighting the functional mapping of some long-range and local circuits of PFC. VIP+ interneurons (VIP) in PFC sends inhibitory inputs to SST+ interneurons (SST), which causes disinhibition of PV+ interneurons (PV), resulting in strong somatic inhibition and weak dendritic inhibition of pyramidal neurons (PN). PFC interneurons and PN are innervated by the hippocampus (HIP) or ventral HIP (vHIP), thalamus (TH), and basolateral amygdala (BLA), while PN sends output to TH, BLA, nucleus accumbens (NAc), and brainstem. Some behavioral correlates of these neuronal circuits are listed, along with the functional role of VIP+ or SST+ interneurons, as well as a subtype of SST+ interneurons expressing oxytocin receptor (OxtrIN).

Early studies of macaque monkeys have revealed PFC as a crucial hub necessary for successful maintenance of working memory (WM), a cognitive process involving information holding and manipulation, which serves as the fundamental backbone for executive functions [2, 3]. The key findings are that in a delayed reaching task, some primate dorsolateral PFC neurons exhibit the increased firing during the delay period when response-related information needs to be held in mind to guide the subsequent execution of correct responses [4, 5]. The delayed and persistent spiking activity that encodes spatial "working memory" signals arises from recurrent excitation among PFC pyramidal neurons [5, 6]. Cortical network models predict that NMDA receptors subserve the recurrent synaptic excitation and persist firing of PFC pyramidal neurons during working memory [7, 8]. In parallel with these neurophysiological studies, neuroimaging studies also implicate the human PFC in higher-order cognitive processing including working memory [9] and sustained attention [10].

Based on anatomical, functional, and connectivity homologies, it is thought that rodent PFC is composed of three cytoarchitecturally defined parts: the prelimbic (PL), infralimbic (IL), and anterior cingulate cortex (ACC) [11, 12]. Electrophysiological and pharmacological evidence further supports the existence of a frontal cortical area in the rat that exhibits increased firing during the delay period in the absence of sensory stimulus that instructs the orienting response, as in primate PFC [13]. Recordings of neuronal ensembles in rats during new task learning further find that the dynamic changes in PFC neuronal activity parallel with behavioral decoding, suggesting that working memory can be mediated by dynamic activation of different neural populations in PFC [14].

PFC projects to distributed subcortical autonomic, motor, and limbic regions (Fig. 1). Tracing studies have found that deep layer PFC pyramidal neurons project to mediodorsal thalamus, lateral hypothalamus, ventral and dorsal striatum, and basolateral amygdala (BLA) [15]. Prefrontal circuitry can dynamically control reward-seeking behavior through projection-specific cue encoding [16]: stimulation of PFC to nucleus accumbens (NAc) neurons promotes conditioned reward-seeking behavior, while activation of PFC to thalamic neurons suppresses both the acquisition and expression of conditioned reward seeking. A specific subset of mPFC projections to NAc neurons encodes the decision to initiate or suppress reward seeking when faced with the risk of punishment [17].

Dorsomedial PFC exerts the top-down control of motor cortex ensembles to inhibit inappropriate responses during a delayed-response task [18]. The neural projection from medial PFC (mPFC) to a brainstem area has been found to control behavioral adaptation to social defeat [19]: social defeat weakens functional connectivity of these two areas, while selective inhibition of this pathway recaptures behavioral effects of social defeat. A spatiotemporal dynamic network, which originates in PFC and ventral striatum, relays through the amygdala and ventral tegmental area (VTA), and converges in the ventral hippocampus (vHIP), is found to encode depression vulnerability in mice subjected to social defeat stress [20].

PFC also receives inputs from diverse regions, including the hippocampus, thalamus, and BLA (Fig. 1). The direct

hippocampal to prefrontal afferents in mice are found to be critical for encoding of spatial cues during working memory, and successful encoding of task-related information is mediated by gamma frequency synchrony between the hippocampus and PFC [21]. Proper vHIP-mPFC signaling is necessary to recall social memories [22]. Reciprocal interactions between PFC and the thalamus play a critical role in high-level cognitive function [23]. Thalamic input amplifies PFC connectivity, sustaining attentional control [24], and enabling sensory selection in divided attention [25]. The reciprocal connection between PFC and BLA is implicated in reward-seeking and fear-related responses, and optogenetic studies have revealed that BLA to PL circuit is critical in governing the selection of behavioral responses amid conflicting cues of reward and punishment [26].

PFC cellular components and synaptic circuits

PFC is composed of pyramidal neurons with wide arbor axons, wide spikes, low discharge rates, and interneurons, many of which having horizontal axonal arbors, narrow action potentials (APs), and high evoked firing rates [27]. PFC fast-spiking (FS) interneurons (presumably expressing parvalbumin, PV+) form contacts on the perisomatic domains of pyramidal neurons, while non-FS interneurons (presumably expressing somatostatin, SST+) contact peridendritic domains [28], enabling PV+ and SST+ interneurons to specialize in the control of the output and input of principal neurons, respectively. PV+ interneurons, which could fire in millisecond synchrony, exert fast and powerful inhibition on principal neuron firing, whereas SST+ interneurons exert weak and more variable inhibitory effects on firing output in behaving mice [29]. PFC in awake mice also has a basic disinhibitory circuit module in which activation of VIP+ interneurons transiently suppresses primarily SST + and a fraction of PV+ interneurons [30]. Such disinhibitory control may serve to amplify local processing and modulate information gating. A subclass of VIP neurons expressing ChAT, ChAT-VIP, directly excites neurons throughout cortical layers via fast synaptic transmission of acetylcholine in mPFC, providing a local source to control attention [31].

Opotogenetics, in vivo electrophysiological recording, and single-cell microendoscopic Ca^{2+} imaging of PFC neurons in behaving animals have revealed the cell-type functional response diversity that contributes to diverse behavioral correlates (Fig. 1). PL pyramidal neurons are found to contain anatomically and molecularly distinct subpopulations that target three downstream regions implicated in social behavior: NAc, BLA, and VTA. Activation of NAc-projecting PL neurons, but not the other subpopulations, decreases the preference for a social target [32]. PV+ interneurons in mPFC also play a key role in social behaviors: activation of mPFC PV+ neurons rescues social memory impairment caused by vHIP inhibition [33]. Dampening thalamic activity causes significant reductions of GABA signaling in the mPFC and concomitant abnormalities in cognition and social interaction, which is ameliorated by selectively activating mPFC PV+ interneurons [34]. BLA inputs also make strong connections onto PFC PV+ and SST+ interneurons, driving feedforward inhibition of PFC pyramidal neurons [35, 36].

In mice performing a reward foraging task, SST+ interneurons in ACC are found to selectively respond at the reward approach, whereas PV+ interneurons respond at reward leaving [29]. In mice performing a PFC-dependent sensory discrimination task, PV+ interneurons are responsive to sensory cues, motor action, and trial outcomes, while SST+ and VIP+ interneurons respond more selectively to motor action or trial outcomes, respectively, and pyramidal neurons show much greater functional heterogeneity with varied responses across cortical layers [37]. This cell-type-specific encoding of task-related signals may be crucial for local computation within the PFC microcircuit to guide goal-directed behavior. Furthermore, SST+ interneurons in mPFC of mice are found to play a primary role in orchestrating the ability to discriminate positive and negative affective states [38]: inhibition of mPFC SST+ interneurons abolishes affective state discrimination, while an increased synchronous activity of PFC SST+ interneurons, which guides the inhibition of PFC pyramidal neurons, is associated with this social cognitive function.

