Chapter 1

Development Period of Prefrontal Cortex

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http://dx.doi.org/10.5772/intechopen.78697

Abstract

This chapter outlines the issues associated with the development of prefrontal cortex in children and adolescents, and describes the developmental profile of executive processes across childhood. The prefrontal cortex plays an essential role in various cognitive functions and little is known about how such neural mechanisms develop during childhood yet. To better understand this issue, we focus the literature on the development of the prefrontal cortex during early childhood, the changes in structural architecture, neural activity, and cognitive abilities. The prefrontal cortex undergoes maturation during childhood with a reduction of synaptic and neuronal density, a growth of dendrites, and an increase in white matter volume. With these neuroanatomical changes, neural networks construct appropriate for complex cognitive processing. The organization of prefrontal cortical circuitry may have been critical to the occurrence of human-specific executive and social-emotional functions, and developmental pathology in these same systems underlies many psychiatric disorders; therefore, if we understand these developmental process well, we could better analyze the development of psychiatric disorders.

Keywords: development, prefrontal cortex, infancy, childhood

1. Introduction

In the past two decades, an increasing number of studies have examined the human frontal lobe and PFC utilizing a wide variety of methodologies including stereology, MRI, minicolumn analysis, and DTI [1]. A number of recent studies have examined the relative size of gray and white matter in the frontal lobe or PFC, while others have examined the volume, neuron density, and columnar organization of functional subregions within the PFC. The frontal lobe includes several anatomical components and different functional areas, and, so it is thought that as a discrete unit can only tell us so much [2].

PFC plays most important roles in executive functions, which includes the organization of several sensory inputs, the maintenance of attention, planning, reasoning, language comprehension, the working memory, and the coordination of goal-directed behaviors [3–6]. Therefore, the functions of PFC are certainly a crucial aspect of what we think of as "human" in cognition [7].

The development of the brain occurs through the interaction of several processes, some of these stages are completed before birth such as neurulation, cell proliferation, and migration, although others continue into adulthood [8]. It is showed that the PFC is one of the last regions of the brain to mature, based on most indicators of development [9], and that the neurons in these areas have more complex dendritic trees than primary somatosensory and primary motor cortex those that mature earlier [10, 11]. Brain development begins in utero in the third gestational week and continues into adolescence [12]. However, lateral regions of the PFC are the latest developing areas that involved in executive functions [9].

When discussing the role of the PFC, other brain regions with which it shares intensive interconnections, including the basal ganglia, thalamus, brainstem, hippocampus, amygdala, and other neocortical regions also play important role [13, 14]. Thus, its intrinsic connections with other areas provide access to emotional responses and other information [5]. The lateral PFC is implicated in language and executive functions, while the orbital and medial regions of the PFC are thought to be involved in the processing and in the regulation of emotional behavior [15]. The lateral orbital PFC, interconnected regions of the basal ganglia, and the supplementary motor area, these regions are called the frontostriatal system, and they work together with many of the cognitive capacities [16].

PFC includes the following Broadman Areas (BA): 8, 9, 10, 11, 12, 44, 45, 46, 47. "The dorsolateral frontal cortex (BA) 9/46 has been functioned in many cognitive process, including processing spatial information [17–19], monitoring and manipulation of working memory [20, 21], the implementation of strategies to facilitate memory [22], response selection [23], the organization of material before encoding [24], and the verification and evaluation of representations that have been retrieved from long-term memory [25, 26]. The mid-ventrolateral frontal cortex (BA 47) has implicated cognitive functions, including the selection, comparison, and judgment of stimuli held in short-term and long-term memory [21], processing nonspatial information [27], task switching [28], reversal learning [29], stimulus selection [30], the specification of retrieval cues [25], and the 'elaboration encoding' of information into episodic memory [31, 32]. BA 10, the most anterior aspect of the PFC, is a region of association cortex known to be involved in higher cognitive functions, such as planning future actions and decision-making [33]. BAs 44 and 45, include part of the inferior frontal and these regions' functions are language production, linguistic motor control, sequencing, planning, syntax, and phonological processing [34, 35].

Finally, the orbitofrontal cortex mostly (BA 47, 10, 11, 13) in the orbitofrontal cortex has been implicated in processes that involve the motivational or emotional value of incoming information, including the representation of primary (unlearned) reinforcers such as taste, smell, and touch [36, 37], the representation of learnt relationships between arbitrary neutral stimuli and rewards or punishments [38, 39], and the integration of this information to guide response selection, suppression, and decision making" [40, 41].

