Trends in Neurosciences

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Review

# Prefrontal Cortex Development in Health and Disease: Lessons from Rodents and Humans

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**The role of the prefrontal cortex (PFC) takes center stage among unanswered questions in modern neuroscience. The PFC has a Janus-faced nature: it enables sophisticated cognitive and social abilities that reach their maximum expression in humans, yet it underlies some of the devastating symptoms of psychiatric disorders. Accordingly, appropriate prefrontal development is crucial for many high-order cognitive abilities and dysregulation of this process has been linked to various neuropsychiatric diseases. Reviewing recent advances in the field, with a primary focus on rodents and humans, we highlight why, despite differences across species, a cross-species approach is a fruitful strategy for understanding prefrontal development. We briefly review the developmental contribution of molecules and extensively discuss how electrical activity controls the early maturation and wiring of prefrontal areas, as well as the emergence and refinement of input–output circuitry involved in cognitive processing. Finally, we highlight the mechanisms of developmental dysfunction and their relevance for psychiatric disorders.**

## PFC: A Cognitive Hub across Mammalian Species

Our successful survival in a permanently changing environment would not be possible without the ability to store and update new evidence, (re-)evaluate our choices, and make decisions. This ability to adapt according to the situation is a product of the cognitive flexibility of our minds. It depends on low-level sensory and motor processes being internally coordinated and endowing the brain with the capacity to adapt internal goals and act accordingly. It is widely thought that such processes involve a neural circuitry that extends over much of the brain, yet it is commonly held that the PFC, the cortical region of the anterior pole of the mammalian brain, is a critical hub. The PFC not only is involved in emotional and social behavior, but provides executive 'top-down' control when behavior is guided by internal states or goals [1]. Accordingly, it is involved in a series of cognitive processes such as attention, salience detection, **working memory** (see Glossary), and inhibitory control, all having as final output the ability to adapt to various conditions and switch between tasks [1].

Despite a wealth of studies, a clear-cut, widely accepted and species-independent definition of the PFC is still lacking [2–4]. Traditionally, **structural** and **functional homology** are used as a basis for brain area classification across species. This enables knowledge to be gained from one species, usually more amenable to invasive interventions, and transferred to other, less-accessible ones, such as humans. The unique relative size, connectivity patterns, parcellation, migration pathways, and layer structure of the human PFC [1,2,5,6] hamper a direct cross-species comparison based on structural homology. Thus, functional homology might be a more fruitful approach for translating PFC studies [7]. For example, while the agranular medial PFC of rats and mice, which is the focus in this review, is not the anatomical equivalent of the primate and human dorsolateral PFC [8], it underlies the same kind of processes (e.g., working memory, decision-making, attention). It can thus be considered its functional homolog [3].

## Highlights

The prefrontal cortex (PFC) comprises a conglomeration of brain areas with a largely heterogeneous cross-species anatomical definition that accounts for numerous cognitive abilities.

Abnormal structure and function of the PFC is linked to lower performance in various cognitive domains and is associated with several neuropsychiatric diseases.

Prefrontal development, while protracted compared with sensory cortices, is similarly controlled by molecular cues that set the proliferation, migration, differentiation, and eventual boundaries of prefrontal neurons.

During development, under the driving force of the hippocampus and thalamic nuclei, prefrontal circuits start to generate characteristic patterns of coordinated electrical activity that dynamically change with age in their cellular mechanisms, spectral structure, and synchrony.

Patterns of electrical activity and connectivity underlie the reorganization of prefrontal areas in line with the maturation of cognitive abilities, such as working memory and decision making.

Miswiring of prefrontal areas, resulting from genetic factors or environmental stressors acting during development, can contribute to cognitive impairment in psychiatric disorders.

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While some of the PFC-dependent abilities listed earlier are typically thought of as exquisitely human, many also exist in a basic form in rodents, although rodents clearly do not have the behavioral complexity or finesse that is characteristic of humans. However, to a certain extent, most mammals adapt and develop flexible strategies to thrive in their environment. The topic of cross-species comparison of the PFC has been reviewed in detail elsewhere [2]. As an additional note, it is worth mentioning that modern transcriptomic approaches might also prove to be insightful for this aim, especially in the context of neural development [9].

In contrast to sensory and motor performance, most cognitive abilities that have been assigned to prefrontal areas emerge late in life in all mammalian species. Correspondingly, it has been proposed that prefrontal areas, at least in some aspects, have a protracted development compared with sensory and motor cortices [10,11]. Abundant knowledge on the structural maturation of the PFC in rodents, monkeys, and humans has been accumulated over decades. By contrast, the picture on the functional development remains patchy and substantial gaps persist, especially for early ages. Technical and ethical difficulties related to pre- and perinatal human investigations might account for part of these gaps (Box 1). While rodents are an **altricial species**, that is relatively easily accessible already at a developmental stage that generally corresponds to human fetal development, it is difficult to relate and translate the timing of neurodevelopmental events in prefrontal areas across species. Some of these events are protracted in humans compared with rodents, and humans and rodents vary considerably in their maturational trajectory (Figure 1). Despite all these obstacles, attempts to uncover the developmental mechanisms of prefrontal function have been emerging in recent years [12,13]. Even if still far from the ultimate goal of direct application of knowledge on prefrontal maturation from animal models to questions about human development, these studies are of high value in elaborating research hypotheses, especially regarding neurodevelopmental diseases.