More recent studies have further revealed the functional role of PFC interneurons in working memory. During a spatial WM task, optogenetically inhibiting PFC SST+, but not PV+, interneurons decreases the long-range synchrony between hippocampus and PFC and impairs working memory accuracy [39], suggesting that SST+ interneurons are uniquely involved in facilitating hippocampal–prefrontal synchrony and prefrontal spatial encoding. Inhibiting PFC pyramidal neurons by optogenetically activating SST+ or PV+ interneurons during the delay impairs working memory performance while activating VIP+ interneurons in PFC improves memory retention [40], which has provided a circuit mechanism underlying memory-guided behavior. PV+ and SST+ interneurons in mPFC are also found to have distinct roles in WM: PV interneurons show weak target-dependent delay-period activity and are strongly inhibited by reward; while SST+ interneurons show strong target-dependent delay-period activity, and only a subtype of them is inhibited by reward [41].

Moreover, in a social fear conditioning paradigm, SST+ interneurons suppress PV+ interneurons and disinhibit pyramidal cells, which consequently enhances PFC output to mediate social fear responses [42]. This disinhibitory

microcircuit in PFC through interactions between interneuron subtypes provides an important circuit mechanism in gating social fear behavior. The relapse of extinguished fear is found to be mediated by a feedforward inhibitory pathway from the ventral hippocampus to the IL cortex, which involves the recruitment of PV+ interneurons in IL [43]. In the avoidance behavior of elevated plus maze, PFC VIP+ interneurons enable cortical circuits to integrate hippocampal inputs, therefore effectively gating the transmission of signals related to open arm avoidance across the hippocampal–prefrontal network [44] (Fig. 1).

Regulation of PFC synaptic function

Monoaminergic regulation of PFC synaptic transmission

PFC is very sensitive to the neurochemical environment (Fig. 2), and monoaminergic modulation of the efficacy of synaptic connections in PFC circuits has profound effects on PFC-mediated executive function, including working memory, regulation of attention, inhibition of inappropriate behaviors, and impulsivity control [45]. Reduced catecholamine transmission has been linked to ADHD, while overamplified noradrenergic transmission is associated with PTSD [46]. The therapeutic actions of psychostimulant methylphenidate for ADHD involve the preferential increase of catecholamine neurotransmission within PFC [47] and dose-dependent, bi-directional regulation of PFC glutamate receptors [48].

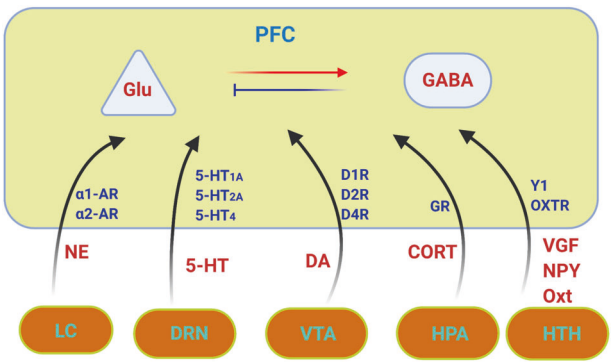

Fig. 2 Plot of PFC regulation illustrating some neurochemical influences on glutamatergic (Glu) excitation and GABAergic (GABA) inhibition in PFC neurons. The major modulators include dopamine (DA) from the ventral tegmental area (VTA), serotonin (5-HT) from dorsal raphe (DRN), norepinephrine (NE) from locus ceruleus (LC), corticosterone (CORT) stress hormone from hypothalamic–pituitary–adrenal (HPA) axis, and neuropeptides, such as VGF nerve growth factor (VGF), Neuropeptide Y (NPY), and oxytocin (OT), from the hypothalamus (HTH). These monoaminergic and hormonal modulations are achieved by activating corresponding receptors. The complex intracellular signaling pathways initiated by each neuromodulator can be found in relevant papers or previous reviews.

Dopamine

Serial section electron microscopy studies suggest that the majority of dopamine synapses in all PFC layers are on pyramidal neurons, but a significant fraction are on GABAergic interneurons [49]. Electrophysiological studies revealed that dopamine selectively modulates PFC excitatory and inhibitory microcircuits. DA depressed inhibitory transmission between FS interneurons and pyramidal neurons, but enhanced inhibition between non-FS interneurons and pyramidal cells [28]. Dopamine also reduces recurrent excitation in layer V pyramidal neurons [50], which may involve the target-specific expression of presynaptic and postsynaptic D1Rs [50, 51]. Dopamine has no effect on excitatory transmission from pyramidal neurons to FS interneurons but increases the excitability of FS interneurons [52]. In an experimental condition mimicking NMDA receptor hypofunction and $GABA_A$ receptor deficiency in schizophrenia, dopamine, by acting on D2 receptors, promoted burst firing in a subset of PFC pyramidal neurons [53].

Stimulation of D1R produces an inverted-U dose response on PFC neuronal firing and cognitive performance during working memory tasks [46]. High levels of D1R activation of cAMP signaling reduce PFC neuronal firing and impairs working memory via opening of HCN channels at excitatory synapses [54]. It suggests that optimal levels of dopamine are essential for PFC function, while excessive dopamine stimulation could be detrimental.

Optogenetic stimulation of VTA neurons to trigger the synaptically released dopamine has revealed a marked and prolonged enhancement of the excitability of PFC PV+ interneurons and a modest and short-lived enhancement of the excitability of PFC principal neurons [55]. Blocking dopamine receptor activation in PFC shortens the VTA excitation of PFC PV+ interneurons and prolongs the VTA excitation of PFC principal neurons, and pharmacological evidence suggests that the dopaminergic effect on PFC principal neurons is through influencing the inhibitory transmission system [55]. These results have unmasked the role of dopamine in regulating the temporal dynamics of excitation/inhibition balance in the VTA-PFC circuit.

Dopamine D4 receptor, which is largely restricted to PFC neurons, is highly implicated in ADHD and schizophrenia [56, 57]. It has been revealed that D4 receptors serve as a homeostatic synaptic factor to stabilize cortical excitability by dynamically regulating CaMKII [58, 59] and the downstream NMDA and AMPA receptor channels [60–62]. In contrast to the activity-dependent, bi-directional effect of D4R stimulation on AMPARs in PFC pyramidal neurons [62, 63], D4 receptors suppress AMPARs in PFC GABAergic interneurons via the unique calcineurin/Slingshot/cofilin signaling mechanism [64]. Moreover, D4R stimulation elicits distinct effects on synaptic-driven action potential firing in PFC

projection neurons versus fast-spiking interneurons, which are differentially altered in neuropsychiatric disorder-related conditions [65]. Stress exposure in D4R knockout mice induces schizophrenia-like behaviors via disruption of GABAergic transmission in PFC [66]. These results have provided a framework for understanding how D4R signaling is involved in the regulation of PFC functions.

D4R is one of the most variable proteins (and genes) in humans. A unique primate-specific feature of D4R is the additional 2–11 proline-rich repeats (most commonly 4) located in the third intracellular loop, which allows more complex simultaneous interactions with other proteins containing the SH3 domain. Interestingly, genetic studies have linked novelty-seeking behavior and ADHD to the long-repeat D4R allele (hD4.7) [57, 67]. Using D4R knockout mice with PFC expression of human D4R variants containing different repeats (hD4.4 and hD4.7), researchers have revealed the impact of hD4 variants on synaptic transmission and network activity in PFC neurons, the proteins interacting with hD4 variants, and the signaling pathways activated by hD4 variants, as well as the behavioral changes caused by hD4 variants [68, 69]. These studies provide novel insights into the functional roles of the remarkable polymorphism of human D4 receptors and shed light on the development of new therapeutic agents for diseases associated with dopaminergic dysfunction (Fig. 2).

