1

The Unique Properties of the Prefrontal Cortex and Mental Illness

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1. Introduction

The prefrontal cortex (PFC) is part of the frontal lobes lying just behind the forehead and is one of the most important areas in the brain. This brain region is responsible for executive functions, which include mediating conflicting thoughts, making choices (between right and wrong or good and bad), predicting future events, and governing social and emotional control. All of the senses feed information to the PFC, which combines this information to form useful judgements. Further, it constantly contains active representation in working memory, as well as goals and contexts. The PFC is also the brain center most strongly implicated in conscience, human intelligence, and personality. Because of its critical role in executive functions, it is often referred to as the "CEO of the brain."

Unfortunately, the PFC is also one of the most susceptible regions to injury and environmental risk factors. As such, the PFC has been the focus of considerable scientific investigation, owing in part to the growing recognition that dysfunction of this region and related networks underlies many of the cognitive and behavioral disturbances associated with neuropsychiatric disorders such as schizophrenia, attention-deficit/hyperactivity disorder (ADHD), drug addiction, autism, and depression. Because all of these diseases are mental disorders related to psychiatric concerns, the prefrontal neuron has been called the "psychic cell" of the brain by the late neuroscientist Dr. Patricia Goldman-Rakic [1, 2]. She famously stated: "Santiago Ramón y Cajal might have envisioned, but likely could not have anticipated, the scientific advances that have allowed the functional validation of the existence of a "psychic cell" in the PFC and its extension to human cognition at the end of the 20th century [2]."

Scientific research on the PFC has been booming and great progress has been achieved since the late 1970s, especially after the "Decade of the Brain" began in 1990. As Dr. Goldman-Rakic stated: "This achievement rests not only on the shoulders of giants but on many small steps in the development of primate cognition, single and multiple unit recording in behaving monkeys, light and electron microscopic analysis of cortical circuitry no less than on the evolution of concepts about memory systems and parallel processing networks,

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among other advance." Indeed, compared to other neocortical regions, recent studies have reported that PFC has several distinct features that make this brain region special for its functions and associated diseases. First, the PFC is widely connected with many other brain regions, particularly those in the limbic system. A recent approach to PFC anatomy defines it on the basis of a combination of cortical types, topology and connectivity. Second, unlike primary sensory cortical regions, such as primary visual cortex (V1), primary auditory cortex (A1) and somatosensory cortex (S1), the PFC lacks direct sensory thalamocortical inputs. However, all of the salient sensory information is indirectly sent to the PFC through other associative cortical regions, such as the parietal cortex and temporal cortex. These characteristic connections make direct testing of PFC function in animals difficult and thus research is much delayed compared to other primary cortical areas. Third, the PFC is densely innervated by monoamine systems, especially the dopaminergic system. This can explain why many of the PFC functions are associated with the functions of dopamine system. Fourth, the PFC has special local circuitry designated for unique functions such as persistent activity for working memory. Fifth, because of these properties, the PFC is mainly associated with psychiatric disorders that are closely related to higher cognitive processes and emotions. The last and the most important is that the executive functions of the PFC develop to their full capabilities throughout the juvenile and adolescent period in humans. This higher brain region, unlike other primary cortical areas, exhibits delayed cortical development until young adulthood. During postnatal development, it gradually takes on its adult form as prefrontal neuron synapses are pruned to the adult level. Further, numerous data show that juvenile and adolescence are time periods of great vulnerability, with special sensitivity to environmental factors in humans, and eruption of neuropsychiatric disorders.

In this chapter, we will focus on the unique properties of PFC circuitry and development. Provide an overview of how during windows of vulnerability the maturation of this specific brain region and environmental factors initiate a series of events that render the PFC exceptionally susceptible to the development of neuropsychiatric disorders such as schizophrenia. Understanding the neurobiological basis is important in the development of more effective intervention strategies to treat or prevent these disorders.

2. The functions of the PFC are defined by its extensive connections with limbic system

The limbic system of the brain consists of many brain structures such as the hippocampal formation, amygdaloid complex, and nucleus accumbens. Limbic system structures are involved in emotions and motivations, particularly those related to survival such as fear, anger, pleasure, and sexual behavior. It is almost impossible to identify specific roles to definite structures, since psychological functions performed are not by single formations but by complexes of the interacting system. Overall, the limbic brain appears to be organized less in terms of precise physiological functions than in terms of elaboration and coordination of varied complexes of behavior [3, 4].

Recent findings in rodents and non-human primates suggest that divergent cognitive processes are carried out by anatomically distinct subregions of the PFC [5-7], although the extent to which these processes can be considered functionally homologous in different

species remains controversial [8]. As part of the limbic system, the PFC is widely connected with many brain structures, particularly those in the Papez circuit. These wide connections make the PFC extremely responsive to stimulation such as emotion, stress, motivation, and learning and memory processes [6, 9-11].