2. Structural development of the PFC

2.1. Development in gestational period

In the third week of gestation, the first brain structure to arise is the neural tube, which is formed from progenitor cells in the neural plate [42]. In the sixth week, neuron production begins. Between gestational weeks 13 and 20, neuronal count increases rapidly in the telencephalon [43], with $5.87 \cdot 10^9$ neurons at 20 weeks in the cortical plate and marginal zone [44]. Through some receptors and ligands, the nerve cells move from the source sites in the ventricular and subventricular regions to the main sites in the brain. Two basic types of cell migration, radial and tangential, have been described, and the most characteristic pattern is radial migration. The peak time period with these events is between 12 and 16 weeks of pregnancy [45, 46].

Cortical organizational events begin in 20 weeks of pregnancy and continues. The basic developmental pattern in the cortical organization includes: (1) neurogenesis and differentiation of neurons, (2) formation and organization of cortical neuron layers, (3) dendritic and axonal branching, (4) formation of synapses, (5) cell death and pruning of synapses, and (6) glial proliferation and differentiation [45].

Primary sulci (superior frontal, inferior frontal, and precentral) are the main regions of the PFC, and develop during gestational weeks 25–26 [42]. The dorsolateral and lateral PFC arise during gestational weeks 17–25 [47]. The dendrites in Layer III and V continue to mature, as spines develop, basal dendritic length increases, and interneurons differentiate in layer IV between 26 and 34 weeks [48].

Synaptogenesis begins around the 20th gestational week. The formation and organization of synapses in the PFC increases after birth, reaches a peak, and is followed by pruning and decline like other neurodevelopmental processes. Also, synaptogenesis occurs later in the PFC than it does in other areas.

After the other developmental stages, the latest developmental event is myelination [45]. Myelination begins in the 29th gestational week with the brain stem, and the development of white matter also follows a caudal to rostral progression like gray matter It continues until adulthood [49]. **Figure 1** shows the main developmental stages of brain intrauterine development.

2.2. Development in infancy

At birth, total brain weight is about 370 g [50]. In a meta-analysis, it is showed that in all PFC areas, neuronal number measurements increase at every age point postnatally (0–72 months). Assessing the cortex as a whole, neuronal number increases 60–70% between 24 and 72 months postnatally [51]. Neuron density is 55% higher in the frontal cortex of 2-year-olds than it is in adults [52].

Total gray matter volume is also greatest at the earlier stages of infancy. During infancy and childhood, gray matter volume in the frontal lobe is positively correlated with total brain

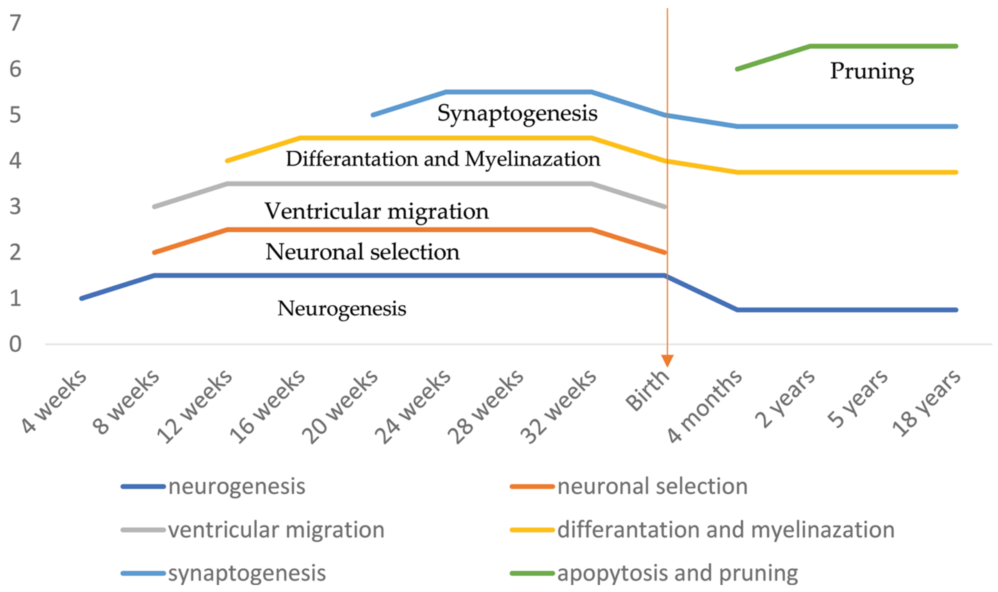

Figure 1. Timeline of brain development.

