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Dopamine effects on stress-induced working memory deficits

Zahra Bahari[a,b], Gholam H. Meftahi[b] and Mohammad A. Meftahi[c]

The prefrontal cortex (PFC) plays a critical role in mediating executive functions and orchestrating the way in which we think, decide, and behave. Many studies have shown that PFC neurons not only play a major role in mediating behavioral responses to stress but are also sensitive to stress and undergo remodeling following stress exposure. Activation of the hypothalamic–pituitary–adrenal axis as a result of stress initiates a flood of alterations in prefrontal neurotransmitter release. Dopamine (DA) neurotransmission in the PFC is involved in the modulation of stress responsiveness. Compelling results show that stressful events are associated with increased DA concentrations in the medial PFC. Excessive DA-ergic activity in the medial prefrontal cortex following stress has a negative impact on working memory and executive functions in rodents, monkeys, and humans, making them unable to processing information selectively and impairing cognitive function. Therefore, an exact understanding of these mechanisms may provide important insights into the pathophysiology of executive dysfunction and novel treatment avenues. The present review provides a summary of the neuronal circuitry involved in alterations of PFC dopaminergic neurons under conditions of stress, and then addresses the interaction of PFC DA with glucocorticoids leading to impairment of working memory under conditions of stress. *Behavioural Pharmacology* 00:000–000

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Introduction

Our ability to manage, update, and act on information in the absence of external cues is important to daily functioning. These executive functions depend on the structural and functional integrity of the prefrontal cortex (PFC), a highly evolved brain region (Dalley *et al.*, 2004; Arnsten and Li, 2005). The PFC creates a mental sketch pad through neuronal networks that can maintain information in the absence of external cues, and use this knowledge to manage our behaviors. Neuroscientists referred to this process as working memory. Working memory helps us to keep in mind an event that has just occurred, or bring to mind information from long-term storage that is no longer present in the environment (Eriksson *et al.*, 2015). The PFC is able to protect this flexible knowledge from interference by external or internal distractions. Furthermore, The PFC also monitors errors, providing us the insight that we are incorrect and need to shift strategies (Arnsten, 2009).

These capabilities depend on appropriate PFC neuronal network connections, which are very sensitive to their neurochemical environment. There is growing evidence that stress can induce changes in PFC neuronal structure and also impairs executive functions such as working memory in rodents and primates (Arnsten, 2009; Holmes and Wellman, 2009). Indeed, studies in humans, monkeys, and rats have shown that acute exposure to mild uncontrollable stress impairs cognitive functions associated with the PFC (Arnsten *et al.*, 2015a, b). Thus, the identification of central stress mechanisms might lead to better treatments for neuropsychiatric disorders. Under stress-free situations, neural networks within the PFC work together to inhibit inappropriate responses (Goldman-Rakic, 1995). However, exposure to stress can disrupt PFC function, markedly impairing working memory (Arnsten *et al.*, 2012). Therefore, stress-induced alterations in PFC function show important neural deficits in the executive function of stressed animals, and also the executive components of many neuropsychiatric diseases.

It is clear that dopamine (DA) neurotransmission in the PFC is involved in the modulation of stress responsiveness. Disruption of DA-ergic transmission under conditions of stress results in cognitive dysfunction. The current review focuses on the DA modulation of PFC neuronal circuits in stressful situations. We begin with a brief note on neuronal organization of the PFC in rodents because the circuitry and physiology of the PFC neurons in rodents are the best characterized. We then discuss four important neuronal pathways in the PFC that are involved in stress-induced responses. It is accepted that the DA-ergic innervation of the PFC originates from the midbrain DA-ergic system (Motahari *et al.*, 2016; Mohammadian *et al.*, 2017). Therefore, we review the reciprocal connections between the midbrain DA-ergic system and PFC. Next, we discuss the increased

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DA-ergic activity within the PFC and midbrain system under conditions of stress. Finally, we review the literature that addresses how changes in DA release impair working memory under conditions of stress.