2.1 PFC connections in the rat brain

The rat PFC is divided into the prelimbic, infralimbic, anterior cingulate, agranular insular cortices, and orbitofrontal areas [12-14]. Each of these subregions of the PFC appears to make individual contributions to emotional and motivational influences on behavior [15]. The PFC has complex functions such as working memory as well as attention, cognition, emotion and executive control [16]. The glutamatergic pyramidal neurons in the anterior cingulate cortex send descending projections to the nucleus accumbens core, the center for reward and emotional processing [13, 17, 18]. Additional descending projections from the PFC to nucleus accumbens, amygdala and other limbic brain regions appear to exert regulatory control over reward-seeking behavior. Therefore, the PFC is a key component of the limbic system with many inputs and outputs, and its heterogeneous cytoarchitectonic structure implies a complex functional organization.

The PFC can also be divided into dorsal and ventral divisions [14] and the attentional and emotional mechanisms appear to be segregated into dissociable prefrontal networks in the brain [16]. The reciprocal relationship between dorsal and ventral PFC may provide a neural substrate for cognitive – emotional interactions, and dysregulation in these systems is clearly related to various mental diseases [11]. It has been reported that the PFC is primarily connected with the mediodorsal thalamic nucleus with distinctions between the dorsal and ventral prefrontal cortices [14]. The dorsal PFC (prelimbic and anterior cingulate cortex) and ventral PFC (infralimbic area) appear to be differentiated with distinct afferent terminations. The dorsal PFC has connections with sensorimotor and association neocortex, while the ventral PFC shows strong connections with the amygdaloid complex and limbic association cortices. The ventral PFC projects heavily to the subcortical limbic structures, including the hypothalamic areas and septum, and of particular interest, the ventral PFC shows more powerful influences on brainstem monoaminergic cells than does the dorsal PFC.

2.2 Different structural features of the PFC in primate versus rodent

The PFC shows enormous variation across species in terms of cytoarchitectonics and connectivities, especially in the presence or absence of a granular zone and the existence of strong reciprocal connections from the mediodorsal nucleus of the thalamus [17, 19, 20]. One major problem about the PFC has been the long-standing debate over what constituents equivalent regions of the PFC between different species [8, 17, 19, 20]. In addition, unlike posterior and temporal regions of neocortex, the PFC receives highly organized indirect inputs from the basal ganglia via striatopallidal and striatonigral projections, and subsequently pallidothalamic and nigrothalamic neurons that project, in a parallel segregated manner, to different areas of the PFC in both rodents and primates [19, 21]. The PFC also receives extensive corticocortical inputs, for example, from parietal cortex and sensory cortical areas, as well as connections from subcortical structures such as the substantia nigra, ventral tegmental area, amygdala, lateral hypothalamus, and hippocampus [19].

The distinctive feature of primate PFC is the emergence of dysgranular and granular cortices, which are completely absent in the rodent. Some of the subregions in the primate PFC do not have a clear-cut homolog in rodents because the rat PFC is entirely agranular [4, 20, 22]. The primate PFC is often divided into different subregions, such as dorsolateral, ventrolateral, medial, and orbitofrontal. These subregions are extensively interconnected, with information to be shared within the PFC circuitries [23]. In addition, information from sensory cortices also converges to the PFC in multiple modalities [24]. Generally speaking, dorsolateral areas receive input from earlier sensory areas; whereas orbitofrontal areas receive inputs from advanced stages of sensory processing from every modality, including gustatory and olfactory [23, 25]. Thus, extrinsic and intrinsic connections make the PFC a site of multimodal convergence of information about the external environment. Furthermore, the PFC receives inputs that could inform it about internal mental states, such as motivation and emotion. As discussed above, orbital and medial PFC are closely connected with limbic structures such as the amygdala, hippocampus, and rhinal cortices [23], as well as the hypothalamus and other subcortical targets that are associated with autonomic responses [26]. Finally, outputs from the PFC, especially from the dorsolateral PFC, are directed to motor systems, and thus the PFC may form or control motor planning. Altogether, the PFC receives inputs that provide information about many external and internal variables, including those related to emotions and to cognitive functions, providing a potential anatomical substrate for the representation of mental states.

2.3 PFC-amygdala connection and interaction

The amygdala is a structurally and functionally heterogeneous group of nuclei lying in the anterior medial portion of the temporal lobe. The amygdala is most often discussed in the context of emotional processes; yet it is extensively interconnected with the PFC, especially with the orbitofrontal cortex and anterior cingulate cortex, as well as diffusely with other parts of the PFC [4, 27]. Sensory information enters the amygdala from visual, auditory, and somatosensory cortices, from the olfactory system, and from the perirhinal cortex and the parahippocampal gyrus [27]. Output from the amygdala is directed to a wide range of target structures, including the PFC, the striatum, sensory cortices, the hippocampus, the entorhinal cortex, and the basal forebrain, and to subcortical structures related to autonomic responses, hormonal responses, and startle [27]. Overall, the bidirectional communication between the amygdala and the PFC provides a potential basis for the integration of cognitive, emotional, and physiological processes into a unified representation of mental states [3, 15, 28].

