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Mechanisms contributing to Prefrontal Cortex Maturation during Adolescence

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Abstract

Adolescence is defined as a transitional period between childhood and adulthood characterized by changes in social interaction and acquisition of mature cognitive abilities. These changes have been associated with the maturation of brain regions involved in the control of motivation, emotion, and cognition. Among these regions, the protracted development of the human prefrontal cortex during adolescence has been proposed to underlie the maturation of cognitive functions and the regulation of affective responses. Studies in animal models allow us to test the causal contribution of specific neural processes in the development of the prefrontal cortex and the acquisition of adult behavior. This review summarizes the cellular and synaptic mechanisms occurring in the rodent prefrontal cortex during adolescence as a model for understanding the changes underlying human prefrontal development.

Keywords

adolescence; prefrontal cortex; interneurons; GABA; dopamine; glutamate; cannabinoid

1. Adolescence in animal models

Adolescence is typically defined as a transitional period between childhood and adulthood. However, it is important to highlight that the exact span of adolescence varies across the different species likely due to genetic, environmental, and social factors. Behaviorally, adolescence is characterized by increased experimentation, changes in social interaction, and cognitive development with the ultimate goal of achieving independence and skills required for survival as an adult (Spear, 2000). Such changes in behavior have been rightly associated with the development and maturation of brain regions and neuronal circuitry involved in the control of motivation, emotion, and cognition. Nonetheless, the precise neurobiological mechanisms underlying the maturation of human behavior during adolescence can only be inferred from psychological and imaging studies in combination with behavioral

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pharmacology and data collected from post-mortem brain samples. Studies in animal models allow us to test hypotheses based on these clinical observations, and determine the causal contribution of specific neural processes in the regulation of each maturational event in acquisition of adult behavior.

Similar to their human counterparts, non-human primates display risk-taking, novelty seeking, and increased vigilance during adolescence (Spear, 2000). In laboratory rodents, adolescence is accompanied by a peak in play behavior, increased exploratory activity and impulsivity, and can be conservatively defined within postnatal days (P) 30 to 50 (Spear, 2000). Despite the behavioral idiosyncrasies of each species, a common developmental theme during adolescence is the acquisition of mature cognitive abilities in the domains of decision-making, behavioral inhibition, and working memory, all of which have been ascribed to the maturation of specific functional domains within the prefrontal cortex (PFC). The PFC integrates contextual and emotional information required for goal-directed behaviors and affect regulation. The importance of understanding the developmental trajectory of the PFC is underscored by multiple findings showing its impaired function in addiction (Chambers et al., 2003) and psychiatric diseases whose onset occurs during the periadolescent period, such as schizophrenia and affective disorders (Hoftman and Lewis, 2011).

We and others have been able to identify clear neurobiological changes occurring during adolescence in rodent models that carry deep significance for PFC maturation. Among these are pre- and postsynaptic differences in neurotransmission and the gain of neuromodulatory capacity that ultimately affect PFC processing of afferent information and output.

2. Anatomical and neurochemical changes in the PFC during adolescence

This review focuses on the developmental changes affecting the PFC because of its well-described role in acquisition of mature cognitive abilities across several species (Fuster, 2001). Indeed, the PFC integrates information from many cortical and subcortical structures including the ventral hippocampus, the amygdala and the mediodorsal thalamus, and also receives neuromodulatory inputs from catecholaminergic and serotonergic nuclei in the brainstem.

Early imaging analyses of developmental trajectories in humans established that the dorsal-ventrolateral cortex and the medial temporal lobe, which includes the hippocampus and the amygdala, undergo significant changes in volume from late childhood to adulthood (Sowell and Jernigan, 1998). During the first two decades of life, the gray matter in the frontal cortex experiences a significant decrease in volume at the same time that temporal structures increase (Sowell and Jernigan, 1998; Suzuki et al., 2005). The consistent thinning of neocortical structures observed in humans in cross-sectional and longitudinal studies (Giedd et al., 1999; Gogtay et al., 2004; Mills et al., 2014; Sowell et al., 2003) occurs at a time of synaptic pruning (Huttenlocher and Dabholkar, 1997; Huttenlocher et al., 1982; Petanjek et al., 2011) of presumably glutamatergic synapses, whereas the increase in temporal lobe's volume is thought to result from the elevated myelination occurring in the hippocampal formation starting in adolescence (Benes, 1989; Benes et al., 1994). Importantly, the

reported anatomical and connectivity changes experienced by frontal structures (Paus et al., 1999) are associated with the protracted maturation of working memory (Satterthwaite et al., 2013) and increased emotional regulation (Gee et al., 2013; Swartz et al., 2014) during adolescence.

To understand whether inputs to the PFC affect its functional maturation, we have focused on the developmental trajectories of specific afferents to the rat PFC, especially the ones where anatomical evidence of a peri-adolescent change has been reported.

