Schizophrenia is a disorder of cognitive neurodevelopment with characteristic abnormalities in working memory attributed, at least in part, to alterations in the circuitry of the dorsolateral prefrontal cortex. Various environmental exposures from conception through adolescence increase risk for the illness, possibly by altering the developmental trajectories of prefrontal cortical circuits. Macaque monkeys provide an excellent model system for studying the maturation of prefrontal cortical circuits. Here, we review the development of glutamatergic and γ-aminobutyric acid (GABA)-ergic circuits in macaque monkey prefrontal cortex and discuss how these trajectories may help to identify sensitive periods during which environmental exposures, such as those associated with increased risk for schizophrenia, might lead to the types of abnormalities in prefrontal cortical function present in schizophrenia.

Key words: GABA/working memory/parvalbumin/pyramidal/cholecystokinin/cannabinoid

Introduction

Substantial evidence supports the view that schizophrenia is a disorder of neurodevelopment, with deficits in cognition often presenting and progressing years before the onset of psychosis. Working memory (WM), the ability to transiently maintain and manipulate a limited amount of information in order to guide thought or behavior, is a prototypical cognitive deficit in schizophrenia. Performance on WM tasks depends, at least in part, upon dorsolateral prefrontal cortex (DLPFC) activity, and both WM performance and associated patterns of DLPFC activity continue to mature through late adolescence, the period during which psychosis onset is most frequent.

In schizophrenia, the DLPFC exhibits altered activation during WM tasks and smaller gray matter volume. Interestingly, the normal decline in DLPFC gray matter that occurs during adolescence appears to be accentuated in schizophrenia, suggesting alterations in the pruning of excitatory synapses that occur during adolescence in the DLPFC of healthy individuals. Together, these findings emphasize the importance of understanding the developmental trajectories of DLPFC circuits that subserve WM because these may reveal which elements of the circuitry are preferentially vulnerable to environmental events at specific stages of development.

Risk for schizophrenia appears to result, in part, from a range of environmental exposures that may occur at different stages of postnatal development, defined for the purposes of this review as the period extending from birth to the end of adolescence. These exposures may include obstetrical complications, minority group position and urban residence during childhood, and frequent cannabis use during early adolescence. Knowledge of how and when these environmental exposures could alter the development of DLPFC circuitry, and thereby contribute to impaired WM, is critical for understanding the pathogenesis of schizophrenia.

Macaque monkeys provide an excellent model system for examining the postnatal refinements in DLPFC circuitry that contribute to WM maturation. As in humans, monkeys exhibit a progressive age-related improvement in WM performance that extends through adolescence. The ability to perform WM tasks first appears between 2 and 4 months of age in rhesus monkeys and then progressively improves to reach adult levels of performance after 3 years of age. This improved performance with age appears to be dependent upon an increased engagement of the DLPFC in task performance. For example, reversible inactivation of the DLPFC does not impair WM performance in monkeys 9–16 months of age, produces modestly disrupted performance in animals 19- to 31-month old, and substantially impairs performance in...
animals over 3 years of age. In electrophysiological studies, some DLPFC neurons exhibit elevated firing rates during the delay period of WM tasks, and the loss of this delay-related activity is associated with errors in task performance. Between 12 and 36 months of age, the proportion of DLPFC neurons that exhibit delay period activity doubles, suggesting that developmental changes in DLPFC circuitry facilitate the recruitment of more neurons to this functional role.

Consequently, in this review, we consider how developmental refinements in glutamatergic and γ-aminobutyric acid (GABA)-ergic circuits in the monkey DLPFC may provide insight into the contribution of different environmental risk factors to the structural and molecular alterations found in the DLPFC in individuals with schizophrenia.

Glutamatergic Circuit Alterations in Schizophrenia

In the DLPFC, pyramidal neurons are the principal excitatory output cells and the targets of the majority of glutamatergic-containing axon terminals. While the number of pyramidal neurons appears to be unchanged in schizophrenia, a reduction in the amount of cortical neuropil has been reported. The reduced neuropil may be the consequence of fewer axon terminals, as suggested by findings in postmortem studies of schizophrenia of lower levels of proteins present in axon terminals, and of fewer dendritic spines, the principal targets of excitatory synapses to pyramidal neurons.