Here, we review recent advances on the development of prefrontal architecture and function in rodents and humans. Rodents are particularly amenable to early investigation and genetic interventions that have been proven to provide deep insights into circuit wiring. We will review findings

## Box 1. Measures for Monitoring Brain Function during Development in Rodents and Humans

The functional properties of the developing brain have been studied with different methodologies leading to different readout measures. One of these measures is brain oscillations, assessed via intra- or extracranial recordings yielding LFP and EEG signal, respectively. These two signals are thought of as mostly being the product of the summation of postsynaptic currents derived from hundreds (LFP) to millions (EEG) of nearby neurons [131]. Brain oscillations are an important functional readout of brain activity, not only because they are readily available in both animal models and humans, but also because they are thought to represent the coordinated activity of neuronal ensembles and, potentially, specific microcircuit configurations [131,132]. While certain aspects of the relationship between EEG and LFP remain not well understood, the main difference between the two is that the EEG signal is spatiotemporally smoother. The EEG signal is thought to be mostly influenced by electrical currents in the apical dendrites of layer V cortical pyramidal neurons and conveys limited information on deep-brain oscillations [131]. To this end, particularly for human studies, the blood-oxygen level-dependent (BOLD) signal obtained with functional MRI (fMRI) is a complementary measure. The BOLD signal is indirectly related to neuronal activity, as it reflects local changes in blood flow [133,134]. It has a poor temporal resolution (on the order of seconds), but allows sampling of deep brain structures. While the relationship between BOLD and EEG/LFP is complex and still debated, BOLD is thought to be correlated with EEG/LFP gamma activity [133,134] and, importantly for developmental studies, with infraslow (<1 Hz) neuronal oscillations [135]. Acquisition of fMRI data during early development, however, is limited, as it usually requires the subject to stay immobile for an extended period of time. Another readout measure of early brain function in animal models is single-neuron activity that is monitored using single-unit activity (SUA) recordings or calcium indicators coupled with multiphoton microscopy. SUA is readily coupled to LFP acquisition. It has submillisecond temporal resolution and provides direct access to what is thought to be the fundamental unit of brain computation [136]. On the flipside, SUA is biased towards detecting action potentials of large neurons with a high firing rate, which leads to a low yield in the low-firing-rate regime of the developing brain. Calcium imaging, conversely, indirectly samples action potentials via their nonlinear effect on intracellular calcium concentration. It has poorer temporal resolution (hundreds of milliseconds to seconds) than SUA recordings and not always allows the detection of single action potentials under behaviorally relevant conditions [136]. However, calcium imaging has superior spatial resolution and allows the sampling of larger numbers of neurons simultaneously as well as easier characterization of specific neuronal (sub)populations [136].

## Glossary

**Adolescence:** the period following the onset of puberty that ends with the transition into adulthood. In humans this roughly corresponds to 11–18 years of age and in mice to 20–40 days of age.
**Altricial species:** a species that is born in an underdeveloped state.
**Functional homology:** similarity of functions subserved by brain areas of different taxa.
**Local field potential (LFP):** electrical field potential that is recorded by intracranial electrodes and is thought to represent the temporal and spatial summation of local postsynaptic potentials.
**Molecular cues:** gradients of molecules that direct the early steps of the formation, migration, and differentiation of neurons.
**Neonatal mouse:** mouse in the first stages of post-birth development. The term is generally used for mice that are younger than 10–12 days of age.
**Network oscillations:** repetitive LFP or EEG patterns of activity that derive from the synchronous activity of local neuronal populations.
**Parvalbumin interneurons:** a class of inhibitory neurons that is particularly abundant in cortical areas towards the brain's posterior pole and that preferentially targets the soma or axon initial segment of pyramidal neurons and other parvalbumin interneurons.
**Sharp-wave ripples:** highly synchronous neuronal firing events that occur primarily in the CA1 area of the hippocampus mostly during consummatory behavior and that have been implicated in memory consolidation.
**Somatostatin interneurons:** a class of inhibitory neurons that is particularly abundant in cortical areas towards the brain's frontal pole and that preferentially targets the dendrites of pyramidal neurons and parvalbumin interneurons.
**Structural homology:** similarity of input/output connectivity and parcellation between brain areas of different taxa.
**Subplate:** a transient layer of neurons in the cortex of placental mammals that emerges early during development and resides underneath the cortical plate. It facilitates the ingrowth of afferents and efferents. In humans, it appears at GW 5–6 and disappears around GW 40 (but persists up to 2 years of age in the PFC). In rodents, it persists as layer Vib.