2.1. Dopamine innervation in the PFC

The role of dopamine in the modulation of PFC transmission was reported shortly after the unequivocal identification of dopamine in the cortex (Thierry et al., 1973). Dopamine innervation in the rodent PFC can be detected early after birth, starting in the deep layers of the cortex (Kalsbeek et al., 1988). This innervation changes qualititatively and quantitatively in fiber caliber and density at different rates within the PFC, reaching a stable state between P20 and P35 for the supragenual region of the PFC. Dopamine innervation continues to develop in prelimbic PFC areas until P60, after which there are no visible changes. Of note, dopamine fibers are found in abundance in layer I and layers V–VI, with fewer fibers in layer III. Similar distribution patterns of dopamine innervation can be detected in the primate PFC with subtle variations depending on the subregion and primate species used in the study. However, dopamine innervation in the primate PFC is typically more extensive at the regional and laminar level than in the rodent PFC (Goldman-Rakic et al., 1989; Lewis et al., 1987; Lewis et al., 1998; Raghanti et al., 2008). A preliminary analysis of the developmental trajectory of dopamine fibers in rhesus monkey suggests that cortical layers experience a peak in dopamine innervation during adolescence, albeit this change was only significant in layer III where the lowest abundance of dopamine fibers is found in this species (Rosenberg and Lewis, 1994). Importantly, the only comparative analysis made among primates suggests that the primary difference in dopamine innervation between apes and other old world monkeys is the more even distribution displayed across cortical layers for the latter (Raghanti et al., 2008). Overall, the anatomical distribution of dopamine innervation would predict that PFC output to subcortical areas through layers V–VI would be highly sensitive to dopamine modulation in all species, whereas the effects of dopamine in layers II–III remain best studied in great apes.

Dopamine terminals in both rodent and primates are remarkably similar at the ultrastructural level forming contacts onto somas, spines, and dendritic shafts, particularly in the distal region of the dendritic tree (Goldman-Rakic et al., 1989; Seguela et al., 1988). Dopamine terminals usually co-exist with an asymmetric (likely excitatory) synapse (Goldman-Rakic et al., 1989; Verney et al., 1990) and have been found closely apposed to dendritic processes and somas of GABA-positive cells (Verney et al., 1990). The highest frequency of such DA-GABA apposition was found within layers V–VI in the rat medial PFC (Benes et al., 1993). Some GABA-positive soma or dendrites in close contiguity with dopamine terminals also receive GABA-positive axonal inputs from local interneurons (Sesack et al., 1995; Verney et al., 1990). Given the number of potential contacts, the exact ontogeny and outcome of each interaction during development has not been fully described, with the exception of a

significant increase in dopamine contacts onto layers V–VI GABAergic cells observed in rats during the transition to young adulthood (P60) (Benes et al., 1996). It was later demonstrated that dopamine terminals preferentially contact a subclass of GABAergic cells that express parvalbumin (Sesack et al., 1998).

The distribution of cortical dopamine receptors in primates and rodents follows closely the anatomical pattern of dopamine innervation (Gaspar et al., 1995; Muly et al., 1998). Overall, almost all pyramidal neurons and GABAergic interneurons in the PFC express both classes of D1 and D2 receptors to some extent (Bouthenet et al., 1987; Gaspar et al., 1995; Muly et al., 1998; Santana et al., 2009). In rodents, approximately 90–80% of D1 and D2 receptors co-localize in pyramidal neurons, with layers V–VI displaying the highest expression level (Santana et al., 2009; Vincent et al., 1993). The few studies measuring dopamine receptor binding have shown that both D1 and D2 receptors increase globally in the frontal cortex until young adulthood (P60) with no reported receptor pruning (reviewed in (Tarazi and Baldessarini, 2000)).

2.2. Hippocampal innervation in the PFC

Afferents originating from the hippocampal formation make monosynaptic contacts onto PFC neurons (Carr and Sesack, 1996; Ferino et al., 1987; Hoover and Vertes, 2007; Swanson, 1981). Of particular interest is the ventral hippocampal-to-PFC glutamatergic pathway, which innervates largely pyramidal output neurons through asymmetric excitatory axospinous contacts (Carr and Sesack, 1996) and a subclass of GABAergic interneurons expressing parvalbumin (Gabbott et al., 2002). More importantly, the integrity of this pathway is needed for sustaining proper working memory processes (Floresco et al., 1997; Friedman and Goldman-Rakic, 1988; Wang and Cai, 2006), a cognitive function that becomes mature during young adulthood (Luna et al., 2004).

Imaging studies in humans have revealed that increases in total hippocampal volume do occur during postnatal development, some of which extend to the late adolescence/young adulthood period depending on the sub-region analyzed (Goddings et al., 2014; Gogtay et al., 2006; Suzuki et al., 2005). Nonetheless, there is a paucity of anatomical information on the timing by which ventral hippocampal innervation to the PFC reaches maturity during adolescence, with the exception of the studies by Benes et al described above (Benes, 1989; Benes et al., 1994). Newer technologies, in particular diffusion tensor imaging tractography, promise to fill this gap in knowledge and address when anatomical hippocampal-PFC connectivity arises during development and whether its integrity shows specific periods of vulnerability (Fani et al., 2015; Robinson et al., 2015).

