



REVIEW ARTICLE

Mechanisms underlying dorsolateral prefrontal cortex contributions to cognitive dysfunction in schizophrenia

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Kraepelin, in his early descriptions of schizophrenia (SZ), characterized the illness as having “an orchestra without a conductor.” Kraepelin further speculated that this “conductor” was situated in the frontal lobes. Findings from multiple studies over the following decades have clearly implicated pathology of the dorsolateral prefrontal cortex (DLPFC) as playing a central role in the pathophysiology of SZ, particularly with regard to key cognitive features such as deficits in working memory and cognitive control. Following an overview of the cognitive mechanisms associated with DLPFC function and how they are altered in SZ, we review evidence from an array of neuroscientific approaches addressing how these cognitive impairments may reflect the underlying pathophysiology of the illness. Specifically, we present evidence suggesting that alterations of the DLPFC in SZ are evident across a range of spatial and temporal resolutions: from its cellular and molecular architecture, to its gross structural and functional integrity, and from millisecond to longer timescales. We then present an integrative model based upon how microscale changes in neuronal signaling in the DLPFC can influence synchronized patterns of neural activity to produce macrocircuit-level alterations in DLPFC activation that ultimately influence cognition and behavior. We conclude with a discussion of initial efforts aimed at targeting DLPFC function in SZ, the clinical implications of those efforts, and potential avenues for future development.

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INTRODUCTION

Since the earliest descriptions of the disorder, cognitive deficits have been widely recognized as a core aspect of schizophrenia (SZ) [1]. These cognitive impairments, present prior to the onset of psychosis and persisting through the disease course, have been shown to be a major source of disability in those affected by SZ [2, 3]. Furthermore, impaired cognition in SZ remains largely treatment refractory [3] despite a concerted effort over the past 30 years to find methods for ameliorating this aspect of the illness. As such, understanding the pathophysiology of impaired cognition in SZ and developing effective treatment for cognitive symptoms are major unmet challenges for contemporary biomedical research, particularly when considering the tremendous personal cost to affected individuals and their families and the substantial economic cost (\$155 billion in the US alone in 2013) to society [4].

The purpose of this review is to summarize the evidence that the dorsolateral prefrontal cortex (DLPFC) plays a major role in the pathophysiology of higher order cognitive processing in SZ via abnormalities in its cellular architecture and associated circuitry. We first present evidence from clinical cognitive neuroscience that the DLPFC is functionally abnormal in SZ. We then describe how these aberrations may broadly affect cognition, behavioral disorganization symptoms, and everyday functioning in the illness. Next, we review findings suggesting that these functional and behavioral disturbances arise from cellular level alterations in

the DLPFC. Finally, we discuss future directions for deepening our understanding of the role of the DLPFC in the disease process of SZ and for developing novel therapeutics to improve cognitive function in people with SZ.

IMPAIRMENTS IN COGNITIVE CONTROL AND WORKING MEMORY: EVIDENCE FOR A PROTOTYPICAL COGNITIVE DISTURBANCE IN SCHIZOPHRENIA

As conceptualized by Alan Baddeley in the 1970's, working memory (WM) is the ability to maintain and manipulate information for brief periods of time in order to guide thought or behavior in the absence of ongoing sensory input [5, 6]. Thus, WM is an essential component of the cognitive control processes that guide goal-oriented behaviors based on context. WM includes multiple subprocesses, including the maintenance of relevant information in the absence of sensory stimuli and the suppression of distractor stimuli not required for the task at hand.

WM is perhaps the most extensively studied cognitive domain in SZ. Results from the first systematic investigation of WM in SZ were reported in 1992 by Park and Holtzman [7], who found lower accuracy in SZ relative to psychiatrically unaffected individuals on an oculomotor spatial delayed-response task. Subsequently, deficits in WM have been frequently observed in SZ (e.g., [8, 9], reviewed by Aleman et al. [10]). Indeed, a meta-analysis of

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187 studies found that individuals with SZ show robust deficits across a wide range of WM tasks [11], with large effect sizes (mean Cohen's $d \approx 1$ for each task). Meta-analytic evidence in first episode SZ individuals also suggests that WM deficits are present in the early stages of illness [12]. Interestingly, these deficits likely have a neurodevelopmental component (as they are present prior to illness onset [13]) as well as a genetic component (since they are found in milder form in unaffected siblings [14–18]). Some studies also suggest that larger WM deficits are associated with worse clinical [19, 20] and functional outcomes [2, 21].

A more recent cognitive construct closely related to WM is cognitive control (CC) [22], the ability to use contextual information to guide behavior in the face of conflicting but often habitual (prepotent) responding. CC processes lie at the heart of the “central executive processes” used to support WM task performance, and since CC requires active maintenance of contextual information, WM and CC are strongly related constructs [23]. CC can be measured using a variety of tasks, including the Stroop [24] and AX-Continuous Performance Task (AX-CPT) [25]. Mirroring WM findings, individuals with SZ show robust deficits in CC across all phases of the illness [25–36]. Like WM, impaired CC in SZ may also have a developmental and genetic origin as these deficits are present prior to onset of psychosis [37] and have been observed (at a smaller magnitude) in unaffected siblings [38, 39]. Preliminary evidence also suggests that functional impairments in CC may predict lack of clinical improvement after one year of standardized treatment in early psychosis [40, 41].

The role of the dorsolateral prefrontal cortex in working memory and cognitive control

The WM network involves a highly interconnected set of nodes located in multiple cortical and subcortical regions [42]. Among these nodes, the DLPFC is a critical region of convergence that both integrates information processing across nodes in the network and provides top-down control of that processing. The DLPFC is a large frontal brain area comprising lateral portions of Brodmann's areas 9 and 46. It is evolutionarily relatively recent, being particularly enlarged in non-human primates and humans [43], and therefore may enable the enhanced complex planning and reasoning abilities characteristic of these species. The highly interconnected nature of the DLPFC, with regions such as the parietal, anterior cingulate and sensorimotor cortices and subcortical nuclei [44], is thought to permit integration of information with “on-line” representations to provide flexible internally driven (as opposed to stimulus-driven) control of behavior [examples in 45, 46].

The importance of the DLPFC in WM was first demonstrated in non-human primate studies in which lesions or reversible cooling of the DLPFC impaired WM performance in a delay-dependent manner [47]. In subsequent single-unit recording studies in monkeys, some DLPFC neurons that responded to specific memoranda were active during the delay period of a WM task, appearing to keep the information online [47–49]. Particular groups of neurons with delay period activity are therefore thought to encode particular features of the stimulus to be remembered [49] and specific information about the rules of the task at hand [50]. Human neuroimaging work in the early 1990s using positron emission tomography (PET) also found DLPFC recruitment during WM tasks [51], confirming the area as a primary WM hub. Notably, activation of the superficial layers of the DLPFC appears to be particularly important during the maintenance, or “delay” phase of WM, whereas encoding and retrieval processes are associated with activity in the inferior parietal lobule and deeper layers of the DLPFC [52–54]. Concordantly, neuronal activity in the DLPFC has been experimentally demonstrated to be predictive of behavioral performance on WM tasks in non-human primates [55], supporting its causal role in the maintenance of WM information. In regard to the WM-related process of CC, based on

electrophysiological work in non-human primates [56] and subsequent imaging studies in humans (reviewed by Miller and Cohen [22]), the DLPFC is thought to support this ability by providing a substrate for online maintenance of rules or goals in order to guide responses, including biasing response away from prepotent tendencies [22].

The DLPFC also plays a critical role in resisting interference from distractors [57]. Distractors are defined as extraneous stimuli that occur during the delay period and compete for the neural processing resources required to maintain the task-relevant stimuli in WM. The ability to filter out these distracting stimuli is critical for WM performance and variations in WM capacity in humans reflect the ability to suppress activation of neural activity related to irrelevant stimuli [58]. The central role of the DLPFC in filtering out distracting stimuli during WM tasks is supported by the following lines of evidence. First, WM performance in monkeys with frontal lobe ablations is further impaired when distractor stimuli are presented [59], suggesting that the absence of the DLPFC is associated with an increased susceptibility to the interfering effects of distractors [60]. Second, relative to neurons in the posterior parietal [61, 62], lateral intraparietal [63, 64] and temporal cortices [65], DLPFC neurons are less likely to be activated by distractor stimuli [57]. Third, silencing of DLPFC pyramidal neurons neighboring those activated by a WM memoranda is associated with successful suppression of distractor stimuli [66]. Finally, increases in distractibility are noted with transient inactivation of the DLPFC, but not the parietal cortex, in monkeys [67]. Together, these data support the notion that relative to other cortical regions, neuronal activity in the DLPFC is more resilient to distractor stimuli during a WM task.