3. Despite the widespread connections with the mediodorsal nucleus of the thalamus, the PFC lacks direct sensory thalamo-cortical connections

As discussed above, the PFC is mainly defined by projections from the mediodorsal nucleus of the thalamus [12, 14, 20]. Specifically, reciprocal and topographically organized connections between the medial PFC and various thalamic nuclei are well known [29-34]. A ventral to dorsal gradient in the PFC is corresponding to a medial to lateral gradient in the dorsal thalamus where the medial prefrontal cortex primarily projects to the midline, mediodorsal and intralaminar thalamus [3, 33, 34]. In general, the cortico-thalamic

projections are largely reciprocated by thalamo-cortical fibers. The midline thalamic nuclei are largely involved in arousal and visceral functions while the intralaminar nuclei subserve orienting and attentional aspects of behavior [3, 14]. The limbic thalamus includes the anterior thalamus, which is part of the Papez circuit, and the mediodorsal thalamic nucleus. The mediodorsal nucleus is a major element within the thalamus of all mammals and undergoes a progressive expansion of cytoarchitectonic differentiation in higher animals, reaching its greatest development in human beings [35]. Importantly, this development parallels the development of the PFC. The mediodorsal thalamic nucleus projects to a large area of the frontal cortex in the rat, including the precentral area, anterior cingulate area, prelimbic area, orbital areas, and the insular areas [29, 36, 37].

Despite the widespread connections between the PFC and mediodorsal nucleus of the thalamus, unlike other sensory cortices, the PFC lacks direct afferent inputs from sensory thalamus. Therefore, research on the PFC is rather delayed compared to the studies on other cortical regions owing to the difficulty in making animal models or direct stimulation.

4. PFC receives rich monoaminergic, especially dopaminergic (DA), and cholinergic (ACh) innervations

Monoamines contribute to stable moods, and an excess or deficiency of monoamines cause several mood disorders. The PFC targets the main major forebrain cholinergic and monoaminergic systems, including noradrenaline (NA)-containing neurons in the pontine locus coeruleus, dopamine (DA)-containing neurons in the ventral tegmental area, serotonin (5-HT) neurons in the raphe nuclei and acetylcholine (ACh) neurons in the basal forebrain [5, 38, 39]. These systems act in turn to modulate cortical networks by influencing both excitatory and inhibitory synaptic transmissions as well as other cortical processing in the PFC [9, 38]. Neuromodulatory input to the PFC from these neuromodulatory systems could also convey information about internal state [40]. Further, the ascending monoaminergic (NA, DA and 5-HT) and ACh systems contribute to different aspects of performance on animal behaviors [40].

When considering the functions of the chemical modulatory inputs to the PFC, a general principle that has emerged in the past decade is the inverted U-shaped function, which links the efficiency of behavioral performance to the level of activity in the DA- and NE-ergic systems [40, 41]. The inverted-U dose response has been demonstrated with pharmacological agents in both animals [42-44] and humans [45]. A major advance in understanding the roles of the neuromodulatory systems is the in vivo measurement of ACh, DA, NA and 5-HT release in the PFC during behavioral tests [5, 46, 47]. This powerful approach directly links PFC functions with specific changes of individual neurotransmitter systems and their interactions in a behavioral task. It is possible that the neuromodulatory systems of the PFC are functionally specialized, and that each of them are engaged by different feedback circuits required for specific information processing. However, a better understanding of the role of each neuromodulator in different cognitive control processes is needed. It is also important to explore whether the regulatory signaling is distributed or localized within the different parts of the PFC neurons [48]. The PFC has a top-down regulatory control over the ascending modulatory systems of the brain, and that in turn, powerfully influences the neuromodulatory functions on the PFC [40, 41]. These projections

widely innervate diverse forebrain regions, including the hippocampus, striatum, amygdala, and thalamus, as well as the entire neocortex. In turn, these neuromodulatory systems likely adjust signal-to-noise ratios in terminal domains to influence information processing and their conjoint activity, and consequently, to affect behaviors.

Among these ascending modulatory systems, the DA system is the most important one that plays a critical role in both normal cognitive process and neuropsychiatric pathologies associated with the PFC [49]. It has been known for several decades that the frontal lobe receives a major dopamine innervation. Furthermore, the PFC receives more DA innervations compared with other cortical regions. In contrast, all other ascending modulatory innervations are more evenly distributed among cortical regions. Researchers, however, have only recently been able to link dopamine afferents to specific cellular targets and neuronal circuits [49, 50]. Understanding the details of this linkage in prefrontal circuits may be important in resolving the various dilemmas concerning the mechanisms of dopamine action or cognitive processes, as well as the validity of the dopamine hypothesis of diseases like schizophrenia [51-54].

