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·Review·

Prefrontal cortical dopamine from an evolutionary perspective

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In this article, we propose the hypothesis that the prefrontal cortex (PFC) acquired neotenic development as a consequence of mesocortical dopamine (DA) innervation, which in turn drove evolution of the PFC into becoming a complex functional system. Accordingly, from the evolutionary perspective, decreased DA signaling in the PFC associated with such adverse conditions as chronic stress may be considered as an environmental adaptation strategy. Psychiatric disorders such as schizophrenia and attention deficit/hyperactivity disorder may also be understood as environmental adaptation or a by-product of such a process that has emerged through evolution in humans. To investigate the evolutionary perspective of DA signaling in the PFC, domestic animals such as dogs may be a useful model.

Keywords: neurodevelopment; neoteny; psychiatric disorder; stress; animal model; synaptic plasticity; environmental adaptation

Introduction

The prefrontal cortex (PFC) is one of the central brain regions that mediate higher cognitive and affective functions[1, 2]. Extensive investigations have unveiled the mechanisms of neuronal network information-processing as well as the genetic and molecular machinery underlying PFC functions. The PFC is also suggested to be evolutionarily the latest component of brain structure, and therefore it plays the most important role in organizing human-specific behavioral traits[1, 3, 4]. Nonetheless, how the PFC evolved into the complex system in humans remains unclear.

The mesocortical dopamine (DA) projection into the PFC from the ventral tegmental area of the midbrain is essential for PFC functions (for an extensive review, see Seamans and Yang[5]). In this article, we propose the hypothesis that the mesocortical DA projection into the PFC is one of the biological substrates involved in the evolution of the PFC. Moreover, this evolutionary process may have resulted in the emergence of psychiatric disorders such as schizophrenia and attention deficit/hyperactivity disorder (ADHD).

Mesocortical DA Regulation of PFC Development

DA innervation of the cortex is more restricted than those of serotonin (5HT) and norepinephrine (NE). NE projections arising from the locus coeruleus and 5HT projections from the dorsal raphe cover almost the entire cortex, from the frontal cortical area to the posterior parts including the visual cortex[6]. In contrast, DA projections are distributed primarily to the frontal and temporal cortex, and other cortical areas lack this innervation[7].

The development and maturation of the cortical areas innervated by DA appear to be slower than other cortical areas lacking DA innervation. A human imaging study has shown that development of the frontal and temporal cortex continues into young adulthood, much later than in other cortical areas[8]. Accordingly, DA receptor expression (both D1 and D2) changes dynamically until early adulthood[9], and this coincides with maturation of the PFC. Such

PFC DA receptor expression dynamics may impact PFC development (e.g. delaying developmental processes if DA signaling affects developmental timing or rate). In addition, the N-methyl-*D*-aspartate (NMDA) receptor has also been suggested to play an important role in neuronal development[10]. Recent studies have shown that the DA receptor is functionally and physically[11, 12] coupled to the NMDA receptor. Thus, lower DA receptor expression during early development could also influence NMDA receptor-dependent developmental processes. Such observations provide the insight that there may be a relationship between delayed cortical development/maturation and the DA projection to the cortex.

Several lines of evidence suggest that DA signaling influences PFC development. First, Lumbe and colleagues examined the development of DA and serotonin (5HT) projections into the PFC in non-human primates at different ages using immunohistological staining to assess the density of fibers containing tyrosine hydroxylase and 5HT that contact PFC pyramidal neurons[13]. They found that the DA projection does not fully mature until early adulthood. In contrast, the 5HT projection is already mature at an early developmental stage. These findings suggest that DA development is an important factor that may determine the timing of PFC development and maturation.