Evidence for dorsolateral prefrontal cortical dysfunction during working memory and cognitive control in schizophrenia

Given the extensive behavioral evidence of WM/CC deficits in SZ and the reliance of these constructs on proper DLPFC functioning, it is expected that alterations at the macro- and microscopic levels of resolution in DLPFC circuitry are responsible for these WM/CC deficits. Indeed, in his early descriptions of SZ, the pioneering psychiatrist Kraepelin postulated that “the mind in dementia praecox is like an orchestra without a conductor” [68]. Kraepelin also suggested that “reasoning” deficits may be linked to pathology of the frontal lobes — laying the initial groundwork eventually (nearly a century later) for a line of research linking deficits in executive function to prefrontal cortical pathology in the disorder.

In alignment with this view, a large body of *in vivo* structural neuroimaging studies of the DLPFC have consistently observed gross macroscopic abnormalities of this region in SZ. These studies, which have been reviewed elsewhere [69–71], suggest that the disorder is characterized by smaller DLPFC gray matter volume, thinner gray matter (for which antipsychotic treatment may be a contributing factor [72, 73]), and lower fractional anisotropy of white matter tracts that connect the DLPFC to other brain regions (e.g., the cingulum bundle) [74]. Evidence further indicates that similar pathology is present (albeit less consistently and to a lesser degree) in people at high risk for psychosis, suggesting these differences are not solely the consequence of antipsychotic treatment and may be influenced by genetic risk factors (reviewed by Andreou and Borgwardt [75]).

Functional neuroimaging studies also suggest that Kraepelin's initial supposition of prefrontal pathology was correct (reviewed by Lesh et al. [35, 76]). This supposition was first supported by early studies by Weinberger et al. [77] and Perlstein et al. [78] demonstrating that individuals with SZ show lower cerebral blood flow in the frontal lobes during the Wisconsin Card Sort Task and N-Back WM Task and continuing through more recent studies using the AX-CPT and other tasks [22, 30–34, 79–82]. Effect sizes

may be moderately high for lower DLPFC activation during CC in SZ; one recent study from our group found effect sizes of Cohen's $d = -0.49$ at baseline and -0.58 at 12-month follow-up for bilateral DLPFC activation deficits during CC in SZ vs. unaffected comparison individuals [33]. Also mirroring the behavioral findings, deficits in DLPFC activation during WM and CC in SZ are present at the onset of the illness, and even prior to psychosis onset in clinical high-risk states [30, 34, 35, 37, 76, 83] (Fig. 1A).

It should be noted that, although task fMRI studies show overall reduced activation in SZ [84], some individual studies have reported increased activity in the illness (e.g., [85–88]). These studies have been interpreted as indicative of an “inverted U” function in the DLPFC, in which increased activity may be seen at low levels of WM demand but decreased activity at higher levels. It is also possible that methodological differences underlie some of these contrasting findings, including small sample sizes and variation in analysis protocols (e.g., matched performance with low performing psychiatrically unaffected participants [86]). For example, a 1999 study that reported increased activation during WM in SZ used a very small sample size ($n = 10$ psychiatrically unaffected participants, 12 participants with SZ) and included a monetary reward for correct answers [85] not present in most other studies of WM in SZ. A 2003 study that reported locally increased activation during an WM task also had a very small sample size ($n = 14$ psychiatrically unaffected participants, 12 participants with SZ) and included performance as a nuisance covariate, potentially regressing out effects of interest related to the expected WM deficits in SZ [88]. Overall, evidence supporting the “inverted U” hypothesis is limited, and meta-analytic evidence suggests that the overarching phenotype in SZ is lower DLPFC activation during WM [84].

The temporal dynamics of WM/CC have also been studied in SZ on millisecond-level timescales by electroencephalography (EEG), which has allowed researchers to examine the degree to which synchronous activity at various frequencies are associated with these processes and to what extent neuronal oscillations are disrupted in the disorder. Of the various frequency bands (e.g., theta, beta), the high frequency, gamma band (~30–80 Hz) shows the strongest evidence for alterations in SZ. Gamma band power in the DLPFC has been shown to increase in psychiatrically unaffected individuals during various cognitive operations, including WM and CC [89–91]. Furthermore, patterns of gamma band activity may be specific for task-relevant information in WM; a 2012 study demonstrated that when a classifier was trained to distinguish between gamma activations that varied according to WM task-relevant load (i.e., items to remember), it was more likely to encode oscillations during the 3 item + 3 distractor condition as load 3 than as load 6 [92]. Prefrontal gamma oscillations, therefore, may specifically encode task-relevant information without incorporating distractor-associated signals. Recordings in non-human primates have also confirmed that dorsal prefrontal gamma frequency oscillations reflect active maintenance of information during WM [93]. Studies in SZ have generally reported lower gamma oscillatory power relative to controls during the maintenance phase of these tasks (e.g., [90, 94], reviewed by Gonzalez-Burgos [95]) (Fig. 1B). In a recent study, anodal tDCS applied to the DLPFC resulted in transient increases in DLPFC gamma activity along with improved performance on a version of the AX-CPT [96]. Notably, lower DLPFC gamma power may provide a translational bridge between the functional impairments in WM/CC in SZ and histopathological analyses of postmortem brain tissue in the disorder as outlined later in this review (Fig. 1C, D).

In addition to structural and functional MRI studies, measurement of regional levels of glutamate and GABA (the primary excitatory and inhibitory signaling molecules of the brain, respectively) has been undertaken using magnetic resonance spectroscopy (MRS). Since brain MRS was first developed in the 1980s, both GABA and glutamate have been measured extensively

in SZ. Most of this previous work has been conducted in the medial prefrontal cortex, for which meta/mega-analyses suggest SZ is associated with lower glutamate [97, 98] but no difference in GABA [99] relative to unaffected participants. For the DLPFC, meta-analyses have not found conclusive evidence for alterations in glutamate [97, 100] or GABA [99] levels in SZ, although the overall number of studies is much smaller relative to the number of medial prefrontal studies and almost all of these previous DLPFC studies have been conducted at 1.5 or 3 T. One study at a higher field strength (7 T) reported lower glutamate in SZ vs. unaffected participants [101], consistent with a recent meta-analysis of 7 T studies of glutamate in the anterior cingulate [102]. Related to WM processes, research suggests that psychiatrically unaffected individuals and individuals with SZ show opposite relationships between DLPFC GABA levels and WM. Specifically, in psychiatrically unaffected individuals, increased GABA predicts better WM [103], whereas in SZ increased GABA predicts worse WM [104]. The reason for this interaction effect is unclear. One speculative possibility is that high GABA concentration represents a homeostatic response to an overall reduction in GABAergic signal. Thus, SZ individuals with higher GABA may actually have more severely disrupted inhibitory circuits (e.g., lower connectivity between GABAergic interneurons and pyramidal cells), resulting in worse WM. The increase in GABA therefore may represent an (unsuccessful) attempt by the brain to restore proper inhibitory function.

A major shortcoming of MRS, however, is its limited spatial resolution. MRS voxel sizes (length/width/height) are typically on the order of centimeters and contain a mix of gray matter, white matter, and CSF. MRS also cannot determine if measured neurotransmitter levels are presynaptic, postsynaptic, and/or involved in metabolic functions not related to neurotransmission. In order to fully understand the circuit level basis for WM deficits in SZ, the DLPFC must be examined at microscale resolutions in postmortem human brain. Following a brief introduction to how specific microcircuits facilitate WM processes in the DLPFC, in the sections below we present a detailed account of postmortem findings that have shaped our understanding of how microstructural aberrations in the DLPFC might lead to circuit-level disruptions during WM in SZ.