Neuronal organization of the prefrontal cortex in rodents

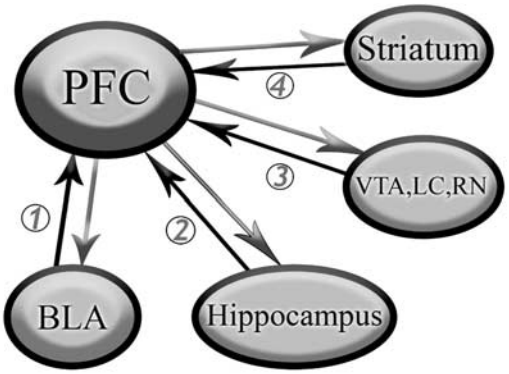
The rodent provides an invaluable model system for studying neural processes underlying complex behaviors, including higher order cognitive and executive functions. The PFC shows many alterations between species in anatomical criteria such as cytoarchitectonics, circuitry, and histology, especially the presence or absence of a granular zone (Uylings *et al.*, 2003; Holmes and Wellman, 2009). The PFC in rats is most commonly divided into two main subregions: the medial prefrontal cortex (mPFC) and the orbitofrontal cortex (Paxinos and Franklin, 2001). These areas are further subdivided into different subregions. The mPFC is comprised of the infra-limbic (IL), pre-limbic (PL), and dorsal anterior cingulate cortex (ACd). The orbitofrontal cortex is comprised of the medial (MO), ventral (VO), and lateral orbital (LO) subregions (Dalley *et al.*, 2004).

Important pathways in the prefrontal cortex that modulate stress

One of the important clues in the better understanding of the neuronal pathways of the PFC in stress situations lies in the answer to the following question: what information reaches the PFC and which brain regions are influenced by this area? The majority of neural connections within the PFC and its anatomical connectivity with the other areas of the brain make it ideally positioned to orchestrate higher order behavioral functions. We will not attempt to describe this extensive network in detail. However, we will discuss four important pathways in the context of PFC modulation of stress (Fig. 1).

The first pathway comprises reciprocal projections between the mPFC and the basolateral nucleus of the amygdala (BLA) (Bacon *et al.*, 1996). As the amygdala is an important region for expression of negative emotions (such as fear memory) and motivational aspects of behavior, the BLA is in a strategic position to mediate our cognitive processes (Davis and Whalen, 2001; Adolphs, 2002; Amaral *et al.*, 2003; Phelps, 2004; Banks *et al.*, 2007). Furthermore, it has been shown that extinction of fear memory requires plasticity in both the mPFC and the amygdala. These brain areas are also key structures in mediating the response to stress. Therefore, the BLA makes a critical contribution in the initiation of fear responses and emotions to stressful events (Akirav and Maroun, 2007; Sadeghi-Gharajehdaghi *et al.*, 2017). There is growing evidence that afferents from the mPFC to the amygdala inhibit the expression of fear, which supports the likelihood that fear extinction may depend on increased neuronal activity in the mPFC (Cho *et al.*, 2013).

Fig. 1



Four important pathways in the context of prefrontal cortex (PFC) modulation of stress. The first pathway is reciprocal projections between PFC and basolateral nucleus of the amygdala (BLA). Second, there is a clear reciprocal relationship between the hippocampus and PFC. Third, PFC also has reciprocal connections with the major brainstem nuclei and midbrain monoaminergic systems, including the ventral tegmental area (VTA), locus coeruleus (LC), and raphe nuclei (RN). Finally, the PFC is highly interconnected with the striatum.

Second, there is a clear direct relationship between the hippocampus and PFC in rodents, monkeys, and humans (Rocher *et al.*, 2004). In rats, the pre-limbic cortex is the PFC region where most of the hippocampal terminals are localized. Exposure to acute stress can impair hippocampal function in rats (Diamond *et al.*, 1992; Shakesby *et al.*, 2002) and subsequently produce working memory impairment in rats and monkeys (Murphy *et al.*, 1996).

Third, the PFC is highly interconnected with striatal regions. Evidence from a range of species suggests that anatomically circuitry linking the PFC and the striatum is involved in various aspects of cognition, including working memory and attention (Christakou *et al.*, 2001, 2004, Dalley *et al.*, 2008). Several studies show that the basal output of DA terminals in the medial striatum is under a tonic excitatory control from the PFC (Karreman *et al.*, 1996).

Finally, the PFC also has reciprocal connections with the major brainstem nuclei and midbrain monoaminergic systems, including dopaminergic (DA-ergic), noradrenergic (NA), or serotoninergic (5HT) neurons, that are activated by stress. Ascending DA, 5HT, and NA neurons, which originate, respectively, from the ventral tegmental area (VTA), the raphe nuclei, and the locus coeruleus, markedly modulate neuronal activity in the PFC (Thierry, *et al.*, 1991).

