EXPERT REVIEW

Aberrant maturation and connectivity of prefrontal cortex in schizophrenia—contribution of NMDA receptor development and hypofunction

Wen-Jun Gao[1]✉, Sha-Sha Yang[1], Nancy R. Mack[1] and Linda A. Chamberlin[1]

The neurobiology of schizophrenia involves multiple facets of pathophysiology, ranging from its genetic basis over changes in neurochemistry and neurophysiology, to the systemic level of neural circuits. Although the precise mechanisms associated with the neuropathophysiology remain elusive, one essential aspect is the aberrant maturation and connectivity of the prefrontal cortex that leads to complex symptoms in various stages of the disease. Here, we focus on how early developmental dysfunction, especially N-methyl-D-aspartate receptor (NMDAR) development and hypofunction, may lead to the dysfunction of both local circuitry within the prefrontal cortex and its long-range connectivity. More specifically, we will focus on an "all roads lead to Rome" hypothesis, i.e., how NMDAR hypofunction during development acts as a convergence point and leads to local gamma-aminobutyric acid (GABA) deficits and input-output dysconnectivity in the prefrontal cortex, which eventually induce cognitive and social deficits. Many outstanding questions and hypothetical mechanisms are listed for future investigations of this intriguing hypothesis that may lead to a better understanding of the aberrant maturation and connectivity associated with the prefrontal cortex.

Molecular Psychiatry (2022) 27:731–743; https://doi.org/10.1038/s41380-021-01196-w

INTRODUCTION

Schizophrenia (SZ) is a neurodevelopmental disorder with both cognitive and social deficits that are resistant to current therapies. To improve the treatment of these impairments, it is essential to clarify the pathophysiological processes underlying the progression of SZ. A large body of evidence indicates a dysfunctional local circuitry, particularly gamma-aminobutyric acid (GABA)ergic deficits within the prefrontal cortex (PFC) [1] and its connections with other brain regions, especially those related to the limbic systems [2]. Over the last two decades, numerous neurophysiological (EEG, electroencephalogram) and neuroimaging (fMRI, functional magnetic resonance imaging) studies of patients with SZ have provided strong evidence for both aberrant local prefrontal network activity and brain-wide dysconnectivity, i.e., abnormal functional integration of information processes in the PFC and the brain [3–10]. While the evidence for dysconnectivity in SZ is strong [9, 11–13], its etiology is complicated, and its mechanisms and significance for clinical symptoms remain subject to debate [9, 14–16]. Nevertheless, in the past two decades, the framework of the dysconnectivity hypothesis has led to significant progress in the field. This dysconnectivity theory hypothesizes that the core neuropathology in SZ is aberrant N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic plasticity and abnormal neuromodulation of NMDAR expression and function by disrupted neuromodulatory transmitters, such as dopamine, serotonin, and acetylcholine [9, 14, 17, 18]. Undeniably, we agree that NMDAR hypofunction is a critical player and a convergence point of the neuropathophysiology of SZ, especially for cognitive and social deficits [19].

However, here we argue against the causal role of neuromodulatory transmitters (such as dopamine, etc.) in the induction of NMDAR hypofunction. On the contrary, based on recent evidence, we hypothesize that NMDAR hypofunction occurs first [20], which in turn causes dysfunctional GABAergic circuitry locally within the PFC and disruptions to the incoming and outgoing connections with other brain regions, including neuromodulatory systems [21]. We agree that this claim remains in debate as substantial literature showing that dopamine and/or other monoamine systems play essential roles in the prefrontal function and synaptic plasticity in both animals and humans [22, 23]. However, evidence from clinical [22, 23] and pre-clinical [15, 16, 24–28] studies supports that the hypothesis of NMDA hypofunction occurs earlier during or before juvenile period [19, 29] compared to dopamine dysfunction appearing at a later stage of adolescence. This raises questions about the sequential changes or logical causal role of NMDAR vs. dopamine hypothesis. More studies on the causal roles of dopamine dysfunction in the disconnected network during earlier periods are needed.

The resulting GABA deficiency and subsequent dopamine/serotonin dysfunction lead to progressive symptoms, including cognitive and social function impairments and psychosis. Current antipsychotic medications that target the dopaminergic system demonstrate minimal therapeutic efficacy in treating cognitive and social deficits in SZ [30]. In contrast, targeting NMDAR dysfunction during early disease stages appears to be a promising avenue for prevention and therapeutic intervention for cognitive

[1]Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA 19129, USA. ✉email: wg38@drexel.edu

Received: 24 October 2020 Revised: 2 June 2021 Accepted: 10 June 2021
Published online: 23 June 2021

and social deficits in various animal models, including the NMDAR antagonist MK-801 model, for SZ [31–33].

Mechanistically, how these two major hypotheses, NMDAR hypofunction and local/long-range dysconnectivity, are initiated and reconciled remains unexplored. A large body of evidence from both animal models and human studies implicates dysfunction of NMDARs in disease development and symptom manifestation of SZ [34–44]. Recent studies, including ours, have suggested that NMDAR hypofunction is likely a convergence point that occurs during the early stage of the disease. This may consequentially initiate GABA deficits [19, 20, 41, 45], leading to aberrant local circuitry and long-range disconnections among different brain regions, including dopamine systems [22, 46], thereby accounting for key clinical features of SZ.

The PFC must precisely filter essential information from the numerous signals it receives from cortical and subcortical brain regions to perform executive functions. Local GABAergic interneurons (INs) are critical for gating incoming information to excitatory neurons [47]. In addition, long-range inputs drive inhibitory neurons to maintain the E/I balance within the prefrontal circuits [48, 49]. The currently limited evidence suggests that distinct afferents may have unique NMDAR subunit compositions with differential functional roles for connectivity during development [50, 51]. It is therefore vital to understand how PFC pyramidal neurons and different IN subtypes are modulated in unique ways across development by distinct afferent inputs from major upstream regulatory centers, including the mediodorsal thalamus (MD) and other thalamic nuclei, as well as other inputs from the limbic systems, such as the ventral hippocampus (vHipp) and basolateral amygdala.

In this review, we focus on recent literature, especially the progress made within the past 10 years, to present (1) clinical evidence of dysconnectivity; (2) the role of NMDAR hypofunction in aberrant local PFC circuitry and long-range dysconnectivity; (3) MD-PFC dysconnectivity and interneuron subtype specificity in SZ; (4) reconciling NMDAR hypofunction with local circuit and global dysconnectivity; and (5) outstanding questions and future perspectives.