LINKING DYSFUNCTIONAL DORSOLATERAL PREFRONTAL CORTICAL CIRCUITRY TO WORKING MEMORY DEFICITS IN SCHIZOPHRENIA

Local circuits in the dorsolateral prefrontal cortex and subprocesses of working memory

In order to develop novel therapeutic avenues for targeting DLPFC function in SZ, it is essential to understand how its activation may be fundamentally affected on a circuit level. Within the DLPFC, neurons in the supragranular layers (e.g., layer 3) appear to play a prominent role in WM processes, especially during the delay period of WM tasks [47–49]. How might these neurons mediate WM processes? Excitatory pyramidal neurons in layer 3, in addition to furnishing a principal axon which projects through the white matter to other cortical regions in the WM network, also give rise to local axon collaterals that primarily target the dendritic spines of other layer 3 pyramidal neurons [105–107]. These connections are thought to provide a local circuit, intrinsic to the DLPFC, for supporting excitatory activity among subsets of DLPFC layer 3 pyramidal neurons during the WM delay period [108, 109]. This interpretation is supported by computational models [110, 111]. In further support of the importance of layer 3 pyramidal neurons in WM function, the dendritic spines of layer 3 pyramidal neurons are enriched in the NR2B subunit of the NMDA receptor which is thought to be critical for delay period activity [109]. In addition, the gamma frequency oscillations that appear to be a neural correlate of WM [112] are primarily generated in layers 2–3 of the DLPFC [93]. These lines of evidence strongly support the role of

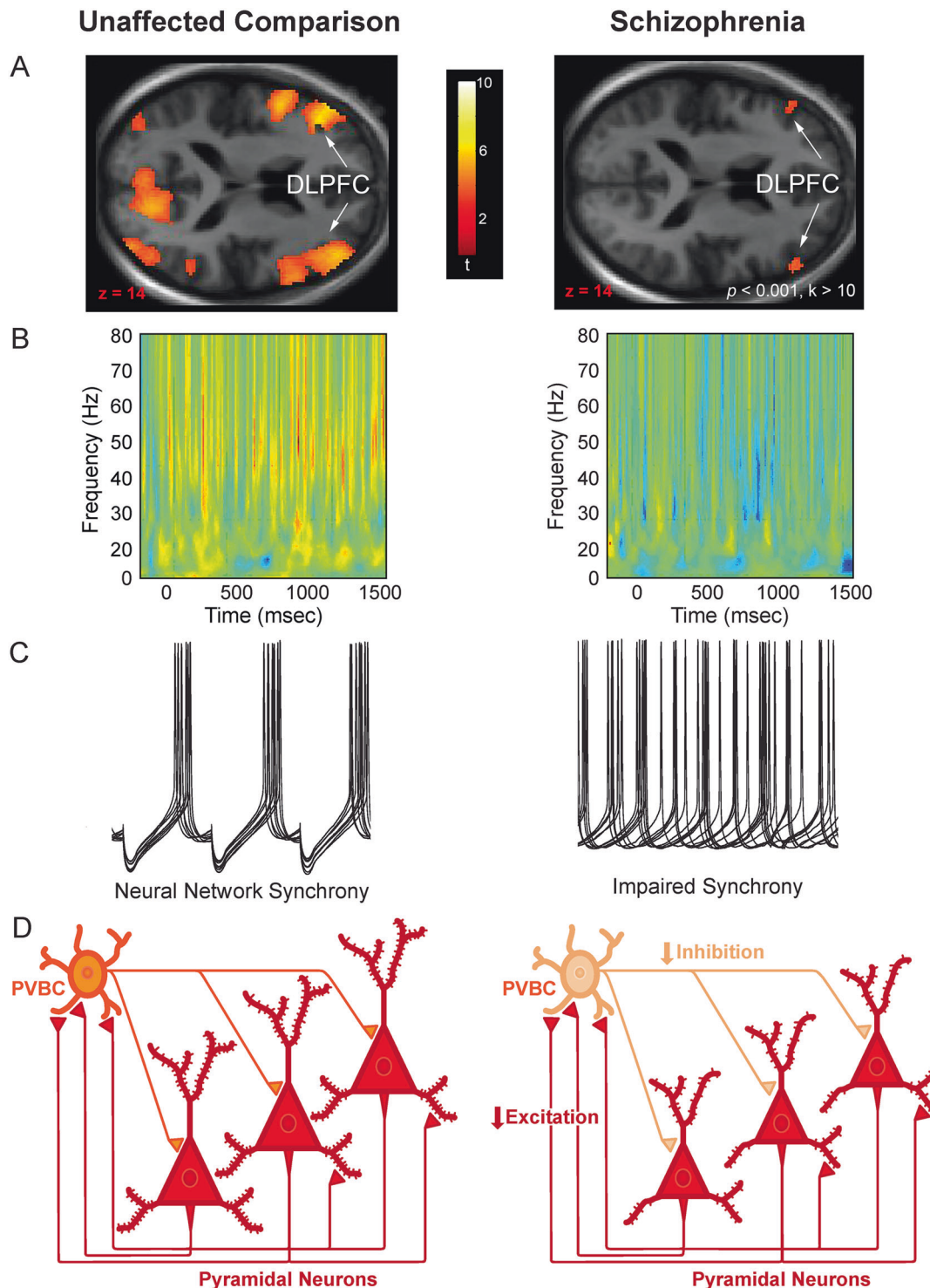


Fig. 1 Findings from psychiatrically unaffected comparison individuals (left) and individuals with SZ (right) at multiple levels of resolution during cognitive control/working memory tasks. A DLPFC activation associated with cognitive control during the AX Continuous Performance Task. Note the lower levels of activation in individuals with SZ. Data taken from a previously published sample [33]. **B** Frequency-time plots of scalp EEG recordings of prefrontal oscillatory activity during the delay period of the Preparing to Overcome Prepotency Task. Warmer colors indicate higher oscillatory power and cooler colors indicate lower power. Note that power in the gamma band (30–80 Hz) is substantially greater in the unaffected comparator group relative to the SZ group. Adapted from [90]. **C** Schematic representation of neural network synchrony (coordinated intracellular membrane recordings from pyramidal neurons) at gamma frequency in psychiatrically unaffected individuals and the hypothesized alteration of this synchrony in SZ. Adapted from [285]. **D** Diagram of local neural circuit in cortical layer 3. In individuals without psychiatric illness, it is posited that inhibition from PV basket cells (PVBCs) synchronizes the recurrent excitatory activity of groups of pyramidal neurons at gamma frequency, but lower levels of both excitation (indexed by smaller somal volumes, fewer dendritic spines, and shorter dendritic arbors, as depicted here) and inhibition (indexed by lower levels of GABA markers within PVBCs and by weaker shading here) could contribute to impaired synchrony in schizophrenia, as depicted in panel (C) (right).

DLPFC layer 3 pyramidal neurons in the generation of activity necessary for WM.

The activity of layer 3 pyramidal neurons during WM tasks is shaped by inhibitory inputs from different classes of GABA neurons. For example, local administration of a GABA_A receptor antagonist in the non-human primate DLPFC impairs WM performance [113] and prevents the activation of neurons that are otherwise engaged by a specific stimulus [114]. Moreover, GABA signaling in non-human primates was found to facilitate interactions between different groups of neurons that are active at discrete time points during a WM task: the presentation of the cue, the delay period, and the response period [115]. Finally, computational models and experimental models of the hippocampus indicate that the gamma frequency activity of large groups of pyramidal neurons is synchronized by inputs from inhibitory interneurons [116].

Among the different subtypes of cortical GABA neurons, parvalbumin (PV)-expressing interneurons have been most extensively studied in relation to WM. The basket cell class of PV interneurons, which are present in high density in layers deep 3 and 4 [117], are a major target of the local axon collaterals of layer 3 pyramidal neurons [118]. These GABA neurons, in turn, provide fast, synaptic inhibition onto the perisomatic region of pyramidal neurons [119]. Based on these targeting properties, PV neurons appear to be positioned to provide strong inhibitory control over the firing of pyramidal neurons. The axons of PV basket cells arborize extensively, enabling them to innervate, and presumably coordinate the activity of, large groups of excitatory pyramidal neurons [120]. Specifically, the strong perisomatic inhibition mediated by PV neurons appears to entrain groups of pyramidal neurons that are responsive to a particular stimulus [121], consistent with experimental data showing that GABA_A antagonism can destroy this stimulus-specific responsiveness [114]. Certain lines of evidence suggest that PV neuron activity is also crucial for generating the cortical gamma oscillations that accompany WM tasks. First, in computational models, the excitation of PV-containing basket cells by pyramidal neurons provides strong, coordinated feedback inhibition onto numerous pyramidal neurons [116]. Upon the termination of this inhibition, the targeted pyramidal neurons share a high probability of firing simultaneously and thus in synchrony [122]. Second, the decay kinetics of PV basket cell inhibition are consistent with a resulting firing rate of pyramidal neurons at gamma frequency [123]. Third, in studies of rodent cortex and hippocampus, activation or inhibition of PV cell activity can induce or suppress gamma oscillations, respectively [124–126]. Thus, these convergent lines of evidence support a central role for PV neurons in the DLPFC microcircuitry that generates the gamma oscillations associated with WM, although causal evidence for the role of PV neurons in gamma oscillations in the primate cortex is still lacking.