2.3. Amygdalar innervation in the PFC

The PFC also receives monosynaptic glutamatergic inputs from the amygdala (Bacon et al., 1996; Krettek and Price, 1977; McDonald, 1996; Verwer et al., 1996), a pathway that is involved in the consolidation of learning and memory, and emotional regulation (Davis and Whalen, 2001). Proper strengthening of the amygdalar-PFC connectivity is thought to be required for PFC modulation of amygdala-dependent behaviors (Garcia et al., 1999; Hariri et

al., 2003). In fact, early life disruption of such connectivity has been correlated to some extent with the severity of affective disorders (Burghy et al., 2012).

Amygdalocortical fibers can be observed shortly after birth with a bilaminar pattern arising in the medial PFC between P12 and P16 in rats (Cunningham et al., 2002; Verwer et al., 1996). This pattern reflects preferential innervation of pyramidal neurons of layers II and V of the PFC, as the majority of these contacts form asymmetric excitatory axospinous synapses (Cunningham et al., 2002), and innervation of GABAergic interneurons through axosomatic and axodendritic contacts (Cunningham et al., 2008; Gabbott et al., 2006). The density of amygdalar innervation continues to increase in both layers II and V up to P65, with layer V of the infralimbic region of the PFC experiencing the greatest increase (Cunningham et al., 2002). These results indicate that the amygdala projection to the PFC increases progressively until early adulthood and is likely to regulate prefrontal output through its action on pyramidal cells and interneurons.

3. Functional remodeling of PFC neurocircuitry during adolescence

The structural changes occurring during adolescence are modest compared to the ones experienced after birth and during childhood, yet magnification of this developmental window reveals that these subtle changes in “hardware” carry a profound significance in the refinement of neuronal signaling. The follow sections will review major findings from our laboratory and others highlighting adolescence as a critical period for the maturation of both glutamatergic and GABAergic transmission in the PFC, particularly due to a differential weight of neuromodulators such as monoamines and cannabinoids. The discovery of dopamine as a bona fide neurotransmitter in the PFC opened the question of whether it played a role in motivated behavior similar to what had been described in striatal circuits. More recently, the cannabinoid system has emerged as a master regulator of PFC plasticity. Both of these systems also display unique age-dependent changes that directly impact PFC activity.

3.1. Modulation of PFC activity by dopamine

Dopamine modulation of PFC activity has been implicated in the regulation of key cognitive processes, many of which mature during adolescence such as working memory, inhibitory control and attention (Goldman-Rakic et al., 2000; Horvitz, 2000; Jay, 2003; O'Donnell, 2003). At the cellular level, dopamine’s action in the PFC is dictated by the functional state of local excitatory and inhibitory activity during cortical maturation (O'Donnell, 2010; Tseng et al., 2009). It has been proposed that dopamine may facilitate the maturation of PFC-dependent cognitive functions by virtue of a D1 receptor-dependent enhancement of prefrontal NMDA transmission (O'Donnell, 2010; Tseng et al., 2009) given the fact that activation of D1 receptors in the PFC improves memory retrieval and working memory (Floresco and Phillips, 2001; Seamans et al., 1998), and co-activation of D1 and NMDA receptors in the PFC is required for appetitive instrumental learning in adult rats (Baldwin et al., 2002).

Dopamine D1 receptor stimulation in the adult PFC can elicit long-lasting plateau depolarizations in pyramidal neurons, an effect that requires NMDA receptor transmission

and postsynaptic calcium-dependent signaling (Tseng and O'Donnell, 2005). Such D1 receptor-mediated facilitation of plateau depolarizations in the PFC emerges only after P45 (Tseng and O'Donnell, 2005) (Fig 1A), when dendritic sodium and calcium regenerative transients become effective in coupling distal apical dendritic activity with somata to sustain plateau potentials in pyramidal neurons (Heng et al., 2011b; Zhu, 2000). Certainly, D1-NMDA interactions could differentially regulate PFC synaptic function depending on the stage of cortical maturation and the level of receptor expression. Thus, an important feature to enable the development of a functionally mature PFC network includes the acquisition of adult levels of D1 (Flores-Barrera et al., 2014; Leslie et al., 1991; Monyer et al., 1994; Tarazi and Baldessarini, 2000; Tarazi et al., 1999; Williams, 1993; Williams et al., 1993) and NMDA receptors combined with intrinsic physiological changes during adolescence (Heng et al., 2011b; Tseng and O'Donnell, 2005; Zhu, 2000). The late adolescent emergence of D1 receptor-mediated facilitation of NMDA receptor transmission (Flores-Barrera et al., 2014; Tseng and O'Donnell, 2005) would therefore have a strong impact in regulating PFC plasticity during the transition to adulthood and the subsequent acquisition of cognitive abilities associated with adult behaviors.

