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GABAergic function as a limiting factor for prefrontal maturation during adolescence

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Abstract

Adolescence is a vulnerable period for the onset of mental illnesses including schizophrenia and affective disorders, yet the neurodevelopmental processes underlying this vulnerability remain poorly understood. The prefrontal cortex (PFC) and its local GABAergic system are thought to contribute to the core of cognitive deficits associated with such disorders. However, clinical and preclinical end-point analyses performed in adults are likely to give limited insight into the cellular mechanisms which are altered during adolescence but are only manifested in adulthood. This perspective summarizes work regarding the developmental trajectories of the GABAergic system in the PFC during adolescence to provide an insight into the increased susceptibility to psychiatric disorders during this critical developmental period.

Keywords

GABA_A; interneurons; parvalbumin; calretinin; adolescence; prefrontal cortex

Your brain “on” adolescence

It is during adolescence when the acquisition of mature cognitive abilities associated with adult behavior occurs. These include working memory, decision-making, and impulsivity control, abilities which are dependent on the functional maturation of the prefrontal cortex (PFC) [1–3]. As one of the last regions in the brain to mature [4], the PFC undergoes protracted remodeling during adolescence at both functional and anatomical levels that are concomitant with increases in connectivity with cortical and subcortical structures. These changes ultimately result in fine-tuning of the excitatory-inhibitory balance required to enable proper integration of afferent information and sustain optimal computational capacity in the PFC [5]. It is therefore conceivable that a dysregulation of the normal maturational processes occurring in the PFC during adolescence could be part of the neural substrate that confers susceptibility to many mental illnesses such as schizophrenia and affective disorders

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[6]. Not fortuitously, the onset of such psychiatric disorders usually occurs during adolescence, and fittingly, their clinical manifestations encompass mild to severe PFC-dependent cognitive impairment [6].

Among the drivers of PFC excitatory-inhibitory balance, the local GABAergic system is of particular interest as it undergoes extensive changes during adolescence at the level of protein expression, modulation by neurotransmitters, and response to afferent drive. Here, we briefly summarize converging findings in rodents and primates on the remodeling of PFC GABAergic function during adolescence with the ultimate goal of deciphering the processes and mechanisms underlying the maturation of prefrontal function. Based on the lessons learned from rodent PFC as a model for associative cortices, we conclude that an afferent-driven mechanism is responsible for the increased functionality of the prefrontal GABAergic system during adolescence resulting in increased inhibitory control of PFC output and optimal fine-tuning of local excitatory-inhibitory ratio. It is through the identification of these and other mechanisms operating during adolescence that a common developmental framework under which psychiatric disorders involving the PFC can be better understood.

Remodeling of GABA_A-mediated inhibition in the PFC during adolescence

The pre- and postsynaptic machinery that controls the signaling, release, and re-uptake of GABA undergoes dynamic changes in cortical circuits during postnatal development in both primates and rodents. Early on, GABAergic function is supported by rapid/linear synaptogenesis of inhibitory terminals, increased expression/activity of GABA-synthesizing enzymes (i.e. GAD1 and GAD2), and upregulation of GABA transporters. In rodents, most of these processes reach a steady state of maturity during the first month of postnatal development, typically within postnatal days (P) 15–30, also defined as the juvenile period [7–12]. Equivalent developmental patterns have been found at the mRNA level in both human post-mortem tissue and non-human primate PFC samples [13–16], suggesting that the structural framework under which increased GABAergic functionality arises during adolescence is well-conserved and is already in place by childhood. Nonetheless, it is clear that past this juvenile stage, additional factors must account for the periadolescent remodeling of GABAergic function observed in the PFC.

Among the postsynaptic changes that could account for the characteristic increase in PFC GABAergic functionality observed during adolescence [17–19] is the subunit composition of GABA_A receptors. In the central nervous system, GABA_A receptors are pentameric and display a typical 2 α :2 β :1 γ stoichiometry [20]. Studies examining the distribution of GABA_A receptor subunits in the cortex have revealed distinct developmental patterns of expression at both the mRNA and protein levels [21, 22]. One of the most consistent findings in the non-human primate dorsolateral PFC has been the developmental increase in α 1 subunit expression concurrent with a progressive reduction of α 2 and α 5 subunits [15, 23, 24]. A recent developmental analysis of GABA_A subunit transcripts expanded this knowledge to layer-specific changes occurring during adolescence [25]. Specifically, while α 1 and α 2 subunits undergo opposite developmental patterns in layer III during the juvenile to adult

transition, robust increases in $\alpha 1$, $\gamma 2$ and δ were found in layer V, with $\alpha 2$ levels in this layer remaining stable throughout development [25, 26]. These findings suggest that a shift from $\alpha 2$ - to $\alpha 1$ -containing GABA_A receptors occurs in the PFC during adolescence. Although the contributing factors triggering these prefrontal changes remain unknown, there is evidence to suggest that an input-dependent mechanism drives the changes in subunit expression in the PFC in a similar fashion to that seen in sensory cortical regions during development [27–31]. Thus, it could be argued that a timely strengthening of specific prefrontal afferents during adolescence is required to promote the expression of $\alpha 1$ -containing GABA_A receptors in the PFC.