Another class of PV GABA neuron, the chandelier cell, gives rise to vertically arrayed sets of axon terminals (termed cartridges) that synapse on the axon initial segment of pyramidal neurons [127, 128]. Based on the location of these synapses, chandelier cell inputs can exert potent inhibitory regulation over the firing of pyramidal neurons [129]. In contrast, although still controversial, some evidence suggests that chandelier cell inputs can also be depolarizing [130]. Indeed, subsequent studies reported that the state of the cortical circuit can influence the nature of chandelier cell inputs: i.e., in quiescent circuits, these inputs can be depolarizing [131]. These and other findings suggest that unlike PV basket cells, PV chandelier neurons may not participate in the generation of gamma oscillations. In addition, at chandelier neuron inputs onto pyramidal neuron axon initial segments, the postsynaptic GABA_A receptors are enriched in $\alpha 2$ subunits which exhibit slower kinetics relative to $\alpha 1$ subunit-enriched GABA_A receptors located postsynaptic to PV basket cell inputs [132]. Thus, the available data suggest that PV basket cells, and not PV

chandelier cells, likely participate in the generation of gamma oscillatory activity in the DLPFC during the delay period of WM tasks.

Inhibition in the DLPFC could also contribute to distractor resistance, possibly through the activity of a second class of GABA interneurons known as somatostatin (SST)-expressing neurons. SST neurons primarily provide inhibition onto the distal dendrites of pyramidal neurons [133]. This inhibition may play a role in gating excitatory inputs to these neurons, as suggested by studies in the rodent hippocampus [134]. SST neurons in layers 2–superficial 3 also appear to be a major target of local axon collaterals of layer 3 pyramidal neurons [118]. The excitation of layer 3 pyramidal neurons during the delay period of a WM task might activate SST neurons that could, in turn, provide inhibition to pyramidal neurons that are not involved in keeping the WM memoranda online. Indeed, in computational models, cells providing the type of dendritic inhibition characteristic of SST neurons are more efficient in filtering out distractor stimuli than is the perisomatic inhibition provided by PV neurons [121]. Thus, SST neurons might contribute to distractor resistance through their ability to suppress the activity of DLPFC pyramidal neurons [135–137] that receive input from task-irrelevant distractor stimuli. This feature of SST neurons might equip the DLPFC to be less sensitive than other cortical regions to the influence of distractors during WM, consistent with the greater abundance of SST neurons in the DLPFC relative to other cortical regions in the non-human primate WM network [138]. While these convergent lines of evidence support a role for SST neurons in distractor resistance during WM, confirmation of this idea requires more evidence from studies in non-human primates.

Overall, the findings reviewed above suggest that the cellular constituents of WM circuitry in the primate DLPFC include (at least in part) layer 3 pyramidal neurons and their interconnected PV and SST interneurons. It is important to note that neuromodulators can also influence the activity of this circuit. For example, dopamine signaling in the DLPFC has long been known to influence WM function [139] and appears to control the firing of neurons exhibiting delay-period activity (see Box 1). In addition, acetylcholine appears to regulate top-down attention crucial for distractor resistance during WM in non-human primates [140]. Other studies have found that acetylcholine influences specific neuronal populations, including SST neurons, in a laminar-specific manner in humans [135, 141]. Therefore, WM impairments in people with SZ likely reflect alterations to one or more of the components of this circuit in the DLPFC. Using results from postmortem tissue studies, we describe the potential contribution (s) of each of these cell types to the WM phenotype in SZ in the following sections.

Alterations in dorsolateral prefrontal layer 3 pyramidal neurons in schizophrenia

Given the important role of layer 3 pyramidal neurons in generating the delay period activity necessary for WM, alterations in this neuronal subtype could be a significant contributor to DLPFC dysfunction in SZ. Indeed, DLPFC layer 3 pyramidal neurons exhibit numerous morphological and molecular anomalies which suggest that SZ is associated with hypoactivity of these neurons. First, pyramidal neurons in layer 3 of the DLPFC of individuals with SZ exhibit smaller somal volumes, shorter dendritic arbors, lower dendritic branching complexity, and lower dendritic spine density relative to matched unaffected comparison individuals [142–146]. These alterations are either not present or present to a smaller degree in pyramidal neurons located in layers 5 and 6 of the DLPFC [147]. Because dendritic spines receive the majority of excitatory inputs to pyramidal neurons [148], the combination of shorter dendrites and lower spine density suggests that layer 3 pyramidal neurons receive a lower level of excitatory input in SZ (Figs. 1D and 2).

Box 1. Role of prefrontal dopamine signaling in cognition and schizophrenia

Although the non-human primate DLPFC lacks native dopamine synthesizing neurons, dopamine afferents from the mesencephalon [286] to the DLPFC [287, 288] appear to critically regulate working memory functions. These dopamine afferents largely target D1 receptors, which are highly abundant in the DLPFC [289]. These receptors are enriched in dendritic spines [290, 291], although they are also located on interneurons [291, 292]. Substantial evidence suggests that dopamine acts in an 'inverted-U'-shaped manner, such that high dose dopamine agonists or antagonists disrupt WM [293–295]. Thus, dopamine afferents are poised to regulate WM function in the non-human primate DLPFC, possibly by regulating the integration of synaptic inputs at the dendrites of pyramidal neurons in layer 3.

In SZ, *in vivo* neuroimaging studies of dopamine in the DLPFC suggest that the illness is associated with higher D1 receptor availability that correlates with poorer performance on WM tasks [296, 297]. In light of findings of fewer dopamine immunoreactive afferents in the DLPFC of SZ [298], findings of higher receptor binding have been interpreted as a compensatory, yet insufficient, response to lower dopamine signaling [296, 297]. Thus, although limited, the available data suggests that SZ is associated with weaker dopaminergic innervation of the DLPFC [299]. The mechanisms that give rise to weaker dopamine signaling in the DLPFC are unclear but lower glutamatergic signaling [300] or perinatal/peripubertal stress [293] may be contributing factors.

Because of the role of dopamine signaling in working memory and putative hypodopaminergic in the DLPFC in SZ, agonism of the D1 receptor remains an attractive therapeutic target for ameliorating cognitive burden in the disease. The development of D1 receptor-acting drugs has been a long, arduous process due to problems with brain bioavailability and a limited therapeutic dose window [301], and no D1 compounds have yet conclusively demonstrated pro-cognitive effects in SZ. A novel partial D1 agonist, however, has shown promise for enhancing the delay-period activity of layer 3 pyramidal neurons [292], which could translate into pro-cognitive benefits in SZ. In order to increase efficacy, some novel approaches are being developed, including synthesis of positive allosteric modulators and compounds with improved pharmacokinetics or pathway specificity [301].

In the absence of increased intrinsic excitability, the lower level of excitatory input is very likely to render layer 3 pyramidal neurons hypoactive in SZ. Indeed, transcriptomic studies of layer 3 pyramidal neurons have reported coordinated downregulation of mitochondrial markers [149, 150], which appears to reflect diminished demand for energy production (rather than an intrinsic dysfunction of mitochondria) in SZ [151]. Further supporting the notion of hypoactive pyramidal neurons in SZ, the expression levels of activity-dependent transcripts are lower in these cells [152–154]. It is worth noting that layer 5 pyramidal neurons, which do not appear to exhibit smaller somal sizes or fewer dendritic spines in SZ [143, 147], also exhibit lower expression of mitochondrial-related transcripts [149]. This alteration may reflect lower activity of layer 5 pyramidal neurons (which are a major target of descending axon collaterals from layer 3 pyramidal neurons [105]) secondary to lower excitatory output of layer 3 pyramidal neurons.