Studies have also investigated the effects of neonatal DA depletion by 6-hydroxydopamine injection into the PFC of rodents. Kalsbeek and colleagues reported that PFC pyramidal neurons in adult rats with neonatal DA depletion are smaller with shorter dendritic lengths[14]. Such morphological changes can be interpreted in two ways: one is that the morphology of mature PFC pyramidal neurons in adult animals that develop without DA signaling resembles that of immature neurons; and the other is that such morphological changes may indicate atrophy of the fully mature form of neurons. However, the latter interpretation is unlikely, since DA depletion is given in the neonatal period before the proliferative growth of neurons. In addition, the PFC volume in rats with neonatal DA depletion is larger than that of normal rats[15], contradictory to the case of atrophy in which shrinkage of neurons and thereby smaller volume are expected, although such enlargement of the volume may be attributed to the proliferation of glial cells, not neurons.

Decreased mesocortical DA transmission has been suggested in the pathophysiology of ADHD[16]. Then, if DA signaling affects PFC development, alterations of its developmental rate would be expected in ADHD children. A magnetic resonance imaging study of ADHD children[17] has revealed that development of the gray matter volume in the PFC is significantly delayed compared to controls. This finding further supports the hypothesis that DA is a biological substrate that promotes PFC development.

Several studies have shown that DA and stimulation of DA receptors facilitate neuronal growth[18-20]. However, these studies used striatal neurons; so, such molecular mechanisms of DA-dependent facilitation of neuronal growth may not necessarily be applicable to PFC neurons. Nevertheless, these studies still support the idea that DA signaling is involved in the regulation of neuronal development.

Collectively, mesocortical DA may play an important role in the PFC developmental process, particularly in regulation of the timing and rate of development and maturation. Thus, PFC development and maturation may be delayed as a consequence of DA innervation, which does not mature until adulthood (Fig. 1). On the other hand, the cortical areas lacking DA innervation develop and mature faster than the PFC. However, this does not mean that DA is the sole determinant of developmental processes in the PFC. Indeed, it is possible that other neurotransmitters are also involved.

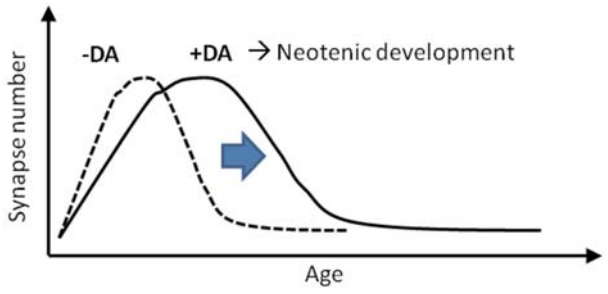

Fig. 1. Schematic illustrating delayed PFC development and maturation in terms of synaptogenesis and elimination of pyramidal neurons with mesocortical DA signaling. In PFC pyramidal neurons, the synapse number increases with growth. Then, during adolescence, synaptic elimination takes place to refine the neuronal networks[22]. This process is delayed with DA innervation, which continues in the PFC until adulthood.

Neotenic PFC Development with DA Signaling

Based on the above evidence, we propose the hypothesis that mesocortical DA signaling is an important biological substrate for evolution of the PFC, enabling neotenic development.

Neoteny is the retention of juvenile traits in adults, and is thought to be an important factor in evolution, as it provides greater flexibility in adapting to the environment by delaying the development of organs for specific functions[21]. Indeed, the sexual maturation of humans takes up to two decades, much longer than in any other animal[22].

The development and maturation of the PFC in terms of synaptic spine density on dendrites of pyramidal neurons have been shown to continue until early adulthood in humans[23], non-human primates[24], and rodents[25]. A more recent study has suggested that the maturational process of the PFC could be even longer, continuing until the thirties in humans[26]. Therefore, neotenic development is one of the most characteristic features of the PFC. Such delayed development may have enabled the PFC to evolve into a highly complex system to mediate an assortment of cognitive and affective functions.