Accordingly, there have been considerable efforts by many groups to understand the cellular mechanisms of DA modulation in PFC neurons [49, 50, 55-60]. Although the results of these efforts sometimes lead to contradictions and controversies, these studies from both in vivo and in vitro experiments have provided some principal features and mechanisms of DA modulation in the PFC circuitry [49]. One principal feature of DA is that, as a neuromodulator, it is neither an excitatory nor an inhibitory neurotransmitter. It becomes apparent that DA's actions in PFC are regulatory and an optimal concentration of DA is required for normal operation of the PFC. Either too much or too little DA will result in serious mental problems that are associated with prefrontal cognitive functions. For example, hyperfunction of the dopaminergic system is believed to be related to several psychiatric disorders [50, 61]. Previous studies in both rats and primates indicate that excessive dopamine activity is detrimental to cognitive functions mediated by the PFC [62, 63]. DA's effects on the PFC depend on a variety of factors, especially activation of different dopamine receptors. There are at least five subtypes of dopamine receptors, D1, D2, D3, D4, and D5. The D1 and D5 receptors are members of the D1-like family of dopamine receptors, whereas the D2, D3 and D4 receptors are members of the D2-like family. The distinct inverted-U dose–response profiles of postsynaptic DA responses are contingent on the duration of DA receptor stimulation, the bidirectional effects following activation of D1 or D2 classes of receptors, the membrane potential state of the prefrontal neurons, and the history dependence of subsequent DA actions [49]. Based on these factors, a theory is proposed for DA's action in the PFC which suggests that DA acts to regulate the information held in working memory and then modulates the cognitive and executive performance of the PFC [49].

5. Unique PFC circuitry for persistent activity – The cellular basis/correlate for working memory

Working memory is the ability to hold an item of information transiently in mind in the service of comprehension, thinking, and planning [64-69]. It encompasses information retrieval, transient storage, and re-update/recycle processing. Thus working memory serves

as a workspace for holding items of information in mind as they are recalled, manipulated, and/or associated to other ideas and incoming information. ''Blackboard of the mind'' has been a useful metaphor for the limited capacity and processing dynamics of the working memory mechanism [64, 69]. Information such as a rule or goal is held temporarily in working memory and used to guide behavior, attention or emotions, dependent on the PFC region(s) involved. In addition to the ability to transiently hold the information 'on-line" for working memory, the PFC is also able to represent information that is not currently in the environment through persistently activated recurrent networks of pyramidal neurons [70]. This process has been referred to as representational knowledge and is thought to be a fundamental component of abstract thought [69].

5.1 Persistent activity in primate studies

The circuitry underlying working memory or representational knowledge in the PFC has been most intensively studied in the past decades. In primates, visuospatial information is processed by the parietal association cortices, and fed forward to the dorsolateral PFC, where pyramidal cells excite each other to maintain information briefly in memory. A major advance in our understanding of PFC and working memory function came in the early 1970s. Electrophysiological studies revealed that neurons in the PFC become activated during the delay period of a delayed-response trial when a monkey recalled a visual stimulus that had been presented at the beginning of a trial [71, 72]. Patricia Goldman-Rakic and her colleagues [69] further discovered and elaborated the PFC microcircuitry subserving spatial working memory using anatomical tracing techniques and physiological recordings from monkeys performing an oculomotor spatial working memory task. They found that the dorsolateral PFC is key for spatial working memory, and many neurons in this region exhibit spatially tuned, persistent firing during the delay period in a spatial working memory task [73]. Goldman-Rakic posited that the delay-related firing arises from pyramidal cells with similar spatial characteristics exciting each other to maintain information in working memory. It quickly became evident that the persistent activity of these prefrontal neurons could be the cellular correlate of a mnemonic event for working memory.

5.2 Physiological and morphological properties of persistent activity

Then, what is the neural basis of persistent activity in the prefrontal neural circuitry? Are the prefrontal cortical circuitries specialized to generate persistent action potentials needed for working memory? What are the microcircuit properties that enable the PFC to subserve cognitive functions such as working memory and decision making in contrast to early sensory coding and processing in primary sensory areas? Although the mechanism remains elusive, a large body of evidence indicates that the PFC is both functionally and structurally specialized with unique properties differing from other cortical areas. It has been hypothesized that persistent activity is generated by sufficiently strong recurrent excitation among prefrontal neurons [69]. Specifically, prefrontal neurons that reside in layer II/III, contain extensive horizontal connections that are characteristic of recurrent connections [69]. Pyramidal cell networks interconnect on dendritic spines, exciting each other via postsynaptic N-Methyl-D-aspartate (NMDA) receptors. NMDA currents are particularly evident in the recurrent network of PFC circuitry [74], and seem to be necessary for delay-related firing in monkeys performing a working memory task [70].

In addition, neurons in the PFC circuitry exhibit distinct morphological properties. In an interesting study, the basal dendritic arbors of pyramidal cells in prefrontal areas of the macaque monkey were revealed by intracellular injection in fixed cortical slices and the spine density in the basal dendrites were quantified and compared with those of pyramidal cells in the occipital, parietal, and temporal lobes [75]. These analyses revealed that cells in the frontal lobe were significantly more spinous than those in the other lobes, having as many as 16 times more spines than cells in the primary visual area (V1), four times more those in area 7a, and 45% more than those in temporal cortex [75]. As each dendritic spine receives at least one excitatory input, the large number of spines reported in layer III pyramidal cells in the primate PFC suggests that they are capable of integrating a greater number of excitatory inputs than layer III pyramidal cells in the occipital, parietal, and temporal lobes. The ability to integrate a large number of excitatory inputs may be important for the sustained activity in the PFC and their role in memory and cognition [75-79]. In addition, Elston et al also presented evidence that the pyramidal cell phenotype varies markedly in the cortex of different anthropoid species. Regional and species differences in the size and number of bifurcations and spine density of the basal dendritic arbors cannot be explained by brain size. Instead, pyramidal cell morphology appears to accord with the specialized cortical function these cells perform. Cells in the PFC of humans are likely more branched and more spinous than those in the temporal and occipital lobes. Moreover, cells in the PFC of humans are more branched and more spinous than those in the PFC of macaque and marmoset monkeys. These results suggest that highly spinous and compartmentalized pyramidal cells (and the circuits they form) are required to perform complex cortical functions such as working memory and executive functions for comprehension, perception, and planning [77]. Because of the high density of dendritic spines in the PFC neurons [75, 76] and presumably more excitatory synapses in the recurrent circuitry in the PFC [80], the PFC is thought to be specialized to generate persistent action potentials (or persistent activity), the presumptive mechanism of working memory [81-87].