Alterations in dorsolateral prefrontal parvalbumin neurons in schizophrenia

As noted above, PV neurons in the middle cortical layers 3–4 are also a major recipient of excitatory inputs from layer 3 pyramidal neurons [118]; thus, hypoactivity of layer 3 pyramidal neurons may subsequently cause activity-dependent alterations to PV neurons in SZ. For example, lower levels of activity-dependent PV mRNA [155–158] and protein [159, 160] are among the most widely replicated findings in postmortem studies of SZ. Importantly, neither the density nor morphology of PV neurons appears to be altered in SZ [156, 159–162], supporting the idea that the lower

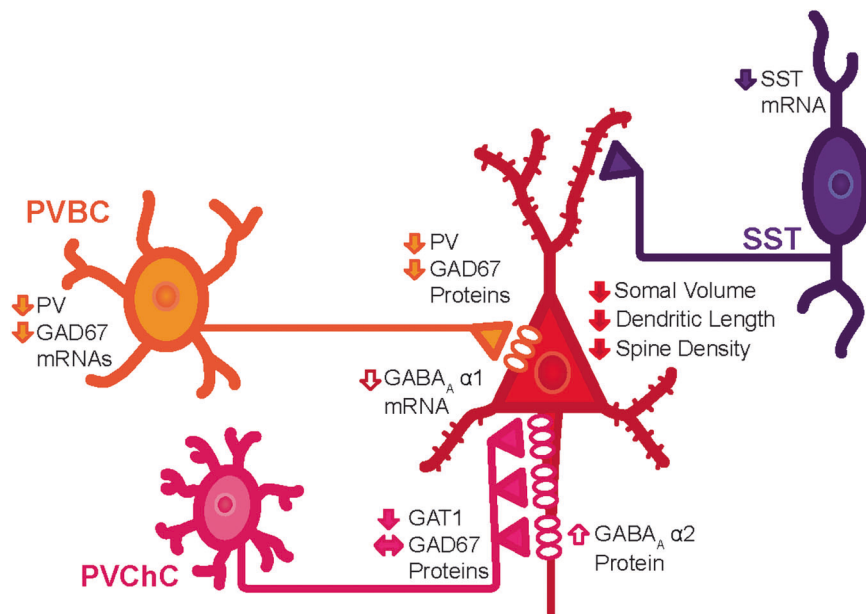


Fig. 2 Summary of cellular and molecular alterations in the DLPFC of individuals diagnosed with SZ identified through postmortem studies. Pyramidal neurons in layer 3 of the DLPFC exhibit smaller somal volumes, shorter dendritic branches, and fewer dendritic spines. Two types of parvalbumin (PV) neurons provide inputs onto the perisomatic region of pyramidal neurons: PV basket cells (PVBC) and PV chandelier cells (PVChCs). The available data suggest that PVBC inputs exhibit lower levels of GAD67 protein, and putatively weaker GABA neurotransmission, in SZ. Postsynaptic to PVBC inputs are GABA_A receptors enriched in the $\alpha 1$ subunit, and mRNA levels for this subunit are also lower in layer 3 pyramidal neurons in SZ, further contributing to weaker PVBC inhibitory inputs. In contrast, GAD67 levels appear to be unaltered in PVChC inputs, but these terminal cartridges exhibit lower protein levels of the GABA transporter, GAT1, and their synaptic targets, pyramidal neuron axon initial segments, exhibit higher protein levels of postsynaptic $\alpha 2$ subunit-containing GABA_A receptors. In concert, these findings suggest that GABA neurotransmission is stronger at PVChC inputs in SZ. Finally, SST neurons, which appear to principally provide inputs onto the dendrites of pyramidal neurons in layers 2–3 of the DLPFC, exhibit lower levels of SST mRNA. Together, these alterations are thought to contribute to the neural substrate of cognitive dysfunction in SZ.

expression of PV is secondary to altered inputs from layer 3 pyramidal neurons.

Consistent with this interpretation, the functional capacity of PV neurons, which can be indexed by measuring cell type-specific expression of transcripts and proteins involved in GABA signaling, appears to be altered in SZ. For example, the expression of GAD67, the principal enzyme responsible for the majority of cortical GABA synthesis, is activity-dependent, and lower levels of DLPCF GAD67 mRNA have been reported in multiple studies of SZ [157, 163–167]. In particular, lower levels of GAD67 mRNA in PV cell bodies [156] and of GAD67 protein in PV axon terminals of PV basket cells have been found in the illness [166, 168] (Fig. 2).

Additional findings lend support to the interpretation that alterations in PV neurons are secondary to weaker excitatory input from layer 3 pyramidal neurons in the DLPCF of SZ. First, levels of KCNS3 mRNA, an activity-dependent potassium channel that is specific to PV neurons in humans [169], are also lower in the DLPCF of SZ [170]. Second, weaker GABA signaling from PV neurons onto pyramidal neurons might be anticipated to result in a homeostatic upregulation of the $\alpha 1$ subunit of the GABA_A receptor that is located in pyramidal neurons postsynaptic to PV basket cell inputs. Layer 3 pyramidal neurons in SZ, however, exhibit lower levels of the mRNA encoding the GABA_A $\alpha 1$ receptor subunit [171]. Therefore, the concordant downregulation of pre- and post-synaptic markers of inhibition by PV neurons onto layer 3 pyramidal neurons in SZ suggests that the inhibitory strength of PV inputs is reduced to compensate for lower excitatory activity of pyramidal neurons in the circuit. This hypothesis is consistent with findings in experimental systems [134, 172].

In contrast to marked downregulations of GAD67 in the axon terminals of PV basket cells, GAD67 protein levels appears to be unaltered in the axon cartridges of PV chandelier cells [173]. Other studies, however, suggest that levels of the GABA membrane transporter GAT1 protein (which is responsible for the reuptake of GABA) are lower in PV chandelier axon cartridges in SZ [174], whereas levels of the GABA_A $\alpha 2$ subunit protein are higher in pyramidal neuron axon initial segments in the illness [175]. In concert, these findings suggest that GABA neurotransmission might be greater in PV chandelier cell inputs to pyramidal neurons in SZ. If as noted above, these inputs are depolarizing in quiescent circuits [130, 176], then the alterations in chandelier cell to pyramidal cell inputs in SZ might reflect a compensatory response to weaker pyramidal neuron activity [177] (Fig. 2).

Alterations in dorsolateral prefrontal somatostatin neurons in schizophrenia

As noted above, the local axon collaterals of layer 3 pyramidal neurons also appear to target SST neurons in layers 2–superficial 3 of the non-human primate DLPCF [133]. Similar to the findings for PV neurons [155, 157] in SZ, multiple studies [155, 157, 178–181] have reported markedly lower levels of SST mRNA in the DLPCF in a large proportion of individuals with SZ. Unfortunately, post-mortem studies of other features of SST neurons in SZ have been limited by several technical challenges. First, SST peptide levels are subject to substantial and rapid postmortem degradation [182], precluding robust proteomic or morphological studies of these neurons [183]. Second, the density of neurons with detectable levels of SST mRNA is ~30% lower in SZ [179]. It is unclear, however, if these findings represent 1) a normal complement of SST neurons in SZ with a subset that fail to express detectable levels of SST mRNA, or 2) a deficit in SST neuron number in SZ. Thus, although SST interneurons are clearly altered in the DLPCF of SZ, the nature of that alteration remains uncertain. One possibility is that like PV neurons, weaker excitatory input to SST neurons from layer 3 pyramidal neurons results in downregulated expression of SST mRNA and possibly GAD67 mRNA within SST neurons. This effect might be strongest in a subset of SST neurons, although a mechanism for such an effect is yet to be discovered.

Possible upstream mechanisms of altered GABA signaling in schizophrenia

As stated above, approximately 50% of the local axon collaterals of layer 3 pyramidal neurons appear to target PV or SST neurons. Therefore, alterations in these two subtypes of GABA neurons in SZ might reflect compensatory responses designed to downregulate inhibition in the face of lower excitatory activity in DLPCF layer 3 pyramidal neurons (Fig. 2). This interpretation is supported by other findings. For example, the μ opioid receptor, which, in rodent hippocampus, is found primarily in SST and PV neurons [184, 185] and mediates hyperpolarization of these neurons [186, 187], is upregulated in SZ [178, 188]; thus, this alteration would also be expected to decrease inhibition from PV and SST neurons. In contrast, other cell types that are not direct targets of layer 3 pyramidal neuron axon collaterals, such as calretinin neurons [118], do not appear to be altered in the DLPCF of individuals with SZ [156, 178, 181, 189]. These findings, in concert with lower levels of markers of GABA neurotransmission, support the idea that convergent transcriptomic alterations take place to downregulate levels of inhibition from GABA neurons to match the lower level of excitation that they receive.

Not all lines of evidence, however, support this hypothesis. For example, although layer 3 pyramidal neurons do not appear to exhibit the same alterations (at least not to the same degree) in the primary visual cortex as they do in the DLPCF in SZ [145], PV and SST mRNAs are significantly lower in the primary visual cortex in SZ [178, 190]. Furthermore, findings of altered ErbB4 splicing [189], and an associated deficit in the density of excitatory inputs onto PV neurons [159], suggest the possibility of a primary pathological process in PV neurons.