Cortical pyramidal neurons can be categorized based on their laminar position and the principal target of their axonal projection. For example, many layers 2 and 3 pyramidal neurons send collaterals within the same cortical area (intrinsic) or between cortical areas (associational) (figure 1A). In contrast, layer 5 pyramidal neurons tend to project to the striatum and other subcortical regions and those from layer 6 tend to project to the thalamus. In the DLPFC of subjects with schizophrenia, dendritic spine density was significantly lower in deep layer 3 pyramidal cells, relative to both normal and psychiatrically ill comparison subjects, whereas spine density was only modestly lower in superficial layer 3 pyramidal neurons and unchanged in pyramidal neurons in layers 5 and 6. Consistent with these findings, the somal volume of deep layer 3 pyramidal neurons was lower in schizophrenia in the DLPFC and other cortical regions, whereas the volume of layer 5 pyramidal neurons was unchanged and the layer 3 findings did not appear to be attributable to medication use or length of illness. In concert, these findings suggest that in the DLPFC and other cortical regions in schizophrenia, basilar dendritic spine density is lower and somal volume is smaller in deep layer 3 pyramidal neurons (table 1), these alterations are specific to or at least most prominent in deep layer 3, and these differences reflect the underlying disease process and not confounding factors.

Postnatal Development of Glutamatergic Circuitry in the DLPFC

Dendritic spine density on layer 3 pyramidal neurons in monkey DLPFC undergoes marked changes across postnatal development. Spine density increases substantially during late gestation and the first 3 months postnatal, reaches a plateau that is maintained until 15–18 months of age and then declines during adolescence until stable adult levels are achieved at 3–4 years of age (figure 2A). Consistent with the findings that dendritic spines are the main site of excitatory synaptic input onto pyramidal cells and that all mature dendritic spines contain an excitatory synapse, the density of excitatory synapses (defined morphologically by the presence of a thick postsynaptic density) changes in a similar age-related fashion in both monkey and human DLPFC (figure 2A). In humans, this synaptic pruning could contribute to the decrease in cortical gray matter thickness that occurs during adolescence. Importantly, the late developmental refinements in excitatory synapse and spine number are more pronounced in layer 3 than in layers 5–6, consistent with the laminar location of pyramidal cell alterations in schizophrenia.

During early brain development, synaptic elimination appears to be directed at synapses that are functionally immature. Immature glutamatergic synapses are relatively weak and their maturation involves an activity-dependent increase in strength of excitation. Such activity-dependent strengthening might underlie synapse stabilization and thus mark for elimination the immature synapses that are not strengthened. Understanding if the synapses that are eliminated during adolescence in the primate DLPFC are functionally immature is essential for determining how synaptic pruning informs the developmental improvements observed in WM ability. For example, if the eliminated synapses are functionally immature, then they may not contribute to, detract from, the functional properties of DLPFC circuitry required for WM. That is, neurotransmission at immature glutamatergic synapses has (1) very low α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor contribution, rendering these synapses silent at the resting membrane potential and (2) relatively high probability of glutamate release, such that these synapses are not able to be repetitively activated without quickly exhausting glutamate vesicle pools. On the other hand, pruning of functionally mature synapses could help constrain the range of inputs that a given pyramidal cell receives and thereby perhaps contribute to the improved accuracy and greater resistance to distracters on WM tasks observed with age.

This question was addressed in a study of living slices of the DLPFC prepared from monkeys of different ages. Excitatory inputs to layer 3 pyramidal neurons in 3-month-old monkeys had immature functional properties, including a higher probability of glutamate release and lower AMPA/NMDA receptor ratio. In contrast, the
excitatory synaptic inputs to layer 3 pyramidal neurons from 15-month-old monkeys (preadolescence and pre-pruning) had mature functional properties that were similar to those observed in neurons from 42-month-old (postadolescence and postpruning) and 84-month-old (adult) animals (figure 2A). Therefore, the contribution of functionally immature synapses appears to decrease significantly before synapse elimination begins and to remain essentially constant thereafter. These data suggest that the substantial remodeling of excitatory connectivity of the primate DLPFC during adolescence primarily involves the elimination of mature synapses and that some other factor, such as the neuronal source of input or the postsynaptic target, somehow tags mature synapses for pruning. For example, of the axon collaterals furnished by layer 3 pyramidal neurons in monkey DLPFC (figure 1A), the intrinsic branches appear to be pruned to a greater degree than the associational branches.40 Although speculative, the elimination of excessive functional glutamatergic synapses might reduce the number of inputs from distracting stimuli during WM performance, improve the circuit’s ability to process relevant stimuli, and thus contribute to the improved WM performance observed during adolescence.