Dopamine regulation of PFC inhibition is also developmentally regulated. Despite the initial *in vivo* studies revealing that dopamine exerts an overall inhibitory effect on PFC activity (Bunney and Aghajanian, 1976; Ferron et al., 1984; Lewis and O'Donnell, 2000), the precise underlying mechanism of such inhibitory action remained unclear and controversial for many decades. In addition to the inhibition mediated by D2 receptor stimulation (Tseng and O'Donnell, 2004), GABAergic interneurons in the PFC also express D1 and D2 receptors (Gaspar et al., 1995; Mrzljak et al., 1996; Muly et al., 1998; Smiley et al., 1994; Vincent et al., 1993), and evidence suggest that part of the inhibitory action of dopamine in the PFC is due to local facilitation of GABAergic activity (Gorelova et al., 2002; Gulledge and Jaffe, 1998; Pirot et al., 1992; Tseng et al., 2006; Tseng and O'Donnell, 2004). Recordings of GABAergic interneurons in the juvenile PFC (P15–35) revealed that only D1, not D2 receptors, increase excitability of fast-spiking interneurons (Gorelova et al., 2002; Tseng et al., 2006). It is during late adolescence (after P50; Fig 1A) that a powerful excitatory action by D2 receptor signaling onto GABAergic activity emerges in the PFC (Tseng et al., 2006; Tseng and O'Donnell, 2007). This is perhaps one of the most interesting and unexpected finding ever described in the field of dopamine. While dopamine control of GABAergic activity in the juvenile/immature PFC is strictly D1 receptor-mediated, the net effect of mesocortical dopamine in the adult PFC is to drive GABAergic firing (fast-spiking and non-fast spiking interneurons) by both D1- and D2 receptor-dependent mechanisms (Tseng et al., 2006; Tseng and O'Donnell, 2007). Thus, the involvement of both dopamine receptors in facilitating prefrontal GABAergic activity presumably causes a powerful inhibitory control in the PFC and influences the timing and spatial selectivity of local ensembles and their computational capacity (Lew and Tseng, 2014).

In summary, the late adolescent acquisition of dopamine-dependent control of excitatory and inhibitory transmission could provide a critical neurobiological step to fine-tuning PFC output activity responsible for the maturation of cognitive processes. A more efficient recruitment of prefrontal GABAergic activity by dopamine will limit PFC neuronal firing in response to asynchronous inputs, whereas the arrival of strong coincident excitatory inputs

(e.g., from the hippocampus) is expected to favor a D1 receptor-mediated facilitation of NMDA receptor transmission (Flores-Barrera et al., 2014) such that the representation encoded in the PFC would be reinforced and synchronized ensembles of neuronal activity would be enabled.

3.2. Glutamatergic control of PFC activity

As summarized above, dopamine-dependent regulation of neuronal excitability in the PFC increases during adolescence in a manner that correlates to some extent with the augmented L-type Ca^{2+} function and postsynaptic PKA-dependent signaling observed after P40 (Heng et al., 2011b). In addition to these postsynaptic changes, it has long been recognized that proper coordination of input-specific presynaptic activity also contributes to PFC maturation during adolescence (Maroun and Richter-Levin, 2003; Tseng et al., 2009). Of particular interest is the developmental regulation of glutamatergic inputs carrying contextual and emotional information from the ventral hippocampus (Floresco et al., 1997; Seamans et al., 1998) and amygdala (Garcia et al., 1999; Gilmartin and Helmstetter, 2010; Milad and Quirk, 2012), as disruptions of these pathways impact the acquisition of cognitive abilities associated with adult behavior (Best and Miller, 2010; Casey et al., 2000; Tseng et al., 2009). Certainly, ongoing remodeling of several anatomical features within the hippocampal-PFC and amygdalar-PFC connectivity continues throughout adolescence (Benes, 1989; Cressman et al., 2010; Cunningham et al., 2002).

At the functional level, changes in PFC response to ventral hippocampal stimulation have been studied for some time in adult animals (Jay, 2003). We have learned from these studies that the monosynaptic hippocampal-PFC pathway is modulated by NMDA receptor transmission and D1 receptor-mediated signaling (Gurden et al., 2000), yet little is known of how its functional connectivity changes during adolescence. Our recent studies in rats revealed that glutamatergic plasticity within the hippocampal-PFC pathway undergoes distinct developmental trajectory from that elicited from the basolateral amygdala. While stimulation of the amygdala induces a form of LTP in the PFC that is already enabled by P30, prefrontal LTP elicited following hippocampal stimulation does not emerge until P50 (Caballero et al., 2014; Flores-Barrera et al., 2014). Notably, both forms of LTP require activation of NMDA receptors in the PFC. Interestingly, an intact GluN2B transmission was required only for sustaining prefrontal LTP elicited from the ventral hippocampus (Flores-Barrera et al., 2014). Together, these results indicate that the delayed strengthening of the ventral hippocampal-PFC pathway is dictated by the late-adolescent expression of GluN2B function in the PFC (Fig 1B).