Clinical evidence of brain-wide dysconnectivity

Since the dysconnection hypothesis for SZ was introduced more than 20 years ago [11, 12, 52], neuroscience has witnessed tremendous advances. The evidence for a systemic dysfunctional integration and connectivity is overwhelming, and now it is widely accepted that SZ is characterized by large-scale cortical (e.g., thalamocortical and corticocortical) dysconnectivity compared with healthy individuals [5, 9, 14]. These findings involve the PFC and key subcortical and associative cortical regions mostly related to the limbic systems [3–5, 7, 9, 14, 53–55]. Combined with the clinical findings, recent modeling of intrinsic and extrinsic connectivity also suggests a specific failure of intrinsic gain regulation within the PFC or modulation of synaptic efficacy in hierarchically subordinate structures [4, 7, 56], which supports the hypothesis of failures in self-monitoring or homeostatic plasticity proposed by Friton et al. [9, 14]. Based on these clinical measurements and modeling, Yang et al. proposed that functional cortical hierarchy between the association and sensory regions underlies preferential network connectivity disturbances in associative vs. primary sensory (e.g., visual and auditory) cortices [56], and even widespread early-stage prefrontal hyperconnectivity [55] in SZ. The neuroimaging correlations of dysconnection appear to be stable over time, enabling the differentiation between patients and control subjects [57]. It has even been proposed that these systemic measures of dysconnection may serve as neurobiological indices for defining SZ patients [9]. However, this raises an intriguing question about the underlying biological trait abnormalities that implicate a failure in the modulation of synaptic efficacy relative to the potential compensatory homeostatic state of abnormalities that produce symptoms and signs [9].

Measures of functional connectivity with EEG or fMRI have also been linked to a genetic basis. A meta-analysis [58] reported that putative SZ risk variants reduced functional connectivity, which is supported by recent studies [59], providing more evidence for the dysconnection hypothesis [9, 52]. Interestingly, dysconnectivity is mostly implicated in the PFC and other association areas, raising the question of how such differential impairment can be explained if biological abnormalities are common across the neocortex. This question has motivated a study of brain dysconnectivity in SZ that combined fMRI with a large-scale cortical network model of the human cortex [56, 60], and an intriguing hypothesis of macroscopic gradients of synaptic excitation and inhibition (E/I) balance across the neocortex that warrants further exploration [7].

The role of NMDA hypofunction in the aberrant local circuit and long-range dysconnectivity of the mPFC

Although there is strong evidence for global functional network dysconnectivity revealed by neuroimaging and neurophysiology, SZ is also clearly linked to disruption of the local prefrontal circuit, particularly imbalanced E/I ratio based on clinical [6, 10, 61], computation [56], and animal [62, 63] studies. Clinical literature from cross-diagnostic analysis indicates a convergent neural mechanism governing E/I balance in patients with SZ [61]. There is also evidence supporting a link between glutamate-mediated cortical disinhibition, effective-connectivity deficits, and computational performance in psychosis [10]. The question is how these two frameworks—global versus localized neural dysfunction—work together to display behavioral phenotypes, particularly cognitive and social impairments in SZ, that are dependent on proper PFC function. To answer this question, we elucidate the basic prefrontal circuitry that functions to execute normal cognition and social behavior, the distinct and prolonged developmental trajectory of the PFC, its unique connections with other brain regions, how NMDAR development and function are intertwined with the development of PFC circuitry, as well as new questions raised and hypothetical mechanisms learned from studies in other cortices for further investigations.

NMDAR in the development of prefrontal GABAergic interneurons

The PFC exhibits laminar connections among diffeent cell types within the local circuitry. As shown in Fig. 1, the excitatory glutamatergic pyramidal cells connect each other to form recurrent excitation and innervate GABAergic INs to initiate feedback inhibition. The pyramidal neurons project to other cortical regions to establish corticocortical connections and subcortical regions as descending innervations. Within the PFC local circuitry, a diverse array of GABAergic IN subtypes regulates cortical activity [64]. The three most abundant INs include fast-spiking (FS) parvalbumin (PV)-INs (which target the perisomatic region of pyramidal neurons), somatostatin-expressing (SST)-INs (which target pyramidal neuron dendrites, gate input-specific information processing, and inhibit PV-INs [65]) and vasointestinal peptide-expressing (VIP) cells (which inhibit SST-INs to induce disinhibition of pyramidal neurons [47, 66, 67]). In addition, the local prefrontal circuitry receives both glutamatergic afferents and non-glutamatergic neuromodulatory afferents from the cortical and subcortical regions to enable feedforward excitation and inhibition [48, 68], while the pyramidal neurons in the PFC project to the limbic systems and other cortical and subcortical structures (Fig. 1) that are different from other cortical regions, such as primary sensory, auditory, and visual cortices.

Despite these seemingly clear connections, exactly how they interact together to affect PFC-associated functions remains to be determined, especially those associated with different subtypes of

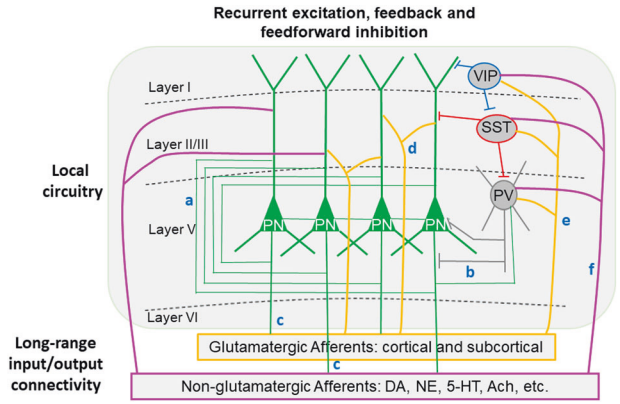

Fig. 1 Illustration showing the simplified local prefrontal circuitry and long-range input/output connectivity. The excitatory glutamatergic pyramidal cells connect to each other to form recurrent excitation (**a**) and innervate GABAergic interneurons to form feedback inhibition (**b**). The pyramidal neurons project to other cortical and subcortical regions to form corticocortical connections and subcortical regions as descending innervations (**c**). In turn, local prefrontal circuitry, including both pyramidal neurons and GABAergic cells are also innervated by cortical and subcortical excitatory glutamatergic inputs (green) to form forward excitation (**d**) and feedforward inhibition (**e**). Both pyramidal neurons and GABAergic interneurons are also regulated by subcortical non-glutamatergic neuromodulatory afferents (pink, **f**) from the dopamine (DA), norepinephrine (NE), serotonin (5-HT), and acetylcholine (Ach) cells. Despite these seemingly clear connections, exactly how they interact to affect PFC-associated functions remains to be determined. There are also many unknowns among these connections, and their roles in behavioral deficits associated with SZ symptoms.