volume, and gray matter ratio with volume shows a decrease with age [53]. Around 6 months of age, dendritic length is 5–10 times greater than at birth and in the middle frontal gyrus, dendritic length is half of adult quantities at 2 years of age [54]. In infants, pyramidal neurons in frontal lobe that mature later, have less complex dendritic trees than regions that mature early, such as primary sensorimotor cortices [11].

At the age of 3 months, synaptic density in the PFC is less than half of what it will eventually reach, and synaptic density in the PFC reaches the net highest value at age 3.5 years, showing a level approximately 50% greater than that in adults [55]. White matter volume also increases from infancy and it is 74% higher in mid-adolescence than infancy [56].

2.3. Development in early childhood

The neuroanatomical structure of the PFC in humans undergoes maturation particularly during early childhood. During this period, the brain quadruples in size and grows to approximately 90% of the adult volume at age 6. The gray matter increases from early childhood until the age of 6–9 [56]. Neuronal density in layer III of the PFC decreases with age between 2 and 7 years, from 55% to about 10% higher in 7-year-olds than in adults [52].

Synaptic density in the PFC decreasing more and more through adolescence [55]. During early childhood, expansion of the dendritic trees of the pyramidal neurons has also been observed [57].

The results of fMRI studies in children suggested that the PFC of children aged 5 years, is also active during performance of the same task as that for the adults. The region and characteristics of the activity are similar in adults and children, but comprehensive comparison could not be done due to technical limitations [58].

2.4. Development in childhood and adolescence

During childhood and adolescence, both growth and then decline in gray matter volume, and increase in white matter volume are observed in brain development. In the longitudinal study of Giedd et al. across ages 4–22, showed that gray matter in the frontal lobe increases in volume during preadolescence including early childhood [59]. However, several studies have reported that during preadolescence, the increase in gray matter volume is observed especially in the PFC among other frontal lobe regions [60]. Inside of the frontal lobe, gray matter in the precentral gyrus develops the earliest, and the superior and inferior frontal gyri mature later. The ventromedial areas commonly reach maturity earlier than more lateral regions as well [9]. The rostral PFC develops more slowly than other regions, maturing into late adolescence and beyond [61]. Additionally, the development of the dendritic systems in rostral PFC matures later than in primary sensory and motor regions, and continue maturing until late adolescence [11]. Regions in the PFC that intercommunicate with Broca's area show an increase in gray matter thickness relative to other regions at between the ages of 5 and 11, it is thought to be associated with the maturation of linguistic capacity [62]. Gray matter volume reaches maximum volume in most of the frontal lobe between 11 and 12 ages [59]. The dorsolateral and medial PFC also expands nearly twice [63] and the dorsolateral PFC reaches adult grades of cortical thickness in early adolescence [8]. However, according to cerebral energy metabolism studies, lateral regions of the PFC and frontal pole mature earlier than the most anterior regions [64]. When the brain increases in size throughout childhood and adolescence, dendritic and axonal growth and synaptogenesis also occur such as many other microstructural changes [51]. Adult neuronal density in the frontal lobe is reached by 10 years of age [52]. Pyramidal neurons in frontal lobe that mature later and they have the most complex dendritic trees in adolescence and adulthood [10].

Moreover, reduction in gray matter volume and synapse elimination continues in the PFC until adolescence and early adulthood [65]. The gray matter density in rostral PFC observed a reduction in between adolescence (12–16 years) and adulthood (23–30 years) like as other prefrontal regions [65]. Although this decrease in gray matter volume in childhood is correlated with age, one study showed that gray matter decreasing in the frontal lobe is significantly and positively associated with verbal memory abilities, independent of the age of the child [53].