**Fig. 1.** Schematic diagram of layer 3 circuitry in monkey dorsolateral prefrontal cortex. (A) The principal axon of layer 3 pyramidal neurons (P) gives rise to local axon collaterals that arborize within the same cortical column, intrinsic collaterals that spread horizontally and arborize in distant columns, and associational projections to other cortical regions either within the same or within the contralateral hemisphere. (B) Innervation of the layer 3 pyramidal neuron in panel A by different classes of GABA neurons. (C) Perisomatic (proximal dendrites, soma, and AIS) GABA inputs to the same layer 3 pyramidal neuron. Abbreviations: AIS, axon initial segment; CB1R, cannabinoid 1 receptor; CCK, cholecystokinin; CR, calretinin; G, GABA; P, pyramidal; PV B, parvalbumin-containing basket neuron; PV CH, parvalbumin-containing chandelier neuron; SST, somatostatin; WM, white matter.
GABAergic Circuit Alterations in Schizophrenia

Multiple studies have consistently found that transcript levels for the 67-kDa isoform of the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD67) are decreased in the DLPFC of subjects with schizophrenia.41 In contrast, messenger RNA (mRNA) levels for the 65-kDa isoform of GAD (GAD65) have been reported to be unchanged, or only slightly lower, in schizophrenia.42–44 DLPFC GABA neurons can be differentiated on the basis of a number of molecular, physiological, and anatomical properties (figure 1B). For example, the neuropeptide cholecystokinin (CCK) is heavily expressed in GABA neurons that do not contain either the calcium-binding protein parvalbumin (PV) or the neuropeptide somatostatin (SST).45 The axon terminals of CCK-containing large basket neurons, which target selectively pyramidal neuron cell bodies, contain type I cannabinoid receptors (CB1R) (figure 1C)46,47; interestingly, mRNA and protein levels of CB1R are lower in schizophrenia.48,49

The affected GABA neurons in schizophrenia also include the PV subclass, which can be subdivided into 2 major types based on the principal target of their axon terminals (figure 1C). Axon terminals from PV basket cells target the perisomatic region (soma and proximal dendrites) and those from chandelier cells exclusively target the axon initial segments (AIS) of pyramidal neurons.50 In the DLPFC of individuals with schizophrenia, although the number of PV neurons appears to be unchanged,51 expression of PV mRNA is decreased.52 Furthermore, approximately half of the PV mRNA containing neurons lack detectable levels of GAD67 mRNA.52 In contrast, the subclass of interneurons that expresses the calcium-binding protein calretinin and comprises ~50% of GABA neurons appears to be unaffected in schizophrenia.52

In the DLPFC of individuals with schizophrenia, immunoreactivity for the GABA membrane transporter (GAT1) appears to be reduced in the characteristic chandelier cell axon terminal arrays referred to as cartridges.53 In the axon initial segment (AIS) of pyramidal cells that receive synaptic inputs from chandelier neuron axon cartridges, immunoreactivity for the GABA<sub>A</sub> receptor α2 subunit, which is normally the dominant GABA<sub>A</sub> receptor α subunit present in the AIS,54 is markedly increased in schizophrenia.55 In addition, the detectability of ankyrin-G, a key structural protein in the AIS, is also lower in the DLPFC in schizophrenia.56 Interestingly, each of these alterations in chandelier neuron connectivity is most pronounced in layer 3. In contrast, the density of PV-labeled axon terminals, presumably from basket neurons, and the expression of the GABA<sub>A</sub> receptor α1 subunit, which is postsynaptic to PV basket cell inputs, are both reduced in DLPFC layer 3 in schizophrenia43,57,58 (table 1). These changes appear to be specific to the pathophysiology of schizophrenia because they are not observed in individuals with other psychiatric disorders or in monkeys exposed chronically to antipsychotic medications.29,58