CLINICAL IMPACT: BROADER CONTRIBUTIONS OF DORSOLATERAL PREFRONTAL CORTEX PATHOLOGY ON COGNITIVE DEFICITS AND CLINICAL SYMPTOMS IN SCHIZOPHRENIA

To this point in this review, we have emphasized the role of the DLPCF in explaining deficits in WM and CC in SZ. The role of the DLPCF in cognition, however, likely goes well beyond these two cognitive domains. Indeed, a consensus view has emerged that the DLPCF, along with the parietal cortex, insula, and medial prefrontal cortex, belongs to a domain-general CC network in the brain that supports performance across a broad range of tasks [35, 191–195]. CC is engaged in support of these systems under a number of conditions, including distraction, high memory loads, and overcoming prepotency. For this reason, the DLPCF may play an essential role in shifting attentional focus according to task demands and/or maintaining task-related goal/rule information [22] to guide task appropriate responding. In fact, the neural mechanisms in non-human primate DLPCF that underlie attentional focus appear to be similar to those underlying the selection of items available in working memory [196]. A reduction in DLPCF function as observed in SZ would thus be expected to have wide ranging effects on cognitive abilities that extend beyond WM. Indeed, a number of studies have shown DLPCF hypoactivation in SZ under high (but not low) CC demands in cognitive domains such as response selection [197], episodic memory [198], language comprehension [199, 200], and emotion processing [201]. Related to this point, in a 2009 meta-analysis Minzenberg et al. [84] observed significantly lower DLPCF activation in SZ across 41 studies covering a variety of executive function tasks, including oddball tasks, mental arithmetic, word generation, WM, and CC. Similarly, in an activation likelihood estimation-based meta-analysis Ragland et al. [202] showed significantly lower DLPCF activation in SZ across 18 episodic memory studies during both encoding and retrieval of information [195].

Reduced DLPCF activation and impaired performance on tasks related to DLPCF function may also have real-life, functional

consequences. To understand how, it may be helpful to first consider the clinical features of SZ. Although the disorder is most well-known for its characteristic positive symptoms (such as hallucinations and delusions), another striking symptom domain is disorganization. The disorganization symptoms of SZ are represented as observable inattention, inappropriate affect, disorganized speech (thought disorder), bizarre behavior, and the inability to initiate or complete complex everyday tasks. Indeed, the pioneering psychiatrist Eugen Bleuler hypothesized that thought disorder, or “loosening of associations,” was close to the primary “organic substrate” of SZ, present over all stages of illness and of principal diagnostic importance [203]. As people with SZ with disorganization symptoms may have difficulties in communication, comprehension, and goal-directed behavior, these symptoms are likely to have deleterious real-life consequences. To this point, a number of studies have reported significant relationships between disorganization and community-based functioning in SZ [204–208].

Conceptually, therefore, it is plausible to hypothesize that disease-related alterations in DLPFC function may contribute to disorganization in the illness. Consistent with this hypothesis, associations have been repeatedly observed between disorganization symptoms and behavioral performance during DLPFC-dependent tasks [27, 31, 208–210] (or similarly, communication disturbances and WM [211]) as well between disorganization and reduced DLPFC activation during CC and WM [78, 80, 82, 212]. Related to this point, when individuals with SZ are asked to speak on high stress topics, their speech is more disorganized than when asked to speak on low stress topics [213], possibly due to stress-induced disruption of DLPFC function [214]. Furthermore, in a 2012 study Yoon et al. [215] found that when whole-brain fMRI data during the AX-CPT was used to classify SZ vs. unaffected comparison participants, SZ individuals that were correctly classified showed stronger disorganization symptoms than misclassified individuals with SZ. Relationships between disorganization and task-associated DLPFC activity in the illness were concisely summarized in a 2014 review [210], which reported significant associations between DLPFC response and disorganization in 7 of the 8 studies examined.

Limited evidence suggests abnormal DLPFC function may also play a role in the expression of the negative symptoms of SZ. Early behavioral studies of WM, for example, demonstrated relationships between WM impairment and negative symptom severity (e.g., [216, 217]). Task-based functional imaging studies have observed relationships between DLPFC hypoactivation and negative symptoms as well (e.g., [201, 218]).

On a final note, given these symptomatic links, it is important to consider the role of DLPFC dysfunction in SZ given the clinically heterogeneous nature of the illness. As described above, evidence suggests that those individuals with SZ for whom disorganization symptoms are most prominent show the most severe deficits in prefrontal function. On the other hand, people with SZ who do not exhibit severe disorganization are likely to exhibit relatively intact levels of DLPFC function.

QUESTIONS FOR FUTURE INVESTIGATION

In the next section, we briefly consider relevant topics for future investigation, including potential avenues for therapeutic investigation.

Diagnostic specificity

Over the past decade, the field has becoming increasingly interested in transdiagnostic approaches to understanding neuronal dysfunction. This is largely due to the rise of directives such as the NIH Research Domain Criteria (RDoC), which seek to understand the neuronal mechanisms of cognitive dysfunction both within and across Diagnostic and Statistical Manual (DSM)-

based diagnostic criteria [219]. Relevant to the present review, therefore, one may ask the question: to what extent are the functional, macrocircuit, and microcircuit level DLPFC abnormalities described for SZ also observed in other psychiatric disorders, particularly in those disorders for which psychosis is a prominent symptom?

At present, approaches towards understanding the diagnostic specificity of DLPFC-related processes (such as WM and CC) have been most extensively applied in studies comparing SZ to bipolar disorder (BD). Behaviorally and functionally, the most common finding appears to be that BD is associated with intermediate performance deficits and prefrontal hypofunction relative to SZ and the unaffected comparison group [31, 32, 220–225]. Performance deficits, furthermore, may correlate with disorganization symptoms across diagnoses [31, 32]. As this line of research remains relatively novel, however, these findings require replication with larger sample sizes. Moreover, the majority of this research has been conducted in Type I BD, so it is unclear to what extent these features are present in Type II BD.

Findings at the cellular level have produced mixed results across diagnoses. For example, one study showed lower dendritic spine density on DLPFC layer 3 neurons in SZ relative to both individuals with major depressive disorder (MDD) and individuals without psychiatric illness (with no difference between people with MDD and unaffected comparison individuals) [145]. A later study found lower spine density in people with BD vs. the unaffected comparison group, a trend-level reduction in SZ vs. unaffected individuals, and no difference between SZ and BD individuals [146]. Similarly, PV mRNA levels have been reported to be lower in both SZ and BD relative to individuals who are psychiatrically unaffected, but not in individuals with MDD [153, 226]. Finally, transcriptomic studies in layer 3 pyramidal neurons found that gene expression alterations were much more prominent in the DLPFC of individuals with SZ than those with BD, but that the presence of psychosis in BD individuals was associated with transcriptome alterations similar to SZ [151, 227]. Nonetheless, additional studies to assess diagnostic and phenotypic specificity are needed.

Cortical regional specificity

Although this review focuses on the DLPFC, it would be overly simplistic to claim that reduced WM and CC abilities and associated disorganization in SZ are solely tied to dysfunction in a single brain region. WM and CC are complex processes that not only involve the DLPFC, but also the anterior cingulate, parietal cortex, ventrolateral prefrontal cortex, and inferior frontal cortex. These regions make up an interconnected brain system known as the frontal-cingulate-parietal network [228], which is broadly involved in executive function. Specific components of this network also make distinct contributions to executive processes, e.g., conflict monitoring in the anterior cingulate [229, 230] and attentional orienting in the superior parietal lobule [231]. Furthermore, although less well-studied, microcircuit-level alterations have been detected in one or more of these regions in SZ [178, 232]. Indeed, data suggest that SZ is associated with alterations to SST neurons and PV basket cells not only in the DLPFC but also other regions of the cortical WM network [168, 178, 233]. The latter findings might be consistent with other findings suggesting that abnormal sensory processing streams, e.g., those investigated using early visual N1 event-related potentials, might also contribute to cognitive deficits in SZ [234]. A multisite study of visual processing deficits in SZ, however, found that abnormalities might be explained by attention lapsing (as indexed by catch trials) [235]. This result suggests a role for dysfunctional cognitive control (in the form of attention lapses) in explaining alterations in perceptual task performance in the disorder. Taken together with evidence presented in this review, therefore, substantial data point to abnormalities within the

DLPFC that act as primary drivers of WM and CC deficits in the disorder given their fundamental roles in these cognitive processes. The specific contributions of sensory processing streams, nonetheless, remains unresolved and is therefore an important direction for future research.

It is also important to recognize that the neuronal substrate of cognitive deficits in SZ almost certainly extends to other brain areas outside of this frontal network, e.g., the hippocampus for episodic memory [195]. As the nature of functional hippocampal abnormalities is variable, however (with some studies showing hypoactivation and others hyperactivation) [195], the exact extent to which it contributes to the overall neurocognitive phenotype observed in the illness is an important future research direction.