The reciprocal connections between prefrontal cortex and the midbrain dopaminergic system

The exact role of DA in the modulation of PFC function under conditions of stress is far from clear. It is accepted that PFC DA innervation originates from the brainstem

mesencephalon (Lindvall *et al.*, 1984; Mohammadian *et al.*, 2017). The midbrain DA neurons originate from the substantia nigra pars compacta (SNc) and VTA, which innervate different brain areas through three major pathways. The first is the nigrostriatal pathway, which originates in the substantia nigra pars compacta and projects to the dorsal striatum and participates in motor control (Grace *et al.*, 2009). The second is the mesolimbic system, which originates in the VTA and projects to the limbic structures such as the ventral striatum (NAc and olfactory tubercle) and amygdala. This pathway has been proposed to be the major mediator for behavioral responses to reward, reinforcement, and responses to emotional and stressful conditions (Pierce and Kumaresan, 2006). The third pathway is the mesocortical DA pathway, which originates from VTA DA neurons and mainly projects to the PFC. Abnormalities of the mesocortical and mesolimbic DA pathways have been proposed to be closely related to the pathophysiology of mental disorders such as schizophrenia (Chu and Zhen, 2010). It was thus important to study the anatomical connectivity of the mesocortical and mesolimbic DA-ergic systems with PFC neurons. Then, we will address several studies that have described close anatomical and functional interactions between the amygdala, NAc, and PFC that coordinate our cognitive behavior.

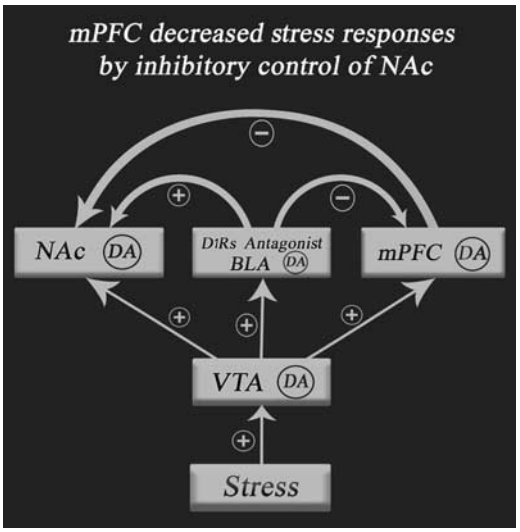
The rodent mPFC is a target of the response to stress-related neurochemicals through connections with the basolateral complex of the amygdala (Porcelli *et al.*, 2008). DA afferent fibers in the mPFC, the BLA, and the NAc originate in the medial posterior part of the VTA. PFC efferent fibers also project to DA cell bodies in the VTA, and the dorsal and ventral regions of the medial striatum (Christie *et al.*, 1987; Sesack *et al.*, 1989). Prefrontal DA depletion or electrical stimulation of output pathways alters the function of the subcortical DA systems (Deutch *et al.*, 1990; Taber and Fibiger, 1995). However, despite experimental support for a triadic interaction (connection between PFC, NAc, and the amygdala) (Barrot, 2014), it is uncertain whether and how DA-ergic neurons in the PFC provide executive control over amygdala-driven responses in the NAc. Jackson and Moghaddam (2001) have identified that microstimulation of the BLA increased glutamate efflux in the PFC and NAc. However, BLA stimulation produced a robust increase in DA efflux only in the PFC and not in the NAc. This increase was not blocked by inhibiting glutamate release in the PFC during the stimulation. Therefore, it seems that the activation of DA release is caused by elevated neuronal activity in the VTA, in which mesoprefrontal DA cell bodies are localized, as opposed to presynaptic regulation by DA of glutamate at the terminal (PFC) level. Nevertheless, there is little evidence for direct projections from BLA to VTA in rodents, although indirect projections through other brain area may cause activation of VTA neurons during BLA stimulation. Moreover, application of an AMPA receptor antagonist in the PFC leads to an increase in NAc DA release during BLA activation. This suggests that the PFC exerts inhibitory control over amygdala-evoked activation of DA output in the Nac (Jackson and Moghaddam, 2001). In addition, Thierry *et al.*, in 1990 have reported a functional connection between VTA and PFC. They showed that electrical stimulation of the VTA (at a frequency of 1 Hz) leads to an inhibitory effect in the majority (80%) of PFC cells in layers 111-VI. Moreover, this inhibitory effect was blocked by the application of sulpiride (a selective D_2 antagonist), but not by SCH 23390 (a selective D_1 antagonist). These data suggest that D_2 receptors play a critical role in the inhibitory effect of DA on PFC cells.