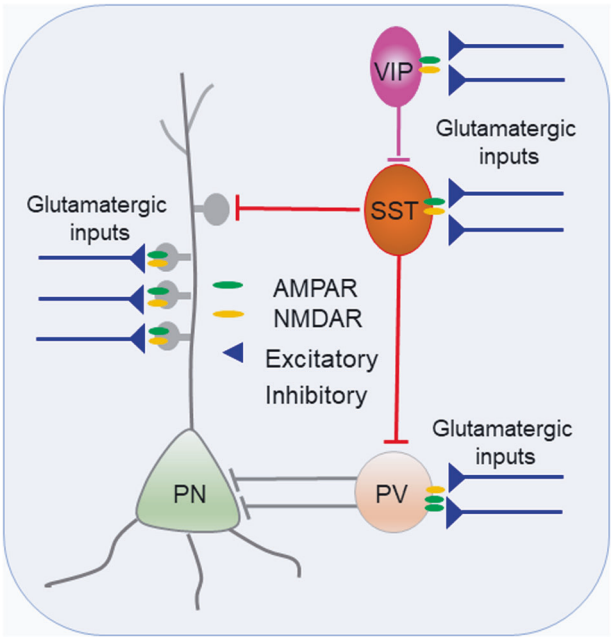

Fig. 2 Prefrontal local circuit. Glutamatergic afferents innervate both excitatory pyramidal neurons (PN) and inhibitory GABAergic IN subtypes [248]. These inputs are capable to generate diverse feedforward control on the prefrontal local network through PV-, SST, or VIP-INs. PV-INs express relatively low levels of NMDARs [51, 94–98], and they are enriched with GluN2A subunits [99–101]. In contrast, SST- and VIP-INs express relatively more NMDARs and are enriched with GluN2B subunits [102–104].

GABAergic INs, such as VIP and SST, even in the normal brain. There are many unknowns among these connections. For example, how does NMDAR hypofunction induce an abnormal neurodevelopment in the local circuitry of different PFC neuronal subtypes and their long-range connections with other brain regions, including both glutamatergic and non-glutamatergic inputs and outputs? Consequently, it remains unclear how these changes may induce behavioral deficits associated with SZ symptoms.

SZ is a neurodevelopmental disorder, and most, if not all, of the functional and structural changes occur during the early stages of postnatal development, especially during juvenile and adolescent periods, as presented in both human [69–71] and animal [63, 72–76] studies. The delayed maturation of the PFC and, in particular, the delayed maturation of GABAergic INs in this region through adolescence critically contribute to susceptibility to cognitive and social deficits [15, 16, 77–85]. Therefore, it is essential to elucidate when and how the local prefrontal circuitry forms and matures across development and the role of different PFC cell types in regulating cognitive and behaviors. It is also essential to understand how various excitatory afferents from cortical and subcortical regions (e.g., thalamus vs. hippocampus vs. amygdala, etc.) regulates the development of synaptic function in PV-, SST-, and VIP-INs vs. pyramidal neurons within the PFC, as illustrated in Fig. 1.

The activity/experience-dependence of synaptic and circuit formation during development, which relies on NMDAR-mediated plasticity, has been extensively studied in somatosensory, auditory, and visual cortices [86–88]. These studies suggest that GluN2B-containing NMDARs are the pillar in the maintenance of critical-period plasticity. In the PFC, the developmental GluN2B-to-GluN2A switch occurs later than in other brain regions and marks the transition from adolescence to adult neural processing and maturation of associative learning abilities [89]. This may leave open a long critical period window for plasticity and may underlie the delayed maturation of the PFC [90]. In addition, existing evidence assists us in speculating that the time course of NMDAR maturation is likely cell-type-specific [91, 92].

For example, the NMDAR hypofunction hypothesis has largely focused on NMDAR expression and function in PV cells [19, 20, 41, 42, 93]. But paradoxically, PV-INs express relatively low levels of NMDARs [51, 94–98] (Fig. 2), and they are enriched with GluN2A subunit [99–101]. In contrast, SST- and VIP-INs express relatively more NMDARs and are enriched with GluN2B subunits (Fig. 3), which have significantly slower decays than NMDARs expressing the GluN2A subunit [102–104]. Previous studies reported that NMDAR subunit composition controls synaptogenesis and synapse stabilization [105]. The distinct composition of NMDAR subunits endows the three types of INs with different magnitudes of plasticity in network activity during cognitive performance. All three types of INs in the PFC are crucially involved in cognitive function, social behavior, and SZ [103, 106–109]. The limited current evidence suggests different IN subtypes show distinct changes in NMDAR function across neurodevelopment. For example, Koppensteinier et al. [92] showed that NMDA-mediated ESPC amplitude in SST-IN increases from adolescence to adulthood. In contrast, the amplitude of NMDA-mediated ESPCs in PV-INs decreases from the juvenile stage to adolescence, consistent with our previous report in rat PFC [95]. However, more research is needed to fully understand NMDAR expression and function in the different IN subtypes across neurodevelopment and how these may go awry in SZ.

Nevertheless, abundant evidence has shown that NMDAR blocker ketamine decreases resting-state functional network connectivity [110] and modulates hippocampal neurochemistry and functional connectivity in health subjects [111]. These effects have not only emphasized the importance of NMDARs in neural connectivity but also neurons in other cortical regions (e.g., ventral tegmental area, VTA) and other cell types (e.g., SST-INs [106]) in NMDAR hypofunction for SZ [42]. Several recent studies have also provided interesting yet inconsistent reports regarding the