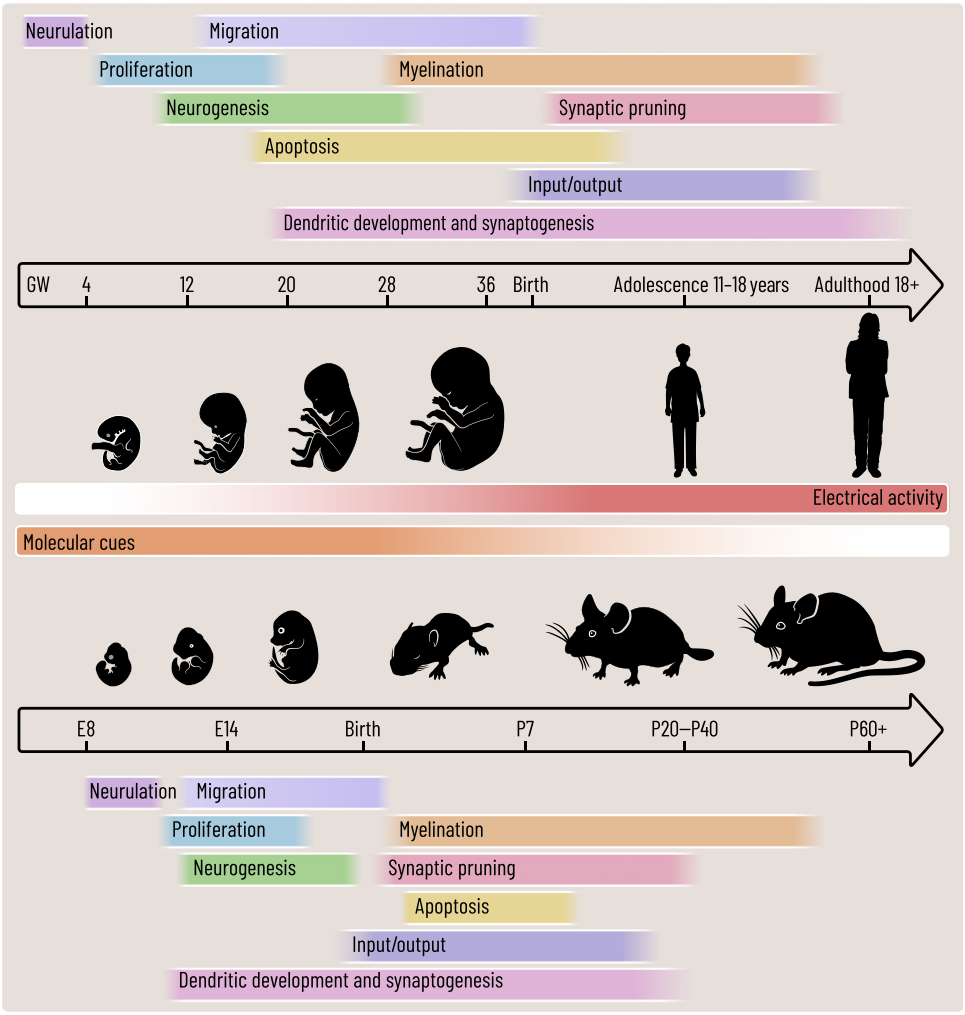


Figure 1. Schematic Representation of the Processes Guiding Human and Rodent Prefrontal Development. The development of the PFC, its local structure, and its input/output connectivity largely follows the same maturational steps in humans and mice. It is initially guided by molecular cues, whose importance declines with age, while the relevance of electrical activity increases throughout development. While the overall development is similar in the two species, individual processes occur at different relative time points and with different time courses. Not only are mice born at a more premature state but, even when accounting for this, synaptogenesis, as an example, is less protracted than in humans, and synaptic pruning occurs at an earlier stage. Abbreviations: E, embryonic day; GW, gestational week; P, postnatal day.

**Supra/infragranular layers:** cortical layers that reside above (layers II/III) or below (layers V/VI) the granular layer of the cerebral cortex (layer IV).
**Synaptic pruning:** a process of excessive synapse removal by glial cells such as microglia and astrocytes.
**Topographic organization:** arrangement of neurons according to sensory receptors (e.g., retinotopic organization of the retina, tonotopic organization of the cochlea) or skeletal muscles (e.g., somatotopic organization of the primary motor cortex).
**Working memory:** cognitive ability that relies on short-term memory and allows the processing of information that is only temporarily stored.

uncovering the structural and functional development of the PFC in relationship to cognitive maturation. Functional assessment mainly but not exclusively relies on the investigation of **network oscillations**. Being aware of the aforementioned cross-species translation pitfalls, we will discuss the mechanisms of disrupted development and their possible implications for disease.

## Molecular Control of Prefrontal Development

Mammals share a similar sequence of developmental events culminating in the formation of the neocortex. In both rodents and humans, the initial processes, including neurulation, proliferation, migration, and differentiation, are mostly under the control of genetic cues, whereas the later events, such as dendritic, synapse, and afferent–efferent development and refinement, are

considered to be largely controlled by electrical activity. However, molecules and activity not only temporally overlap in shaping cortical development but also interact with each other during this process [14,15].

Neocortical maturation starts at about day 16 of gestation in humans [16] and embryonic day (E) 7 in rodents, with neurulation followed by regional specification and expansion of the PFC. The process is controlled by intrinsic transcription factors and extrinsic growth factors that tightly interact to delimit the prefrontal boundaries [17]. Once the neural tube is formed, at around 5 weeks of gestation in humans and E10 in rodents, neurons destined to form the neocortex are born as neuroblasts. Their proliferation is a long-lasting process with an area-specific dynamic that generally peaks between 6 and 18 weeks gestation in humans [18] and E10 and E15 in rodents [19]. Excitatory neurons are generated from apical progenitors located in the ventricular zone as result of a complex interplay of cell-autonomous mechanisms and local and long-range environmental cues [20,21]. Towards the end of the neurogenic period, glial cells are generated [22]. Similar to other neocortical areas, the PFC expands and the generated neurons migrate under the influence of Fgfs radially (for glutamatergic pyramidal neurons) and of Dlx and Gad1 tangentially (for GABAergic interneurons) [23,24]. Initially [gestational week (GW) 10–12 in humans and E11–E12 in rodents], the PFC comprises the marginal zone, the cortical plate, and the **subplate**, a transiently expressed layer of heterogeneous neurons located at the border with white matter [25]. In the human PFC, the subplate is the thickest layer at GW 17–25. It persists longer (i.e., 6–12 months after birth in humans) than in the primary sensory cortices and it has been hypothesized to have a critical role in the development of prefrontal circuitry [26]. The migrating cortical neurons build the layers in an 'inside-out' spatial–temporal pattern with the earliest born neurons forming deep layers and later-born neurons embedded in upper layers [27]. The migration of prefrontal neurons is controlled by many signaling pathways that are largely common to all neocortical areas and have been reviewed elsewhere [24].