A change in the subunit composition of NMDA receptors has been shown to directly impact plasticity in cortical circuits (Zhao et al., 2005) with a decreasing contribution of GluN2B to that of GluN2A transmission over the course of postnatal development (Dumas, 2005; Wang et al., 2008). However, recent studies have challenged this traditional view by highlighting that GluN2B-containing NMDA receptors are key for a variety of PFC-dependent functions in adult animals including working memory processes (Wang et al., 2008; Wang et al., 2013) and trace fear conditioning (Gilmartin et al., 2013). Accordingly, we found that GluN2B transmission in the PFC does emerges late in adolescence (Fig 1B) to enable the expression

of hippocampal-to-PFC LTP in an input-specific manner (Fig 1C) (Flores-Barrera et al., 2014). Interestingly, the functional acquisition of GluN2B transmission in the PFC was observed only at glutamatergic synapses driving the apical dendrite of layer V pyramidal neurons after P50 (Fig 1B) (Flores-Barrera et al., 2014). Note that this compartment-specific developmental event takes place ~20 days after major structural remodeling of apical dendritic length and complexity has been completed (i.e., P30; (Heng et al., 2011b; Zhu, 2000)), and ~1week after the apical dendrite becomes functionally coupled to the soma (i.e., P42; (Zhu, 2000)). The slow kinetic of GluN2B-containing NMDA receptors (Vicini et al., 1998) certainly provides a functional advantage for computing input integration (Wang, 1999) and selectively amplify contextually salient information originating from ventral hippocampus. Thus, the late adolescent incorporation of GluN2B transmission into a functionally mature apical dendrite could be seen as a key neurobiological step towards PFC maturation by virtue of enhancing the input-specific capacity of afferent integration and processing.

In addition to LTP, ventral hippocampal stimulation can potentiate GABAergic transmission in the PFC (see below section 3.3) and subsequently induce a form of LTD that also emerges around P50 (Fig 1C) (Caballero et al., 2014; Thomases et al., 2014). Interestingly, plasticity elicited from the basolateral amygdala typically results in prefrontal LTP instead of LTD (Caballero et al., 2014; Thomases et al., 2014) despite the fact that amygdalar inputs do drive feedforward inhibition in the PFC via activation of local interneurons (Dilgen et al., 2013). It is therefore conceivable that ventral hippocampal inputs exert a much powerful control of prefrontal GABAergic plasticity than those from the basolateral amygdala. Thus, the late-adolescent onset of hippocampal-dependent LTP and LTD could contribute to the functional maturation of PFC processing of context-dependent information through an input-specific remodeling of pre/postsynaptic mechanisms. More research is warranted to identify the precise role of LTP and LTD at later stages of brain maturation.

3.3. Local GABAergic regulation of PFC activity

In addition to the different mechanisms contributing to the refinement of glutamatergic activity in the PFC, local GABAergic transmission also undergoes major functional remodeling during adolescence. The most consistent changes in prefrontal GABAergic function are at the level of local GABAergic interneurons, specifically those expressing the calcium binding proteins parvalbumin (PV) and calretinin (CR) (Caballero et al., 2013; Erickson and Lewis, 2002; Fung et al., 2010). These two populations show opposite developmental patterns during adolescence (Fig 2), such that PV interneurons upregulate their expression whereas CR decreases sharply during this period (Caballero et al., 2013). Given that PV expression strongly depends on glutamatergic signaling (Behrens et al., 2007), our results indicate this switch in dominance may be partially due to the observed increase in excitatory inputs selectively impinging upon PV-positive, fast-spiking interneurons during adolescence (Caballero et al., 2013). Moreover, these events coincide with a period of increased GABAergic activity onto layers V–VI pyramidal neurons detected as a 30% increase in the frequency of spontaneous postsynaptic inhibitory potentials (Cass et al., 2014). Together, these findings indicate that maturation of PV-positive/fast-spiking interneurons is likely responsible for the periadolescent increase in GABAergic transmission

observed in the PFC (Fig 2). The contribution of other populations of GABAergic interneurons in this process remains to be determined.

Among the postsynaptic factors that could account for the observed periadolescent increase in GABAergic transmission is the subunit switch in GABA-A receptors from α2 to α1. Such compositional changes have been shown to result in fast inhibitory transmission in other cortical regions due to the properties of α1-containing GABA-A receptors (Vicini et al., 2001). Recently, these subunit changes have been observed in the monkey dorsolateral PFC (Datta et al., 2014; Hashimoto et al., 2009), and are also likely to be driven by the advent of specific excitatory inputs to the PFC.