Furthermore, it has been appreciated that several types of interneurons reside in the PFC and interact with pyramidal cells. Using simultaneous recordings in monkeys, it has been revealed that the inhibitory interactions between neurons at different time points are relative to the cue presentation, delay interval and response period of a working memory task [88, 89]. These data indicate that pyramidal – interneuron interactions may be critical to the formation of memory fields in PFC [88]. The PFC network activity is 'tuned' by inhibitory GABAergic interneurons so that the contents of working memory are contained, specific and informative. For example, when pyramidal cells are active they excite GABAergic interneurons that suppress the firing of pyramidal cells in another microcircuit, and vice versa [88, 89]. These findings suggest an important role of inhibition in the PFC: controlling the timing of neuronal activities during cognitive operations and thereby shaping the temporal flow of information [90].

6. Delayed development or maturation of the PFC

6.1 Synaptogenesis, synaptic remodeling and maturation

Development is a complex process involving changes in white matter and the establishment of neuronal connections in the brain, both of which are influenced by genetic and

environmental factors. Generally speaking, the development of the nervous system occurs through the interaction of several processes, some of which are completed before birth, while others continue into adulthood [91]. For example, proliferation and migration of cells mostly occurs during fetal development, although in postnatal development, the formation of neuronal circuits, along with neuronal death and the rapid formation and elimination of synapses, occurs in the cerebral cortex, including the PFC [92-95]. It is known that synaptic density in the brain increases with age, and it occurs as a result of trillions of neurological connections, commonly called "wiring." Neuronal firing creates a network that is permanently established with repetitive experiences. Connections no longer being used or relied upon are eliminated through a process called synaptic pruning. Although the development of neural connections in the brain is not fully understood, it is clear that the time courses of such neuronal and synaptic formation and elimination are considerably different across diverse cortical areas, with the PFC generally being one of the latest [96]. Therefore, the childhood development of the cerebral cortex may be characterized by neuronal death and the elimination of unused synapses during a defined time window such as adolescence. 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 but decreasing gradually through adolescence [96]. Developmental changes in cellular morphology have also been observed during early childhood, including expansion of the dendritic trees of the pyramidal neurons [97].

6.2 Delayed maturation of the PFC

PFC development in humans begins from the neural tube, which is an embryonic structure that eventually becomes the brain and spinal cord. PFC experiences one of the longest periods of development of any brain region, taking over two decades to reach full maturity in humans, i.e., PFC exhibits a significant delayed maturation compared to other brain regions [98-100]. As children explore their environments and begin to develop speech, motor skills, and a sense of themselves as separate human beings, the PFC undergoes rapid growth during infancy [101]. Several characteristic functions of the PFC, such as planning, reasoning, and language comprehension, change dramatically as a function of age throughout childhood and adolescence [102]. The processes involved in the development of these PFC functions have been debated for several decades at the level of both brain and behavior, and it has been established that changes in structural architecture and cognitive maturation occur concurrently throughout childhood development [103]. Complete frontal cortex development takes many years, and new functions are added well beyond the childhood years. Accumulating evidence suggests that early childhood appears to be comparably important for functional neural development of the PFC [104]. While the most dramatic structural changes in the healthy human brain are thought to occur in the perinatal period [96], there is a growing body of evidence suggesting that adolescence is also a period of substantial neurodevelopment [105]. Understanding the brain maturation over adolescence and early adulthood is particularly important, given that it is a peak period of neural reorganization that contributes to both normal variation and the onset of some major mental illnesses, such as schizophrenia [106, 107]. Despite support for pronounced changes in both the structure and function of the brain during adolescence, the relationship among these changes has not been fully examined.

6.3 Adolescence is a critical period for PFC maturation – Molecular and cellular alterations in the PFC circuitry

To encourage the establishment of new neuronal connections, the frontal lobe must be stimulated. While frontal cortex development is significantly influenced by genetics, environmental factors play a pivotal role. Children who are exposed to varied environments; encouraged to solve problems; challenged to reason; and engaged in different games, songs and memory tasks will benefit from these stimulations that facilitate the development of the PFC. Conversely, children with sensory processing disorders often struggle with the reasoning and decision making tasks controlled by the PFC, and damage to the PFC results in an inability to control impulses and learn from experiences with reward and punishment.