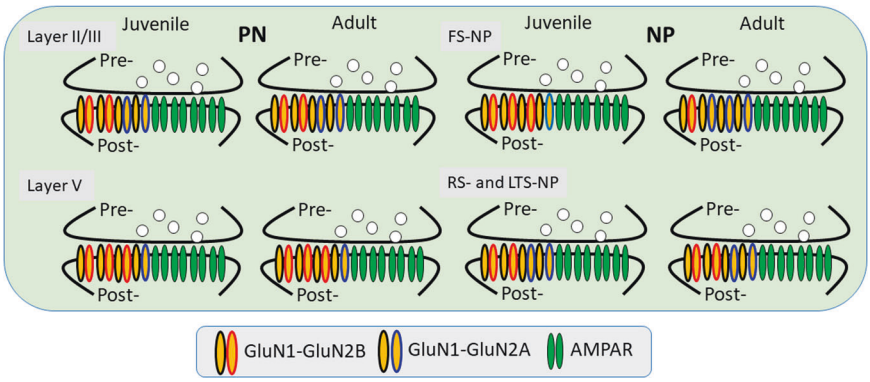

Fig. 3 Schematic model showing the development of NMDAR subunits in different types of PFC neurons. Layer II/III pyramidal neurons (PN) exhibit an equal amount of GluN2A and GluN2B subunits, whereas layer V pyramidal neurons express more GluN2B subunits during the juvenile to adulthood development. In contrast, in the GABAergic interneurons (non-pyramidal neurons (NP), fast-spiking (FS) interneurons exhibits clear GluN2B-to-GluN2A subunit switch whereas regular spiking (RS) and low-threshold spiking (LTS) interneurons exhibit similar NMDAR subunit expression to the layer II/III pyramidal neurons. In summary, except a subset of FS-NPs, which show a sharp increase of GluN2A and decrease of GluN2B, all other cells exhibit no GluN2B-to-GluN2A switch during postnatal development, differing from other brain regions [95, 155, 185, 249].

relationship between NMDAR function and proper connectivity in the PFC. For example, Flores-Barrera et al. reported a late adolescent expression of GluN2B in the apical (but not basal) dendrites in mPFC layer 5 pyramidal neurons, with vHipp inputs requiring postsynaptic PKA and D1 signaling for GluN2B maturation [112]. In contrast, by deleting GluN2B in PFC pyramidal neurons, Miller et al. showed a selective enhancement of MD-PFC but not a vHipp-PFC pathway in layer 2/3 pyramidal neurons, and that activation of MD-PFC pathway induces anti-depressive behaviors in young adult mice [113]. This enhanced connectivity is consistent with a clinical report of increased connectivity during the early stage of the disease [55]. It provides causal evidence that NMDAR dysfunction can lead to aberrant functional connectivity.

Notably, the mPFC is a convergent target of multiple long-range inputs, including those from vHipp and MD [114, 115]. Given that these long-range inputs innervate pyramidal neurons [116] and INs [48, 68, 117] in both layers 2/3 and 5 (Fig. 1), these findings raise important questions regarding how NMDAR hypofunction affects the excitatory activity from the MD and other long-range inputs, which in turn, shape the local inhibitory circuitry formed by different subtypes of INs within the PFC, and whether altered MD activity influences the inhibitory circuit formation among INs.

Recent studies have suggested an afferent-specific role of NMDARs for the circuit integration of INs [118] and input-specific NMDAR-dependent potentiation of dendritic (i.e., SST-INs) GABAergic inhibition [119]. Tonic GABAergic activity also facilitates dendritic calcium signaling and short-term plasticity [120]. Dendritic NMDARs in PV-INs even underlie super-linear integration of feedback excitation from local pyramidal neurons and thus enable strong and stable neuronal assemblies [121]. Consequently, NMDAR ablation in corticolimbic PV-INs induces hippocampus-PFC functional hypoconnectivity after adolescence in a mouse model for SZ [63]. Therefore, we expect an input- and cell-type-specific, as well as age-dependent, modulation, as we and others have reported that cortical INs are differentially modulated by their inputs, including glutamatergic and monoaminergic fibers [21, 50, 122–126] (see Fig. 1).

MD-mPFC dysconnectivity and interneuron subtype specificity in SZ

The MD is a major upstream regulatory center to the PFC [127–130]. Excitatory afferents from the MD reach PFC cortical layers far earlier during development than the maturation of GABAergic INs and synapses [117] (Fig. 4). In addition, the MD and PFC share extensive reciprocal connections [114, 131] with SZ patients demonstrating reduced connectivity between these two brain regions [5], which is associated with cognitive and social deficits [49]. Recent studies indicate that the MD plays distinct roles in sophisticated cognitive processes [116, 130, 132–134] and social dominance [135]. In particular, MD inhibition in mice disrupts thalamofrontal connectivity and working memory [49, 131, 136], and goal-directed behavior [129, 137]. In adulthood, we recently reported that acute chemogenetic inhibition of MD activity results in a significant reduction in GABAergic signaling and increased E/I ratio within the mPFC, as well as abnormalities in cognitive and social behaviors. Furthermore, by selectively activating PV-INs in the mPFC with a chemogenetic tool, E/I balance was restored, and working memory and social deficits were ameliorated. These findings highlight the importance of thalamocortical activation of PV-INs in PFC-dependent behaviors [68].

Thus far, our study, as well as work from others, has mainly focused on PV cells in normal adult animals [42], leaving the role of SST and VIP cells in MD-mediated PFC function untested. In fact, we do not even know how MD inputs directly regulate SST and VIP-INs despite the dense distribution of both SST and VIP cells [138–141], as well as MD fibers [114, 142, 143] in superficial layers of the PFC. SST and VIP mRNA and peptide levels are both decreased in the PFC of patients with SZ [107, 144]. In addition, both cell types are critically involved in cognition [67, 145–147]. It is thus essential to understand how MD and other inputs' activity regulates different PFC INs during development and to determine whether MD inputs are essential for the reduction of SST and VIP in animal models for SZ. It is conceivable that the MD, as a major source of glutamatergic inputs, plays a critical role in the development of NMDARs in both pyramidal neurons and different subtypes of INs in the PFC (Fig. 4).

Reconciling NMDAR hypofunction with local and global dysconnectivity

A basic question that has haunted the field is what causes GABA deficits and abnormal connectivity in neurodevelopmental disorders, such as SZ? It is known that in response to normal and abnormal stimulation, synapses mediating local and long-range connections between different cell types exhibit sequential alterations through different mechanisms during development. More importantly, during adolescent development, GABAergic cell function becomes dominant compared to pyramidal neurons