Our lab has studied the identity of the excitatory inputs that prompt maturational changes in GABAergic transmission in the PFC during adolescence. These studies have revealed the excitatory afferents from the ventral hippocampus to the PFC undergoes functional changes during adolescence (Thomases et al., 2013). Rats younger than P40 were not able to induce the typical hippocampal-induced inhibition observed in animals older than P45 or P60. Importantly, the adult pattern of inhibition was fully dependent on GABA-A receptor transmission as it was blocked with local application of picrotoxin in the PFC (Thomases et al., 2013). Whether specific PFC inputs (e.g., ventral hippocampus) trigger the maturation of GABAergic interneurons or prior GABAergic maturation is needed to enable PFC processing of hippocampal inputs remains unknown (Caballero and Tseng, 2012).

In any case, we do know that disturbances in dopamine and cannabinoid systems as well as NMDAR-mediated transmission during adolescence are sufficient to elicit a state of PFC disinhibition that can be traced to a disruption in prefrontal GABAergic signaling (Cass et al., 2014; Cass et al., 2013; Thomases et al., 2014; Thomases et al., 2013). In addition, the age-dependent maturation of PFC GABAergic function could explain the adolescent acquisition of cognitive functions and emotional regulation subserved by different PFC domains. One such functional implication is the hippocampal gating of amygdalar inputs in the PFC, which can only be detected after P40 (Thomases et al., 2014) and might be critical for the developmental acquisition of PFC control over amygdala-dependent processes.

3.4. PFC modulation by cannabinoids

The CB1 receptor undergoes a clear developmental regulation during postnatal development, which is accompanied by relative changes in the concentrations of endogenous cannabinoids (Berrendero et al., 1998). More specifically, CB1 receptor mRNA expression decreases from juveniles to adults in the cerebral cortex of rats (Berrendero et al., 1998). Similarly, we have found the levels of CB1 receptor mRNA decrease sharply during adolescence particularly in the limbic/associative regions of the PFC (Heng et al., 2011a). Although the functional impact of this reduction has not been fully examined, a developmental loss of CB1 receptors would predict an important change in the known endocannabinoid-mediated modulation of both glutamatergic and GABAergic transmission in the PFC (Auclair et al., 2000; Bacci et al., 2004; Bodor et al., 2005; Fortin and Levine, 2007; Harkany et al., 2004). Accordingly, we have found that glutamatergic synaptic transmission onto layer V pyramidal neurons in the adult PFC is subjected to less CB1 receptor-dependent presynaptic inhibition than the PFC of their juvenile/early adolescent counterparts (Heng et al., 2011a). Future studies are

needed to assess whether a similar downregulation of CB1 receptor-dependent modulation of GABAergic function occurs in the PFC during adolescence. CB1 receptor expression can be found in PFC GABAergic interneurons (Tsou et al., 1998), in particular among the cholecystokinin-positive and calbindin-positive subpopulations (Eggan et al., 2010; Marsicano and Lutz, 1999; Wedzony and Chocyk, 2009).

The neurobiological significance of a developmental regulation of CB1 receptor expression and function during adolescence is not entirely understood, in part due to our limited knowledge of the specific neuronal circuits developing during adolescence. However, insights can be gained from epidemiological studies showing an association between cannabis abuse during adolescence and increased risk of developing psychosis and cognitive impairments later in life (Caspi et al., 2005; Henquet et al., 2005; Meier et al., 2012), although such a link is not cannabis specific (Chambers et al., 2003). Despite the complex mixture of natural cannabinoids present in cannabis (Elsohly and Slade, 2005), a common finding from these studies is the negative impact observed on cognitive functions associated with working memory and decision making processes (Kanayama et al., 2004; Meier et al., 2012; Schweinsburg et al., 2008; Solowij et al., 2002), many of which are refined during adolescence and depend on PFC maturation. Similar PFC-dependent deficits have been observed in rodent models following chronic exposure to CB1 receptor agonists during adolescence (O'Shea et al., 2004; Raver et al., 2013; Renard et al., 2013; Schneider and Koch, 2003; Schneider et al., 2008). Based on these studies, it has been proposed that a sustained elevation of CB1 receptor signaling in the PFC by exogenous cannabinoids could contribute to the cognitive deficits seen in chronic cannabis abusers (Caballero and Tseng, 2012; Realini et al., 2009). Our recent studies in rats indicate that the neuronal deficits induced by repeated cannabinoid exposure (i.e., CB1 receptor agonist administration) during adolescence are at the level of PFC GABAergic circuitry, an impairment that is strictly age-dependent such that GABAergic functionality is unaffected when cannabinoid treatment occurs in adulthood (Cass et al., 2014). Such specific windows of susceptibility to cannabinoids suggest that untimely CB1 receptor stimulation during adolescence hinders the proper development of the PFC. The exact mechanisms by which CB1 receptor signaling enable PFC maturation remain to be determined.

