Review

Biological Psychiatry

Layer 3 Excitatory and Inhibitory Circuitry in the Prefrontal Cortex: Developmental Trajectories and Alterations in Schizophrenia

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ABSTRACT

Convergent evidence suggests that schizophrenia is a disorder of neurodevelopment with alterations in both early and late developmental processes hypothesized to contribute to the disease process. Abnormalities in certain clinical features of schizophrenia, such as working memory impairments, depend on distributed neural circuitry including the dorsolateral prefrontal cortex (DLPFC) and appear to arise during the protracted maturation of this circuitry across childhood and adolescence. In particular, the neural circuitry substrate for working memory in primates involves the coordinated activity of excitatory pyramidal neurons and a specific population of inhibitory gamma-aminobutyric acid neurons (i.e., parvalbumin-containing basket cells) in layer 3 of the DLPFC. Understanding the relationships between the normal development of—and the schizophrenia-associated alterations in—the DLPFC circuitry that subserves working memory could provide new insights into the nature of schizophrenia as a neurodevelopmental disorder. Consequently, we review the following in this article: 1) recent findings regarding alterations of DLPFC layer 3 circuitry in schizophrenia, 2) the developmental refinements in this circuitry that occur during the period when the working memory alterations in schizophrenia appear to arise and progress, and 3) how various adverse environmental exposures could contribute to developmental disturbances of this circuitry in individuals with schizophrenia.

Keywords: Cortical development, Dorsolateral prefrontal cortex, Excitation/inhibition balance, Parvalbumin interneurons, Pyramidal cells, Schizophrenia

http://dx.doi.org/10.1016/j.biopsych.2016.05.022

SCHIZOPHRENIA AS A DEVELOPMENTAL DISORDER

Multiple genetic liabilities (1–5) and perinatal environmental exposures (6,7) suggest that the neural substrate for schizophrenia may be present from early stages of development (8–10). Other environmental exposures, such as urban residence during childhood and repeated cannabis use during adolescence (11), suggest that alterations in later developmental processes may also contribute to the disease process (9,12,13).

The appearance of certain core cognitive features of schizophrenia well before the onset of psychosis also supports the idea that schizophrenia is a neurodevelopmental disorder (14–16). For example, at 7 years of age, individuals who were later diagnosed with schizophrenia displayed deficits in tests indexing reasoning and conceptualization. These individuals subsequently began to fall behind their peers in other aspects of cognitive function, such as working memory (WM), and this developmental lag progressively worsened through puberty (16).

WM, the ability to transiently maintain and manipulate a limited amount of information to guide thought or behavior, depends on the activity of a distributed neural network. A number of cortical, thalamic, and striatal regions are active during WM tasks (17–19), and alterations in these regions have been reported in patients with schizophrenia (20–22). A key node in this network, the neural circuitry of the dorsolateral prefrontal cortex (DLPFC), has been a major focus of investigation in healthy monkeys and humans (23–25) and in patients with schizophrenia (17,26) (Table 1). In monkeys and humans, both WM performance and DLPFC circuitry undergo protracted patterns of maturation that continue through late adolescence, and greater activation of the DLPFC is associated with improved WM performance during these periods (27–29). Understanding the developmental trajectories of DLPFC circuits that subserve WM may reveal which elements of the circuitry are preferentially vulnerable—and when they are most vulnerable—to the environmental events associated with an increased risk for schizophrenia.

NEURAL SUBSTRATE FOR WM

WM in monkeys appears to require the coordinated activity of excitatory pyramidal neurons and a specific population of inhibitory gamma-aminobutyric acid (GABA) neurons in DLPFC layer 3 (24). Layer 3 pyramidal cells furnish widespreading, horizontal axon collaterals that terminate in stripe-like arrays (30,31). These axon collaterals almost exclusively target the dendritic spines of other pyramidal cells (32). These

 ISSN: 0006-3223

Table 1. Dorsolateral Prefrontal Cortex Circuitry: Cell Type–Specific Functions, Alterations in Patients With Schizophrenia, and Developmental Trajectories