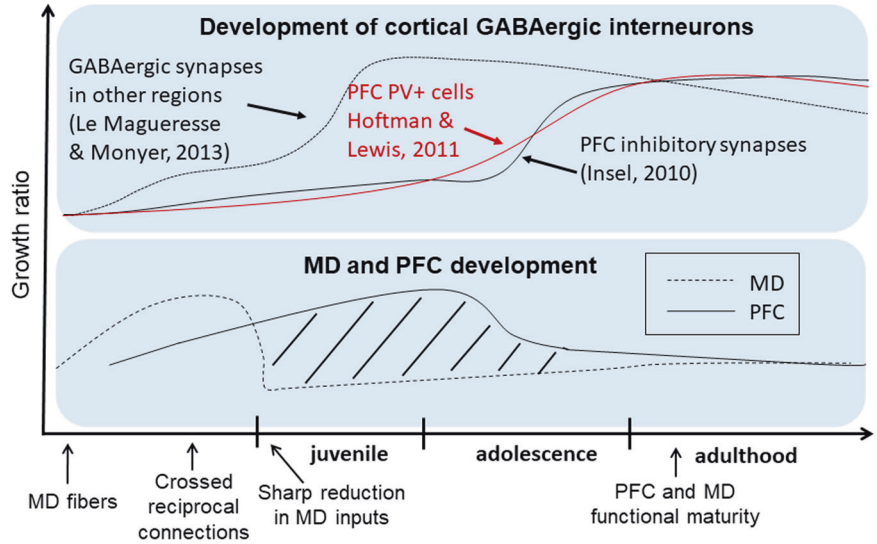

Fig. 4 Developmental trajectory of cortical GABAergic interneurons and maturation of MD and PFC. Upper panel: Distinct developmental trajectories of GABAergic inhibitory synapses and PV+ cells in the PFC (red and black lines) vs. other brain regions (dashed line) [75, 97, 250]. Lower panel: MD afferent density (dashed line) and volume of the PFC (solid line). Dashed lines represent the different developmental window between MD activity and PFC function. Lower panel is modified from [117], and copyright is permitted for reuse of the figure.

because they are receiving more glutamatergic innervations [78]. For example, PV cells are enriched with excitatory inputs during adolescent development, and ErbB4 splicing regulates the pruning of these excitatory synapses [148–151]. This effect is both activity- and NMDAR-dependent, and disruption of any of these processes produces SZ-like cognitive and social deficits [20, 78, 149, 152, 153].

NMDARs significantly contribute to information transfer and integration at synapses during repetitive activity and to the generation of persistent activity of neural assemblies for working memory function [90, 154–156]. The mechanisms for changes in NMDAR function, number, and subunit composition at a given synapse and cell type, as well as the identity and function of auxiliary subunits of NMDARs in the developing rodent PFC [51, 95, 96, 155, 157], remain understudied compared to other cortical regions [158–160].

NMDAR hypofunction and dendritic spine plasticity

Given the unique biophysical properties and development of NMDARs in the PFC, especially the high level of GluN2B [7, 90], the plasticity of NMDAR-mediated synaptic transmission is crucial to the circuit formation and maturation of the PFC. A growing body of evidence suggests the existence of synaptic pathology in SZ [15]. NMDAR hypofunction in pyramidal neurons appears to be responsible for spine density alteration of cortical pyramidal cells as SZ-related spine density reduction is induced by GluN1 knockdown in the pyramidal neurons [20, 161, 162]. Pharmacologically, subchronic PCP treatment decreases the number of dendritic synapses in the rat PFC [163, 164], but the underlying mechanisms remain to be determined. However, it has been demonstrated that mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonist ketamine [165]. A remarkable recent rodent study provides additional support with in vivo dendritic spine monitoring in the PFC [166]. Specifically, prolonged exposure to chronic unpredictable stress increases "depressive-like behaviors" in mice and causes a retraction of dendritic spines in the mPFC. Interestingly, these changes are effectively normalized by systemic administration of ketamine [166], highlighting the importance of NMDAR in regulating dendritic spine plasticity in the PFC.

PFC dysconnectivity and NMDAR hypofunction in non-human primate and human studies

Prior neural recording studies in monkey PFC also characterized how blocking NMDAR alters physiological signals in prefrontal neurons related to working memory and executive control. Specifically, blocking NMDAR weakens delay period activity associated with working memory [154], reduces the strength and task selectivity of neural signals reflecting executive control in rule-based tasks [167, 168], and modifies prefrontal oscillations reflecting trial outcome [169]. In particular, blockade of GluN2B in the dlPFC markedly reduces the persistent firing of the delay cells needed for neuronal representations of visual space [154, 170]. However, studies probing how NMDAR hypofunction affects prefrontal function in non-human primates remain limited [171]. Two different NMDAR antagonists, PCP and MK-801, have been often used in rodent behavioral studies, while ketamine has been often used in non-human primates to induce cognitive disturbances [171–176]. Moreover, non-human studies tend to use acute and bolus injection of NMDAR antagonists equivalent to those achieved in human subjects, in which ketamine produced resting brain hyperconnectivity and SZ-like cognitive deficits [177, 178]. Systemic administration of ketamine also reduces the persistent firing of delay cells in primates. This effect may explain why this drug can mimic or worsen SZ's cognitive symptoms [170].

In a recent study, Zick et al. further reported that blocking NMDAR-mediated synaptic transmission by PCP in primates disrupts the spike timing in prefrontal circuits that lead to activity-dependent synaptic disconnection of these circuits over time, potentially linking synchrony and connectivity deficits in SZ [179]. Administration of ketamine also yields a circuit-level mechanism that links NMDAR hypofunction to synaptic connections to behaviors, including decision-making biases [180]. Based on these observations, although the causal biology underlying SZ remains not well understood, it is predicted to involve a malfunction in how neurons adjust synaptic connections in response to patterns of activity in networks [181].

Interestingly, a recent study reported that the effects of NMDAR antagonists on prefrontal cortical connectivity model early rather than chronic SZ [4] (also see [110, 111, 182, 183]), emphasizing their critical roles in neurodevelopment. However, despite the

progress, compared with rodent studies, how NMDA hypofunction affects the development of prefrontal circuitry and synaptic connectivity in non-human primates remains to be determined. In the primate dlPFC, the density of excitatory synapses decreases by 40–50% during adolescence [184], but whether this significant change is associated with NMDAR-mediated transmission is unknown. Gonzalez-Burgos et al. reported that during early postnatal development (3-month-old monkey), excitatory inputs to layer 3 pyramidal neurons exhibited immature properties, including higher release probability, lower AMPA/NMDA ratio, and higher expression of GrinN2B subunits compared to preadolescent (15 months old) and adult (42 or 84 months old) monkeys. These findings indicate that functionally immature synapses' contribution to prefrontal cortical development significantly decreases before adolescence begins, at least for monkey PFC layer 3 pyramidal neurons [184]. These findings are slightly different from those reported in the rodent mPFC, as shown in Fig. 3 [90, 95, 155, 185]. Whether there exists a laminar difference of NMDAR subunit development in non-human primate PFC remains to be determined.