Postnatal Development of GABAergic Circuitry

Cholecystokinin- and Cannabinoid 1 Receptor Basket Neurons

Endogenous cannabinoids synthesized by pyramidal neurons act in a retrograde fashion to inhibit neurotransmitter release from axon terminals containing CB1R.59
In the case of CCK axon terminals enriched with CB1R, activation by cannabinoids suppresses the release of GABA, decreasing inhibition from those terminals onto their targets (frequently pyramidal neurons). The density of CCK-positive basket cells is most prominent in layers 2–superficial 3 at birth and falls to a constant adult-like level by 1 year of age. In the monkey DLPFC, the overall level of CB1R immunoreactivity robustly increases during the prenatal and perinatal periods and then remains stable throughout postnatal development. However, laminar-specific developmental changes are present in innervation density; in layers 1–2, CB1R immunoreactivity decreases during the first postnatal year (not shown), whereas in layers deep 3 and 4, CB1R immunoreactivity increases during adolescence (figure 2B). In contrast, CB1R mRNA expression is highest at birth, markedly decreases during the first 3 postnatal months and then remains stable through development and into adulthood (figure 3) with a distinct peak in CB1R mRNA expression in layer 2. Thus, the relative levels and laminar distribution of both CB1R immunoreactivity and mRNA exhibit distinctive patterns and different rates of change, eventually achieving peaks of mRNA expression in layer 2 and of CB1R-immunoreactive axons in

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**Fig. 2.** Schematic summary of developmental trajectories of excitatory and inhibitory markers of neurotransmission in the middle layers of monkey dorsolateral prefrontal cortex and the timing of risk factors for schizophrenia. (A) Developmental trajectories of excitatory synapse number and functional maturation (Colors for trajectory curves are within the same color family as figure 1C). (B) Developmental time course of presynaptic and postsynaptic markers of GABA neurotransmission (Colors for trajectory curves are within the same color family as figure 1C). (C) Timing of exposures that increase the risk of schizophrenia from conception through adolescence. Abbreviations: AIS, axon initial segment; CB1R, cannabinoid 1 receptor; GAT1, GABA membrane transporter; mos., months; PV, parvalbumin.
These findings suggest a shifting role of CB1Rs in cortical circuitry that might contribute to the functional maturation of the DLPFC and to age-specific vulnerabilities to cannabis exposure during both the perinatal and the adolescent periods of development (figures 2B and C).

**PV-containing Basket Neurons**

The density of the PV-positive axon terminals of basket neurons changes markedly during postnatal development, increasing steadily from 1 month of age to adulthood (figure 2B). These developmental changes in the number of PV-positive boutons most likely reflect a shift in the detectability of basket axon terminals with immunocytochemical techniques, secondary to a change in the concentration of PV protein within the terminals, because the total number of inhibitory synapses, and the axonal arbors of basket cells specifically, appear to remain relatively constant over this same period of development.

**PV-containing Chandelier Neurons**

The chandelier class of PV-containing GABA neurons also exhibits developmental changes in the expression of biochemical markers. During postnatal development, the density of chandelier neuron axon cartridges immunoreactive for either PV or GAT1 changes markedly in monkey DLPFC. Although the precise time course differs for the 2 markers, the density of labeled cartridges is low in the newborn, increases to reach a peak prior to the onset of puberty and then declines markedly during adolescence to adult levels (figure 2B). Because cartridges are readily visualized with the Golgi technique over this same time period, the changes in PV- and GAT1-immunoreactive cartridges likely reflect developmental shifts in the concentration of these proteins.

In the adult cortex, the majority of GABA<sub>A</sub> receptors containing the α2 subunit are found in pyramidal cell AIS. The detectability of GABA<sub>A</sub> α2 subunits at the AIS undergoes substantial changes during postnatal development. As shown in figure 2B, the density of pyramidal cell AIS immunoreactive for the α2 subunit protein is very high in the postnatal period and then steadily declines through adolescence into adulthood. Because GABA receptors including the α2 subunit have a higher affinity for GABA and slower deactivation times than receptors containing the α1 subunit, this decrease in the density of α2-labeled AIS may reflect a change in the strength and speed of GABAergic transmission at the AIS during postnatal maturation rather than a reduction in the number of GABAergic synapses onto the AIS.