Role of thalamocortical connectivity

The DLPFC is a highly connected brain region. Among its vast array of connecting fibers are prominent reciprocal connections with the mediodorsal nucleus (MDN) of the thalamus. Interest in the role of MDN-DLPFC connectivity in cognition stems from early studies which found that MDN lesions induce similar cognitive deficits to those observed following damage to the prefrontal cortex [236], including deficits in WM function [237]. Postmortem neuroanatomical studies of the MDN in SZ have not shown consistent differences between individuals with SZ relative to those without psychiatric illness in cell number or MDN volume, although sample sizes for these studies are small [238]. Functionally, research in mice suggests the MDN may influence WM by amplifying DLPFC connectivity in order to maintain information during the delay period [239]. Human neuroimaging studies have also found increased activation of the thalamus during WM tasks as well as reduced activation and connectivity between the thalamus and prefrontal cortex in SZ relative to unaffected comparison individuals [240, 241]. Due to limitations of fMRI contrast and resolution, it is unclear if these deficits are specific to the MDN. Combining high field MRI with recent improvements in thalamic parcellation schemes [e.g., 242] may help shed light on the nature of thalamic abnormalities in SZ.

Role of corticostriatal connectivity

In addition to the thalamus, the DLPFC is also connected to the associative striatum, to which it sends efferent projections as part of a cortico-striatal-thalamic feedback loop. The potential role of the striatum in the pathophysiology of SZ has long been appreciated due to its high density of dopaminergic axon terminals and dopamine D2 receptors, as the dopamine system is targeted by all currently FDA-approved antipsychotics. It is now well-established that SZ is associated with dysregulated dopaminergic signaling, and particularly increased dopamine synthesis and release in the striatum [243, 244]. MRI studies further suggest that the illness is associated with disrupted prefrontal-striatal structural and functional connectivity [245–249]. Reduced functional connectivity, furthermore, may be associated with response to antipsychotic treatment [246, 247]. One other possibility suggested by rodent studies is that alterations in prefrontal pyramidal neurons could lead to downstream hyperdopaminergia in the striatum that is sensitive to the effects of antipsychotics [250]. Thus, alterations to the DLPFC in SZ, causing cognitive dysfunction in the disorder, may subsequently lead to hyperdopaminergia and contribute to the emergence of positive symptoms.

In addition to positive symptoms, frontostriatal dysconnectivity may play an important role in cognitive deficits in SZ. For example, aberrant functional connectivity has been observed between the DLPFC and striatum during WM in the illness [251, 252]. Reduced connectivity of this circuit may reflect a relative inability of the DLPFC to regulate the basal ganglia during cognition [252]. Later work in individuals without psychiatric disorders suggests that effective connectivity between the DLPFC and striatum may be

particularly important during the encoding phase of WM as it may signal object novelty [253]. Overall, however, despite clear links between striatal dopamine and SZ, how frontostriatal connectivity contributes to the DLPFC-associated cognitive processes in the disorder remains poorly understood.

Antipsychotic effects

Any understanding of DLPFC structure and function in SZ would be incomplete without considering the effects of antipsychotics. Structural imaging studies suggest that people with SZ given antipsychotic treatment have thinner cortices relative to antipsychotic-naïve individuals (including a study in a very large ($n = 4474$) sample) [73, 254, 255], although some evidence suggests cortical thickness is reduced in antipsychotic-naïve people with SZ (relative to people without a major psychiatric illness) [256, 257] and may also occur before illness onset (i.e., prior to medication use) [258].

Neuroimaging studies have also reported antipsychotic effects on prefrontal function. A 2017 meta-analysis of longitudinal fMRI studies across various tasks found that the most commonly observed antipsychotic effect was prefrontal normalization (i.e., activation and connectivity patterns that more closely resembled those in psychiatrically unaffected individuals), although the authors of this meta-analysis noted that the included studies were generally naturalistic and therefore did not include placebo groups [259]. Results were also regionally heterogeneous and usually not replicated. A cross-sectional study of CC also found that people with SZ treated with antipsychotics showed levels of DLPFC activation halfway between unmedicated people with SZ and psychiatrically unaffected people [73]. D2 receptor blockade-induced homeostatic increase in prefrontal dopamine release may be a potential mechanism underlying antipsychotic effects [260]. Given that antipsychotic medication is generally ineffective at treating cognitive symptoms, however, it should be noted that these medications are not expected to completely normalize DLPFC activation during WM, CC, or other prefrontal cortex-mediated processes in SZ.

Importantly, the bulk of the cellular level findings described above do not appear to reflect the influence of antipsychotic medications, at least as assessed by comparisons of human participants on or off these medications at time of death and by studies in non-human primates exposed chronically to typical or atypical antipsychotics at doses that produce serum levels associated with therapeutic efficacy in humans. Studies in non-human primates exposed to antipsychotics, however, did find smaller brain tissue volumes [261], suggesting that antipsychotics might contribute to smaller DLPFC volume in SZ.

Potential avenues for therapeutic investigation: psychopharmacology

As described in this review, SZ and WM deficits are associated with disrupted GABAergic signaling. It therefore follows that drugs targeting this receptor may help restore normal function. In a preliminary proof-of-concept study, the subunit selective GABA_A receptor agonist MK-0777 improved WM and CC performance as well as increased frontal gamma band power during CC [262]. A larger clinical trial, however, failed to show cognitive benefits of the drug [263]. This apparent lack of clinical benefit might be due to the relatively weak partial agonist activity of MK-0777 or other limitations in study design [264].

As SZ is also associated with reduced glutamatergic signaling, another approach has been to develop agonists for the NMDA receptor. As recently reviewed in a meta-analysis of 25 clinical trials of NMDA receptor-acting agents in SZ [265], a small but significant improvement (standardized mean difference = 0.16) in WM was observed across all trials. It is unclear, however, if this result is clinically meaningful (e.g., improves functional outcomes). In addition, other strategies to augment signaling through

NMDARs have been investigated in preclinical models and early stage clinical trials, including agents which inhibit the synthesis of endogenous compounds that block NMDARs [266, 267].

Other neurotransmitter systems, including dopamine signaling in the DLPFC, have been targeted by pharmacologic interventions (Box 1). A limitation inherent in developing compounds that target neurotransmitter systems, however, is that these synthesized molecules are generally less effective at modulating these systems relative to endogenous ligands, for a variety of reasons (e.g., availability, kinetics, affinity, desensitization). It is also unclear if the “normalization” of these systems actually affects the underlying pathology that initiated the cascade of events leading to the disorder. Moreover, these pharmacologic interventions lack regional-specificity contributing to a host of off-region engagements. An alternative approach may be to develop pharmacologic ways of inducing long-lasting microstructural changes that may be more closely tied to disease pathogenesis.

For example, as discussed in this review, SZ is associated with lower dendritic spine density on excitatory pyramidal neurons. One mechanism by which this is thought to occur is chronic inflammation and microglial hyperactivation [268] (Box 2). The clinical features of SZ emerge during late adolescence, a period of brain development during which synaptic pruning is particularly robust. When amplified by an inflammatory stimulus (e.g., environmental stress), microglial activation could be exaggerated during this period, increasing pruning beyond normal levels. Interestingly, a recent finding in neuronal cultures derived from cortical tissue of individuals with SZ found links between abnormalities in microglial-like cells and synapse elimination. Cultures with variants in C4A associated with SZ risk also showed increased neuronal complement disposition and microglial synaptic engulfment. Finally, the antibiotic minocycline prevented pruning, hinting at a potential therapeutic avenue of investigation [269].

If inflammation-induced cortical over-pruning and subsequent loss of excitatory drive is intimately tied to the etiology of SZ, it follows that pharmacologic agents that reverse or prevent this process may have clinical utility. Indeed, significant improvement in visual learning/memory, attention, and/or executive function in SZ has been observed in trials of the anti-inflammatory compounds minocycline and pregnenolone [270]. Notably, however, a 2018 trial of 12 months of minocycline treatment in patients showed no effect of the antibiotic on DLPFC activation associated with WM [271]. The compound also showed no effect on symptoms.

On a final note, a limitation of the majority of clinical trials in SZ is that most do not incorporate functional measures of cognition as biomarkers. For example, effects of treatment on DLPFC function during relevant tasks (e.g., WM) or prefrontal gamma oscillatory activity [262] are rarely included as endpoints. Including such biomarkers might be necessary to determine if treatments are indeed appropriately engaging their intended targets [272].

