Molecular Modulation of Prefrontal Cortex: Rational Development of Treatments for Psychiatric Disorders

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Abstract

Dysfunction of the prefrontal cortex (PFC) is a central feature of many psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), schizophrenia and bipolar disorder. Thus, understanding molecular influences on PFC function through basic research in animals is essential to rational drug development. In this review, we discuss the molecular signaling events initiated by norepinephrine and dopamine that strengthen working memory function mediated by the dorsolateral PFC under optimal conditions, and weaken working memory function during uncontrollable stress. We also discuss how these intracellular mechanisms can be compromised in psychiatric disorders, and how novel treatments based on these findings may restore a molecular environment conducive to PFC regulation of behavior, thought and emotion. Examples of successful translation from animals to humans include guanfacine for the treatment of ADHD and related PFC disorders, and prazosin for the treatment of PTSD.

Keywords

prefrontal cortex; spatial working memory; norepinephrine; dopamine; stress

Introduction

Dysfunction of the prefrontal cortex (PFC) is a central feature of many psychiatric disorders (reviewed in Arnsten, 1998; Arnsten, 2007b), and the associated cognitive dysfunction often predicts patients' functional outcome in society (e.g. Bowie et al., 2010; reviewed in Green, 2006). Thus, it is critical to understand the molecular influences that modulate PFC function in order to develop intelligent medications for psychiatric disorders. Basic research on PFC mechanisms in animals has already led to the successful translation of two treatments for human PFC disorders: guanfacine (Intuniv™) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), and prazosin for the treatment of Post-Traumatic Stress Disorder (PTSD). This review will briefly describe the molecular influences that strengthen

PFC function under optimal conditions, and those that weaken PFC function during uncontrollable stress and in psychiatric disorders, and how understanding these pathways can provide therapeutic targets for drug development.

Higher cognitive functions of the prefrontal cortex

The PFC commands a range of "executive functions" to modulate behavior, thought and affect to produce thoughtful and purposeful actions (Goldman-Rakic, 1995; Goldman-Rakic, 1996). The PFC generates representational knowledge, which allows us to maintain specific information as well as rules and goals in mind to execute cognitive control over our actions and thoughts (Goldman-Rakic, 1995; Goldman-Rakic, 1996; Miller & Cohen, 2001). This "mental sketch pad" also rapidly updates the contents of working memory to remain relevant to the situation at hand (Goldman-Rakic, 1995; Goldman-Rakic, 1996). The PFC is highly interconnected with the rest of the brain (Figure 1), which allows it to receive pertinent information and in turn, appropriately modulate information processing in other regions (reviewed in Arnsten & Castellanos, 2002; Ghashghaei & Barbas, 2002; Goldman-Rakic, 1996; Middleton & Strick, 2000; Selemon & Goldman-Rakic, 1985; Selemon & Goldman-Rakic, 1988). In addition, the PFC projects to subcortical arousal systems, and thus can regulate monoamine and cholinergic inputs to other regions as well as onto itself (Arnsten & Goldman-Rakic, 1984; Aston-Jones, Rajkowski, & Cohen, 2000; Berridge & Waterhouse, 2003; Jodo, Chiang, & Aston-Jones, 1998; Robbins, 2005; Sara & Herve-Minvielle, 1995).

Spatial working memory as a model to study molecular modulation of prefrontal circuits

Much of the research on the molecular mechanisms of PFC function has focused on spatial working memory as a model of PFC function. The pioneering work of Goldman-Rakic has delineated the cellular circuitry underlying spatial working memory (Goldman-Rakic, 1995), allowing us to address the molecular mechanisms that strengthen or weaken these networks. Spatial working memory is mediated by the dorsolateral PFC (DLPFC), and specifically, the region surrounding the principal sulcus in monkeys. These studies have been performed in monkeys performing an oculomotor delayed response (ODR) spatial working memory task (Figure 2A), while single units are recorded in the DLPFC (Figure 2B). In this task, the monkeys are required to continually update their working memory for a specific location during the delay periods, when the cues are no longer present in the environment.