Once the neurons reach their final destination (in humans around birth to the end of the first year; in rodents at the first to second postnatal week), their axons extend and the dendrites arborize to enable the assembly of prefrontal circuits. Growth cones of developing axons are instructed by guidance molecules, such as semaphorins, to reach their targets. Subsequently, synaptic contact formation is mediated by adhesion molecules [28]. Further, genes such as Reln have been reported to control the synaptogenesis of prefrontal pyramidal neurons [29], whereas Erbb4 regulates dendritic spine formation on prefrontal interneurons [30]. During this period, overproduction of synaptic contacts and wiring occur, but synaptic density peaks relatively late in the PFC (2–4 years of age in humans and after the fourth postnatal week in rodents) compared with sensory cortices [18,31,32]. Newly established connections are highly dynamic and refined as development advances. In the PFC, this process extends until **adolescence** [~16 years in humans, postnatal day (P) 20–40 in rodents], and in humans, particularly in layer III, it leads to the most dramatic and long-lasting decrease of synaptic density [25,33,34]. While **molecular cues**, such as semaphorins, Cdk5/p35, Disc1, and Dcc, modulate to a certain extent the pruning of branches [35], the refinement of connectivity is considered to be mainly controlled by electrical activity (see next section).

The molecular orchestration of early developmental processes in prefrontal areas is prone to disruption that, despite efficient compensatory mechanisms, might lead to abnormal function and, ultimately, cognitive impairments. The molecular underpinnings and downstream pathways of prefrontal development as well as their disruption in neuropsychiatric disorders have been recently reviewed [36,37].

## Early Patterns of Electrical Activity in the PFC

During the developmental time window of decreasing influence of molecular cues and increasing influence of electrical activity, the neocortex generates patterns of electrical activity with unique features (Box 2). Knowledge on the early electrical activity of the PFC is rather recent and considerably sparser than that available for sensory cortices and the hippocampus.

**Topographically organized** sensory cortices display spontaneous patters of activity with highly stereotypical motifs [38–40], but such network-level descriptions of early prefrontal activity remain largely elusive. However, recent studies in **neonatal mice**, conducted with and without anesthesia (Box 3), identified transient bouts of beta–low-gamma rhythmic oscillations as an early prefrontal activity signature with important functional correlates [12,41,42]. This activity is generated by pyramidal neurons residing in **supragranular layers** of the PFC ($PYRs_{II/III}$) [41,43,44], is elicited by light activation of $PYRs_{II/III}$, and occurs naturally in response to incoming stimuli from the hippocampus [12,45]. Unpublished results from our group suggest that this oscillatory motif persists and evolves smoothly from the first postnatal week throughout adulthood, gradually becoming longer, faster (the average frequency increases from ~15 Hz up to ~50 Hz), and of higher amplitude [44]. This maturation parallels and might be caused by the unfolding of inhibitory feedback [44] (Figure 2). Similar to other neocortical areas, inhibition shifts from an early environment in which **somatostatin interneurons** dominate the GABAergic landscape, to one in which **parvalbumin interneurons** progressively gain relevance ([46,47] but see also [48]). Across the first 3 postnatal weeks, the strength of somatostatin-to-pyramidal neuron synapses decreases, whereas the opposite occurs for parvalbumin interneurons [46]. Of note, early bouts of gamma activity are also present in the rodent barrel [49] and visual [50,51] cortices, but distinct mechanisms underlie their generation.

While it remains unclear what kind of information (if any) is carried by early prefrontal activity or the extent to which it serves as a functional output source for downstream areas, its relevance for the refinement of prefrontal circuits and behavior has been highlighted by a number of recent studies. In developmental mouse models of mental disorders, beta–gamma prefrontal oscillations are impaired from the first postnatal days up to adulthood, leading to cognitive deficits [42,52]. Severely

### Box 2. General Features of Early Brain Activity

Brain activity in the developing brain has several unique functional properties. The most directly observable is the alternation between long periods of electrical silence (i.e., an isoelectric LFP/EGG trace and the almost complete absence of spiking) and sporadic bursts of activity. In the EEG literature, this phenomenon takes the name *tracé discontinu*. Such isoelectric electrical traces are unparalleled in the healthy adult brain, as they are indicative of *bona fide* neuronal silence and not, for instance, uncorrelated neuronal activity. This unique property of immature brain activity appears to be a brain-wide phenomenon and has been described not only in human newborns and preterm babies [137] but also in other species that are phylogenetically far apart such as rodents [138] and fishes [139].

Rodent studies have shown that, at birth, these waves of activity travel in the occipitofrontal direction [140]. Transient bursts of activity have been particularly well characterized along sensory pathways according to their frequency (i.e., the number of deflections occurring in 1 s), amplitude (i.e., the magnitude of deflections), and power (i.e., the oscillatory amplitude at a defined frequency and during a defined temporal window). The oscillatory bursts have been shown to share some characteristic features: they organize neuronal firing in the infraslow timescale [141]; they are subplate and acetylcholine dependent [38]; they are periphery driven but develop before the sensory pathway is mature [39,40,50,51]; and they become longer [142–144], less correlated [48,142,143], and more periphery independent as the brain matures [145,146]. These early patterns of spontaneous activity in brain sensory areas have been shown to be homeostatically regulated [40] and to instruct the further development of adult sensory activity [39]. While it remains a matter of debate whether they carry any sensory information (see [146,147] for one perspective and [138,148] for the other), their disruption is detrimental to the development of sensory perception [149,150] and local circuitry [151]. The exact way in which early activity influences adult sensory perception is still debated. It has been hypothesized that spontaneous activity might present the specific brain area with activity statistics that are similar to those that it will be exposed to once it is fully developed [139]. From a predictive coding perspective, this would be akin to serving the role of providing the correct priors.