In order to establish this hypothesis, an intrinsic correlation between evolutionary and developmental processes is required. Indeed, it has been suggested that evolution and development have strong relationships, as reflected in the field of evolutionary developmental biology or "evo-devo"[27]. One of the key concepts of evo-devo is heterochrony, which refers to changes in the timing and rate of development of organisms, including neoteny. Genetic (e.g. homeobox genes) and morphological evidence that supports the critical roles of such heterochronic processes in evolution has been reported[28-33].

Reduced PFC DA Signaling as an Environmental Adaptation Strategy in Evolution

Our hypothesis predicts that mesocortical DA signaling plays an important role in neotenic development, and thereby the evolution of the PFC, especially when DA signaling is lower than normal. In this regard, it is important to note that although decreased DA signaling is usually considered deficient and abnormal from the perspective of conventional neuroscience, it could be advantageous from the evolutionary perspective. How could decreased DA signaling in the PFC, which has been shown to cause cognitive and affective dysfunction [5, 34], be advantageous?

Stress alters DA release in the PFC in rodents and primates[35]. Although brief, acute stress temporarily increases DA release in the PFC[36], more severe, chronic stress decreases basal DA tone regardless of the stress type (e.g. restraint[37] or cold[38]) in adult animals. However, the effects of chronic stress on PFC DA release in the adult brain may differ from that in the developing brain. For instance, Giovanoli and colleagues[39] recently reported that exposure of adolescents to chronic stress affects 5HT, but not DA, in the PFC. This study provides additional insights into our hypothesis. First, this study assessed the content but not the release of DA and 5HT in the PFC. The absence of a change in DA concentration in the PFC with stress suggests that chronic stress affects the release but not the synthesis of DA. In addition, in this study, the effects of chronic stress in adolescence were examined in adulthood; but the effects of stress may not be persistent, but could be reversible and recover with time. Therefore, delayed PFC development with decreased DA release may be evident only when organisms are under chronic stress, and once the situation improves, the developmental rate may return to normal. Finally and most importantly, this study used variable stress procedures (5 different stressors, applied on alternate days, between postnatal day 30 and 40). Stress-induced changes often differ depending on the environment in which stress is generated. For instance, chronic restraint but not unpredictable stress induces amygdala-dependent brain and behavioral changes[40]. This suggests that the environment in which stress is generated determines how the stress-induced changes take place, whereas stress (e.g., stress hormones) and associated changes such as decreased DA release may rather signal or trigger subsequent environment-dependent changes. The unpredictable stress procedure was probably developed for animal studies, given that animals tend to show habituation against repeated exposure to identical stressors, making unpredictable stress more convenient in the experimental setting. However, it is important to note that it is uncommon in real life (both in humans and animals) for stressful environments to change rapidly from day to day. In our hypothesis, an adaptation process would take place under

a particular environment that causes stress for a prolonged period. Therefore, even if the stress exposure is sufficiently long, adaptation may not occur when the environment is rapidly changing.

Many studies have been conducted to reveal *how* chronic stress decreases DA signaling in the PFC (i.e. Tinbergen's proximate view, which questions a mechanism of function of a system[41]), and many of the molecular and cellular mechanisms underlying this process are known[34]. In contrast, *why* DA signaling is decreased in the PFC by chronic stress (i.e. Tinbergen's ultimate view, which questions an evolutionary origin of function of a system[41]) has not yet been explored. However, there must be a reason that DA signaling in the PFC is decreased by chronic stress.

Rodents and primates are estimated to have diverged ~100 million years ago[42]. Given that chronic stress induces similar, if not identical, cognitive and affective deficits as well as associated brain changes such as decreased DA signaling both in rodents and primates, these "disadvantageous" phenotypes were already present in mammals before this divergence, and have been maintained for >100 million years. Darwinian evolutionary theory (natural selection)[43] suggests that, if the chronic stress-induced decrease in DA signaling in the PFC and the consequent changes in PFC-dependent cognitive and affective processes were disadvantageous for survival, such phenotypes should have vanished. Therefore, even though decreased DA signaling and altered PFC function have major disadvantages in the normal environment, such phenotypes may still be advantageous for survival in specific environments that cause chronic stress.