Noradrenaline

The noradrenergic system in PFC is involved in many physiological and psychological processes, including working memory and mood control [46]. Endogenous norepinephrine (NE, also called noradrenaline), by acting on α1-ARs, exerts complex effects in PFC: NE increases the firing of some PFC pyramidal neurons via presynaptic excitation of glutamate release under basal conditions, but when high levels of α1-AR stimulation occur, such as with stress exposure, NE suppresses PFC neuronal firing through the opening of K^+ channels on spines [70]. Stimulation of α2A-ARs enhances the spatially tuned, delay-related firing of PFC neurons and strengthens working memory networks through inhibition of cAMP and closing HCN (hyperpolarization-activated cyclic nucleotide-gated) channels [71]. The interaction of HCN channels and cAMP regulating proteins in dendritic spines of PFC is considered to be a potential substrate of working memory [72].

Activation of α1-ARs or α2-ARs suppresses NMDAR currents in PFC pyramidal neurons by distinct mechanisms: the α1-AR effect depends on the $PLC/IP_3/Ca^{2+}$ pathway, whereas the α2-AR effect depends on PKA and the microtubule-based transport of NMDARs that is regulated by ERK signaling. Moreover, the effects of α1-ARs and α2-ARs are differentially modified by RGS4 [73], a member of the RGS family protein that plays an important role in modulating GPCR signaling [74] and an identified schizophrenia susceptibility gene [75, 76] (Fig. 2).

Serotonin

PFC receives a major serotonergic projection, which is dysfunctional in individuals who show impulsive aggression and violence [77]. Aberrant serotonergic neurotransmission has long been implicated in the pathogenesis of neuropsychiatric disorders associated with PFC dysfunction, including schizophrenia, depression, and anxiety [78]. Most clinically effective antipsychotic drugs, antidepressants, and anxiolytics all exert potent effects on the serotonin system. The pleiotropic functions of serotonin are afforded by the concerted actions of multiple serotonin receptor subtypes [79].

A series of studies have revealed the synaptic functions of serotonin receptors in PFC and how dysfunction of the serotonin system contributes to mental illnesses [80–89]. One of the key targets of serotonin receptor signaling is the glutamatergic system. It has been found that $5\text{-}HT_{1A}$ receptors in PFC pyramidal neurons suppress NMDAR function by disrupting the microtubule/kinesin-based dendritic transport of NMDA receptors [83], while this effect of $5\text{-}HT_{1A}$ is opposed by $5\text{-}HT_{2A/C}$ signaling [82]. In the human PFC, serotonin suppresses monosynaptic excitatory connections from pyramidal cells to interneurons [90]. At thalamocortical synapses, $5\text{-}HT_{2A}$ activation enhances NMDA transmission, gates the induction of NMDAR-mediated temporal plasticity, and facilitates associated cognitive functions [91].

Another main target of serotonin receptor signaling is the GABAergic system. $5\text{-}HT_2$ receptors inhibit $GABA_A$R-mediated currents in PFC pyramidal neurons through phosphorylation of $GABA_A$ receptors by the activation of anchored PKC [87], while $5\text{-}HT_4$ receptors modulate GABAergic signaling bi-directionally, depending on the basal PKA activation levels that are determined by neuronal activity [80]. Serotonergic regulation of GABA transmission in PFC is subject to the alteration by corticotropin-releasing factor (CRF) in response to stressful stimuli [89] or chronic antidepressant treatment [86]. In addition to pyramidal neurons, serotonin also affects GABAergic fast-spiking interneurons in PFC by enhancing their excitability and gamma frequency temporal integration via $5\text{-}HT_{2A}$ suppression of an inward-rectifying potassium conductance [92]. These studies have provided unique and complex mechanisms for serotonin receptors to dynamically regulate synaptic transmission and neuronal excitability in the PFC network in physiological and pathophysiological conditions (Fig. 2).

Hormonal regulation of PFC synaptic transmission

Stress hormones

Stress hormones exert complex and profound effects on the synaptic structure and function in PFC neurons (Fig. 2). Glucocorticoid action in the PFC shows marked functional heterogeneity. Glucocorticoid receptor (GR) knockdown in IL induces compromised stress adaptation and depression-like behavior, while GR knockdown in PL increases HPA axis responses to acute stress but does not affect stress sensitization or helplessness behavior [93], highlighting the region-specific impact of PFC on stress coping and emotional control.

Exposing animals to an acute stressor, such as forced swim, foot shock, or restraint, produces significantly enhanced glutamatergic transmission in PFC circuitry [94–97]. One mechanism is related to the enhancement of a readily releasable pool of glutamate vesicles via a non-genomic mechanism mediated by membrane receptors [95]. Acute stress, via acting on GR, also induces a delayed potentiation of NMDAR- and AMPAR-mediated synaptic currents, which is correlated with the increased level of synaptic NMDAR and AMPAR subunits [96, 98]. Serum- and glucocorticoid-inducible kinases (SGKs), an immediate early gene activated by the stress hormone, are shown to be involved by enhancing Rab4-mediated trafficking of glutamate receptors from early endosomes to the plasma membrane in PFC neurons [98, 99]. The GR-induced upregulation of SGK and glutamatergic signaling in acutely stressed animals is blocked by inhibition of HDAC6, a unique member of the HDAC family that directly regulates the GR chaperone protein, heat shock protein 90 (HSP90) [97]. Interestingly, reduced SGK expression is found in postmortem brains of PTSD patients, and inhibition of SGK in rat PFC produces helplessness- and anhedonia-like phenotypes [100].

Adhesion molecules that anchor glutamate receptors at the synaptic surface are also implicated in the acute stress-induced enhancement of GluR2 membrane trafficking and memory facilitation [101]. In addition, acute foot shock stress increases spine density and induces dendritic remodeling in medial PFC, which can be partially blocked by chronic treatment with the antidepressant desipramine [102, 103]. This effect of stress and antidepressant is linked to the alteration of key genes involved in synaptic plasticity and spine structure [104].

In contrast to the positive effects of acute stress, chronic stress (e.g., 21-day restraint stress) produces impaired dendritic branching, atrophy, and spine loss in PFC pyramidal neurons [102, 105], and such structural reorganization is reversed after 3-week cessation of stress [106]. Chronic stress impairs synaptic plasticity by reducing LTP induction in the hippocampus–PFC connection [107], and repeated social stress during mid-adolescence significantly decreases synaptic activity and intrinsic excitability of mPFC neurons [108]. Chronic exposure to corticosterone also causes the reduction of NR2B and GluR2/3 subunit expression in ventromedial PFC [109].

A prominent loss of GluR1 and NR1 subunit expression has been found in PFC pyramidal neurons from repeatedly stressed animals, which leads to the depression of AMPAR- and NMDAR-mediated synaptic currents [110]. This stress-induced loss of glutamate receptor expression is attributable to the increased ubiquitin/proteasome-mediated degradation of GluR1 and NR1 that is controlled by E3 ubiquitin ligases Nedd4 and Fbx2, and inhibition of proteasomes or knockdown of these E3 ligases in PFC prevents the loss of glutamatergic responses and recognition memory in stressed animals [110]. The transcription of Nedd4 is upregulated by repeated stress via an epigenetic mechanism involving the elevated histone deacetylase 2 (HDAC2) and the ensuing suppression of histone methyltransferase Ehmt2 (also known as G9a) that catalyzes the repressive mark H3K9me2 [111]. The impairment of glutamate receptors and excitatory transmission in the PFC of chronically stressed animals is blocked by HDAC2 inhibitors [111].

There are many additional molecules that have been implicated in governing the effects of chronic stress in PFC. One key player is the mTORC (mammalian target of rapamycin complex) signaling pathway. Decreased levels of mTORC are found in the PFC of humans with the major depressive disorder [112], and the fast-acting antidepressant ketamine increases mTORC signaling in rat PFC [113]. REDD1, an endogenous inhibitor of mTOR, shows the elevated expression in the PFC of animals exposed to chronic unpredictable stress and the PFC of post-partum depressed humans [114]. REDD1 knockdown renders animals to have greater resilience to the chronic stress-induced spine shrinkage and AMPAR current reduction [114].