### Box 3. Anesthesia in the Developing Brain

Anesthesia is a behavioral state that is characterized by loss of consciousness, retrograde amnesia, immobility, and analgesia. Its neuronal correlates in the adult brain have long been characterized. With few exceptions (e.g., when ketamine is the main anesthetic), anesthesia induces a dramatic change in the dominant brain dynamics that are picked up by scalp EEG (mostly cortical activity). While during wakefulness low-amplitude and high-frequency oscillations prevail in the EEG signal, anesthesia shifts the regime towards slower oscillations of higher amplitude [152]. This phenomenon is so robust that it underlies the most common strategies used to monitor anesthesia depth during surgery [153]. Several of the pioneering studies on early brain activity, especially in rodents, were conducted under anesthesia. One might therefore ask to what extent such results are representative of what occurs in the non-anaesthetized brain. Anesthesia's effect on the immature brain is strikingly different from the adult case. In rodents, until the beginning of the second postnatal week, rather than slowing the dominant cortical rhythm, anesthesia enhances the discontinuity of the signal, leaving most of its spectral/dynamical properties relatively untouched [154]. Anesthetics increase the naturally occurring periods of electrical silence in several cortical and subcortical regions in a dose-dependent manner [154]. This is accompanied by a global decrease in firing rate and broadband suppression of LFP power that leaves the ratio of fast:slow oscillations relatively unaffected [154]. Similar findings have also been reported from scalp EEG recordings in humans of roughly equivalent age (i.e., preterm or newborn babies) [154,155]. The lack of frequency-specific effects of anesthesia on the immature brain is in stark contrast to what occurs in the adult brain and is thought to underlie the particularly poor performance of EEG-based anesthesia-depth monitoring methods in newborn babies [156]. In rodents, anesthesia begins to favor slow oscillations at the expense of faster ones around P12 [144], when activity starts to be continuous [144] and slow waves during sleep emerge [157]. In babies, such a shift occurs around 4 months of age, when anesthesia starts to induce theta and alpha oscillatory activity [158]. Of note, the age-dependent differences in how anesthesia impacts the brain somewhat resemble those of developmental changes in sleep patterns. At adulthood, deep non-rapid eye movement (REM) sleep favors slow and delta waves over faster frequencies [159]. By contrast, in preterm babies and in rats of less than 2 weeks of age, sleep increases signal discontinuity [160].

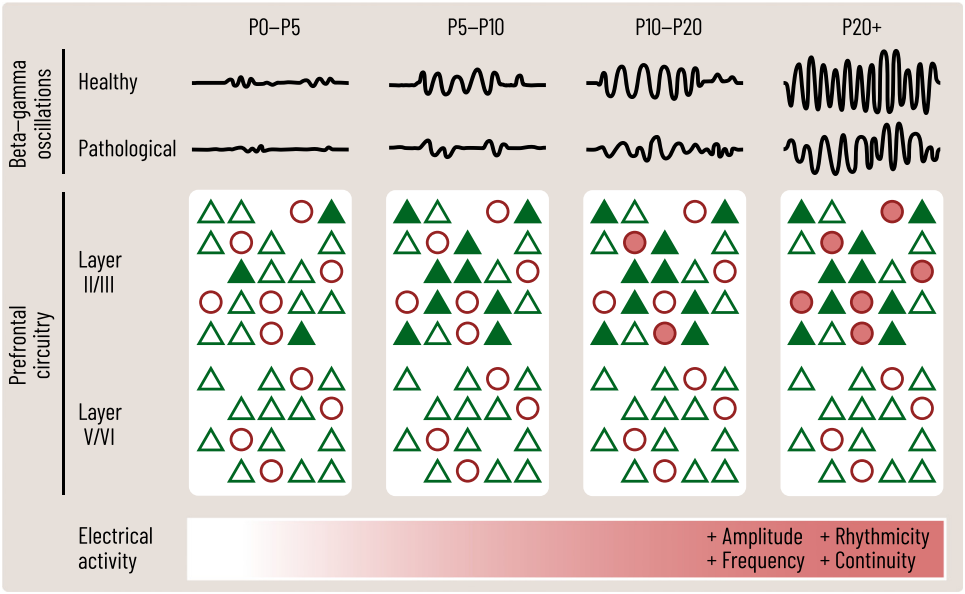


Figure 2. Schematic Representation of the Development of Beta–Gamma Prefrontal Oscillations in Health and Disease. Developmental time windows (top) refer to mice, indicated as postnatal days. Bouts of beta–gamma oscillations are one of the hallmarks of early prefrontal activity. In mice, they are mainly generated by layer II/III pyramidal neurons. In the first stages of development, when brain activity is highly discontinuous, these oscillations are slow (~15 Hz), have low amplitude, and are mostly bolstered by pyramidal neurons. As brain activity gradually becomes continuous and inhibition takes on a larger role, prefrontal oscillations increase in amplitude and frequency (~50 Hz). In mouse models of mental disorders that are often characterized by deficits in layer II/III pyramidal neurons, these rhythms are impaired throughout life, in a manner that is predictive of later-emerging cognitive deficits. In mouse models of schizophrenia, this impairment occurs in the form of beta–low-gamma oscillations of smaller amplitude and a more fragmented nature. Green triangles and red circles represent pyramidal and inhibitory neurons, respectively. Filled shapes depict neurons that are thought to actively participate in the generation of beta–gamma oscillations. Abbreviation: P, postnatal day.