	Proposed Circuit Function in Working Memory	Alterations in Patients With Schizophrenia	Postnatal Developmental Trajectories	Reference(s)
Pyramidal Neurons	Recurrent excitation among layer 3 pyramidal neurons	↓ Dendritic spine density	↑ Perinatal dendritic spine density ↓ Peripubertal dendritic spine density	(57–59,91–93)
		↓ Somal and dendritic arbor size	↔ Changes in size	(54,55,91,92)
		↓ $GABA_A$ α1 mRNA	↑ $GABA_A$ α1 mRNA	(75,76,135,136)
		↑ $GABA_A$ α2-IR AIS; ↑ $GABA_A$ α2 mRNA	↓ $GABA_A$ α2 mRNA	(75,137)
PVBCs	Feedback inhibition of layer 3 pyramidal neurons	↑ μOR mRNA	↓ μOR mRNA	(138)
		↓ PV mRNA and protein	↑ PV protein levels per terminal	(72,74,139)
			↔ Terminal density during postnatal development	(100)
PVChCs	Regulation of pyramidal neurons: 1) blockade of back-propagating action potentials and 2) depolarization	↓ GAT1 immunoreactive cartridge terminals	↓ Terminal density during postnatal development	(100,137)
		? PV protein levels in PVChC terminals currently unknown	↔ PV protein levels per terminal	(100)

AIS, axon initial segment; $GABA_A$, gamma-aminobutyric acid type A receptor; GAT1, gamma-aminobutyric acid membrane transporter 1; IR, immunoreactivity; mRNA, messenger RNA; PV, parvalbumin; PVBC, parvalbumin basket cell; PVChC, parvalbumin chandelier cell; μOR, μ opioid receptor.

extensive, reciprocal, glutamatergic connections are thought to provide the anatomic substrate required for the activity of spatially segregated (but functionally related) clusters of pyramidal cells during the maintenance phase of WM tasks (24,33,34).

The axons of DLPFC layer 3 pyramidal cells also give rise to local collaterals that arborize in the vicinity of the cell body; the targets of these terminals are equally divided between pyramidal cell dendritic spines and the dendrites of a subpopulation of GABA interneurons that express the calcium-binding protein parvalbumin (PV) (35,36). These PV interneurons include basket cells (PVBCs), which innervate the perisomatic region (i.e., soma and proximal dendritic shafts and spines) of pyramidal cells. These inputs provide feedback inhibition that shapes the activity of pyramidal cell subpopulations during WM tasks (Figure 1A) (37–40). The divergent connections of PVBCs also result in the coordinated inhibition of multiple pyramidal cells. The fast and simultaneous decay of this inhibition synchronizes the firing of pyramidal cells, producing oscillatory network activity in the γ frequency range (30–80 Hz) (41–44). The potential importance of γ oscillations for supporting WM (45) is suggested by findings that the power of prefrontal γ synchrony increases in proportion to WM load (46,47).

Other neural elements in the DLPFC might also influence the function of this circuit. For example, the axon terminals of another subpopulation of PV interneurons, chandelier cells (PVChCs) or axoaxonic cells, form distinctive vertical arrays called cartridges that exclusively target the axon initial segments of pyramidal cells. In contrast to the conventional strongly hyperpolarizing role of PVBCs, the impact of PVChC inputs on pyramidal cell function in rodents appears to depend on stage of development, brain region, and level of network activity (48–52). For example, chandelier cell inputs can be depolarizing under certain conditions (48–50). In addition, PVChCs are reported to prevent ectopic action potential backpropagation, especially during γ oscillations in vitro (53). PVBCs and PVChCs therefore appear to uniquely shape the activity of postsynaptic pyramidal cells.

EXPLORING THE ROLE OF DEVELOPMENT IN DLPFC CIRCUITRY DYSFUNCTION IN PATIENTS WITH SCHIZOPHRENIA

The findings reviewed above suggest that understanding the normal development and alterations in schizophrenia of the DLPFC circuitry that subserves WM could provide new insights into the nature of schizophrenia as a neurodevelopmental disorder. Consequently, in this article we 1) review evidence of alterations in DLPFC layer 3 circuitry in patients with schizophrenia; 2) consider how these circuitry elements are normally refined during the developmental periods when the WM impairments in patients with schizophrenia arise and progress; and 3) discuss how adverse environmental exposures could produce developmental disturbances in DLPFC layer 3 circuitry underlying WM deficits in patients with schizophrenia.

Altered Connectivity of DLPFC Layer 3 Circuitry in Patients With Schizophrenia

A number of studies in the postmortem human brain provide convergent evidence that schizophrenia is associated with alterations in multiple elements of the WM circuitry in DLPFC layer 3. The interpretation of postmortem studies of schizophrenia needs to consider the potential effects of antipsychotic medications, nicotine, substances of abuse, suicide, and other factors that are frequently comorbid with schizophrenia. In the findings reviewed below, the effects of these factors have been accounted for using convergent approaches described in detail elsewhere (26,54,58).