Neuropeptides

The neuropeptide precursor VGF plays a critical role in depression and antidepressant efficacy [115]. Reduced levels of VGF have been found in the PFC of MDD patients and the PFC of chronically stressed mice [116]. VGF in PFC regulates susceptibility to stress and the antidepressant response to ketamine and infusion of VGF C-terminal peptide TLQP-62 to PFC produces sustained antidepressant responses [116].

Neuropeptide Y (NPY), a stress modulatory transmitter, has been associated with PTSD. NPY in IL cortex, acting on NPY Y1 receptors, increases inhibitory synaptic transmission onto IL projection neurons and dampens their excitability, resulting in the significant impairment of fear extinction memory [117].

The "prosocial" hormone oxytocin (OT) plays a key role in regulating social and emotional behaviors through a population of SST+ interneurons that express the oxytocin receptor (OxtrIN) in mPFC. Silencing OxtrIN of female mice or deleting Oxtr gene in mPFC results in sociosexual deficits [118], while OxtrIN in male mice regulates anxiety-related behaviors by interacting with the co-expressed corticotropin-releasing-hormone-binding protein (CRHBP), an antagonist of the stress hormone CRH [119] (Fig. 2).

PFC dysregulation and diseases

Transcriptomic meta-analyses of the human cerebral cortex across major neuropsychiatric disorders, including autism (ASD), schizophrenia (SZ), bipolar disorder (BD), and depression (MDD), have found the shared transcriptional dysregulation underlying convergent molecular neuropathology, such as a gradient of synaptic gene downregulation and astroglial gene upregulation in ASD, SZ, and BD (ASD >SZ = BD), and dysregulation of the HPA axis and hormonal signaling in MDD [120]. Synaptic plasticity deficits in the PFC of animal models have been linked to clinical findings from human patients with frontal cortical dysfunction, including the decreased functional connectivity in prefrontal–limbic circuits, executive function and memory deficits, inflexible and maladaptive behaviors [121]. In what follows, we will summarize mechanisms of synaptic transmission dysregulation in the PFC and pathophysiological implications in a few neurodevelopmental, neuropsychiatric and neurodegenerative diseases linked to the impairment of social, emotional, and cognitive processes.

Autism

Autism is a prevalent neurodevelopmental disorder characterized by core symptoms, such as social deficits and stereotypic behaviors. The importance of PFC in autism is demonstrated by structural, functional, and genomic studies. Postmortem studies have found focal patches of abnormal laminar cytoarchitecture and cortical disorganization of neurons, but not glia, in the prefrontal and temporal cortical tissue from a majority of young children with autism, with the clearest signs of abnormal expression of excitatory neuronal markers in deep cortical layers 4 and 5 [122]. Many of the high-level executive functions controlled by PFC are impaired in autism. Transcriptomic analysis of autistic brains has found 444 genes showing significant expression changes in PFC, but only 2 in the cerebellum [123].

Haploinsufficiency of the *Shank3* gene, which encodes a scaffolding protein at postsynaptic density of glutamatergic synapses, has been causally linked to autism [124, 125]. High-resolution MRI has found that loss of *Shank3* in mice results in disrupted local and long-range prefrontal and frontostriatal functional connectivity, which is predictive of social communication deficits [126]. In PFC pyramidal neurons of *Shank3*-deficient mice, NMDAR function and synaptic distribution are significantly diminished, which is caused by a marked loss of actin filaments at glutamatergic synapses due to the altered Rac1/PAK/cofilin signaling [127]. Inhibiting cofilin or activating Rac1 rescues the social deficits and NMDAR hypofunction in *Shank3*-deficient mice [127] (Fig. 3), suggesting that targeting actin regulators to restore actin-based NMDAR synaptic delivery could be a therapeutic option for autism [128]. Chemogenetic activation of PFC pyramidal neurons in *Shank3*-deficient mice also restores social preference behaviors and elevates glutamatergic synaptic function [129]. Moreover, the reduced synaptic plasticity in the hippocampus–mPFC pathway and impaired social recognition memory and attention in *Shank3*-deficient rats are attenuated by oxytocin treatment [130].

Another prominent genetic link to autism spectrum disorders and intellectual disability is the microdeletion or microduplication of the human 16p11.2 gene locus [131, 132]. A 16p11.2 deletion mouse model, $16p11^{+/-}$, exhibits NMDAR hypofunction in PFC pyramidal neurons [133]. Chemogenetic activation of PFC pyramidal neurons leads to the amelioration of cognitive and social impairments and the restoration of NMDAR function in $16p11^{+/-}$ mice [133]. On the other hand, a 16p11.2 duplication mouse model, $16p11^{dp/+}$, exhibits deficient GABAergic synaptic transmission and elevated excitability in PFC pyramidal neurons [134]. Restoring the expression of Npas4, a key regulator of GABA synapses [135, 136], ameliorates the social and cognitive deficits, as well as GABAergic synaptic impairment and neuronal hyperexcitability in $16p11^{dp/+}$ mice [134]. Synaptic dysfunction and excitation/inhibition imbalance are identified as a common pathophysiological feature of multiple ASD models [137–139].

Large-scale genetic screenings have revealed that many of the identified top-ranking autism risk factors are genes implicated in synaptic homeostasis, transcriptional regulation, and chromatin remodeling pathways [140–142]. Epigenomic studies show that PFC neurons from subjects with autism exhibit the altered H3K4me3 peaks at numerous genes regulating neuronal connectivity, social behaviors, and cognition, often in conjunction with altered expression of the corresponding transcripts [143]. A recent series of studies have shown that targeting epigenetic enzymes to adjust gene expression and ameliorate synaptic defects in PFC is a potential strategy to normalize behavioral phenotypes associated with autism [144–147].

In PFC of *Shank3*-deficient mice, the loss of histone acetylation and upregulation of HDAC2 have been identified