A developmental shift in GABA_A receptor subunits could have profound biological impact given that $\alpha 1$ subunits confer specific properties to GABA_A function, namely, faster decay times, which ultimately promote fast synaptic inhibition [27, 32]. Accordingly, PFC GABAergic function in rodents increases during adolescence, as measured by the frequency of inhibitory postsynaptic currents (IPSC) onto output pyramidal neurons [33] and local field potential recordings of GABA_A-mediated prefrontal responses to afferent drive *in vivo* [18, 19]. Pyramidal neurons recorded from non-human primates also experience a postnatal increase in IPSC frequency with decreased IPSC decay time [23, 34], consistent with an elevated expression of the $\alpha 1$ subunit. Together, these findings would predict the emergence of a functional dominance of fast-spiking interneurons over their non-fast-spiking counterparts in regulating PFC inhibition during adolescence given that $\alpha 1$ and $\alpha 2$ subunits are predominantly postsynaptic to these interneuronal populations, respectively [35].

Changes in Ca⁺⁺-binding protein-expressing interneurons in the PFC during adolescence

Local GABA-producing interneurons are the effectors of GABAergic transmission in the PFC. Analysis of GABAergic populations in PFC has revealed that the vast majority of local interneurons express one of the Ca⁺⁺-binding proteins parvalbumin (PV), calretinin (CR), and calbindin (CB) [36, 37]. Aside from being useful neurochemical markers, the prevalence of calcium-binding proteins in interneurons suggests that the regulation of calcium dynamics is of central importance for the activity of these cells [38, 39]. This has been best illustrated for PV, as it participates in neurotransmitter release [40–43] and its expression levels in the hippocampus correlate with permissive learning states [44]. Notably, PV-positive interneurons have a fast-spiking phenotype whereas CR and CB-positive cells are either regular- or irregular-spiking, or exhibit a low threshold-spiking pattern, all of which can be broadly defined as non-fast spiking neurons [45–51]. It is important to bear in mind that the electrophysiological profiles described early on were mostly based on the analysis of recordings obtained from juvenile animals. Only recently has the field been able to assess the physiological properties and modulation of interneurons in adults and to reveal that the powerful excitatory control of GABAergic activity by dopamine does not emerge until late adolescence in the PFC [17, 52–57]. Our studies have found that the expression of PV and CR show opposite patterns in the rodent PFC during adolescence [17], such that PV shows a developmental increase in expression which is paralleled by a decrease in CR. We found no changes in CB expression over the adolescent transition to adulthood. However, it cannot be

discarded that concurrent increases or decreases in CB-expressing interneuronal subpopulations (e.g. cholecystokinin- and somatostatin-positive cells) balances out the amount of CB. These general patterns have also been found at the mRNA level in the PFC from non-human primates and in post-mortem human samples, [58, 59] suggesting that these trajectories are conserved in the mammalian PFC.

At the physiological level, only PV-positive/fast-spiking interneurons in the PFC show changes in their intrinsic and synaptic excitability during adolescence. Of particular interest is the doubling in the frequency of spontaneous excitatory postsynaptic currents onto PV-positive/fast-spiking interneurons that was not observed in the non-fast spiking population [17]. Such augmentation of excitatory synaptic transmission onto interneurons could contribute to the increase in PV through an activity-dependent mechanism. This has been best exemplified in sensory cortical regions, where chronic deprivation of afferents results in a significant decrease in PV expression [60–64]. Thus, the normal developmental trajectory of specific populations of GABAergic interneurons in the PFC could be regulated by concurrent intrinsic and synaptic events triggered by strengthening of prefrontal afferents during adolescence, such as those from the ventral hippocampus, mediodorsal thalamus, and basolateral amygdala [5].