Immunoreactivity for ankyrin-G, βIV spectrin, and gephyrin (a scaffolding protein that regulates the clustering of GABA<sub>A</sub> receptors containing α2 subunits at the AIS) also exhibits substantial changes during postnatal development (figure 2B). The densities of ankyrin-G- and βIV spectrin-immunoreactive AIS were greatest at birth and then sharply declined to reach relatively stable values by 1 year of age. In contrast, the relative density of gephyrin-immunoreactive AIS did not appear to change through the first 2 postnatal years but then sharply declined through adolescence and into adulthood.

The high density of AIS with detectable levels of ankyrin-G immunoreactivity in the first 3 postnatal months may reflect the recruitment to this location of a portion of the large number of GABA synapses that are formed in the monkey DLPFC during this developmental epoch. Given the general role of spectrins in maintaining membrane integrity and elasticity, high levels of βIV spectrin during early postnatal development might ensure the stability of AIS structure while prefrontal cortical thickness is increasing. The high density of gephyrin-immunoreactive AIS during early postnatal development is accompanied by a high density of AIS immunoreactive for GABA<sub>A</sub> receptors containing the α2 subunit, consistent with the role of gephyrin in clustering this type of GABA<sub>A</sub> receptor. In contrast, during this same developmental epoch, the densities of PV- and GAT1-immunoreactive chandelier cell axon cartridges...
are very low. At presynaptic terminals, PV is thought to reduce Ca$_{2+}$-dependent GABA release and the amount of GAT1 is inversely correlated with the availability of GABA at the synapse. Together, these findings suggest that both the release of GABA from chandelier axon cartridges, and its persistence in the extracellular space at AIS, is very high during early postnatal development. In concert with the high density of both gephyrin- and GABA$_A$ $\alpha_2$-immunoreactive AIS, these findings suggest that both presynaptic and postsynaptic factors are shifted to maximize GABA neurotransmission at pyramidal cell AIS during the first month of postnatal development.

These changes in the presynaptic and postsynaptic markers at the chandelier-pyramidal neuron synapse are likely to have a substantial effect on GABA neurotransmission. For example, PV is a slow calcium buffer that does not affect the amplitude, but accelerates the decay of Ca$_{2+}$ transients in GABA nerve terminals. Thus, PV decreases the residual Ca$_{2+}$ levels that normally accumulate in nerve terminals and facilitate GABA release during repetitive firing. Studies in PV-deficient mice have demonstrated that a decrease in PV increases residual Ca$_{2+}$ and favors synaptic facilitation. Furthermore, the enhanced facilitation of GABA release from fast-spiking neurons with reductions in PV is associated with increased power of gamma oscillations. Similarly, the blockade of GABA reuptake via GAT1 prolongs the duration of inhibitory postsynaptic currents (IPSCs) when synapses located close to each other are activated synchronously; the resulting prolongation of IPSCs increases the probability of IPSC summation and enhances the total efficacy of IPSC trains. The upregulation of the postsynaptic GABA$_A$ receptors that contain $\alpha_2$ subunits would be expected to increase the efficacy of the GABA that is released from chandelier neurons. Thus, the combined reduction of PV and GAT1 proteins in chandelier cell axon cartridges, and of postsynaptic GABA$_A$ receptors in pyramidal neuron AIS, during adolescence is likely to substantially change the strength and kinetics of GABA neurotransmission at the AIS during the types of repetitive neuronal activity associated with WM.