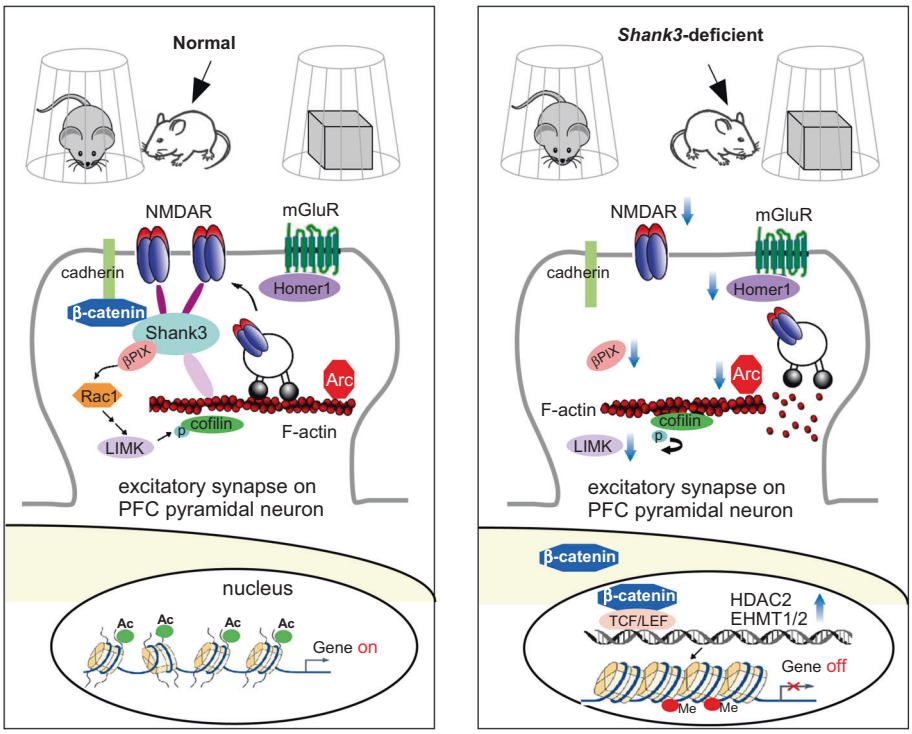

Fig. 3 Schematic diagram illustrating a potential mechanism underlying the social deficits in Shank3 autism models. Normally, Shank3 crosslinks NMDARs to the actin cytoskeleton, and binds to the adhesive junction-associated protein β-catenin. Loss of Shank3 leads to the translocation of β-catenin from synapses to the nucleus, inducing the upregulation of histone modifiers HDAC2 and EHMT1/2. The ensuing transcriptional suppression of actin regulators, such as βPIX (Rac1 activator) and LIMK, and synaptic plasticity genes, such as Arc and Homer1 (mGluR anchor), results in the disruption of actin filaments (via cofilin-mediated depolymerization) and the diminished actin-based synaptic delivery of NMDARs in PFC pyramidal neurons. Consequently, the autism-like social preference deficits are manifested. Treatment with HDAC or EHMT inhibitors restores or elevates many target genes, which collectively leads to the normalization of NMDAR synaptic function in PFC and the rescue of social deficits [127, 145, 146].

[145]. Systemic administration of the class I HDAC inhibitor romidepsin or MS-275 leads to the robust and persistent alleviation of social deficits, as well as the restoration of actin regulators and NMDAR function in PFC [144, 145]. A histone acetylome-wide association study (H3K27ac ChIP-seq) of human ASD postmortem samples also reveals common "epimutations" on genes involved in synaptic transmission, ion transport, and histone deacetylation [148]. Moreover, the repressive histone mark H3K9me2 and its catalyzing enzymes EHMT1/2 are selectively increased in the PFC of *Shank3*-deficient mice and autistic human postmortem brains [146]. Inhibition of EHMT1/2 rescues social deficits and restores PFC NMDAR function in *Shank3*-deficient mice via restoring the expression of plasticity gene *Arc*, which encodes the activity-regulated cytoskeleton-associated protein Arc [146]. The nucleocytoplasmic shuttle protein involved in both cell adhesion and transcriptional regulation, β-catenin, is found to link the loss of Shank3 in the synapse to the upregulation of HDAC2 and EHMT1/2 transcription in the nucleus [145, 146] (Fig. 3).

Another identified high-risk factor for autism is the *Cullin 3* (*Cul3*) gene [141], which encodes a core component of the E3 ubiquitin ligase complex that mediates proteasomal degradation [149]. Loss of *Cul3* in the forebrain or PFC leads to social deficits and NMDAR hypofunction, while loss of *Cul3* in the striatum leads to stereotypic behaviors and cell-type-specific alteration of neuronal excitability in striatal circuits [147]. One of the misregulated proteins resulting from forebrain *Cul3*-deficiency is Smyd3, a histone methyltransferase involved in gene transcription. Inhibition or knockdown of Smyd3 ameliorates social deficits and restores PFC NMDAR function in forebrain *Cul3*-deficient mice [147]. These studies have demonstrated how aberrations in molecular and epigenetic pathways implicated in autism are interconnected.

Schizophrenia

Schizophrenia (SZ) is a chronic psychiatric disorder that is characterized by delusions, hallucinations, disorganized speech and behavior, and negative symptoms [150]. SZ has been linked to both aberrant PFC development during embryonic stages and disrupted PFC maturation in later adolescence driven by environmental stressors, making

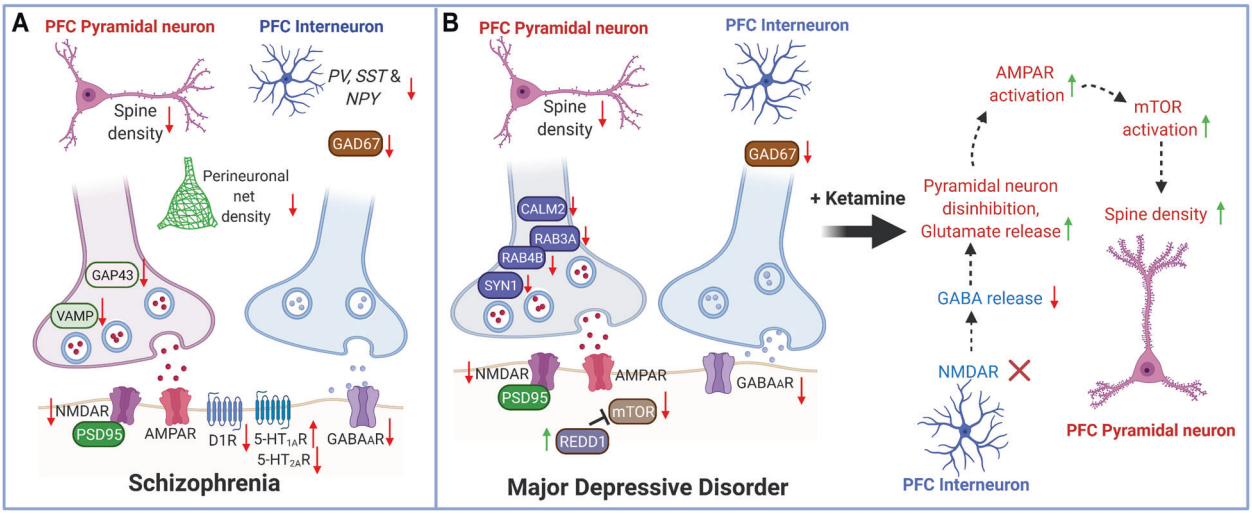

Fig. 4 Schematic diagram illustrating the synaptic changes in PFC of schizophrenia (SZ) and major depressive disorder (MDD). NMDAR hypofunction, GABA deficiency, dopamine hypoactivity, serotonin dysregulation, and dendritic spine loss are major aberrations in SZ PFC. The reduced density of perineuronal nets (PNN) may contribute to the destabilization of synapses. A similar reduction on NMDAR, GABA system, and spine density is found in MDD PFC. Some presynaptic molecules involved in transmitter release, including CALM2, SYN1, RAB3A, RAB4B, are also diminished in MDD PFC. In addition, mTOR signaling is decreased in MDD PFC because of the elevated expression of the endogenous inhibitor REDD1. The fast-acting antidepressant ketamine primarily blocks NMDARs on PFC interneurons, leading to the disinhibition of PFC pyramidal neurons and the increase of mTORC signaling, resulting in the restoration of dendritic spines in MDD PFC.

SZ a unique disorder with two critical susceptibility periods [151]. SZ patients exhibit reduced gray matter in the frontal cortex, evidenced by MRI studies [152, 153]. It has been suggested that SZ is driven by disrupted cortical synaptic pruning [154] because its symptoms tend to appear late in adolescence corresponding with the developmental period in which PFC connectivity undergoes maturation [155]. One hypothesis is that psychosocial stress in late development drives microglial overactivation, leading to the increased synaptic pruning in PFC [156]. In accordance with these theories, SZ patients display significant reductions in dendritic spine density in PFC [157], and lower density of perineuronal nets (PNN)— extracellular structures that stabilize synapses, also suggesting synaptic loss or destabilization [158]. SZ patients show reduced blood flow in PFC during task performance [159] and reduced functional connectivity between PFC and other brain regions when performing a cognitive task [160].

SZ etiology has a strong genetic component, and many high-risk SZ genes identified by GWAS studies are highly enriched in the mid-frontal lobe [161], form protein interactions in fetal dorsolateral (DL) and ventrolateral PFC [162], and/or are functionally implicated in synaptic transmission [162, 163]. Proteomic analysis of SZ DLPFC samples identified 15 differentially expressed proteins, 7 of which were synaptic [164]. These studies suggest synaptic dysfunction in PFC as a core mechanism in SZ.