In addition, as gray matter volume declines during childhood and adolescence, cross-sectional and longitudinal studies have reported that white matter volume in the PFC increases significantly as fiber tracts grow and myelinate during childhood [49, 59]. From ages 7 to 16, the frontal lobe experiences an increase in white matter volume [53]. In the white matter, it was found that diffusion along fiber tracks was more and more anisotropic with age (range 6–19 years) in a number of prefrontal regions, including right lateral, and medial, rostral PFC [66]. White matter is primarily constituted of axons covered in myelin produced by oligodendrocytes, and myelination increases nerve transmission rapidity [67], thereby, reduces the effects of travel distance variability in networks and facilitating synchronous impulsion of neurons [68]. For this reason, increase in white matter volume in the PFC and distributed networks, may provide a structural basis for cognitive functions [69]. Additionally, macro and microstructural changes in gray and white matter both continue during developmental process, even after adolescence, and these structural changes are parallel to behavioral changes [70].

The myelination of the frontal lobe can continue into the 3rd decade of life [71]. The anteromedial aspect of the frontal lobe is one of the last regions, to myelinate postnatally [72].

When reviewed the fMRI studies, many of these studies have reported that the responsible regions in the PFC show age-related increases in activity through development in school-age children and adolescents [73–75]. In the Kwon et al. study, they observed an age-related linear increase in activity in the lateral PFC during the n-back working memory task from 7 to 22 years of age [73]. In contrast, in the brain regions less critical to the tasks tested has also been reported age-related decrease in neural activity [75]. These patterns of age-related activity changes are thought to indicate a developmental shift in functional neural organizations more focal, fine-tuned systems [76].

3. Cognitive development of PFC

PFC mediate several cognitive abilities and they develop fundamentally during early childhood in terms of age-related improvements, and functional neural systems for each function become more separable through development [58]. In this section, we reviewed cognitive abilities and their development which are mediated by the PFC.

3.1. Attentional development

The attention properties fall into five basic categories: alertness, set, spatial attention, sustained attention, and interference control [77].

Although by 3 years of age, children can make the occasional perseverative error; they inhibit instinctive behaviors well [78]. Improvements in speed and accuracy on impulse control tasks can be observed up to 6 years of age [78, 79]. However, an increase in impulsivity occurs for a short period around 11 years of age, children aged 9 years and older are able to monitor and regulate their actions well [80].

The components of attention seem to develop gradually toward full maturity at about 12 years, with maximum development between the ages of 6 and 9 [81, 82].

3.2. Memory

Neuropsychological and functional neuroimaging evidence implicated the importance of the PFC, supports particularly the development of episodic memory [83]. Functional neuroimaging studies consistently show increasing in PFC activation that supports the formation [84] and retrieval of episodic memories [85].

Although the frontal lobe damage usually does not cause loss of perceptual memory, it does in some cases especially if the lesion involves the left prefrontal cortex that causes the inability to encode and retrieve serial tasks [86], stories [87], and verbal material [88]. Particularly, if the lesion includes the orbitolimbic region, it can cause the presence of spontaneous confabulation and false recall or recognition [87].

In the recent study, the PFC contribution to subsequent memory (SM) in children, adolescents, and young adults was investigated. It is showed that regions in the lateral PFC showed positive SM effects, whereas regions in the superior and medial PFC showed negative SM effects. Both positive and negative SM effects increased with age. The magnitude of negative SM effects in the superior PFC partially mediated the age-related increase in memory. Functional connectivity between lateral PFC and regions in the medial temporal lobe (MTL) increased with age during successful memory formation [83]. In the study of Qin et al., they examined age-related changes in brain activity associated with memory-based arithmetic and found increased working of memory-based strategies for solving arithmetic problems across a period of 14 months in children ages 7–9. Paralleling these behavioral findings, increased functional connectivity between the lateral prefrontal cortex (IFG/MFG) and the hippocampus was observed [89].

3.3. Working memory

Working memory is the one of neural functions for temporary storage and manipulation of information [90]. It is necessary for other cognitive functions, such as language comprehension, reasoning, and learning [91]. Behavioral measures showed that working memory systems improve fundamentally during early childhood [92].

Kaldy and Sigala [93] observe that 9-month-old infants can integrate the visual features of an object with its location as part of the content of working memory. On the conclusion of findings, they speculate that the early development of the *what-where* integration in working memory [93].