4. Summary and Conclusions

The progressive structural and neurochemical adjustments combined with distinctive physiological changes occurring in the PFC during adolescence are crucial for establishing appropriate information processing mechanisms that can support more complex behavioral outcomes. As reviewed here, susceptibility to developmental insults is certainly high during the periadolescent transition period, an impact that is likely to disrupt PFC maturation and functioning through adulthood (Cass et al., 2014; Cass et al., 2013; Thomases et al., 2014; Thomases et al., 2013). We propose that any early developmental event capable of altering the mechanisms underlying the protracted trajectory of PFC maturation and functional remodeling could result in abnormal assembly of PFC circuits, which would not become apparent until adolescence when proper fine tuning of PFC GABAergic activity is integrated to enable input selectivity and increase PFC output capacity (Lew and Tseng, 2014).

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Highlights

- Adolescence occurs in mammals as a period for acquisition of prefrontal maturity
- Dramatic functional changes occur in the prefrontal cortex during adolescence
- Prefrontal maturation is required to support complex behavioral outcomes
- Preventing such maturation leads to an inadequate control of prefrontal output

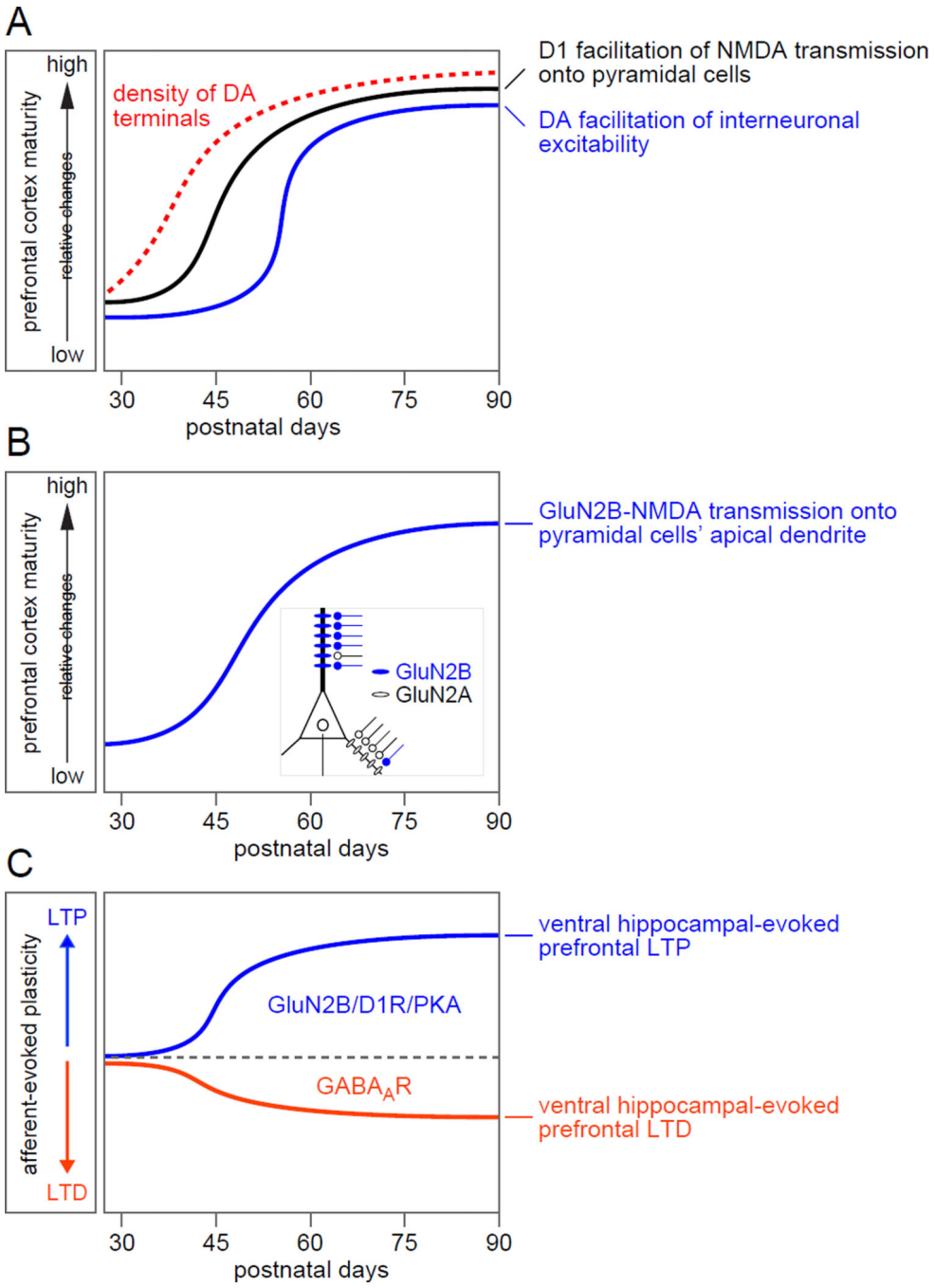

Figure 1. Postnatal development of dopamine and glutamatergic transmission in the PFC