NMDAR hypofunction, prefrontal E/I balance, and global dysconnectivity

Despite extensive information regarding the regulation of NMDAR function and trafficking in cultured neurons and expression systems [186, 187], much remains to be explored about the molecular basis of activity-dependent NMDAR plasticity in vivo, especially during different stages of development [188]. A significant challenge is determining the precise contribution of NMDAR in a cell-type- and afferent/pathway-specific manner, as recently reported in the prefrontal neurons [151, 189]. The new technologies described in the future directions would be vital in addressing this challenge and the outstanding questions enlisted below. A recent review study has provided strong evidence of cell-type actions for NMDAR hypofunction [42]. Specifically, NMDAR hypofunction can produce SZ-related effects through action on various circuits and cell types, including not only prefrontal pyramidal neurons and PV-INs, but also VTA dopamine neurons and other brain regions [42], as illustrated in Fig. 1.

Still, all of these assumptions depend on how NMDAR hypofunction leads to global E/I imbalance, local circuit dysfunction, and regional dysconnectivity that underlie SZ [6]. Postmortem work indicates IN dysfunction involves the altered interplay of GABA and glutamate across the brain [190]. NMDARs on GABAergic INs, especially PV-INs, form the cornerstone of the NMDA hypofunction model of SZ [10, 19, 42, 191], and are critical for the regulation of E/I balance in neural microcircuits [192].

An important recent discovery is the macroscopic gradients of synaptic E/I in the neocortex [7]. Areas of the neocortex differ not only due to their input-output patterns but also their physiological properties. Specifically, when cortical regions were plotted by rank order of SST cell to PV cell ratio values, the ratio of SST- to PV-INs is surprisingly low in primary sensory and motor areas and high in association areas, including frontal areas, revealing a macroscopic gradient of synaptic inhibition in the mouse cortex. Notably, PV cells are twice as abundant as SST cells in V1, but SST cells are four-fold more numerous than PV cells in frontal areas per this ratio calculation [7]. Importantly, there is an increasing gradient of synaptic excitation along the cortical hierarchy, including the expression level of GluN2B that plays a crucial role in the NMDAR-dependent recurrent excitation that supports cognition [90, 154–156]. However, a gradient of NMDAR-dependent excitation in a multiregional cortex, especially those in SST cells, remains elucidated in future research [7]. The notion of macroscopic gradients has begun to be applied to studies of mental disorders. For instance, SZ is characterized by large-scale cortical dysconnectivity [14].

Interestingly, dysconnectivity is primarily implicated in the PFC and other association areas, raising the question of how such differential impairment can be explained if biological trait abnormalities are common across the neocortex [56]. Still, the relationship between macroscopic gradients and NMDAR hypofunction leading to global E/I balance and local circuit dysfunction remains to be determined. Given the selective role of GABAergic INs in NMDAR hypofunction hypothesis [19, 192], and the gradient GluN2B ratio [193] and regional difference of NMDAR-mediated currents between PFC and V1 [155], we predict that an NMDAR hypofunction condition will likely produce a regional difference in E/I balance, contributing to the various symptoms of SZ. Indeed, recent theoretical accounts have proposed E/I imbalance as a possible mechanistic, network-level hypothesis underlying neural and behavioral dysfunction across neurodevelopmental disorders, particularly SZ [61].

Investigation of the link between NMDAR homeostatic plasticity and the molecular mechanisms governing NMDAR trafficking [194, 195] may serve to bridge the gap in our understanding of how these processes integrate activity over multiple timescales to support cognitive functions. While emerging evidence suggests that activity-dependent regulation of NMDARs plays an essential role in behaviors, further studies are needed to test the role of NMDAR plasticity in neuropsychiatric conditions, such as the NMDAR dysregulation implicated in SZ [186].

In summary, mechanistically, pyramidal cells and IN subtypes can be regulated in response to activity levels via various mechanisms (Box 1, Fig. 5). Therefore, the maturation of different inputs to the PFC during juvenile and adolescent development can stimulate the neurons and neuronal network, leading to distinct changes in protein expression levels depending on the identity of the postsynaptic cell. One such family of proteins is the NMDAR subunits, which are known to vary among IN subtypes and pyramidal neurons. NMDAR subunit composition is important for plasticity and regulation of cortical development during critical juvenile and adolescent periods. Therefore, alteration of input and output activity during development is expected to disrupt GABAergic circuitry and neuronal connectivity with other brain regions, with cell-type- and input/output-specific effects on synaptic plasticity and underlying molecular changes. Eventually, these homeostatic changes could lead to a shift of threshold for plasticity, i.e., metaplasticity, and consequently, a set-point adaption.

Conclusion and future directions

Aberrant neural network connectivity has been widely recognized as constituting major functional and structural changes in the neuropathophysiology of SZ. However, what an aberrant circuitry actually looks like remains an enigma. Brain cells are highly plastic, allowing an organism to learn and adapt to its environment, including response to mutant genes and risk factors. This ongoing plasticity is essentially unstable during development, leading to aberrant circuit activity. Homeostatic plasticity provides a compensatory mechanism in controlling neuronal network activity and stability. Many of these homeostatic modifications may occur not only within the subcellular neuronal compartments but also in different levels of connections from synaptic inputs at both excitatory and inhibitory cells to modulation of neuronal outputs, as proposed in a recent review [232]. Here we have summarized the current progress, and we outline the outstanding questions in Box 2, and future directions.

New technologies for SZ studies

Technology has opened new frontiers in the study of the pathophysiology of mental disorders, including SZ. Specifically, recent technical advances have enabled us to map not only local synaptic connections among different cell subtypes [233], but also their up and downstream connectivity [234, 235], as well as their

Box 1. How NMDAR hypofunction may contribute to the abnormal inhibition, disrupted synaptic plasticity, and dysconnection—lessons learned from the studies in other brain regions and the hypothetical mechanisms (Fig. 5)

Despite the progress reviewed above, the mechanisms underlying how NMDAR hypofunction may contribute to abnormal inhibition, disrupted plasticity, disconnection, and eventual behavioral deficits remains elusive. However, significant progress has been made in other cortices, and we propose to test these hypothetical mechanisms in the PFC circuitry, as illustrated in Fig. 5. Beyond their well-established role as Hebbian signals for long-term potentiation and depression (LTP and LTD) of fast synaptic transmission [158, 159, 196–201], NMDARs themselves are also dynamically regulated by an activity-dependent LTP [188, 202]. Specifically, the unique functional properties of the NMDAR, including high Ca^{2+} permeability, negative slope conductance that enables signal amplification, and slow NMDAR-EPSP kinetics, make NMDAR plasticity a powerful mechanism for the fine-tuning of information encoding and storage [7, 156]. Since Ca^{2+} is a secondary messenger, NMDAR plasticity has far-reaching implications beyond amplitude changes of NMDAR-mediated synaptic responses [188].