If decreased DA release delays PFC development, then chronic stress during development would also delay PFC maturation. There is no direct evidence to support this idea, and further investigation is needed. However, there are reports that children exposed to stress due to family problems exhibit delayed physical[44] and mental[45] development, indirectly supporting our hypothesis.

If chronic stress and associated brain changes have played a role in the evolution of the brain, such stress-induced alterations should be inheritable. A brief report of transgenerational inheritance of stress-induced alterations appeared in 1970[46]. However, this study was largely ignored until recently when the transgenerational inheritance of epigenetic changes was confirmed. Behavioral changes caused by neonatal[47] or adult[48] exposure to stress have been recently reported again, confirming that stress-induced changes are inheritable. It appears that the inheritance of these environmentally-induced (or acquired) phenotypes involves epigenetic mechanisms[47, 48]. Since these studies have followed two or three generations at most, it is still unclear whether such stress-induced epigenetic changes can be translated into equivalent genetic changes for inheritance across generations. Nevertheless, domestication processes in chicken[49] and silkworm[50] have been reported to involve epigenetic inheritance. Importantly, these studies raise the question of why stress-induced changes, which are thought to be "deficits" and therefore disadvantageous phenotypes, are inherited and the biological mechanisms mediating them are still found in organisms.

Taken together, chronic stress could be a driving force for PFC evolution, and the consequent decrease of DA signaling may provide greater flexibility to the PFC for developing into a more complex system with neotenic development to adapt to or overcome severe environmental conditions (Fig. 2).

Psychiatric Disorders Associated with Lower PFC DA Signaling

Decreased PFC DA release has been implicated in psychiatric disorders such as ADHD[51] and schizophrenia[52]. The third implication of our hypothesis is that such disorders may not necessarily be considered deficits, but could rather be understood as an environmental adaptation strategy (i.e. ADHD) or a by-product of adaptation (i.e. schizophrenia) that has emerged through evolution in humans.

ADHD

ADHD is one example of a psychiatric condition that could illustrate the beneficial effects of decreased DA signaling in the PFC. ADHD is a childhood-onset condition with core symptoms consisting of hyperactivity, impulsivity, and attention deficit (short attention span). These behaviors have been associated with decreased DA release in the PFC in animal studies[53-55]. Although these symptoms

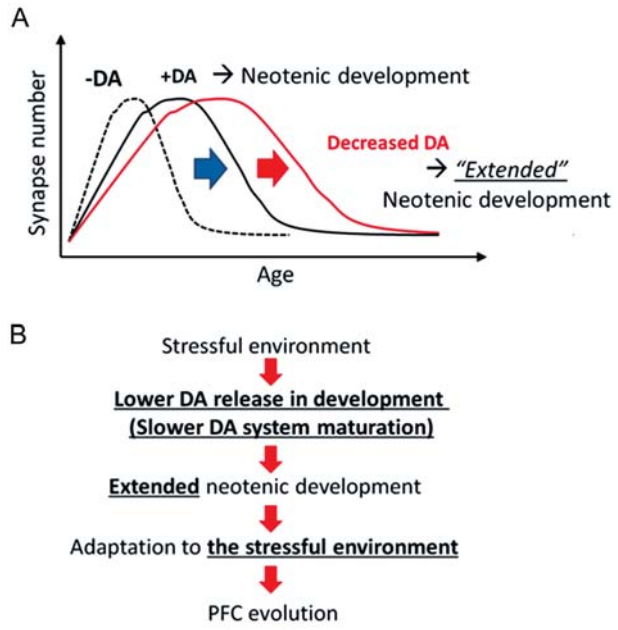

Fig. 2. Diagrams illustrating the process that, from an evolutionary perspective, lower mesocortical DA may play a beneficial role in the PFC. A: Schematic of the extension of delayed PFC development and maturation expected with lower DA signaling during the developmental process. B: Flowchart of the hypothetical evolutionary process of the PFC with mesocortical DA signaling driven by severe, chronic stress.