While the monkey is performing the ODR task, pyramidal neurons in the DLPFC exhibit persistent firing during the delay periods for cues in a particular direction, called the "preferred direction," but show no increase or even suppressed firing for other directions, called the "non-preferred directions" (Goldman-Rakic, 1995) (Figure 2C). This pattern of firing is considered to be the cellular basis for spatial working memory. Persistent firing during the delay period is thought to arise from recurrent excitation among networks of PFC pyramidal cells with shared spatial properties, such as those cells receiving inputs for the 90-degree location in space (Goldman-Rakic, 1995; Goldman-Rakic, 1996) (Figure 2D). These cells reside in layer III of the cortex, where pyramidal cells make horizontal connections (Kritzer & Goldman-Rakic, 1995) that are likely mediated predominantly via NMDA receptors with some contribution from AMPA receptors (reviewed in Wang, 2001; Wang, Yang, Gamo & Arnsten, unpublished data). The specificity of the contents of working memory is further refined by lateral inhibition from GABAergic interneurons, such as basket cells, which inhibit networks representing other locations in space (Rao, Williams, & Goldman-Rakic, 1999; Rao, Williams, & Goldman-Rakic, 2000) (Figure 2D). The recurrent firing of pyramidal cell networks depends upon their effective synaptic contacts at dendritic spines; the strength of these connections is dynamically modulated via intracellular signaling events within these spines (e.g. Figure 2E), termed Dynamic Network Connectivity (DNC) (reviewed in Arnsten, Paspalas, Gamo, Yang, & Wang, 2010). While this mechanism allows

rapid and precise updating of information according to changing environmental demands, it is also vulnerable to a variety of genetic and environmental insults, such as occur in psychiatric disorders and during exposure to stress.

PFC function varies according to arousal state

Beginning with the key work by Brozoski et al. (1979), it has been shown that the PFC is powerfully modulated by its neurochemical environment (reviewed in Arnsten, 2007a; Brozoski, Brown, Rosvold, & Goldman, 1979; Robbins & Arnsten, 2009). The DLPFC is especially sensitive to the catecholamines – dopamine (DA) and norepinephrine (NE) – which are released into the PFC according to one's state of arousal or in response to environmental events. Thus, these powerful influences may have evolved to coordinate cognitive state with environmental demands. The catecholamines have an inverted-U-shaped influence on DLPFC function, such that too little or too much impairs function, while moderate levels are required for optimal function (Figure 3).

The primate PFC receives NE projections from the locus coeruleus (reviewed in Berridge & Waterhouse, 2003; Levitt, Rakic, & Goldman-Rakic, 1984; Porrino & Goldman-Rakic, 1982). The NE system is thought to be involved in optimizing goal-directed behavior, where NE neurons fire according to one's arousal state and selective attention (reviewed in Aston-Jones, Rajkowski, & Cohen, 1999). They show 1) silence during rapid eye movement sleep, 2) low, tonic firing during slow wave sleep and drowsiness, 3) moderate, tonic firing with phasic responses to relevant stimuli during non-stressed waking, and 4) high tonic firing during stress (reviewed in Aston-Jones et al., 1999). Interestingly, NE neurons can also respond to irrelevant stimuli during fatigue or stress, but inhibit these responses during non-stressed waking (reviewed in Aston-Jones et al., 1999). Appropriate NE firing to environmental stimuli is likely regulated by the PFC (Arnsten & Goldman-Rakic, 1984; Aston-Jones et al., 2000; Berridge & Waterhouse, 2003; Jodo et al., 1998; Sara & Herve-Minvielle, 1995), while high tonic firing during stress exposure requires activation from the amygdala (Goldstein, Rasmusson, Bunney, & Roth, 1996).