Luciana and Nelson's study showed that in normal children, aged 4–8 years, the prefrontal working memory system emerges at around the age of 4 and improves between 5 and 7 years of age [94], and capacity of visual short-term memory increases also substantially between 5 and 11 years of age [95]. Additionally, age-related improvement of working memory for phonological information has also been observed during early childhood from 4 years of age [96]. Consistent with these findings, fMRI studies in children indicated that the lateral PFC functions in healthy children as young as 4 years, and the neural systems of this area responsible for working memory gradually mature at 4–7 years of age [97]. In conclusion all of them, the child reaches the mature level of performance by age 10–12 years [77].

In the development of working memory, not only PFC plays role, but also stronger fronto-parietal connectivity underlies the development of working memory. Edin et al. indicated that the weak connectivity among subregions of the PFC might also be important for the functional development of the PFC [98]. It can be summarized that functional maturation of the PFC is tightly linked to changes in several other brain regions [99].

3.4. Planning

The effective planning is crucial to self-organization and it involves setting a goal, formulating a checklist of tasks necessary to achieve it, and executing each one until the goal is achieved. Studies suggest that children and adolescents are identified as deficient in planning skills, which is not surprising given that executive functions improve especially through adolescence [100, 101]. The failure to formulate plans, especially new plans, is generally accepted as being a common feature of prefrontal syndromes. Especially, the symptom appears unique to dysfunction of the prefrontal cortex [77].

Simple planning skills are observed by 4-year-olds [102]. Similarly by 4 years of age children are skillful of create new concepts [103]. When the aims are made clear, at the age of 6 years children can make detailed plans [104]. Planning and organizational skills develop rapidly between 7 and 10 years of age [105] and gradually after into adolescence [102]. Young children use simple strategies, which are usually ineffective but between 7 and 11 years of age strategic behavior and reasoning abilities become more organized [106]. The planning seems to develop at about 12 years with the plateau and around 12–13 years of age, regression from conceptual strategies to piecemeal strategies may occur and it suggesting a developmental period in which cautious and conservative strategies are preferred. Improving of strategies and decision making continues during adolescence [107]. Studies have reported improved the planning skills into the 20s [108, 109]. In addition, the inter-correlations observed between planning skills and other neuropsychological tasks and IQ, during adolescent development of planning abilities [110].

3.5. Temporal integration

Temporal integration is the ability to organize temporally separate items of perception and action into goal-directed thinking, speech, or behavior. This ability derives from the joint and temporally extended operation of attention, memory and planning. In neural terms, it derives from the cooperation of the prefrontal cortex with other cortical and subcortical regions. In a study, age-dependent comparisons were made between 9–10- and 13–14-year-olds and these findings suggested that children used a similar strategy as adults and indicate a stabilizing and optimalizing process by the age of approximately 13–14 years with respect to subjective rhythmization [111].

In conclusion, the temporal integration seem to develop at about 12–13 years as same as development of working memory and planning [77].

3.6. Inhibitory control

Inhibitory controls the ability to suppress information and actions that are inappropriate situations and it is important for several cognitive abilities and adaptive behaviors [99]. The children aged 2.5 years were able to inhibit the prepotent tendency on the spatially incompatible trials and by 3 years, they were correct 90% of the time [112].

Several studies have demonstrated that performance on the cognitive tasks that requires inhibitory control, improves throughout childhood over the ages of 4 years [6, 99, 109].

The fMRI studies suggest a change in the recruitment of rostral PFC (BA10) in situations of response inhibition during late childhood and adolescence. An increase in BOLD signal in this region [113] initially and then a decrease in BOLD signal [114] seems consistent with the anatomical findings suggesting that gray matter volumes in the frontal cortex [59].

In summary, the ability inhibitory control develops both anatomically and functionally significantly during early childhood.

3.7. Language

The spoken language is based on the exercise of temporal integration and the cognitive functions. For this reason, language has been found to be adversely affected in a variety of ways by frontal damage [115].

In early childhood, increase in speed and verbal fluency of language is observed, particularly between 3 and 5 years of age [102, 116]. Processing speed and fluency continues to improve during middle childhood [80, 102] with significant gains in processing speed observed between 9–10 and 11–12 years [117]. Improvements in efficiency and fluency occur during adolescence [107, 117].

However, higher cognitive functions such as language and intelligence continue to develop into the 3rd decade of life, supported by the lateral prefrontal cortex, which does not seem to reach full maturity until that time [77].