simplified dendritic arborization as well as decreased spine density and firing rate of $PYRs_{II/III}$ underlies these abnormalities [31,42]. Further, selective disruption of this neuronal population recapitulates the phenotype of a pan-pyramidal neuron genetic mutation [52,53]. Intriguingly, excessive microglial pruning has been suggested as being upstream of these deficits [31,42]. It is therefore tempting to speculate that the interplay between activity and microglial phagocytosis might be one of the mechanisms through which early activity sculpts the developing prefrontal circuits. If reduced early $PYRs_{II/III}$ activity is deleterious, the opposite effect is equally detrimental. Unpublished results from our group suggest, for instance, that a protracted but subtle increase of $PYRs_{II/III}$ firing across the first two postnatal weeks results in long-term prefrontal microcircuit disruption and an excitation/inhibition (E/I) imbalance that worsens over time, equally leading to cognitive and social deficits [43]. Similar deficits have also been described in mouse models of autism spectrum disorder, which are characterized by increased prefrontal activity [54–56]. Another important piece of the puzzle is the role of inhibitory neurons in prefrontal development. Sparse experimental evidence suggests that developmental ablation of NMDA receptors on corticolimbic interneurons or disruption of MGE-derived interneurons results in altered prefrontal gamma activity [57,58].

Such a level of definition is difficult to attain in human studies. However, electroencephalography (EEG) recordings revealed patterns of coordinated activity in newborns and premature babies (Box 2). For example, early prefrontal activity and connectivity within the frontal networks of premature babies are reduced and relate to individual neurological performance [59,60]. Moreover, delayed maturation of prefrontal activity patterns has been shown to predict impaired behavioral abilities [61]. From the disease perspective, at adulthood, altered prefrontal activity in the gamma band is a robust biomarker for cognitive deficits in mental disorders [62,63]. Reduced spine density of layer III pyramidal neurons in schizophrenia patients has been proposed as an underlying disease mechanism [64]. Thus, converging evidence highlights the impact that $PYRs_{II/III}$ and early fast prefrontal activity have on the refinement of the prefrontal circuitry and the behavioral functions it subserves. Further studies are needed to uncover whether and how processes described in rodents relate to human circuit development.

## Input–Output Circuitry of the Developing PFC

The functional maturation of the PFC during early stages of development is driven by other cortical and subcortical regions. Among them, the hippocampal, thalamic, ventral tegmental area (VTA), and striatal projections play critical roles.

### Hippocampus

The hippocampus not only generates patterns of coordinated activity before the PFC but also critically contributes to its functional maturation [12,45]. In rodents, starting from the first postnatal days, distinct activity patterns characterize the hippocampal **local field potential (LFP)**. The most prominent are **sharp-wave ripple** events, which dominate hippocampal activity in the first postnatal week [65]. These hippocampal events are preceded by bursts of synchronous firing occurring in the entorhinal cortex, which, in turn, seem to be triggered by myoclonic movements [66]. Another hippocampal pattern is the network oscillations, whose dominant frequency ranges from theta to the beta–low-gamma range [12,45,65]. They organize single-unit firing around 8 Hz [52] and are driven by sensory [67] and motor [68] signals.

Already at neonatal age, the CA1 area of the intermediate and ventral hippocampus [45] represents a major source of glutamatergic input for the developing PFC [12,45,69]. Sharp waves induce a strong and long-lasting increase in prefrontal firing and a broadband increment of LFP power in neonatal mice [45]. Hippocampal theta bursts are relayed via monosynaptic axonal

projections to the deeper layers of PFC, where they boost intracortical coupling and the emergence of prefrontal oscillatory rhythms [12,45].

Disruption of hippocampal inputs to the PFC has life-long consequences for cognitive performance. Poorer working memory in schizophrenia patients and mouse models has been related to abnormal prefrontal–hippocampal communication [70,71]. This dysfunction emerges early in life and persists throughout the entire development, switching from insufficient to excessive hippocampal drive [52,72,73]. Correspondingly, developmental rescue of prefrontal–hippocampal communication in a mouse model of mental illness restores working memory deficits [74].

While probing the functionality of the hippocampal–prefrontal pathway in human babies is challenging, a study on newborns reported a temporal–frontal gradient in brain communication and maturation that might represent a functional equivalent of early rodent hippocampus–PFC synchrony [75]. Further, connectivity between the PFC and temporal areas is impaired in infants carrying mutations that predispose to mental disorders [76,77].