The immediate responses to risk factors involve both translational and posttranslational modifications, such as receptor trafficking related to epigenetic regulation (e.g., epigenetic histone acetylation, methylation, phosphorylation via activator or repressor) (Fig. 5a–c) [88, 203]. These changes will likely result in similar synaptic scaling of both AMPA- and NMDA-EPSCs in prefrontal neurons, as previously reported in visual cortical neurons [204, 205]. Importantly, activity-dependent NMDAR plasticity appears to be a universal mechanism; it occurs in not only excitatory but also inhibitory synapses, including effects on NMDA/AMPA ratio and E/I balance in different cell types and connections [206, 207] (Fig. 5b, d). Further, NMDAR-dependent effect is also observed on behavioral representation, as pioneered in the study of primary visual cortex [160, 208–210].

While most studies support the postsynaptic locus of NMDARs, the existence and functional role of NMDARs localized to the presynaptic site has received significant attention in both PFC [211] and other cortical regions [212–215]. There is evidence from different brain regions that presynaptic NMDARs act as coincidence-detectors and play an essential role in some forms of spike-timing-dependent plasticity [212, 216–218]. The subunit composition of presynaptic NMDARs can also be developmentally regulated, thereby modulating the inducibility of spike-timing-dependent plasticity [219]. A recent study illustrated the distinct roles for pre and postsynaptic NMDARs in visual circuit development and revealed extensive transsynaptic regulation of form and function [220]. Our research indicated that, in response to NMDAR blockade during adolescence, these presynaptic receptors themselves underwent plastic changes differentially in the FS INs vs. pyramidal cells in the PFC [221]. Still, it remains unclear whether presynaptic NMDARs from distinct long-range afferents or cell types within the PFC have different identities and functions.

Although we have focused primarily on the mechanisms and implications of rapid, synapse-specific NMDAR plasticity, mounting evidence mainly from the sensory cortices indicates that NMDARs can participate in homeostatic plasticity [202], This process acts over relatively longer timescales and can underlie metaplasticity [197, 208, 222–226], as illustrated hypothetically in the PFC in Fig. 5. Specifically, visual experience-dependent homeostatic plasticity of excitatory synapses observed in superficial layers of the visual cortex is dependent on NMDAR function. Interestingly, both strengthening of synapses induced by visual deprivation and weakening by the reinstatement of visual experience were blocked in the absence of functional NMDARs. This finding suggests that sensory experience-dependent homeostatic adaptation depends on NMDARs, supporting the sliding threshold model of plasticity and input-specific homeostatic control observed in vivo [208]. Especially during adolescent development, NMDAR subunit-dependent homeostatic plasticity in inhibitory neurons occurs in cell-type and input-specific manner through a sliding threshold mechanism [197, 198], such as differential LTP induction in SST vs. LTD in PV cells, respectively (Fig. 5d, e). Similarly, homeostatic plasticity of GABAergic neurons and their synaptic connections with excitatory neurons also occur, although the molecular mechanisms remain to be determined [119, 227, 228]. NMDAR hypofunction would weaken or disrupt both normal Hebbian plasticity between prefrontal INs and long-range afferents, meanwhile, reshape the homeostatic plasticity in the mPFC and its connections with downstream targets. These homeostatic changes in plasticity, in turn, induce threshold shift and/or disconnectivity, resulting in a reduced metaplasticity [222, 229] (Fig. 5F). Consequently, an aberrant local circuit and dysfunctional connections are formed, a new set point with a narrower dynamic range for information is adopted, and abnormal behavioral changes follow under an aberrant connectivity condition [230, 231] (Fig. 5g).

Box 2. Outstanding questions

- When and how is local prefrontal circuitry formed and matured during development, especially during juvenile and adolescent periods? What are the roles of different subtypes of INs in the regulation of cognitive and social functions during adolescent development? What are the roles of NMDARs in the development of local prefrontal circuitry among the different subtypes of INs?
- Past studies focused on the roles of DA, GABA, NMDARs in genetic and neurodevelopmental models for SZ. Many aspects of the circuit- and cell-type-specific connections, as well as input/output specificity, remain unclear or unexplored, especially those related to homeostatic plasticity and metaplasticity. For example, the pre and postsynaptic NMDARs in different subtypes of INs, particularly SST and VIP cells, and their roles in development, remain untested.
- For the PFC, given the most important factor is prolonged and delayed maturation during adolescence, all findings reported in other brain regions, especially those from the sensory, auditory, and visual cortices, usually do not completely apply to the PFC. Therefore, the key question is to elucidate the unique properties among each brain region, given the potential macroscopic gradient differences.
- One critical issue is the monoamine systems in the mPFC, which exhibit prominent delayed maturation, and macroscopic gradient distribution compared with other regions. How these neuromodulatory systems are affected by NMDAR hypofunction during development is barely explored. Are the NMDAR hypofunction and neuromodulation mutually dependent on each other or mutually exclusive in the dysfunctional status? We propose that during the early (e.g., juvenile and adolescent) stages of development, NMDAR hypofunction dominates the process of dysfunction, which in turn results in differential impairments in a system-specific manner, and in adulthood, both NMDAR hypofunction and DA dysfunction co-exist and impact each other.
- Given the large number of genetic mutations associated with symptoms of SZ, it is unlikely that a single locus for pathology exists at the cellular or synaptic level. How a complex substrate induces a distinct behavioral phenotype that represents a genuinely "brain-wide" aberrant function and disconnection, deserves to be explored.

molecular phenotypes and neuronal activity in animal models. These techniques include the transcriptomic approach RNAseq [236] for molecular phenotype, neurological tracing methods, such as Tracing the Relationship of Inputs and Outputs (TRIO) and cell-type-specific tracing of the relationship between input and outputs (cTRIO) [237, 238], iTango for neuromodulatory circuits [239], optogenetics [240], and chemogenetics [241], as well as calcium imaging and various fluorescent indicators [242, 243]. These technologies will provide novel insights into the understanding of what an aberrant circuit and dysfunctional connectivity look like under different etiological conditions and whether the alterations due to different etiology share similar or different mechanisms in a global scale of input-output level connectivity and macroscopic gradient of whole brain activity.