In addition to these defined subcircuits of the VTA, several other regions strongly innervate the VTA, including glutamatergic inputs from the PFC and the lateral hypothalamus (Rossetti *et al.*, 1998). In-vivo recordings showed that activation of glutamatergic neurons projecting from the PFC to the VTA also increases burst-firing of VTA DA neurons (Tong *et al.*, 1996). Therefore, the glutamatergic descending pathways of the PFC are believed to modulate the release of DA in subcortical areas. Additional complexity is added by the fact that a subset of midbrain DA neurons may also co-release the excitatory neurotransmitter glutamate (Stuber *et al.*, 2010; Hnasko *et al.*, 2010, 2012) or GABA (Stamatakis *et al.*, 2013). However, the underlying mechanism(s) of glutamate released by DA-ergic neurons is far from clear.

Changes in dopaminergic activity within the prefrontal cortex and the mesolimbic system under conditions of stress

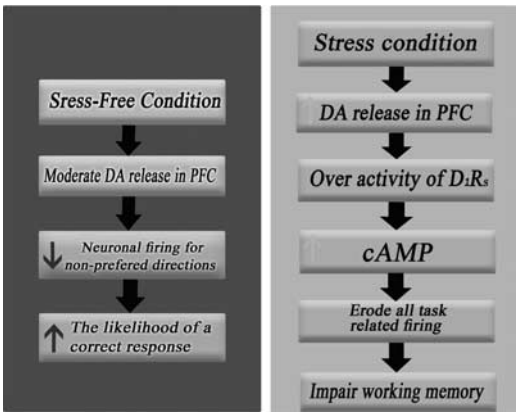
Stressful events increase DA-ergic activity within the mesolimbic system (Brischoux *et al.*, 2009; Ungless *et al.*, 2010). For example, DA release in the NAc and PFC increases during social threat (Tidey and Miczek, 1996). Foot-shock and acute restraint stress increase the firing of DA-ergic neurons in the VTA (Anstrom and Woodward, 2005; Brischoux *et al.*, 2009). Many studies have indicated that DA in the mPFC exerts an inhibitory influence on DA release in the NAc and suppression of the mesocortical DA-ergic pathway facilitates stress-induced activation of DA release in the NAc (Fig. 2) (King *et al.* 1997). These observations suggest that the mPFC decreases neurophysiological stress responses. Therefore, pathological outcomes of stress develop when these responses overcome the inhibitory control of the mPFC. The ability of mesocortical DA to suppress activation of the NAc DA release under stressful conditions has been identified in different stress-induced psychopathologies including schizophrenia and depression (Pascucci *et al.*, 2007). Moreover, the BLA is involved in the modulation of mPFC affective responses to stress (Fig. 2).

Fig. 2



The role of the basolateral nucleus of the amygdala (BLA) D1 receptors in modulating nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) DA responses to stress. Under stress conditions, the release of dopamine (DA) increases in the VTA, leading to increased activity of DA-ergic neurons in the mPFC, the BLA, and NAc. An intra-BLA injection of a D1 receptor (D1R) antagonist (SCH 23390) increases stress-induced NAc DA release, but attenuates mPFC DA release. These observations suggest that hyperactivity of DA-ergic neurons in the mPFC exerts an inhibitory influence on DA release in the NAc. Therefore, pathological outcomes of stress develop when the stress responses overcome the inhibitory control of the mPFC.

Fig. 3



Dopamine (DA) release in the prefrontal cortex (PFC) and subsequent events under stress-free and stressful conditions. Exposure to stress produces high levels of DA release in the PFC. Overactivity of DA1 receptors (D1Rs) subsequently increases the generation of cAMP, leading to suppression of all task-related firing in all directions in the PFC network, and also impairs working memory. However, moderate levels of D1R stimulation under stress-free conditions increase spatial tuning by reducing neuronal firing for non-preferred directions. Therefore, moderate levels of D1R stimulation increase the likelihood of a correct response.