The synaptic pathology of SZ in the PFC is complex, involving disrupted glutamatergic, GABAergic, dopaminergic, and serotonergic transmission (Fig. 4A). There is strong support for NMDA hypofunction in SZ, as treatment with NMDAR antagonists, such as MK-801 or phencyclidine, can induce SZ-like symptoms in both human subjects [165] and in animals [166]. NMDAR-mediated connectivity between PFC and hippocampus is impaired in SZ, which is suggested as a mechanism underlying working memory deficits [167]. Blocking NMDARs with MK-801 injection leads to the impairment of mPFC-dependent cognitive flexibility and hippocampus–mPFC pathway-dependent spatial working memory [168].

Paradoxically, MK-801 drives the increased release of glutamate in the mPFC, though the antipsychotic medications clozapine and haloperidol are both able to block MK-801-induced glutamate release in PFC of rats [169]. NMDAR antagonists may elicit this paradoxical response by primarily blocking NMDA receptors on GABAergic interneurons, thereby promoting disinhibition of pyramidal neurons [170]. It has thus been postulated that the NMDA hypofunction in SZ mainly occurs in cortical GABAergic interneurons [165]. Postmortem schizophrenia studies have revealed supporting evidence [171], including the reduced density of NR2A-expressing PV interneurons in cortical layers 3 and 4 [172] and the reduced density of GAD67- and NR2A-coexpressing neurons in layers 2 and 5 of the anterior cingulate cortex [173].

In rats treated with NMDAR antagonists, PFC neurons display elevated and irregular spiking activity and the reduced coordinated burst firing, suggesting that NMDA hypofunction in PFC may drive disorganized network activity [174]. In agreement with this, monkeys performing a SZ-relevant cognitive task exhibit reduced synchronous firing and disrupted connectivity in PFC neurons after the administration of an NMDAR antagonist [175]. PFC-specific inhibition of either NMDA or GABA transmission produces working memory deficits in rats, suggesting that either system could contribute to working memory deficits in SZ [176]. Several biochemical indicators of NMDA dysfunction are reported in SZ PFC, including the reduced expression of several synaptic plasticity-related genes [177], and the significantly lower postsynaptic expression of the NMDAR subunit NR1 and PSD95 [178]. Reduced expression of the presynaptic vesicle protein VAMP has also been reported in SZ PFC [179], while other presynaptic markers appear unchanged [177, 179].

Several well-replicated cellular indications of disrupted GABAergic synaptic transmission have been reported in PFC of SZ patients, including the decreased GAD67 expression and reduced gamma oscillations, suggesting deficient GABA synthesis and GABAergic synaptic transmission, respectively [180]. While no change in the number of PV+ cells [181] or the density of GABAergic synaptic inputs on DLPFC neurons [182] is observed in SZ patients, the reduced PV expression is reported both at the individual cellular level [181] and specifically within presynaptic boutons of PV+ basket cells [182]. Furthermore, expression analysis of DLPFC from SZ patients indicated the reduced expression of several GABA-related genes, including neuropeptides and both presynaptic and postsynaptic markers [183]. Inhibiting GABAergic transmission in the PFC of rats produces several behavioral phenotypes mirroring SZ symptomology [184]. The evidence implicating GABAergic deficits in PFC as a core mechanism in SZ-related cognitive dysfunction has been reviewed previously [185].

Dopamine modulation of PFC, which also plays a major role in working memory [186], is thought to contribute to PFC dysfunction in SZ. In a mouse model carrying a genetic risk factor for neuropsychiatric disorders, adolescent isolation stress induces DNA hypermethylation of the tyrosine hydroxylase (TH) gene in mesocortical dopaminergic neurons, causing the reduced TH expression and cortical dopamine release, leading to SZ-associated behavioral abnormalities [187]. D2R activation leads to long-lasting NMDAR hypofunction, resulting in the profound disruption of functional connectivity between the hippocampus and PFC [167]. D2R overexpression in mouse striatum causes the reduced inhibitory synaptic input to PFC pyramidal neurons, suggesting that the deficit in PFC GABAergic function in schizophrenia could be secondary to alterations in the striatal dopamine system [188]. On the other hand, D1R activation in PFC facilitates the maintenance of long-term potentiation (LTP) of glutamatergic transmission, as well as the induction of long-term depression (LTD) of glutamatergic transmission, indicating its bi-directional modulation of synaptic plasticity in mPFC [189]. Computational models predict that an imbalance of D1R/D2R activation in the PFC may underlie the associated cognitive, positive, and negative symptoms of SZ [190]. Positron emission tomography studies indicate that radioligand binding to D1R is reduced in PFC of SZ patients, and the extent of the reduction correlates directly with the severity of SZ-related negative symptoms [191]. Further postmortem studies have confirmed the reduced D1R expression in PFC of SZ patients [192].

In addition to dopamine, serotonin dysfunction in PFC is also implicated in SZ, as 5-HT receptors are the major targets of many atypical antipsychotics used to treat SZ, such as clozapine and olanzapine. A systematic review of literatures reported the increased expression of 5-HT_{1A} and the reduced expression of 5-HT_{2A} receptors in PFC of SZ patients [193]. PET studies in SZ patients have similarly shown the reduced 5-HT_{2A} availability in the frontal cortex [194]. The novel antipsychotic drug lurasidone restores the diminished NMDAR function in PFC pyramidal neurons from the phencyclidine (PCP) model of schizophrenia via antagonizing 5-HT_7 receptors [195], which may underlie its effect on reversing cognitive impairment in SZ. The exact mechanisms by which serotonin dysfunction in PFC contributes to SZ pathophysiology remain to be further elucidated. Collectively, the existing evidence suggests a model whereby the disruption of NMDA and GABA transmission in PFC, which is partially driven by aberrant dopamine and serotonin neuromodulation, produces excitation/inhibition imbalance and network dysconnectivity in SZ (Fig. 4A).

Emerging studies have revealed the epigenetic alterations in SZ [196]. ATAC-seq analysis of SZ DLPFC shows that genetic regions with high chromatin accessibility are highly enriched in heritable genetic risk factors for SZ [197]. In agreement with this, two histone markers associated with transcriptional activation (H3K4me3 and H3K27ac) are enriched at SZ genetic risk variants [198]. Broadly disrupted DNA methylation profiles are also reported in SZ PFC [199]. Epigenetic dysregulation of 5-HT_{2A} receptor has been demonstrated in the human frontal cortex [200]. In a rat model of SZ, abnormal epigenetic repression of the NMDAR subunit *Grin2b* in PFC drives glutamatergic synaptic deficits [201]. Upregulation of *HDAC1* is found in the PFC of human SZ patients and *Hdac1* overexpression in PFC is associated with SZ-like phenotypes in mice [202]. These findings suggest that epigenetic dysregulation of selective genes may play an important role in SZ.

Depression

Substantial evidence indicates that mPFC dysfunction plays a critical role in the pathology of major depressive disorder (MDD) [203]. MDD patients display the reduced glucose metabolism in DLPFC [204], and the significantly reduced mPFC volume spanning across dorsomedial PFC, ventromedial (VM) PFC, and ACC [205]. While both DLPFC and VMPFC are involved in MDD, they play different roles: damage to VMPFC is associated with low levels of depression, and damage to DLPFC is associated with high levels of depression [206]. The PFC has also emerged as a hub for MDD treatment, as repeated transcranial magnetic stimulation (rTMS) therapy targeting the left PFC appears effective in mitigating depression symptoms [207].