Like other GABA neurons, the effect of GABA released from chandelier neuron axon terminals is mediated by binding to postsynaptic GABA$_A$ receptors, which results in the opening of chloride ion channels. The developmental shift from excitatory to inhibitory effects of GABA depends on the chloride electrochemical gradient set up in part by the sodium-potassium-chloride cotransporters, NKCC1, and KCC2, which exhibit opposite developmental trajectories. For instance, in the neonatal brain, elevated expression of NKCC1, which pumps chloride into the cell, coupled with low expression of KCC2, which extrudes chloride from the cell, results in high intracellular chloride concentrations relative to those observed in the adult brain. In the adult brain, high expression KCC2 coupled with lower expression of NKCC1 results in the extrusion of chloride from the cell. Thus, in the adult brain when GABA$_A$ receptors are activated, chloride ions flow along a concentration gradient into the cell, resulting in membrane hyperpolarization and reduced probability of cell firing. However, a recent study found that KCC2, while readily detectable in the cell body of adult pyramidal neurons, was apparently absent in the AIS of neocortical pyramidal neurons. Consistent with this observation, Szabadics and colleagues found that the release of GABA from chandelier neuron axon terminals resulted in depolarization of pyramidal cells in an in vitro slice preparation. In fact, the chandelier cell-mediated depolarization was so powerful that in ~50% of the cases in which a single chandelier cell was stimulated, the postsynaptic pyramidal cell was depolarized to the point of firing an action potential. Consistent with these findings, microapplication of GABA near the AIS of neocortical pyramidal cells was found to be excitatory. Furthermore, the excitation of pyramidal cells by chandelier cells was found in both rodent and human neocortex. Studies using recording techniques that were able to exclude potential methodological confounds showed that both basket and chandelier neurons are inhibitory in the hippocampus, but that neocortical chandelier cells are able to produce GABA-mediated excitation. While chandelier neurons have long been considered to be powerful inhibitors of pyramidal cell output, these findings suggest that under certain conditions, chandelier neurons might provide depolarizing excitatory inputs to pyramidal neurons. Although schizophrenia does not appear to be associated with an alteration in the developmental trajectories of NKCC1 and NKCC2, an association between schizophrenia and disturbances in the expression of kinases that regulate the activity of these transporters has been reported. These findings suggest that an indirect disease-related effect on sodium-potassium-chloride cotransporter function somehow alters the chloride concentration gradient and may affect GABA signaling at the AIS.

**Developmental Trajectories of Postsynaptic GABA$_A$ Receptor Subunits**

GABA$_A$ receptors are heteropentameric structures most commonly composed of $2\alpha:2\beta:1\gamma$ subunits or 1 $\delta$ subunit in place of $\gamma$. At the postsynaptic level, $\alpha_1$, $\beta_2$, $\delta$, $\gamma_1$, and $\gamma_3$ subunits in primate DLPFC GABA$_A$ receptors have similar laminar patterns of expression and undergo similar developmental trajectories, which are distinct from those followed by GABA$_A$ $\alpha_2$, $\alpha_4$, $\beta_2$, and $\gamma_2$ subunits. For example, expression of mRNAs encoding GABA$_A$ receptor $\alpha_1$ and $\alpha_2$ subunits in monkey DLPFC exhibit opposite trajectories across postnatal development, including significant differences between prepubertal and adult animals (figure 3). This divergent trajectory is shaped by a gradual postnatal increase of $\alpha_1$ subunit mRNA expression that does not reach stable peak levels.
until adulthood, and by a progressive decline of α2 subunit mRNA from its highest levels in neonates to the lowest levels of expression in adult animals. In human DLPFC, mRNA levels for the GABA\(_A\) α1 and α2 subunits also display opposed postnatal developmental trajectories.

Functionally, increased α1 subunit expression during development might be important for establishing the network properties required to efficiently generate the gamma oscillations (~30 to 80 Hz) associated with WM. The faster kinetics of inhibitory inputs to pyramidal neurons during postnatal development are consistent with increased α1 subunit expression at inhibitory synapses on pyramidal neurons, such as those made by PV-containing basket neurons. Faster inhibition by PV-containing neurons across postnatal development might contribute to an improved ability for PV neurons to synchronize the firing of large populations of pyramidal neurons at high frequencies. Therefore, increasing levels of GABA\(_A\) α1 subunits at the synapses between PV-containing basket neurons and pyramidal neurons during postnatal development might contribute to a greater capacity for generating cortical gamma band oscillations and developmental improvements in WM performance.