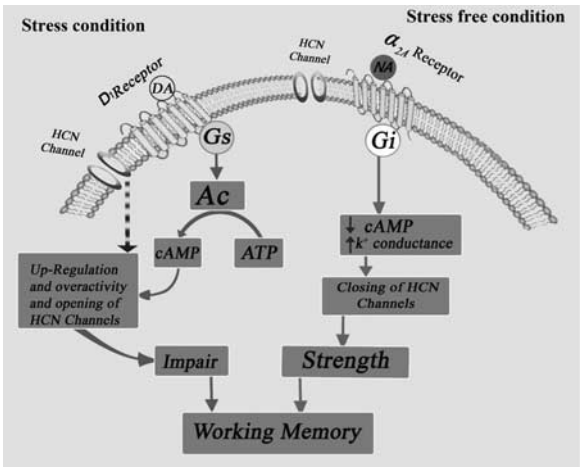
The BLA, along with the NAc and mPFC, receives a DA projection from the VTA. Stevenson and Gratton (2003) showed that an intra-BLA injection of a D1 receptor antagonist (SCH 23390) increased stress-induced NAc DA release, but attenuated the mPFC DA stress response. However, application of a D2/D3 receptor antagonist (raclopride) had no effect on either the NAc or the mPFC DA responses to stress. They concluded that BLA DA modulates the NAc and mPFC DA stress responses by activation of the D1 receptor subtype. They also suggested that BLA DA modulates stress-induced NAc DA release indirectly by modulating the mPFC DA response to stress.

How do changes in dopamine release impaired working memory under stress conditions?

Extensive evidence suggests an important role for DA in PFC functions such as working memory (Meyer-Lindenberg, *et al.*, 2005). Pharmacological blockade of D1Rs in both monkeys and rodents significantly impairs spatial working memory (Vijayraghavan *et al.*, 2007). Exposure to stress produces high levels of DA release in the rodent PFC. Overactivity of D1Rs subsequently increases the generation of cAMP under stressful conditions, suppresses PFC network firing and impairs working memory (Zahrt *et al.*, 1997). Moderate levels of D1R stimulation increase spatial tuning by reducing neuronal firing for non-preferred directions, but higher levels of D1R stimulation, in stressful situations, suppress all task-related firing in all directions (Fig. 3). The detrimental effects of high levels of D1R stimulation during stress are particularly important to understand as D1Rs are altered in disorders such as schizophrenia and the symptoms of such disorders are often precipitated or exacerbated by stress. Similarly, administration of high dosages of D1R agonists onto dl-PFC neurons also reduces delay-related firing by increased cAMP, and impairs spatial working memory in rodents and monkeys.

However, it is not understood how D1R stimulation reduces PFC neuronal firing. It has been proposed that D1R stimulation can reduce glutamate release from axon terminals (Gamo *et al.*, 2015) or alter opening of calcium channels (Yang and Seamans, 1996). D1Rs may also reduce the firing of PFC neurons by increasing the open probability of hyperpolarization-activated cyclic nucleotide-gated (HCN) cation channels through cAMP (Vijayraghavan *et al.*, 2017). HCN channels are expressed widely in the CNS and involved in various neuronal activities, including the control of neuronal rhythmic activity, setting the resting membrane potential, as well as dendritic integration (Wahl-Schott and Biel, 2009). HCN channels also participate in the regulation of spontaneous activity of DA neurons in the CNS. It has been shown that HCN channels are controlled by both membrane voltage and the binding of cyclic nucleotides to their cyclic nucleotide binding domain. Hyperpolarization of the membrane potential (< -70 mV) activates the HCN channels and mediates the K^+ and Na^+ influx to combat post-

Fig. 4



Intracellular signaling pathways activated by stress exposure impair working memory in the PFC. Under stressful conditions, high levels of dopamine (DA) release and subsequent D1 receptors (D1R) stimulation activate adenylyl cyclase (AC) to produce cyclic AMP. Then, the high level of cAMP opens hyperpolarization-activated cyclic nucleotide-gated cation channels (HCN channels) on dendritic spines, impairing and weakening all network connections in the PFC. The overactivity and opening of HCN channels leads to a reduction in the firing rate of PFC neurons by shunting network inputs and/or reducing temporal summation. As a result, PFC neurons are unable to accurately represent information in working memory. However, under stress-free or optimal situations, appropriate network connections for working memory are strengthened by α2A-receptor inhibition of cAMP–HCN channel signaling.