MDD is associated with aberrant synaptic transmission in PFC, affecting both GABA and glutamate systems (Fig. 4B). A meta-analysis of GWAS studies identified 102 genetic risk variants in MDD patients, many of which display high expression in the frontal cortex and are enriched in biological pathways related to synaptic transmission [208]. Diminished expression of several synaptic genes, including CALM2, SYN1, RAB3A, RAB4B, and TUBB4, is observed in PFC of MDD patients, along with reduced spine density in layers II/III of DLPFC [209]. Protein expression levels of the NMDA subunits NR2A/NR2B and PSD95 are also reduced in the PFC of MDD patients [210], and RNA-sequencing analyses of postmortem DLPFC from MDD patients similarly revealed the downregulation of genes related to glutamatergic transmission [211]. Moreover, an optogenetic study reveals that activating D1R-, but not D2R-, expressing PFC pyramidal neurons produces rapid and long-lasting antidepressant and anxiolytic responses, and disruption of D1R activity blocks the rapid antidepressant effects of ketamine [212].

In addition to the disrupted glutamatergic transmission, there is also evidence for GABAergic impairment in MDD. Microarray analyses of PFC tissue from MDD patients indicate the downregulation of genes related to GABAergic signaling, including multiple $GABA_A$ receptor subunits [213]. In addition, protein levels of GAD67, the primary enzyme responsible for GABA synthesis, are reduced in MDD PFC, and PET imaging studies reveal lower GABA levels in PFC of MDD patients [214]. RNA-seq of postmortem DLPFC tissue from individuals who died by suicide also revealed the downregulation of $GABA_AR$ γ2 subunit [215]. Interestingly, mice carrying heterozygous deficiency of the $GABA_AR$ γ2 subunit in the forebrain display depression-like behavioral phenotypes [216] and the reduced surface expression of NMDA and AMPA receptor subunits in mPFC that could be restored via ketamine treatment [217], suggesting that GABAergic impairment could affect glutamatergic signaling in MDD PFC. Studies in mice indicate that scopolamine, an effective antidepressant medication acting on muscarinic acetylcholine receptors, enacts its antidepressant effects via targeting somatostatin-expressing GABAergic interneurons in mPFC [218], further implicating the prefrontal cortical GABA system in MDD. The density of PNNs is also reduced in the PFC of stressed mice [219] and rats [220], suggesting that PNNs may be disrupted in MDD, similar to SZ.

The NMDAR antagonist ketamine produces rapid antidepressant effects in those with treatment-resistant depression [221], and its therapeutic efficacy appears to be dependent upon its effects on PFC, along with its connecting regions. In rodents, low doses of ketamine have been shown to drive the increased glutamate release [222] and glutamate cycling [223] in PFC. Electrophysiological recordings similarly indicate that ketamine elevates the frequency of excitatory postsynaptic currents (EPSC) in mouse PFC pyramidal neurons [224]. In human MDD patients, ketamine administration similarly increases glutamate/glutamine cycling in PFC [225]. The paradoxical increase in glutamate activity driven by ketamine initially appeared to be mediated by the loss of NMDA-mediated excitation of GABA interneurons, resulting in disinhibition of pyramidal neurons [170] (Fig. 4B). However, deletion of the NMDAR subunit GluN2B from mPFC pyramidal neurons in vivo produces antidepressant-like effects, while also preventing ketamine's effects on behavior, EPSC, and the induction of mTOR activation in mouse mPFC [224], suggesting that ketamine enacts direct effects on pyramidal neurons via GluN2B antagonism.

The ketamine-induced elevation in PFC glutamate release promotes AMPA receptor activation, which is necessary for ketamine's antidepressant effects; pre-administration of the AMPAR receptor antagonist NBQX prevents ketamine's antidepressant-like behavioral effects in mice [226]. NBQX treatment also prevents ketamine's induction of mTOR signaling, suggesting that mTOR activation is mediated by AMPA receptor activation [227]. mTOR inhibition is sufficient to prevent the ketamine-dependent induction of synaptogenesis in PFC and antidepressant-like behavioral effects in rats [113]. The mTOR activation of BDNF and synaptogenesis in PFC appear to be involved in Ketamine's therapeutic function because transgenic mice carrying a mutant form of BDNF that cannot translocate to dendrites do not display ketamine-dependent synaptogenesis nor antidepressant-like behavioral responses [228]. Notably, the significantly reduced protein expression level of mTOR and several downstream signaling molecules is reported in postmortem PFC tissue from depressed patients [112]. Mice expressing a non-phosphorylatable mutant copy of the signaling molecule eIF4E (eukaryotic initiation factor 4E), which is activated downstream of mTORC1, display depression-like behaviors

[229], further implicating the mTOR signaling pathway in MDD. The ketamine metabolite hydroxynorketamine similarly produces antidepressant effects in mice when administered exclusively in the PFC, and this effect is dependent upon the activation of BDNF, and downstream TrkB and mTORC1 signaling [230]. Furthermore, direct activation of the mTORC1 pathway via NV-5138 produces antidepressant effects in rats, suggesting that mTORC1 activation alone may be sufficient to alleviate depressive symptoms [231].

Collectively, these studies suggest that in MDD patients, the PFC is characterized by diminished expression of glutamatergic and GABAergic receptors, accompanied by a reduction in dendritic spine density. Ketamine treatment thus enacts its therapeutic effects by transiently promoting glutamate release in PFC to activate AMPA receptors, which in turn activates the downstream mTOR signaling pathway and promotes BDNF expression, leading to synaptogenesis and elevated glutamatergic transmission (Fig. 4B).

In addition to the involvement of PFC synaptic dysregulation in depression, epigenetic changes have been described in the PFC of individuals with MDD. Twenty genes are found to be differentially methylated in PFC of MDD patients from a genome-wide methylation analysis, including hypermethylation of *Grin2a* [232]. HDAC inhibitor produces antidepressant-like effects in mice [233]. DNA methyltransferases have also been implicated in depression [234]. Elevated DNA methylation is observed in the PFC of rats subjected to learned helplessness stress, which is reversed by antidepressant imipramine treatment [235]. Moreover, systemic administration of DNA methyltransferase inhibitors induces antidepressant-like effects in rats [236]. These findings suggest that pharmacological targeting of epigenetic enzymes may be a novel treatment strategy for depressive symptoms.

Alzheimer's disease

PFC is one of the first regions to be affected in clinical AD, which may explain the early occurrence of the impairment of PFC-mediated cognitive processes, such as working memory and attention. Aging is the leading risk factor for developing AD, so many studies have focused on revealing neurobiological changes that affect synaptic integrity with aging and why the aged brain is vulnerable to AD. In aged PFC, the cAMP/PKA pathway is disinhibited, and PKA inhibition provides an effective approach for treating age-related cognitive decline [237]. The marked loss of PFC persistent firing in aged monkeys is also partially restored by inhibiting cAMP signaling or blocking HCN or KCNQ channels [238]. Age-related increase in PKA phosphorylation of tau at serine 214 in monkey PFC is thought to confer risk for degeneration of glutamatergic synapses [239]. From aging monkey studies, it is found that PFC is particularly vulnerable to calcium dysregulation and tau phosphorylation [240]. The loss of thin spines in monkey PFC, which are particularly plastic and linked to learning, is selectively correlated with age-related cognitive impairment [241]. Aβ infused into the monkey brain induces accelerated cortical aging by triggering the specific loss of dendritic thin spines in the PFC [242].