Potential avenues for therapeutic investigation: neuromodulation

Modulation of DLPFC activity is another potentially exciting avenue for improving cognition in SZ. At present, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are the two most widely investigated methods for SZ, although the overall body of literature in this area remains small.

tDCS is a well-tolerated, safe, noninvasive technique that applies low current stimulation via scalp electrodes. A number of studies have demonstrated that anodal tDCS over the DLPFC enhances cognitive performance in individuals without a psychiatric illness [273–275]. In SZ, overall evidence suggests that anodal tDCS may have modest positive effects on cognition [273, 276, 277] with WM showing the most significant effects

Box 2. Role of the neuroimmunology in the pathogenesis of prefrontal cortical dysfunction in schizophrenia

Links between the immune system and SZ have been postulated for over a century [302], and evidence is mounting that neuroimmune mechanisms and associated neuroinflammatory processes may play a role in the pathogenesis of SZ [303]. Genotyping studies have revealed associations between variants in genes encoding immune system-related proteins (e.g., major histocompatibility complex/complement component 4A (C4A) and SZ [304, 305]. Elevated levels of pro-inflammatory cytokines (e.g., IL-6) have consistently been observed in the disorder [306] (as well as other disorders), and postmortem studies reveal higher levels of immune-related markers in the DLPFC of SZ [307–310]. A meta-analysis of older PET studies in SZ also reported increased binding potential of the 18 kDa translocator protein (TSPO), a putative marker of microglial activation, albeit with a small effect size (standardized mean difference = 0.31) and only when ascertained by TSPO binding potential but not volume of distribution [311]. In contrast, however, studies using quantitative modeling approaches, studies with second generation TSPO ligands with enhanced signal to noise ratio, and/or studies that control for a genetic variant that leads to non-binding of the tracer in both participants with SZ and unaffected comparator participants have found no evidence for increased TSPO in SZ [312, 313]. Finally, prenatal maternal neuroimmune activation may also increase future SZ risk, as evidenced by studies linking maternal illness with future SZ in offspring [303]. Consistent with these findings, multiple postmortem studies have shown elevated levels of immune-related transcripts in the DLPFC of individuals with SZ [314].

An unanswered question is if alterations in immunological markers observed in SZ are a consequence and/or a cause of the disease. A study in mice found an association between maternal immune activation and increased dopaminergic signaling in adult offspring [315], and a preliminary PET imaging study in non-human primates found increased striatal expression of a presynaptic dopamine marker in monkeys born to dams treated with a compound that activated the maternal immune system during pregnancy [316]. A few studies have also linked loss of gray matter volume in chronic SZ with cytokine levels [317–319]. On a microstructural level, increased microglial activation may also induce excessive synaptic pruning, potentially contributing to prefrontal dysconnectivity [269]. Early phase clinical trials of anti-inflammatory compounds (e.g., aspirin, cyclooxygenase-2 inhibitors) have also shown mixed efficacy at treating SZ symptoms [320].

Neuroimmune changes may contribute to cognitive symptoms of SZ as well. One study found that abnormally high levels of blood C-reactive protein were associated with poor cognitive functioning in a sample of 369 individuals [321]. Another study reported negative associations between cytokine levels and WASI scores across SZ-spectrum, bipolar-spectrum, and psychiatrically unaffected participants, after adjusting for diagnosis, age, and sex [322]. Interestingly, a later structural imaging study found associations between abnormally increased choroid plexus volume with cytokine (specifically, IL6) expression, lower gray matter volume, structural connectivity, and Brief Assessment of Cognition Score in the illness, suggesting potential mechanistic links between peripheral immune signaling and neurocognition [323]. Overall, however, how neuroimmune mechanisms contribute to cognitive dysfunction (including WM and CC-related processes) in SZ is unclear.

One hypothesis suggests that genetic risk factors, including common variations in the complement C4 gene that may produce higher levels of C4A in SZ [324], could lead to higher complement activity that contributes to hyperactive microglia in prodromal phases of the disease. According to this hypothesis, during adolescent development, dendritic spine pruning (which is normally mediated by microglia) is excessive [325, 326] and contributes to fewer dendritic spines observed in layer 3 pyramidal neurons in SZ [145]. Fewer dendritic spines and presumptive deficits in excitatory inputs onto layer 3 pyramidal neurons could contribute to downstream deficits in the PV and SST subtypes of GABA neurons. The convergence of these alterations in the WM microcircuitry in the DLPFC could then lead to the cognitive deficits seen in the disorder. While this hypothesis is a tantalizingly parsimonious explanation for the pathophysiology of DLPFC dysfunction in SZ, much more experimental evidence is required to substantiate this hypothesis. Furthermore, evidence for cognitive deficits present during childhood (ages 7–13) in those who later develop schizophrenia suggest that changes in local circuit/structure function, including spine density, might significantly pre-date adolescent brain development and schizophrenia onset [327]. Finally, it is unclear whether these potential alterations to neuroimmune function arise due to genetic risk factors or environmental insults during adolescent or earlier neurodevelopment. Pathogenic processes that contribute to DLPFC dysfunction remain an important area for new discoveries in schizophrenia research.

among various cognitive domains [277]. Interestingly, however, a meta-analysis in individuals without psychiatric disorders suggests that tDCS effect sizes are larger when administered during the study phase of a cognitive task (compared to the performance phase) [278]. It is possible, therefore, that larger effect sizes in SZ will be observed if the effects are measured following stimulation, as opposed to during stimulation. Indeed, our group found that when anodal prefrontal tDCS is administered during a WM task in

SZ, performance and gamma power was enhanced during a CC task that was performed immediately following stimulation [96].

With repetitive transcranial magnetic stimulation (rTMS), brain regions are excited by repeated magnetic pulses. The most recent review of rTMS effects on cognition in SZ revealed mixed findings, with 4 studies showing enhancement and 8 studies reporting no significant effects [279]. A study combined rTMS with fMRI also showed no effect of stimulation on DLPFC activation during WM [280]. Given the higher cost, greater participant discomfort, and increased difficulty of administration for rTMS vs. tDCS, based on these mixed findings we believe that tDCS may ultimately hold more promise as a method for cognitive enhancement in SZ.

Finally, it should be noted that prefrontal stimulation may also improve negative symptoms in SZ, as demonstrated by a 2018 meta-analysis of 24 studies that reported improvement after stimulation with moderate effect sizes (0.64 for rTMS, 0.50 for tDCS) [281].

Potential avenues for therapeutic investigation: cognitive training

As defined by Keshavan et al. [282], cognitive training (CT) is “an intervention that uses specifically designed, behaviorally constrained cognitive or socio-affective learning events delivered in a scalable and reproducible manner to potentially improve neural system operations.” Methodologically, CT involves performing cognitive tasks designed to activate neuronal circuits and enhance their function through neuroplasticity. In relation to “neural system operations” associated with DLPFC function, some evidence suggests potentially promising effects of intensive training in SZ. For example, in a 2014 study Subramaniam et al. [283] found that 1 h of daily computerized auditory/verbal processing and emotional identification exercises improved 2-back WM performance and associated DLPFC BOLD response in SZ relative to a computer games control condition, and a 2019 meta-analysis found that left prefrontal activation was the most commonly observed finding across 16 studies that combined neuroimaging with CT [284]. This meta-analysis, however, also found no significant overlap in the specific brain regions responding to CT, perhaps due to variation in training protocols and tasks. The mechanisms of cognitive enhancement following CT in SZ, therefore, may be variable and remain poorly understood.

CONCLUDING REMARKS

It has been over a century since Kraepelin posited that SZ was a disorder of the frontal lobes. Since then, anatomical, physiological, and behavioral evidence have converged on a common substrate, localized to the DLPFC, that underlies many of the cognitive deficits observed in the illness. Further, these lines of research are well-interconnected, in that neuroanatomical abnormalities of the DLPFC in SZ can be plausibly linked to aberrant neuronal function to ultimately produce the distinctive neurocognitive phenotypes associated with the disease. Studies of SZ have also helped to identify many potential approaches to novel therapeutic strategies that might be tested for efficacy using well-characterized functional biomarkers that combine neuroimaging and cognitive testing. We anticipate that these therapeutic strategies will eventually make significant inroads towards alleviating the devastating disease burden of SZ, from preempting the emergence of psychosis in at-risk states to improving cognition in chronic illness.

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AUTHOR CONTRIBUTIONS

Authors JS, SJD, DAL, and CSC conceptualized and wrote the paper.

ADDITIONAL INFORMATION

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