PFC development is thus characterized by maturational processes that span the period from early childhood through adolescence to adulthood [108, 109], but little is known whether and how developmental processes differ during these phases. In the past two decades, numerous studies have been focused on detail changes in the functional maturation of the PFC circuitry. For example, it is now clear that the underlying synaptic refinement process in the PFC is not completed until late adolescence and early adulthood [110, 111], which coincides with the period when symptoms of schizophrenia typically begin to emerge [112]. Indeed, our study indicated that the NMDA receptor subunit NR2B-to-NR2A shift does not occur during prefrontal development. The NMDA receptor-mediated currents in the recurrent synapses of the PFC exhibit a 2-fold longer decay time-constant and temporally summate a train of stimuli more effectively than those in the primary visual cortex [74]. Pharmacological experiments suggest a greater contribution by NR2B subunits at prefrontal synapses than in the visual cortex. Therefore, the biophysical properties of NMDA receptors in PFC may be critically important to the generation of slow reverberating dynamics required for cognitive computations [74]. However, the enriched NR2B subunit in the PFC appears to be a double-edged sword - important for normal working memory but easy to be targeted by detrimental stimulation. In addition, we also reported that parvalbumin-containing fast-spiking interneurons in the PFC undergo dramatic changes in glutamatergic receptors during the adolescent period, including both NMDA receptors and calcium-permeable AMPA receptors [113, 114]. Furthermore, Tseng and O'Donnell found significant changes in the susceptibility of interneurons to dopaminergic D2 receptor modulation during adolescence. Importantly, D2 agonists were effective only in adult but not in prepubertal animals [115]. Many other late occurring changes in GABAergic neurons, GABAergic neurotransmission and $GABA_A$ receptors have also been demonstrated [112, 116, 117]. Similarly, developmental trends have been reported for the dopaminergic [118] and glutamatergic systems [119] and for interactions of these neurotransmitters with GABAergic interneurons. It is possible that these prominent changes may make fast-spiking cells particularly sensitive and vulnerable to epigenetic or environmental stimulation, thus contributing to the onset of psychiatric disorders, including schizophrenia, bipolar disorder, and depression.

While these findings suggest important evidence on late-occurring anatomical and physiological modifications, the precise implications of these changes for coordinated network activity in the PFC are unknown. It is believed that these anatomical and physiological changes impact critically upon the functional properties of large-scale cortical networks [120, 121]. The alterations in GABAergic neurons during adolescence may be of particular relevance for synchronous oscillations because GABAergic interneurons and their

interactions with excitatory neurotransmission have been shown to be critical for the generation of high-frequency oscillations [122-132]. Following early developmental periods, changes in the amplitude of neural oscillations and their synchronization continue until early adulthood, suggesting ongoing modifications in network properties. One of the most replicated findings is the alteration in resting-state oscillations. In the adult brain, resting-state activity is characterized by prominent alpha oscillations over occipital regions while low (delta, theta) and high (beta, gamma) frequencies are attenuated. During adolescence, there is a reduction in the amplitude of oscillations over a wide frequency range, particularly in the delta and theta band, while oscillations in the alpha and beta range become more prominent with age [133]. Interestingly, these changes occur more rapidly in posterior than in frontal regions and follow a linear trajectory until age 30 [133]. Alteration in the amplitude of oscillations is accompanied by modifications in the synchrony of resting-state oscillations. Thatcher et al investigated modifications in the coherence of beta oscillation in children and adolescents between 2 months and 16 years of age. During development, beta-band coherence increased over shorter distances while long-range coherence did not vary with age [134]. Uhlhaas et al further reported that until early adolescence, developmental improvements in cognitive performance were accompanied by increases in neural synchrony [121]. This developmental phase was followed by an unexpected decrease in neural synchrony that occurred during late adolescence and was associated with reduced performance. After this period of destabilization, a reorganization of synchronization patterns occurred with a pronounced increase in gamma-band power and in theta and beta phase synchrony. These findings provide evidence for the relationship between neural synchrony and late brain development that has important implications for the understanding of adolescence as a critical period of brain maturation [121].

7. Diseases associated with the development of PFC – Mental illness

7.1 What is a mental disorder?

Mental illness refers to a wide range of mental health disorders that affect people's mood, thinking and behavior. Examples of mental illness include schizophrenia, ADHD, depression, bipolar disorders, anxiety disorders, autism spectrum disorders, obsessive-compulsive disorder, eating disorders, and addictive behaviors. As repeatedly discussed above, the PFC plays a critical role in cognitive functions and cortical inhibition, especially for insight, judgment, the ability to inhibit inappropriate responses, and the ability to plan and organize for future events. Therefore, PFC dysfunction is greatly associated with disorders/deficits in cognitive and executive functions that are seen in most mental illnesses.

Many people have mental health concerns from time to time, but this only becomes a mental illness when clear signs and symptoms cause severe stress and affect people's ability to function properly. A mental illness can make people miserable and can cause problems in daily life, such as at work or in personal relationships. Signs and symptoms of mental illness vary, depending on the particular disorder. In most cases, mental illness symptoms can be managed with a combination of medications and counseling such as psychotherapy. Most major or serious mental illnesses tend to have symptoms that come and go, with periods in between when the person can lead a relatively normal life, i.e., episodic illness. The most common serious mental disorders are schizophrenia, bipolar disorder, and depression.