However, although these cutting-edge tools are useful in model organisms, primarily rodents, and even non-human primates, critical advances in human brain disorders are seriously hindered by our lack of ability to monitor and manipulate circuitry in safe and minimally invasive ways. Clinical intervention with novel cell- and circuit-specific tools are required to focus on research designed to elucidate the aberrant circuit and connectivity of PFC in patients with SZ [10]. The ambitious "Research Domain Criteria" project initiated by The National Institutes of Mental Health aims to develop new tools in assessing behavior and neurobiological measurements encompassing positive and negative valence systems, cognitive systems, social systems, and arousal/regulatory systems. These comprehensive analyses of these systems at the cellular, brain network, physiological, and behavioral levels will likely yield the direct information associated with the aberrant connectivity of SZ [244]. Other clinical tools, such as proton magnetic resonance spectroscopy (^{1}H-MRS for tissue glutamate and GABA), PET/SPECT, Mismatch negativity/P300/gamma-band oscillations [245, 246], post-mortem neurochemical/biochemical findings remain useful in elucidating the pathological alterations in neural circuit and connectivity [44]. All these measures offer noninvasive endophenotypes or biomarkers that may find a powerful application in SZ research [247].

Concluding remarks

It is increasingly clear that synaptic plasticity can occur at various levels of connections during both learning and homeostatic

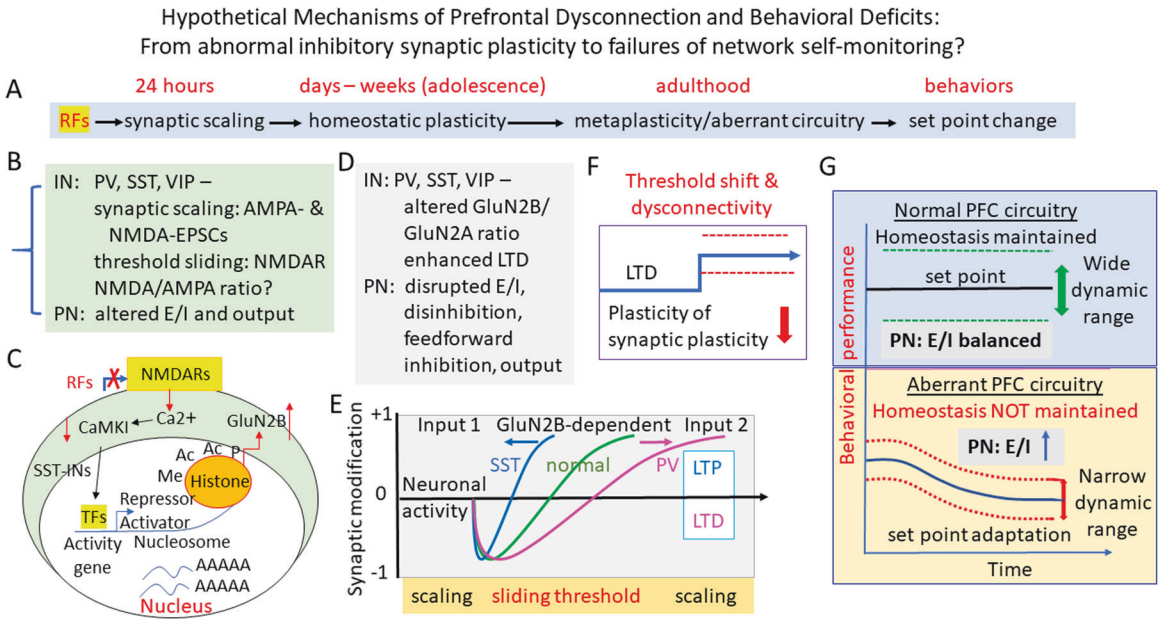

Fig. 5 A summary illustration of the perspective mechanisms associated with dysconnectivity and behavioral deficits—from abnormal synaptic function and plasticity to failures of self-monitoring. a Timeline of synaptic- and circuit-specific alterations and behavioral changes during developmental dysconnectivity. **b**–**g** In response to normal and abnormal stimulation, synapses mediating local and long-range connections between different cell types exhibit sequential alterations through different mechanisms during development. The immediate responses (within 24 h) to risk factors (RFs) are associated with both translational and posttranslational modifications, such as receptor trafficking (**b**) related to epigenetic regulation (e.g., epigenetic histone acetylation, methylation, phosphorylation via activator or repressor) (**c**) [88, 203], resulting in changes in excitatory synaptic strength/synaptic scaling of both AMPA- and NMDA-EPSCs [204, 205] in prefrontal neurons which consequently disrupts E/I balance in the local prefrontal circuit. **d**, **e** Later on, especially during adolescent development, NMDAR subunit-dependent homeostatic plasticity in inhibitory neurons occurs in cell-type and input-specific manner through a sliding threshold mechanism [197, 198], such as differential LTP induction in SST vs. LTD PV cells, respectively. NMDAR hypofunction would weaken or disrupt both normal Hebbian plasticity between prefrontal interneurons and long-range afferents, meanwhile reshape the homeostatic plasticity in the mPFC and its connections with downstream targets. **f** These homeostatic changes in plasticity (as described in **d**, **e**), in turn, induce threshold shift and/or disconnectivity, resulting in a reduced metaplasticity [222, 229]. **g** Consequently, an aberrant local circuit and dysfunctional connections are formed, a new set point with a narrower dynamic range for information is adopted, and abnormal behavioral changes follow under an aberrant connectivity condition [230, 231]. IN interneuron, PN pyramidal neuron, PPF paired-pulse facilitation, PPD paired-pulse depression, RFs regulatory factors, TFs transcription factors.

adaptation, including different cell types in the PFC and their input and output connectivity. It is clear that excitatory and inhibitory neurons undergo complementary forms of functional and structural plasticity in order to maintain an optimal E/I balance and ultimately regulate network stability. Yet, many outstanding questions remain unanswered. It is essential to understand whether excitatory and inhibitory neurons display different forms of homeostatic plasticity by using different sensors and effectors of neuronal or network activity, and how different forms of homeostatic plasticity, at either the pre or postsynaptic sites, are merged to form a newly adapted set-point for behavioral performance. It is likely that each cell type will alter its input-output relation within the network in a different way, and thus the type of stimulus or the level of network activity will be altered towards specific forms of functional and structural homeostasis and metaplasticity, especially during the development. We conclude that the aberrant prefrontal cortical circuitry and dysconnection in SZ are attributed to the "all roads lead to Rome" NMDAR-mediated plastic changes during development, ranging from abnormal synaptic plasticity to an adapted set point with dysfunctional self-monitoring. Targeting this process during the early stages is likely more effective in preventing or treating the disease.

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ACKNOWLEDGEMENTS

This study was supported by NIH R21MH110678, the NIH R01MH085666, NARSAD Independent Award 2015, and Pennsylvania Commonwealth 4100072545 (CURE 2016) to WJG.

AUTHOR CONTRIBUTIONS

WJG, SSY, NRM, and LAC wrote and edited the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to W.-J.G.

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