are problematic in modern human society such as school life, and therefore have to be treated, they still yield clear advantages for survival in severely stressful environmental conditions where life is threatened[56]. Hyperactivity enables constant exploration of the environment for the faster detection of threats. Similarly, attention deficit with inability to sustain attention to a particular target enables shifting of attention and scanning from one object to another to monitor threats. Impulsivity also allows rapid responses to escape from dangers.

How delayed maturation with decreased DA signaling in the PFC is associated with ADHD is still unclear. For instance, in animals living in the wild, faster maturation appears to be advantageous to escape from predators. Nevertheless, ADHD-like behavioral changes with decreased DA release in the PFC can be considered as a trade-off mechanism, such that delayed maturation exposes animals to more dangers, but ADHD-like behavioral changes reduces them.

Schizophrenia

Reduced DA function in the PFC has been suggested in schizophrenia[52]. In addition, stress appears to be an important factor, such that stress exposure often precedes the first episode of symptoms as well as exacerbating or precipitating symptoms[57, 58].

Various environmental and social conditions can be sources of stress. From the conventional viewpoint, environmental and social enrichment is usually considered beneficial, whereas a poor environment and social isolation are deficient for social organisms. However, it is important to note that exaggerated environmental and social enrichment can also be stressful. For instance, people living in cities, where the environmental complexity is great, are exposed to stronger stress than those living in rural areas[59]. Commuters during rush hours also suffer high-intensity stress[60]. Therefore, crowding within a group can be stressful to social organisms. Stress with excessive social crowding is particularly interesting, since it can generate evolutionary pressure to cope with such conditions, by developing an adaptation strategy to better assess the behavior or mental states of others, i.e. a theory of mind (ToM)[61, 62]. Indeed, PFC activity has been shown to be associated with ToM[63]. Mirror neurons, which become active during both motor action and the observation of such action by others, are found in the PFC[64]. The mirror neuron circuit, involving the PFC and DA release in this region, plays an important role in understanding the behavior and emotional states of others[65]. Therefore, one scenario is that stress with overcrowding in a tribe may cause decreased DA release in the PFC, which is a signal or trigger to develop a strategy, ToM, as an adaptation to this specific stressful environment through evolution.

In this process, decreased DA may be just a signal or trigger for adaptation by delaying development, and thereby providing a longer adaptation period. Therefore, delayed development by itself does not yield specific adaptation. How adaptation takes places depends on the specific environment, such that adaptation could involve as many changes as there are stressful environments to which organisms are required to adapt. Indeed, stress is associated with various environmental factors (sych as social isolation, social crowding, social defeat, physical pain, and restraint), such that adaptation to stressful environments

does not involve only one change, but can include as many changes as there are different stressful environments. How the system changes for adaptation depends on the types of stressors. Therefore, adaptation to stressful environments can vary, and the psychiatric conditions that emerge from such processes could also be variable and different. The evolution of such an adaptation strategy most likely needs multiple generations. Thus, this argument does not imply that organisms with decreased PFC DA release immediately develop advantageous strategies, including ToM, as adaptive responses to stressful environments.

ToM deficits have been reported in schizophrenia[66, 67] and autism[61]. Nevertheless, the bases of these deficits may differ between the disorders. Crespi and Badcock have suggested that schizophrenia and autism are diametrically opposite psychiatric conditions, autism associated with underdeveloped ToM, and schizophrenia associated with overdeveloped ToM[68]. Overdeveloped ToM can passably explain the positive symptoms of schizophrenia such as paranoia and delusions. Schizophrenic patients often claim that they are controlled by TV, or neighbors are spying on them. These claims illustrate that patients peculiarly find that inorganic objects have minds like living organisms, or have a distorted understanding of the mental state of others.