Although the exact cause of most mental illnesses is unknown, it is becoming clear that many of these conditions are caused by a combination of genetic, biological, psychological and environmental factors.

1. Genetics: Many mental illnesses have family histories, suggesting that the illnesses may be passed on from parents to children through specific genes. Many mental illnesses are linked to multiple problem genes that are still largely unknown. The disorder occurs from the interaction of these genes and other factors, such as psychological trauma and environmental stressors – which can influence or trigger the illness in a person who has inherited a susceptibility to the disease.
2. Biology: Mental illnesses have been linked to an abnormal balance of neurotransmitters, mis-wired neuronal connections in the network, and disrupted communications between neurons within the brain. When neuronal signals cannot be properly transmitted within the brain, particularly within the brain region such as PFC, signs and symptoms of a mental disorder will emerge.
3. Psychological trauma: Some mental illnesses may be triggered by psychological trauma suffered as a child, such as severe emotional, physical or sexual abuse, etc.
4. Environmental stressors or risk factors: Certain stressors or risk factors – such as a brain injury, dysfunctional family life, substance abuse, or a life threatening event – can trigger a disorder in a person who may be at risk for developing a mental illness.

7.2 Circuit basis for cognitive dysfunction in mental illness

The cognitive operations of the PFC are especially vulnerable to physiological, genetic and environmental factors. They can be altered by changes in arousal state such as fatigue or stress [135] and are profoundly impaired in most mental illnesses [40, 136-139]. However, it is unknown how these functions are affected. There are many questions that need to be answered. Specifically, for example, what are the specific genes that are involved in a mental disorder such as schizophrenia or depression? There are some high risk genes identified for an individual disease. However, it is unclear how these identified genes interact to other factors and how these susceptible genes are triggered by aforementioned psychological trauma or environmental risk factors, and consequently result in a domino effect in the brain. A large body of evidence indicates that the onset of a mental disorder is triggered by a risk factor but the pathological process of a mental illness is complex and unclear. Apparently, many mental illnesses are associated with impaired brain development, especially broken PFC circuitry.

As discussed above, PFC cognitive functions rely on networks of interconnected pyramidal cells [1, 2, 69], as well as GABAergic interneurons [112, 116, 140]. Recent studies reveals that neuronal connections in the PFC network are influenced by powerful molecular events that determine whether a network is connected or disconnected at a given moment, thus determining the strength of cognitive abilities [70]. These mechanisms provide great flexibility, but also confer vulnerabilities and limit mental capacity. A remarkable number of genetic and/or environmental insults to these molecular signaling cascades are associated with cognitive disorders such as schizophrenia [77, 138, 139, 141-144], ADHD [145, 146], depression [100, 101, 147-149], and autism spectrum disorder [150-155]. These insults can dysregulate network connections in the PFC and weaken its capabilities in cognitive control. It is evident that many genetic and environmental insults would have an impact on signaling molecules within PFC networks [70] and its highly linked limbic systems.

Alterations in PFC circuitry are therefore associated with a variety of cognitive disorders, ranging from mild PFC impairment (e.g. anxiety disorder, depression, normal aging) to severe deficits (e.g., schizophrenia, bipolar disorder, Alzheimer's disease).

The question is that what causes a circuit disorder? Mental disorders such as schizophrenia and mood and anxiety disorders are mostly diseases of early life; their onset tends to occur during adolescence or early adulthood, when the brain is still developing. Because of page limits and the complex etiology and pathological process in different mental disorders, it is not possible for us to describe all aforementioned mental illnesses in detail in this chapter. So next we use schizophrenia as an example to illustrate the role of PFC in this devastating disorder.

7.3 Disrupted development of PFC circuitry in schizophrenia

Schizophrenia is a disorder of cognitive neurodevelopment with characteristic abnormalities in working memory attributed, at least in part, to alterations in the circuitry of the PFC. Schizophrenia is associated with altered PFC circuits, arising from both developmental insults in utero, and continuing in the mature brain, for example with impaired neural circuitry and synaptic connectivity in late adolescence and adulthood. Various environmental exposures from conception through adolescence increase risk for the illness, possibly by altering the developmental trajectories of prefrontal cortical circuits.

Several lines of evidence support the notion that a substantial reorganization of cortical connections takes place during adolescence in humans. A review of neurobiological abnormalities in schizophrenia indicates that the neurobiological parameters that undergo peripubertal regressive changes may be abnormal in this disorder. An excessive pruning of the prefrontal corticocortical, and corticosubcortical synapses, perhaps involving the excitatory glutamatergic inputs to pyramidal neurons, may underlie schizophrenia [99, 106]. Several developmental trajectories, which are related to early brain insults as well as genetic factors affecting postnatal neurodevelopment, could lead to the illness. These models would have heuristic value and may be consistent with several known facts of the schizophrenic illness, such as its onset in adolescence. For example, a person with schizophrenia usually experiences a psychotic break in early adulthood, which is a time when the number of cortical synapses is being pruned. The disorder might result from the excessive loss of synapses in a critical cortical pathway when the normal process overshoots.