(A) D1 receptor modulation of NMDA transmission in deep-layer pyramidal neurons increases after P45 to reach steady state, adult level by around P60 (Tseng and O'Donnell 2005; Flores-Barrera et al., 2014). A similar pattern of dopamine (DA) innervation was observed in the PFC. Dopaminergic fibers can be found in deep layers soon after birth, yet the density of DA innervation in the prelimbic cortex continues to increase until P60 (Kalsbeek et al, 1988). Similarly, DA modulation of GABAergic activity in the PFC undergoes developmental regulation such that D1 and D2 receptor-mediated facilitation of

interneuronal excitability becomes markedly enhanced after P50 (Tseng and O'Donnell 2007). **(B)** GluN2B-NMDA receptor transmission begins to emerge in the apical dendrite of layer V pyramidal neurons in the PFC around P45 (Flores-Barrera et al., 2014). This developmental change is required to strengthening PFC processing of ventral hippocampal inputs (Flores-Barrera et al., 2014) and to enable the increased D1 receptor modulation of NMDA-mediated responses described in **A**. **(C)** PFC processing of ventral hippocampal drive is also developmentally regulated as revealed by the mechanisms contributing to the induction of prefrontal LTP and LTD following high-frequency stimulation of the ventral hippocampus (Caballero et al., 2014; Flores-Barrera et al., 2014). While prefrontal LTP is dependent on local GluN2B-NMDA transmission, D1 receptor (D1R) activation and protein-kinase A (PKA) signaling, prefrontal LTD relies on the recruitment of local GABAergic interneurons and GABA-A receptor ($GABA_AR$)-mediated transmission.

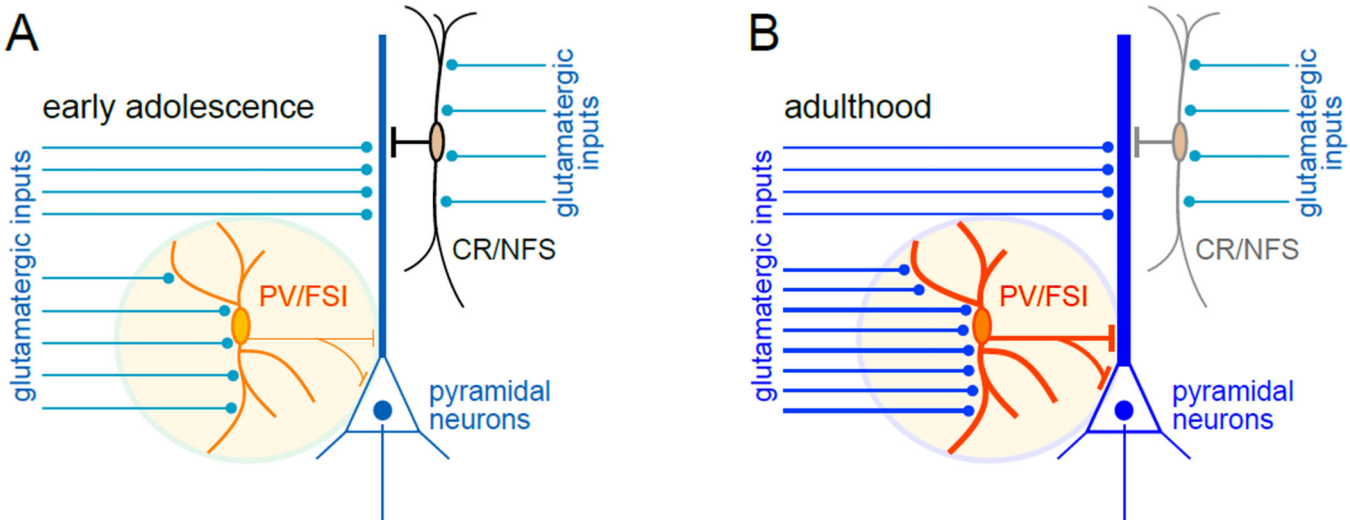

Figure 2. Periadolescent changes in GABAergic function are associated with shifts in dominance of GABAergic populations in the PFC

(A) Early adolescent rats exhibit lower levels of PV expression in the PFC when compared to adults, a developmental hallmark that is associated with diminished glutamatergic transmission onto PV-positive, fast-spiking interneurons (PV/FSI). On the other hand, the expression of CR in the PFC is higher during early adolescence and lower in adulthood. However, the levels of glutamatergic transmission onto CR-positive, non-fast spiking interneurons (CR/NFS) remain unchanged throughout adolescence. **(B)** In the adult PFC, the frequency of glutamatergic synaptic activity onto PV/FSI increases significantly in tandem with a marked upregulation of PV expression. No developmental changes are observed in glutamatergic transmission onto CR/NFS, yet there is a robust decrease of CR expression in adults. The identity of such glutamatergic inputs remains to be defined.