Some of the schizophrenic symptoms may emerge as a by-product of the evolutionary process of ToM function as an adaptation strategy for stress associated with overcrowding within a group. This speculation is also consistent with the evolutionary psychiatric hypotheses proposed by Burns that schizophrenia emerged as a by-product in the evolution of human social behavior[69], by Stevens and Price that schizophrenia is an advantageous evolutionary phenotype playing the role of splitting a group when the population becomes too large[70], and by Saugstad that the less clear cerebral lateralization in schizophrenia is associated with late, slow maturation of the cortex[71]. On the other hand, social isolation can also be stressful, which could generate an evolutionary pressure for an adaptation strategy against isolation. Such evolutionary pressure may be the basis of the autistic phenotype.

Predictions and Experimental Approaches

Predictions Based on the Hypothesis

Our hypothesis suggests that cortical areas such as the visual cortex where DA innervation does not develop mature faster than cortical areas such as the PFC with DA innervation, since mesocortical DA signaling is involved in the development of the PFC neuronal network, but the mesocortical DA system does not mature until adulthood. Development of the PFC consequently continues until adulthood when the mesocortical DA system also matures. Our hypothesis therefore predicts that PFC development and maturation are accelerated by the augmentation of mesocortical DA signaling (e.g. pharmacological treatment such as psychostimulants). In contrast, PFC development and maturation are extraordinarily delayed by the attenuation of mesocortical DA signaling (e.g. pathological changes suggested in ADHD delayed development of the PFC[17] or DA fiber depletion by 6-OHDA).

Such a prediction appears to be partly supported by recent studies suggesting that addictive drugs that increase DA release accelerate aging[72-77]. These studies have shown that chronic abusers of amphetamines, cocaine, and alcohol exhibit cognitive decline and greater cortical atrophy indicative of accelerated aging. A study by Cheng and colleagues has shown that heroin abusers exhibit lower telomerase activity, which results in shorter telomeres, the biological marker of aging. Moreover, such lower telomerase activity is correlated with PFC gray and white matter thickness in abusers[78]. The possibility of accelerated aging by DA agonists is also interesting in relation to ADHD treatments in which DA agonists such as methylphenidate have been used. Given that ADHD may involve delayed development[17], the therapeutic effects of DA agonists in ADHD may be achieved not only by increased DA transmission, but also by accelerating aging. Indeed, development and aging could be distinct processes, and therefore the mechanisms involved in aging may not necessarily be similar to the mechanisms involved in neuronal development and maturation.

Empirical Approach

Several experimental approaches may confirm or refute the hypothesis. Many studies have already investigated the effects of physical, pharmacological, and psychological manipulations that alter PFC DA release on PFC function. However, very few have examined the impact of these manipulations on PFC development. Thus, investigations focusing on changes in the developmental trajectory of

PFC neuronal networks (timing and speed of synaptic growth and pruning, which could be measured by dendritic spine quantification[79] or expression of synapse-associated molecules such as synaptophysin[80]) caused by manipulations such as local DA depletion with microinfusion of 6-OHDA into the PFC, chronic exposure to stress (e.g. maternal deprivation[81]), and repeated psychostimulant administration given at an early stage of development in animals, would be promising for testing the hypothesis.

Domestic Animals: a Model of PFC Evolution with DA

An alternative approach to investigating the evolutionary role of mesocortical DA in the PFC may lie in the use of domestic animals.