firing hyperpolarization, whereas membrane depolarization produces the opposite effect (Wahl-Schott and Biel, 2009). HCN channels are also regulated by cyclic nucleotides including cAMP and cGMP. Both cAMP and cGMP could bind directly to the cyclic nucleotide-binding domain of the HCN channel, increasing channel opening. Although both cAMP and cGMP enhance the activity of HCN channels, however, the affinities of HCN channels are about 10-fold higher for cAMP than for cGMP. HCN channels are co-localized with D1Rs on the heads and necks of dendritic spines near incoming synapses in the superficial layers of monkey PFC, the layers that form the cortical–cortical networks (Wang *et al.* 2007). It is likely that these suppressing functions occur in dendritic spines through cAMP effects on HCN channels (Fig. 4) (Paspalas *et al.*, 2012). Previous research has shown that cAMP reduces PFC neuronal firing by increasing the open state of HCN channels on dendritic spines. Therefore, hyperactivity of HCN channels in the presence of cAMP shunts nearby inputs. This shunting might arise from opening of K^+ channels (Kv7 channels), leading to a hyperpolarizing M current (Delmas and Brown, 2005).

Inconsistent with these reports, however, some data have shown that the impairment of working memory by stress exposure or excessive D1 receptor activation can be inhibited by blocking cAMP activity or HCN channels in the PFC (Wang, *et al.*, 2007; Vijayraghavan, *et al.*, 2017). Furthermore, administration of a cAMP analog, Sp-cAMPS, impaired working memory (Taylor, *et al.*, 1999). At the cellular level, application of high doses of the D1 agonist (Sp-Camps) or a phosphodiesterase inhibitor decreased the firing rate of neurons, in monkeys performing a working memory task, whereas blockade of the cAMP or HCN channels restored normal firing patterns (Wang, *et al.*, 2007). Furthermore, there is some evidence that the HCN channels and α_{2a}-adrenoceptors are co-localized in dendritic spines in the PFC, and that stimulation of postsynaptic α_{2a}-adrenoceptors strengthens working memory through inhibiting cAMP, closing HCN channels, and strengthening the functional connectivity of PFC networks.

In contrast, stimulation of D1Rs in the superficial PFC, increases intracellular levels of cAMP. Thus, there is activation of D1Rs and a subsequent increase in cAMP levels, leading to an upregulation of HCN channel activity. Overactivity of HCN channels weakens the functional connectivity of PFC networks. Therefore, activation of D1Rs will be accompanied by a selective inhibition of irrelevant afferent information such as noise from non-preferred spatial pathways. However, the modulation of the activity of HCN channels by D1Rs in the PFC and its physiological significance remain unclear and n more evidence is need to support this hypothesis. Several studies have shown that pharmacological blockade, using an HCN channel blocker ZD7288, or knockdown of HCN channels in the rat pre-limbic PFC, restores spatial working memory performance and PFC network tuning during stress (Ramos *et al.* 2005; Wang *et al.* 2007). These beneficial actions are reversed by agents that increase cAMP signaling at both the cellular and behavioral levels.

In addition to high levels of DA release in the PFC, depletion of DA release also impairs working memory performance and cognitive functions (Arnsten and Goldman-Rakic, 1998). Several studies have shown that the administration of either a high-dose D1/5R antagonist or a D1/5R agonist (SKF38393, SKF81297, A77636) impaired performance after systemic or intra-PFC infusions, whereas low doses of the agonist improved performance (Cai, 1997; Zahrt *et al.*, 1997; Gamo *et al.*, 2015). Therefore, it is accepted that there is an inverted U-shaped influence of D1R activity on PFC neuronal networks (Arnsten, 2009). Taken together, moderate levels of DIRs activity improve PFC function, whereas higher levels impair PFC function.

Recordings from DA neurons have uncovered two general types of cells: those that fire based on the value of a stimulus (value cells) and those that fire based on its salience (salience cells) (Matsumoto and Hikosaka, 2009; Bromberg-Martin *et al.*, 2010). Schultz (1998) investigated DA value cells and reported that these cells fired in association with prediction error, elevating their activity to unexpected rewards or to signals that predict reward,

reducing activity when a reward is predicted but does not happen, and showing a very limited response to expected rewards. Bromberg-Martin *et al.* (2010) showed that salience cells, by contrast, increased their activity to either rewards or punishments, for example, showing elevated firing to a mildly aversive air-puff. According to the general location of these different kinds of neurons, it is believed that DA salience cells project to the dorsal PFC, whereas DA value cells project to the ventromedial and orbital PFC and the NAc.