### Striatum

The PFC is involved in the formation of corticostriatal circuits that are relevant for motor skill acquisition, action selection, and planning. Already in the first postnatal week, the connectivity between the mouse neocortex and striatum is established, including a direct monosynaptic afferent pathway and indirect efferents via the mediodorsal thalamus (MD) [78]. This connectivity shapes striatal development and synaptogenesis [79]. The striatum is particularly sensitive to cortical inputs early in life, and this responsiveness decreases with age [56]. Early cortical hyperactivity, as described in mouse models of autism disorders, results in imbalanced striatal circuit development and behavioral abnormalities, such as repetitive behavior and increased anxiety [55,56]. The downstream striatal response to excessive cortical activity is twofold: at the beginning of the first postnatal week, it induces striatal hyperactivity and hyperconnectivity in cortical–striatal circuits, whereas the contrary occurs towards the third postnatal week [55,73]. Further, according to preliminary results, selectively increasing the firing of pyramidal neurons from P4 to P14 leads to an imbalanced prefrontal network, decreased corticostriatal connectivity at adulthood, and behavioral abnormalities reminiscent of autism spectrum disorder [54]. On the flipside, transiently increasing the activity of D2 dopamine receptors in the mouse striatum impacts prefrontal development and PFC-dependent cognitive abilities [80]. While connectomics investigations on the homology of corticostriatal circuits between mammalian species warrant some prudence when translating mouse data to humans [81], similar deficits have also been reported in the clinical human literature. Altered prefrontal and striatal activity is present in a correlated fashion in schizophrenia patients during the prodromal phase [82,83]. Moreover, corticostriatal connectivity is similarly disrupted in humans and mice carrying a genetic mutation in the NF1 gene, which predisposes to autism spectrum disorders [84].

### Thalamus and VTA

Several anatomical and lesion studies have documented the relevance of afferents from the MD and VTA to the PFC during development, but their early function is poorly understood. In rodents, a monosynaptic connection between the MD and PFC is already in place at P1, when the lamination of prefrontal deep layers is still immature and virtually absent in the more superficial ones [85,86]. This innervation pattern distinguishes the PFC from primary sensory cortices, where thalamic axons initially target the subplate and only around P3–P4 invade the newly formed cortical layers [10,85,86]. It is thus tempting to hypothesize that the early thalamic innervation of prefrontal layers contributes to the development of the supragranular layers. Despite the critical role of prefrontal–thalamic communication for executive functions in adult mice [87,88], and the fact that in

humans prefrontal–thalamic communication is disrupted in young adults carrying a 22q11.2 deletion [77], lesions of the rodent MD in the first postnatal weeks lead to only mild cognitive impairment [86]. More thorough functional investigations of this pathway throughout development are necessary. Similarly, the contribution of the ventral midline thalamus to the development of prefrontal circuits, and in particular of the nucleus reuniens, remains largely unknown, despite experimental data documenting the synchronization of the two areas in neonatal mice [89].

In rats, dense innervation from the VTA to the PFC has been described as already having a trophic function during the first postnatal week [90]. Dopaminergic axons reach the prefrontal subplate at embryonic stages of development [91]. After birth, these axons start to invade the cortical layers starting from layer VI and progressively reaching the more superficial ones [91]. At P4–P6, the VTA projections are thought to be functional but continue to grow in density, particularly in the superficial layers, where they reach maturity only weeks later. Developmental studies on the behavioral relevance of this pathway are scarce, but its neonatal lesioning has been found to alter behavioral responses to stress [92].

## Adolescent PFC as Substrate of Cognitive Maturation

With ongoing development from childhood to adulthood, prefrontal areas undergo massive changes as result of gray matter decrease, white matter augmentation, and myelination processes, which have been reviewed elsewhere [93]. In the human PFC, the exuberant synapse formation is followed by a decrease in spine density [18,94]. A similar phenomenon occurs in the PFC of mice, in which spine density and turnover both peak around P30 [33,34]. **Synaptic pruning** in the PFC is protracted compared with other neocortical areas and accompanied by augmented myelination [95]. This anatomical reorganization of the PFC during adolescence has profound functional implications that have been documented both in humans and rodents. Imaging studies showed that adolescents have less-focal patterns of activation than adults [96]. At this age, the PFC becomes more strongly linked to sensory and subcortical brain areas [97,98]. EEG recordings documented a frequency change of activity at rest, with a decrease at slower rhythms (0–7 Hz) and an increase at faster ones (7–30 Hz) [99,100]. Besides synaptic pruning [33,34] and refinement of oscillatory entrainment [12,101], major changes in cellular interactions in the adolescent rodent PFC have been documented. Parvalbumin expression increases [102] and the composition of GABA and NMDA receptors changes compared with earlier ages [103,104]. These developmental processes promote gamma oscillations, the power of which increases at adolescence [100,105]. Diverse experience (e.g., environmental exploration, sexual experience, social interactions, play behavior) profoundly impacts the development of prefrontal areas and contributes to the refinement of connectivity [106,107].

Flexible adaptation to new situational tasks, salience detection, attention, recognition memory, and working memory improve considerably around adolescence and have been linked, as highlighted above, to the functional development of the PFC [108,109]. These changes in cognitive processing mirror the dramatic reorganization of prefrontal networks during adolescence [110]. While several abilities, such as working and recognition memory, gradually improve with age, risk behavior is thought to peak at adolescence [111]. The mechanisms underlying this difference between the two developmental trajectories are largely unknown, but one of the leading hypotheses is that the risk-seeking behavior of adolescents results from the imbalance between early-maturating subcortical areas, involved in reward, and later-developing prefrontal areas, guiding control behavior [110]. The development of the reward-controlling dopaminergic system has been extensively investigated and reviewed elsewhere [112]. While starting in early childhood, the interactions between the dopaminergic system and the PFC strengthen during late development. The ingrowing dopaminergic innervation as well as the density of D1 and D2 receptors in

the PFC of both rodents and humans peaks during adolescence [113,114]. Dopamine has been shown to facilitate inhibitory circuit function and to decrease the E/I balance [115,116]. It may bias behavior towards risk and sensation seeking as well as cognitive flexibility, some of the most characteristic traits of adolescent behavior.