3.8. Social behavior

Social cognition defines to identify and interpret social signals, and the use of those signals to guide the flexible performance of appropriate social behaviors given in changing situations [118]. The PFC is connected with several cortical and subcortical regions of the brain, including nucleus accumbens (NAc), amygdala, ventral tegmental area (VTA), hypothalamus, and regions of the cortex involved in processing sensory and motor inputs. PFC is also connected with which regions known as social brain, so PFC has been played rol in also social behavior [119, 120]. Many studies have demonstrated the importance of the vmPFC for social motivation and reward. The vmPFC is also engaged with social acceptance feelings and is activated learning with cues of related with social reward [121, 122]. The lateral PFC is also a part of a network that process in the social domain, such as imitation, abstract social reasoning, and resolving conflict in social cues [123].

The mPFC is responsive to social stimuli in developing infants [124]. In particular, the mPFC activates at the infant with viewing a mothers smile, or hearing infant directed speech [125]. Studies with children and adolescents focus on amygdala and findings of these studies showed an association between cerebral maturation and increased regulation of emotional behavior; the latter mediated by prefrontal systems [126, 127]. In another study, findings suggest that the adult brain better modulated OFC activity based on attention demands, while the adolescent brain better modulated activity based on the demands of emotion. So, if there were no attentional demands, emotional content of the stimuli-induced higher activity in ACC, OFC and amygdala in the adolescents compared with the adults [128]. These fMRI results show that both the brain's emotion processing systems develop during adolescence.

3.9. Theory of mind and mentalizing

Theory of mind (ToM) is the ability of an individual to mean the feelings, motives, opinions, and emotions of another on the basis of his or her expressions. It is a necessary ability for meaningful social interaction [77]. Some studies have investigated the development of mentalizing, which to have been associated with rostral PFC.

When investigating the development of ToM, children develop an understanding of desires, goals, and intentions at around 18 months firstly, and then the understanding of many mental states such as wanting, knowing, pretending, or believing is available in implicit form to 2-year-olds. Typical tests of mentalizing develop at about 4 years old in children [129]. At the age of 6 years, all typically developing children understand the tasks, involving more complex scenarios [130].

A functional MRI study investigated the development of mentalizing by the task and found that children (between 9 and 14 years old) engaged frontal regions includes medial PFC and left inferior frontal gyrus more than adults did in this task [131]. In another study, adolescent (12–18 years) and adults participants (22–37 years) were scanned with functional MRI and the results showed that adolescents activated part of the medial PFC more than adults did, and adults activated part of the right superior temporal sulcus more than adolescents did. These results suggest that the neural strategy for mentalizing changes between adolescence and adulthood. Although the same neural network is active, the relative roles of the different areas change, with activity moving from anterior (medial prefrontal) regions to posterior (temporal) regions with age [132].

4. Conclusion

In this chapter, we have attempted to link structural and functional findings of developmental studies to PFC. Our knowledge and understanding of the neural mechanisms, a growing body of evidence, point to the PFC as a central regulator. The review of the developmental literature indicates that, in the child, the cognitive and emotional functions of the prefrontal cortex develop in apparent synchrony with its structural maturation. The long-term development of executive functions is likely to be aligned with neurophysiological changes, particularly synaptogenesis and myelination in the prefrontal cortex.

All of cognitive functions seem to reach a relative plateau of maturity at about the age of 12 years. For example, development of attention reach maturity at about age 12, Working memory and planning seem to develop also at the same pace and toward the same plateau (about 12 years). Temporal integration development depends on both working memory and planning and it develops at the same time with the others. However, higher cognitive functions such as language and intelligence continue to develop into the third decade of life. In summary, these functions develop gradually, between 5 and 10 years of age, to reach completion at about age 12.

In the future, longitudinal studies will be required to verify our understanding of cognitive development. With the structural and functional neuroimaging studies, we are now in the position to concurrently track the development of neural systems and cognitive functioning, greatly enhancing our understanding of brain-behavior relationships.

It is known that abnormalities of PFC is associated with many of psychiatric disorders such as attention deficit and hyperactivity disorder, schizophrenia, obsessive compulsive disorder, depression, autism, etc. As we know more about the prefrontal cortex, we think that we could better understand these psychiatric disorders and could develop new treatment options.

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