The mRNAs of αα and δ subunits of the GABA\(_A\) receptor also show opposed developmental trajectories, even though these 2 subunits coassemble to form extrasynaptic receptors in the cortex that mediate tonic inhibition. Interestingly, the developmental increases in δ and α1 subunits were quite similar in the same monkeys, and these 2 subunits can coassemble to form functional receptors. GABA\(_A\) α1 subunits have also been found extrasynaptically, consistent with the typical localization of δ-containing receptors. In concert, these findings support the idea that δ-containing GABA\(_A\) receptors in the adult DLPFC coassemble with α1 subunits and that the α subunit composition of extrasynaptic GABA\(_A\) receptors in the primate DLPFC changes with development.

Environmental Exposures During Sensitive Periods and the Risk of Schizophrenia

A range of early life environmental exposures may increase the risk for the later development of schizophrenia. While some of these risk factors cover an extended period of development, their impact on the risk of developing schizophrenia may be amplified during discrete periods of postnatal development that have enhanced sensitivity due to the high rate of change in specific elements of DLPFC circuitry. For example, the apparent dose-related effect of cannabis use on schizophrenia risk may be most prominent with repeated exposure prior to the age of 16 years, which corresponds with the developmental period when CB1R protein levels are increasing in the middle layers of the DLPFC, suggesting that vulnerability to cannabis exposure is most pronounced when these cortical circuits are being refined. Activation of CB1R by exogenous cannabinoids, such as the principal psychoactive component in cannabis, Δ9-tetrahydrocannabinol, suppresses GABA release from the axon terminals of CCK neurons (figure 1C). The repetitive use of cannabis during adolescence may blunt the developmental increase in CB1R protein that normally occurs during this period of development, perhaps contributing to the lower levels of CB1R protein observed in schizophrenia. Furthermore, unlike the synapse-specific depolarization-induced suppression of inhibition that normally occurs when a pyramidal neuron synthesizes endogenous cannabinoids on demand in response to synaptic activity, exogenous cannabinoids may persistently and widely suppress CB1R-containing inputs onto pyramidal neurons in a non-specific manner. This widespread suppression of GABA release from CCK neurons may subsequently contribute to excessive pyramidal cell activity, resulting in altered excitatory-inhibitory balance. To prevent runaway excitation and cell injury, affected pyramidal neurons may compensate by evoking an exaggerated pruning of excitatory synapses and eliminating dendritic spines in order to restore excitatory-inhibitory balance in the DLPFC; such a scenario might account for the lower pyramidal neuron spine density present in schizophrenia. Moreover, the output of CCK neurons also influences the activity of PV neurons, suggesting that cannabis use during adolescence could indirectly disrupt the normal development of PV basket and chandelier cells in schizophrenia.

This complex and protracted maturation of local neural circuits, especially in layer 3 of the DLPFC, provides a number of opportunities for any disturbances, even subtle ones, to have their effects amplified because they alter the trajectories of the developmental events that follow. Indeed, the similarities between the components of DLPFC circuitry that exhibit marked changes during postnatal development and those reported to be altered in postmortem studies of schizophrenia suggest that the alterations of these markers in schizophrenia reflect a disturbance in their patterns of development and might explain how a range of environmental factors (figure 2C) could all be associated with an increased risk of schizophrenia later in life. That is, different exposures might each alter, albeit in different ways, the neural circuitry that is essential for WM function, resulting in WM performance levels in schizophrenia that resemble the immature levels seen in children. The different environmental exposures during discrete sensitive periods of development could thus each alter the maturation of DLPFC circuitry, leading to a common outcome of impaired cognition in schizophrenia but with differences in the nature and severity of the impairment across individuals depending upon the type and timing of the exposure.
Recently, it has been suggested that schizophrenia be reconceptualized as a syndrome with psychosis as a late, potentially preventable outcome of the illness. The findings summarized in this review highlight that DLPFC circuits are dynamic in their structural and molecular properties from birth through adolescence, with substantial changes in occurring in markers of both glutamatergic and GABAergic neurotransmission. Importantly, in the primate DLPFC, these developmental trajectories appear to be temporally associated with a range of environmental risk factors for schizophrenia. This association raises the possibility that early intervention to interrupt or reverse pathological circuit development may help reduce the decline in cognitive function and alter the course of the illness.

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