On the flipside, the high adaptability of the adolescent PFC might make it particularly vulnerable to abnormal formation and refinement of connections [112,117]. The considerable scientific interest in the adolescent PFC results from the dynamics of numerous psychiatric disorders, such as schizophrenia, anxiety, and depression, with onset of symptoms towards the end of this developmental period [95]. In line with the increased hormonal stress response, stressful experience of various kinds (e.g., social isolation, drug abuse) has a particularly strong impact at adolescence [118]. A prominent example of disease with adolescent onset and dual genetic–environmental etiology is schizophrenia [119]. Substantial efforts in schizophrenia research have focused on the development of strategies for risk prediction and early intervention [120]. One candidate is the coordinated oscillatory activity and neuronal dynamics [121,122] that reflect the altered connectivity of prefrontal circuits [123]. E/I imbalance and abnormal long-range connectivity have been hypothesized to underlie the behavioral deficits in schizophrenia patients and animal models of disease [124,125]. Weaker gamma band activity has been detected in high-risk individuals during the prodromal phase [122]. Moreover, interneuron hypomyelination throughout development has been related to cognitive inflexibility in a schizophrenia rat model [126].

Mirroring the profound dysfunction of prefrontal circuits, cognitive impairment represents a serious, life-long burden of mental illness [127]. Even before the emergence of clinical symptoms, poorer executive abilities have been detected in adolescent offspring of schizophrenia patients [128]. Similarly, memory deficits have been reported in mouse models of disease at juvenile age [42,72]. Adolescence has been proposed as a critical period for prefrontal function similar to that characterized in sensory systems [129]. Consequently, it might offer an appropriate time window for intervention/rescue. Understanding the mechanisms underlying prefrontal dysfunction at this stage as well as the identification of reliable biomarkers represent two critical steps for the development of future therapies and diagnostics.

## Concluding Remarks and Future Perspectives

Overviewing its functional complexity, the developing PFC appears as a neurobiological double-edged sword: it enables amazing complex cognition and social behavior, yet it underlies devastating symptomatology. While the maturation of PFC-dependent behaviors has been extensively investigated, the mechanisms of functional development of the PFC are less well understood. The knowledge gap is due to: (i) the lack of prefrontal homology across mammalian species; (ii) the protracted dynamics of developmental processes; and (iii) the absence of direct experimentally addressable links with the environment that differentiate the PFC from other neocortical areas (e.g., V1, S1, A1). Despite these difficulties, recent studies provided first insights into the wiring mechanisms of prefrontal areas and highlighted the role of genetic cues and electrical activity in health and psychiatric diseases.

The principles of PFC development have just begun to be uncovered. Several key questions still need to be addressed (see Outstanding Questions). The developmental features of disorders such as schizophrenia and autism remain largely unexploited partly because the principles of prefrontal development are poorly understood. To overcome this, at least two steps are necessary. First, clearer definitions of how prefrontal areas and developmental time windows compare across mammalian species would facilitate the translation of findings between species [2,4]. This will allow clearer understanding of the relevance of animal-model findings for human disease

## Outstanding Questions

How do molecules and signaling pathways interact to achieve the correct parcellation and structure of prefrontal areas? Are distinct molecular programs responsible for the structural differences across mammalian species?

How does (multi)sensory maturation impact the development of prefrontal areas and behavioral performance? When does sensory information reach the PFC? How is it represented? Does this occur at the same time for all sensory modalities? Is it equally as important for PFC maturation as the hippocampal drive? When does the PFC's role as a multisensory integration area begin?

Is there a human correlate to beta/low-gamma mouse rhythms?

Which mechanisms link prefrontal development and the emergence of cognitive flexibility, working memory, and attention? Is prefrontal function at early stages of development (perinatal, childhood) a prerequisite for the maturation of cognitive performance?

How do projection-defined prefrontal populations of neurons initially assemble to encode diverse tasks? How do they enable the switch between tasks?

Which specific prefrontal features (e.g., $PYR_{II/III}$ firing, power or rhythmicity of beta/gamma rhythms) are relevant for cognitive development? What is the minimal set of these features that should be restored in a mouse model of cognitive impairment to restore impaired cognitive abilities?

Do different prefrontal neuronal subpopulations, projecting to different brain areas, follow developmental trajectories with different time courses?

Does the PFC during 'critical periods' of augmented vulnerability (i.e., perinatal age and adolescence) show characteristic signatures of neuronal and network activity across species that might serve as biomarkers for disease?

How does behavioral maturation map onto biomarkers of functional maturation (e.g., prefrontal oscillations)?

and hopefully enable the identification of meaningful biomarkers. Second, we advocate for a detailed dissection of cellular and network interactions during development using recent powerful technologies such as high-density recordings, imaging, and optogenetics. Towards translation to humans, EEG/magnetoencephalography (MEG) approaches should be complemented by the investigation of human brain organoids [130], which appear to be a powerful tool for modeling cellular interactions, neural circuit dysfunctions, and the complex genetic landscape related to neurodevelopmental pathologies.

How is the crosstalk between the PFC and basal ganglia tuned across development? Do specific patterns of activity, topographically organized firing, or firing rates code the weight of the areas? How does this change over development, especially at adolescence when risk-taking behavior is a dominant trait?

## Acknowledgments

This work was funded by grants from the European Research Council (ERC-2015-CoG 681577 to I.L.H.-O.), the German Research Foundation (Ha 4466/10-1, Ha4466/11-1, Ha4466/12-1, SPP 1665, SFB 936 B5 to I.L.H-O.), and Landesforschungsförderung Hamburg (LFF-FV76 to I.L. H.-O.). I.L.H-O. is funding member of the FENS Kavli Network of Excellence. We thank Guido Hegasy (www.hegasy.de) for help with figure preparation.

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