Developmental window for common neurobiological processes in rodent and primate underlying PFC maturation during adolescence

Absolute comparisons of neurobiological changes between primate and rodent are constantly prevented by the nature of starting material and the technology available to study it. Human studies often use post-mortem samples, followed by mRNA detection either by microarrays, quantitative RT-PCR, or *in situ* hybridization histochemistry. Conversely, the possibility of direct physiological measures combined with the ample availability of tissue for protein immuno-detection in rodents allows the systematic dissection of neurobiological mechanisms underlying specific developmental changes. The integration of all of these approaches help us uncover which neuronal processes in the PFC are conserved between humans and rodents such that insights on common neural substrates underlying PFC development in animals provide testable hypotheses on the vulnerability of human adolescence.

Among the most conserved variables thus far measured in cross-sectional, post-mortem studies, a robust increase in PV mRNA and a decrease in CR mRNA have been found in the human dorsolateral PFC [58]. As discussed above, the rodent PFC also experiences similar patterns of PV and CR expression occurring between P35-55 (roughly corresponding to human adolescence or the period spanning 12–20 years of age), as measured by protein expression [17] (Fig 1). If linear, this would suggest that five days in rodents are equivalent to 3 human years; however it is possible that non-linear relationships occur within this rapidly changing period. Nonetheless, the changes in interneuron patterns observed from adolescence to young adulthood support a functional remodeling of the GABAergic system in both species as part of the developmental program necessary to achieve adult PFC functions. By using this developmental framework to study the mechanisms underlying

increased GABAergic function during adolescence, we have found that embedded within this period is a shorter window during which environmental insults permanently arrest PFC maturation [19, 33]. These findings provide a set of neurobiological mechanisms underlying the increase in GABAergic function during adolescence and validate this period as one of extended susceptibility for the PFC.

Practical considerations for adolescence susceptibility

Data from our recent studies in rodents reveal that the PFC undergoes massive functional remodeling during adolescence (i.e., P35-55). However, it is the local GABAergic system that renders the PFC labile during this developmental period. In fact, any experimental manipulation that either directly or indirectly compromises the activity of GABAergic interneurons in the PFC during adolescence prevents the acquisition of inhibitory control that normally occurs in the adult PFC through an increase of local GABAergic function [19, 65, 66]. Thus, the functional maturation of the GABAergic system during adolescence is part of the neural substrate that confers adult properties to the prefrontal circuit through a change in the excitatory-inhibitory balance. Given the complex social and environmental challenges individuals encounter during adolescence, it is not entirely unexpected that particular risk factors alter the trajectory of this inhibitory component and render the PFC hypofunctional. Most troubling, however, is the indication that any transient insult during this developmental period leads to behavioral and physiological consequences that persist into adulthood [19, 33, 65–68]. It remains to be determined why these deficits are enduring and, more importantly, if they can be reversed or ameliorated. Recent studies suggest that interneuron transplants in the ventral hippocampus can indeed correct some developmental alterations relevant to psychiatric disorders [69, 70]. We hypothesize that maturation of specific PFC afferents during adolescence promotes a type of long-term plasticity in GABAergic interneurons necessary to integrate growing cortico-cortical inputs resulting from the increasing environmental demands occurring during this period. The absence of such maturation would render the system unable to match the computational demands posed by parallel developing circuits, ultimately altering PFC output and control over subcortical structures. More research is needed to determine whether specific PFC afferents promote GABAergic maturation during adolescence and the precise molecular mechanism by which this developmental event occurs. Our recently published studies indicate that the excitatory input from the ventral hippocampus is essential for eliciting the periadolescent emergence of PFC GABAergic inhibition. Accordingly, ventral hippocampal stimulation elicits an age-dependent plasticity in the PFC that relies on local GABA_A receptor-mediated transmission [18]. This timeline agrees with the maturation of the ventral hippocampus itself [71–73] and the course of fronto-temporal connectivity [74], which is consistent with hippocampus dysfunction in disorders of mood and cognition that arise during adolescence [75]. The anatomical and physiological characterization of other neurotransmitter and neuromodulatory pathways during adolescence and adulthood will prove to be essential to understanding their role in the acquisition of mature GABAergic properties in the PFC.

Concluding Remarks and Future Perspectives

Whether this critical period in PFC development is circumscribed to adolescence or encompasses the period up to adolescence remains to be determined. In any case, our data indicate that the PFC is resilient to the same variety of environmental insults by young adulthood (>P65 in rats) [19, 33, 65, 66], suggesting that the period of vulnerability closes after the first two thirds of adolescence (P50 in rats). Thus, a delicate balance between the challenges meant to stimulate cortical integration and the extent to which they can be met by each individual genetic, phenotypic, and experiential background is necessary for proper PFC development.

