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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.

Contents

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 pharmacology and data col-

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lected 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 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) 30–50 (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, 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). However, 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 cor-