Although psychosis always emerges in late adolescence or early adulthood, we still do not understand all of the changes in normal or abnormal development prior to and during this period. It is particularly unclear what factors alter the excitatory-inhibitory synaptic balance in the juvenile and what changes induce the onset of cognitive dysfunction. Current studies suggest that problems related to schizophrenia are evident much earlier. The emerging picture from genetic and epigenetic studies indicates that early brain development is affected. Many of the structural variants associated with schizophrenia implicate that neurodevelopmental genes or epigenetic factors are involved with neuronal development [156-159]. A remarkable number of genetic insults in schizophrenia involve proteins found at prefrontal synapses. There are well-established genetic changes associated with NMDA receptor signaling [160-162], DA [51, 163-165], GABA [112, 116, 140, 166], and α7 nicotinic receptors [167-170]. More recently, a number of high-risk genes are found to be associated with schizophrenia [171]. Four out of the top 10 risk gene variants most strongly associated with schizophrenia are directly involved in DA-ergic systems, including the catechol-o-

methyltransferase gene (COMT) [142, 172-177], neuregulin 1 (NRG1) [178, 179], disrupted in schizophrenia 1 protein (DISC1) [157, 180], and dystrobrevin-binding protein 1 (dysbindin) [181-184]. Many of these gene variants are involved in brain development, such as reelin, or influence more ubiquitous brain transmitters such as glutamate or GABA [171, 184-189]. These postnatal developmental trajectories of neural circuits in the PFC identify the sensitive adolescent period for vulnerability to schizophrenia [112].

Furthermore, recent data from developmental cognitive neuroscience highlight the profound changes in the organization and function of PFC networks during the transition from adolescence to adulthood. While previous studies have focused on the development of neuronal components in gray matter, as well as axonal fibers and myelination in white matter [190], recent evidence suggests that brain maturation during adolescence extends to fundamental changes in the properties of cortical circuits that in turn promote the precise temporal coding of neural activity. Specifically, schizophrenia is associated with impaired neuronal synchronized activity that occurred during PFC maturation, suggesting an important role of adolescent brain development for the understanding, treatment, and prevention of the disorder [120].

These findings, although intriguing, are limited in that they do not reveal the changes before psychosis. At present, the diagnosis of schizophrenia is based primarily on the symptoms and signs of psychosis. Recently, it has been proposed that schizophrenia may progress through four stages: from risk to prodrome to psychosis and to chronic disability [191]. Obviously, the key to prevent or forestall the disorder is to detect early stages of risk and prodrome. Therefore identification of novel biomarkers, new cognitive tools, as well as subtle clinical features is urgently needed for early diagnosis and treatment [191, 192]. Animal studies, particularly developmental models, will certainly help to reveal the neurodevelopmental trajectory of schizophrenia, yield disease mechanisms, and eventually offer opportunities for the development of new treatments. As Thomas Insel pointed out in a recent review of schizophrenia [191]: "This 'rethinking' of schizophrenia as a neurodevelopmental disorder, which is profoundly different from the way we have seen this illness for the past century, yields new hope for prevention and cure over the next two decades."

8. Summary

The cognitive and executive functions of the prefrontal cortex (PFC) develop to their full capabilities throughout the juvenile and adolescent period in humans. The PFC is critical for cognitive functions and cortical inhibition, especially for insight, judgment, the ability to inhibit inappropriate responses, and the ability to plan and organize for the future. This higher brain region, unlike other primary cortical areas, exhibits unique connectivity and delayed cortical maturation. During postnatal development, it gradually takes on its adult form as prefrontal neuron synapses are pruned and neuronal connections are reformatted to adult level. Further, numerous data show that juvenile and adolescence are time periods of great vulnerability, with special sensitivity to risk environmental factors, and eruption of neuropsychiatric disorders. We have provided an overview of the unique properties and connectivity of the PFC circuitry and alterations during the juvenile and adolescent development under both normal and abnormal conditions. Understanding the neurobiological basis is important in the development of more effective intervention strategies to treat or prevent mental disorders such as schizophrenia.

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10. Conflict of interest

The authors claim no financial conflicts of interest.

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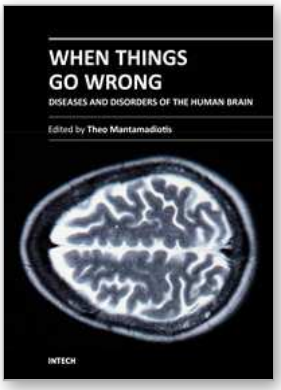

When Things Go Wrong - Diseases and Disorders of the Human Brain

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In this book we have experts writing on various neuroscience topics ranging from mental illness, syndromes, compulsive disorders, brain cancer and advances in therapies and imaging techniques. Although diverse, the topics provide an overview of an array of diseases and their underlying causes, as well as advances in the treatment of these ailments. This book includes three chapters dedicated to neurodegenerative diseases, undoubtedly a group of diseases of huge socio-economic importance due to the number of people currently suffering from this type of disease but also the prediction of a huge increase in the number of people becoming afflicted. The book also includes a chapter on the molecular and cellular aspects of brain cancer, a disease which is still amongst the least treatable of cancers.

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