As clinical research improves on identification of prodromal symptoms and risk factors for psychiatric disorders, the preclinical research done in animal models suggests there might be a potential window for intervention up to early adolescence before the full manifestation of mental illness. By timely manipulation of specific inputs to the PFC, either pharmacologically and/or through cognitive/behavioral therapy, it might be possible to encourage the maturation of the PFC GABAergic system, restore the excitatory-inhibitory balance, and improve PFC function.

What are the molecular mechanisms enabling the GABA_A-dependent, afferent driven-plasticity in the PFC and what makes them uniquely timed during adolescence? If the ventral hippocampal-prefrontal pathway is involved in the acquisition of adult GABAergic functionality in the PFC during adolescence [17, 19], it raises the possibility that other glutamatergic inputs could similarly play a role. Intriguingly, the basolateral amygdalar innervation of the PFC is qualitatively similar to that of the ventral hippocampus, yet the plasticity elicited from this amygdalar-prefrontal pathway is entirely GABA_A-independent [18]. Thus, it remains to be determined whether these and other PFC afferents differentially contribute to the development and increased functionality of specific GABAergic populations, and how this information feeds into PFC computation and output. Additionally, sex differences in acquisition and performance of cognitive tasks [76, 77] imply that sex hormones can change the balance of excitation and inhibition in the PFC. In fact, recent evidence suggests that estradiol concentrations in adult women have profound effects on the neural circuits involving the PFC, amygdala, and hippocampus [78–80]. The role of gonadal hormones in shaping the maturation of GABAergic circuits during adolescence demands more attention, particularly in light of nuclear and non-nuclear hormone receptors being expressed in specific GABAergic populations [81, 82].

In conclusion, a mechanistic analysis of the contributing factors capable of enabling PFC maturation during adolescence will provide a much needed neurobiological framework for understanding the trajectory and onset of mental disorders during adolescence.

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Trends Box

Adolescence is a transitional developmental period characterized by refinement of executive functions associated with the protracted development of the prefrontal cortex (PFC).

Interestingly, adolescence is also a period for the onset of psychiatric disorders of affect and cognition, yet the neurobiological mechanisms underlying this vulnerability remain unclear.

Defining the developmental correspondence between humans and rodents is a necessary step to study the neural substrates that confer such developmental vulnerability.

The prefrontal GABAergic system of rodents experiences dramatic functional changes during adolescence whose arrest leads to an imbalance of the excitatory-inhibitory transmission and a hypofunctional PFC.

The systematic dissection of this model will be valuable for understanding the rules governing normal prefrontal development in humans and ameliorating the burden of developmental disorders.

Outstanding Questions Box

Which afferents drive GABAergic interneuron development in the prefrontal cortex during adolescence? Do different afferents control specific interneuron subsets?

Can GABAergic deficits resulting from developmental insults be rescued by strengthening specific afferents?

Do established genetic risk factors alter the normal maturation of prefrontal GABAergic system during adolescence?

Do gonadal hormones and other steroids interact with adolescence to alter the course of GABAergic transmission in the PFC?

Figure 1.

Adolescence constitutes a critical period for the refinement of GABAergic function in the prefrontal region of both primates and rodents. **(A)** Among the variables thus far measured in human cross-sectional, post-mortem studies, a robust increase in the mRNA of parvalbumin (PV) and a decrease in calretinin (CR) have been observed in the frontal lobe (i.e. dorsolateral PFC) [58]. In addition, it has been suggested that this period is accompanied by a relative increase in PFC inhibitory synapses (adapted from Insel, 2010 [83]). This apparent effect is based on the consistent loss of asymmetric synapses (mostly excitatory) observed in primate PFC during development, which occurs to a greater degree than in symmetric synapses (mostly inhibitory) effectively changing the ratio [84]. **(B)** The rodent PFC experiences similar patterns in PV and CR protein expression between P35-55 (rat) without any significant change in interneuron numbers. Using this framework, a major change in PFC GABAergic functionality can be detected during adolescence as measured by the increased frequency of inhibitory postsynaptic currents (IPSC) onto pyramidal neurons. This observed enhancement in GABAergic transmission during adolescence may be supported by the sharp increase in the frequency of excitatory postsynaptic currents (EPSC) onto PV-positive/fast-spiking interneurons (FSI). The nature of such excitatory input(s) remains to be defined. In fact, any excitatory projection to the PFC could in principle promote the activity-dependent increase in FSI function. These observations exemplify a set of neurobiological mechanisms underlying the functional increase of GABAergic transmission during adolescence in both rodent and human PFC.