Vijayraghavan *et al.*, (2007) reported that administration of a DA receptor agonist improved tuning to preferred remembered locations in the delay period of the spatial working memory task in rhesus monkeys. Therefore, it seems that the physiological role of DA in PFC is to strengthen mental representations (Arnsten, 2011). In contrast, there is little information about how DA modulates prefrontal sensory signals that precede and give rise to such sustained activity.

Stress can impair working memory by interaction of dopamine and glucocorticoid receptors

Stress is a major source of environmental determinants of psychopathology and impairs cognitive functions associated with the PFC. Thus, the identification of central stress mechanisms is fundamental to the understanding of disease processes and to the development of increasingly effective therapies. During stressful conditions, activation of the hypothalamic–pituitary–adrenal (HPA) axis causes the adrenal cortex to release glucocorticoids, which travel through the bloodstream and cross the blood–brain barrier to activate glucocorticoid receptors (GRs) throughout the brain (De Kloet *et al.*, 2005a, 2005b; Ehteram *et al.*, 2017; Mortazaei *et al.*, 2018). GRs are abundantly present in the PFC of rats and primates. Intra-PFC infusion of a GR antagonist (RU 38486) reverses stress-induced impairments on the delayed spatial win-shift task, a test of prefrontal-dependent executive function (Butts *et al.*, 2011). This finding suggests that glucocorticoids can damage PFC function through direct actions at GRs. However, it is likely that glucocorticoids also indirectly exacerbate working memory impairments through interactions with the DA-ergic systems. One mechanism of interaction between glucocorticoids and DA is the extraneuronal catecholamine transport system. These transporters are located on glial cells and remove excess DA from the synapse, helping to optimize stimulation of DRs. Corticosterone blocks DA-ergic transporters in the PFC (Grundemann *et al.*, 1998a, 1998b), resulting in increased extracellular DA levels. Thus, stress-induced glucocorticoid release in the PFC could lead to overstimulation of the D1Rs, producing PFC dysfunction. Glucocorticoids also modulate DA release in the PFC. DA-ergic cells in the VTA and PFC express GRs that become saturated during stress (Ahima and Harlan, 1990), altering the firing of DA-ergic projections. Interestingly, however, glucocorticoid effects on DA release in the PFC appear to be locally driven, rather than a result of actions in the VTA. In-vivo microdialysis experiments show that infusion of a GR antagonist (RU 38486) into the PFC suppresses stress-induced DA release, but infusions into the VTA have no effect (Butts *et al.*, 2011). Therefore, GRs make a specific contribution in the PFC in modulating the magnitude of stress-induced DA efflux.

In addition to the direct effects of stress on DA-ergic neurons in the PFC, activation of the HPA axis following stress can indirectly affect the activity of the PFC through its effect on other regions of the brain. For example, during stress, HPA axis activation leads to stimulation of the VTA, causing excess DA release into the PFC (Shansky and Lipps, 2013). When DA binds to the D1Rs, its downstream signaling cascades lead to working memory impairment. Accordingly, these impairments can be reversed by intra-PFC infusions of a D1 antagonist (Zahrt *et al.*, 1997), as well as by infusions of cAMP and PKA inhibitors (Taylor *et al.*, 1999).

Concluding remarks

Stressful events can lead to significant impairments in working memory. A substantial literature has shown that DA signaling pathways within the PFC are altered by stress. The data obtained from primates and rodents have shown that the impairment of executive functions such as working memory is driven by increased DA-cAMP–HCN channel signaling, which may be further modulated by changes in cortisol levels. In summary, stress exposure leads to weakened PFC networks. However, little is known about how DA alters PFC cell firing in animals performing tasks that involve the PFC.

Beyond intracellular signaling pathways that are activated by stress, the present review has provided critical insight into the interaction of PFC DA with glucocorticoids under stressful conditions. Ample evidence shows that the PFC is a key target of stress, and that stress-induced PFC dysfunction is markedly associated with neuropsychiatric illnesses. Therefore, further insights into identification of the molecular mechanisms that alter PFC function under stressful conditions could provide the foundation for a new era in psychiatry. Further studies are needed to achieve a more detailed understanding of the molecular mechanisms involved in stress-induced PFC dysfunction.

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Conflicts of interest

There are no conflicts of interest.

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