Domestication is a process of selective breeding that reduces aggression and facilitates sociality in animals due to decreased intra- and inter-species competition for resources. Such domestication is not necessarily achieved by human hands only, but could be a self-generated, i.e. self-domestication, as has been suggested in bonobos[82]. In particular, domesticated animals exhibit neotenic features (delayed development, maintaining juvenile morphological features into adulthood) and higher cognitive function and sociality, which are associated with PFC activity, than wild animals[82]. In particular, domesticated animals include laboratory rodents (e.g. ICR mice, Sprague-Dawley rats), which are commonly used in biomedical research. It is possible that PFC function and associated DA transmission in the PFC differ significantly between laboratory mice/rats and wild rodents (e.g. MSM mice). Comparison between laboratory and wild rodents for associations between cognitive function and social behavior and PFC neuronal network morphology, plasticity, volume, and DA levels would be promising. In support of this approach, a recent study by Takahashi and colleagues has reported differences in social behavior between laboratory and wild mice[83].

The use of dogs as a model for understanding human social behavior has been proposed[84, 85]. The advantages are as follows. Individuals diagnosed with psychiatric disorders are considered to have abnormal social relationships partly because they are a minority within the population, and do not fit into a society where the majority of (normal) individuals lack phenotypes associated with disorders. A similar relationship can be applied to domestic and wild animals. In particular, the social behavior of dogs is quite distinct from that of wild animals. Such social behavior in dogs that appear to have evolved as human companions may be considered as "abnormal" behaviors from the viewpoint of wild animals.

Dogs also vary in their neotenic features. Some breeds such as huskies and corgis in adulthood have a less neotenic appearance and look closer to the wild-types such as jackals and coyotes, whereas other breeds such as Saint Bernards and Great Pyrenees exhibit a stronger neotenic appearance, maintaining a juvenile-like appearance as adults[86]. In particular, neotenic appearance and cerebral DA level are correlated in dogs[86, 87]. Thus, breeds close to the wild-type and displaying a less neotenic appearance have higher cerebral DA levels than those with a more neotenic appearance[86, 87], further supporting our hypothesis of a relationship between lower DA levels and neoteny. Another advantage of using dogs for investigation is that they have a clear phylogeny, which enables investigators to follow their evolution relatively easily.

It is also interesting to note that unlike in humans, spontaneously-occurring neurological disorders such as Alzheimer's disease or Parkinson's disease are extremely rare, if they occur at all, in wild animals including non-human primates without artificial genetic or pharmacological manipulation. Dogs are an exception. They show spontaneously and endogenously-occurring Alzheimer's disease-like alterations in their brains[88] which, although not necessarily related to neotenic development of the PFC with DA signaling, illustrate that dogs have acquired a brain system that is closer to that of humans than other wild animals through evolution by domestication. Therefore, dogs could be a good model to understand how evolutionary change pertains to the emergence of human-specific brain disorders[89].

Conclusions

We have proposed a hypothesis that mesocortical DA plays a specific role in the development and evolution of the PFC. However, our hypothesis has several limitations. For instance, DA transmission in the PFC is regulated by brain areas such as limbic structures[90] and diencephalic nuclei including the habenula[91]. These structures and other parts

of the brain that regulate PFC DA release are relatively conserved across species (i.e. evolutionarily old brain areas), suggesting that, although this possibility cannot be excluded, decreased DA levels in the PFC may not be a consequence of altered regulatory mechanisms by other brain structures, but is more likely the result of an intrinsic change within the PFC selected through evolution. In addition, since our hypothesis is based on disorder models such as ADHD, schizophrenia, and chronic stress, it may be that these disorders involve brain mechanisms other than DA and PFC. However, this problem may be partly overcome by using multiple disease models. Thus, each disorder involves various mechanisms, and the differences between these mechanisms may create different conditions in the disorders, although one mechanism is common across the disorders (e.g. ADHD involves mechanisms A, B, and C, whereas schizophrenia involves mechanisms A, D, and E, and chronic stress involves mechanisms A, C, and F...). If the argument (i.e. role of DA in PFC development) is supported by all of these different conditions of disorders, then, the mechanism in this argument is most likely the one that is common across the disorders (i.e. DA change in the PFC), but not other mechanisms.

In conclusion, an evolutionary perspective for understanding the role of neurochemicals such as DA and their relation to brain disorders may open a new venue in neuroscience.

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