Cholinergic system is crucial for cognitive processes, and deficient acetylcholine (ACh) function has been implicated in AD. A major AD therapy is acetylcholinesterase (AChE) inhibitors, which act to enhance cholinergic function by prolonging the action of endogenously released ACh. AChE inhibitors produce a strong and persistent reduction of synaptic NMDAR responses in PFC pyramidal neurons via nicotinic ACh receptors [243]. Activation of muscarinic or nicotinic ACh receptors in PFC pyramidal neurons also enhances inhibitory synaptic transmission through PKC-dependent mechanisms [244, 245]. The cholinergic regulation of NMDA and GABA function is impaired in transgenic mice overexpressing mutant β-amyloid precursor protein (APP) [243, 245, 246]. Aβ-induced loss of RACK1 (an anchoring protein for activated PKC) distribution in the membrane fraction of cortical neurons is found to underlie the impairment of muscarinic regulation of PKC [247]. In aged monkeys with naturally occurring cholinergic depletion, low-dose muscarinic M1R stimulation enhances delay firing in dorsolateral PFC neurons and improves working memory via a mechanism involving KCNQ channels [248]. These studies suggest that restoring cholinergic regulation of PFC synaptic activity and neuronal excitability might help to treat AD-associated cognitive disorders.

The brain noradrenergic system is also critical for cognition and noradrenergic dysfunction is a critical early step in AD progression [249]. A recent study has found that β-amyloid oligomers bind to an allosteric site on α2-ARs to redirect norepinephrine signaling to activate the pathogenic GSK3β/tau cascade [250]. Guanfacine, a specific α2-AR antagonist, has been used to treat cognitive disorders linked to PFC dysfunction [251].

The systematic search for global gene expression changes in PFC during the course of AD has found a temporally orchestrated increase of genes involved in synaptic activity during the very early pre-symptomatic stage, probably representing a coping mechanism against increased β-amyloid levels, and the decreased expression of these synaptic genes in later Braak stages, suggesting a reduction in synaptic activity that coincides with AD neuropathology and cognitive impairment [252]. Studies of postmortem human brains have found a significant association between cognitive decline and the loss of synaptic proteins in PFC, such as SNAP25, SNAP47, SV2C, SYT2, and GRIA3

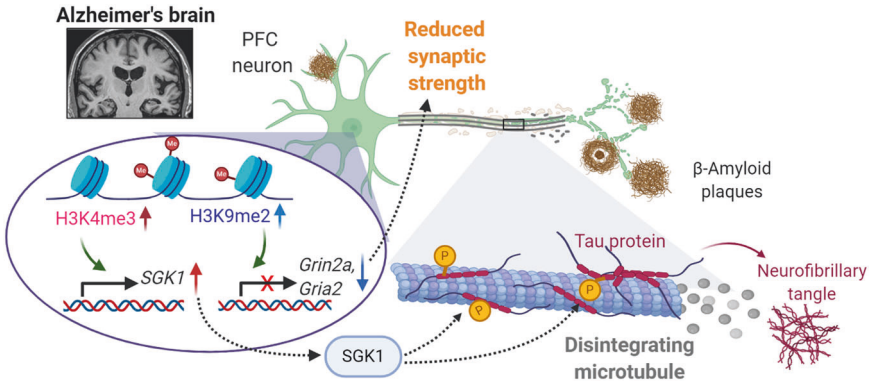

Fig. 5 Schematic diagram illustrating the potential epigenetic mechanisms underlying gene dysregulation and synaptic deficits in PFC of AD. The elevation of repressive histone mark H3K9me2 in AD leads to the downregulation of genes involved in synaptic transmission, such as AMPAR subunit Gria2 and NMDAR subunit Grin2a, resulting in the reduction of synaptic strength [256]. On the other hand, the elevation of permissive histone mark H3K4me3 in AD leads to the upregulation of genes involved in cell stress, such as serum- and glucocorticoid-inducible kinase 1 (SGK1), resulting in hyperphosphorylation of tau, disintegration of microtubules, and disruption of vital protein transport [260]. Targeting histone methyltransferases to normalize histone modification or key target genes is the potential new therapeutic strategy for treating synaptic and cognitive deficits in AD.

[253, 254], suggesting that these PFC synaptic markers are predictive molecular fingerprint for neurodegenerative diseases, and understanding the basis of synaptic impairment is the most effective route for early intervention and prevention of cognitive decline.

Both AD patients and symptomatic AD mouse models show impaired synaptic plasticity in PFC, which is related to the impaired NMDAR function [255]. The diminished transcription of NMDA and AMPA receptors in late-stage AD mouse models has been linked to the EHMT1/2-mediated repressive histone methylation at their promoters [256]. Treatment of AD models with specific EHMT1/2 inhibitors reverses the increased H3K9me2 enrichment at genes involved in neuronal signaling (e.g., *Grin2b* encoding NR2B subunit and *Gria2* encoding GluR2 subunit), restores glutamate receptor expression and excitatory synaptic function in PFC, and rescues the impaired recognition memory, working memory, and spatial memory [256] (Fig. 5).

In addition to the downregulation of genes involved in synaptic transmission and synapse organization, there is also prominent upregulation of genes involved in cell stress, immune response activation, and cell death in PFC of AD patients [257–259]. A recent study has found that H3K4 trimethylation (H3K4me3), a histone mark for gene activation, is significantly elevated in PFC of human AD postmortem tissues and AD mouse models, and inhibiting H3K4-specific methyltransferases, including MLL1-4 (also named as KMT2A-D) and SETD1a/b, leads to the substantial recovery of glutamatergic synaptic function in PFC pyramidal neurons, and the significant improvement of memory-related behaviors in mutant Tau transgenic mice [260]. One of the top-ranking genes elevated by the abnormally high H3K4me3 in PFC of AD patients and mouse models is *SGK1*, which encodes the stress-responsive kinase SGK1. A short treatment with the specific SGK1 inhibitor results in the significant reduction of hyperphosphorylated tau (a pathological hallmark of AD) and the recovery of synaptic receptor expression and glutamatergic transmission in PFC, as well as the restoration of recognition and spatial memories, in mutant Tau transgenic mice [260] (Fig. 5). These results suggest that targeting histone methylation enzymes may represent a novel therapeutic avenue for normalizing the aberrant epigenetic regulation of gene transcription in PFC that underlies cognitive deficits in AD.

Concluding remarks

Overwhelming evidence has indicated that PFC is a uniquely important brain region for the highest level of executive function, which drives self-regulatory and goal-directed behaviors [261–263]. Dysregulation of PFC synaptic transmission directly contributes to the impairment of social, affective, motivational, and cognitive function associated with brain disorders including autism, schizophrenia, depression, and Alzheimer's disease. Studies in animal models have revealed critical neural circuits, biological pathways, and molecular players that converge to control the excitatory and inhibitory signals in PFC networks. Novel epigenetic mechanism-based strategies have been proposed as potential avenues of therapeutic intervention for mental diseases linked to PFC dysfunction.

There are many open questions that await to be further explored in future studies, and a few examples are listed as follows:

(1) What makes PFC so special in terms of the organizational and cellular function? Circuit mapping with modern technologies has revealed the links of specific pathways and cell types to particular behavioral aspects. How specific and robust are such links? Is it likely that complex cognitive and emotional behaviors usually need to recruit multiple circuits and neuronal populations? What are the differential roles of PFC and its connecting regions in the control of these behaviors?

(2) How does PFC integrate the influences of monoaminergic systems, stress hormones, and neuropeptides in different conditions? What effects of these neuromodulators are unique to PFC synaptic function? How much does the aberrant modulation of PFC contribute to the pathophysiology of neurodevelopmental, neuropsychiatric, and neurodegenerative diseases?

(3) What are the convergent and divergent factors causing PFC synaptic dysfunction in autism, schizophrenia, depression, and Alzheimer's disease? Is PFC synaptic dysregulation directly linked to behavioral abnormalities in these illnesses?

(4) How are the synaptic, epigenetic, and transcriptomic alterations mechanistically connected in each of PFC-involved brain disorders? What is the translational potential of the epigenetics-based treatment strategies found in preclinical models for human patients with these disorders?

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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