The primate PFC receives DA projections from the ventral tegmental area and substantia nigra (Domesick, 1988; Fallon, 1988; Garris, Collins, Jones, & Wightman, 1993; Goldman-Rakic, Lidow, Smiley, & Williams, 1992; Levitt et al., 1984; Lewis, Campbell, Foote, Goldstein, & Morrison, 1987; Lewis, 1992; Lewis, Hayes, Lund, & Oeth, 1992; Porrino & Goldman-Rakic, 1982). Tonic firing of DA neurons may reflect arousal state, while phasic responses are likely associated with reward, for example, during the presentation of a spatial cue in a spatial working memory task (reviewed in Arnsten, Vijayraghavan, Wang, Gamo, & Paspalas, 2009; Schultz, Apicella, & Ljungberg, 1993). In fact, many DA neurons respond phasically to reflect prediction error of rewards (Schultz, 1998). However, a subset of DA neurons fire in response to aversive stimuli (Matsumoto & Hikosaka, 2009), which may increase DA release in the PFC during stressful situations. Rodent studies have also shown catecholamine release to be enhanced in the medial PFC during acute stress (Deutch & Roth, 1990; Finlay, Zigmond, & Abercrombie, 1995; Goldstein et al., 1996; Roth, Tam, Ida, Yang, & Deutch, 1988).

These catecholaminergic projections target the PFC in a lamina and synapse-specific manner, allowing them to precisely modulate PFC network connectivity at those levels. NE and DA neurons target post-synaptic terminals in the superficial and deep layers of the cortex (Aston-Jones et al., 1999; Goldman-Rakic et al., 1992; Levitt et al., 1984; Lewis et al., 1987; Lewis & Morrison, 1989), with DA neurons shown to specifically contact dendritic spines (reviewed in Goldman-Rakic, Leranth, Williams, Mons, & Geffard, 1989; Goldman-Rakic et al., 1992; Smiley & Goldman-Rakic, 1993). These projections target receptors that are also distributed in a lamina and synapse-specific manner, as described

below, which further refine the specificity of catecholaminergic modulation and consequent intracellular signaling within PFC circuits.

Once released, the catecholamines initiate a network of intracellular cascades that can rapidly strengthen or weaken the connectivity within PFC networks (Figure 4). Too little release of catecholamines during fatigue or boredom suspends PFC function, likely to conserve energy, as maintenance of working memory is an energy-intensive process (Friedman & Goldman-Rakic, 1994;Swartz, Halgren, Simpkins, & Mandelkern, 1996). PFC function may also be reduced during stressful, dangerous situations when rapid, instinctual or habitual reactions mediated by the amygdala and striatum are enlisted in place of slow, thoughtful responses by the PFC (reviewed in Cahill & McGaugh, 1996;Hu et al., 2007;McEwen, 2004;Wickens, Horvitz, Costa, & Killcross, 2007). In contrast, moderate release of catecholamines occurs during optimal arousal conditions, which would strengthen PFC cognitive abilities (see below; also reviewed in Arnsten, 2009a;Arnsten et al., 2010).

Patients with psychiatric disorders are especially vulnerable to stress-induced PFC impairment (e.g. Hammen & Gitlin, 1997), but such impairment occurs under normal circumstances as well, e.g. when getting a call from a doctor with bad news about a loved one. In today's society, it would certainly be useful for PFC function to remain intact during stress, e.g. when restraining ourselves from road rage or remaining calm during a disagreement with a boss. However, this system has evolved to promote survival when one's physical safety is threatened, e.g. when fleeing from an approaching tiger or freezing at the sight of a bear in the woods. Enhancing the functions of the amygdala and hippocampus during such situations may also enhance long-term memories that would promote survival during a similar circumstance in the future.

Modulation of PFC function under optimal arousal conditions

Under optimal arousal conditions, moderate levels of NE and DA regulate PFC network inputs such that signals for relevant information are enhanced, while those for irrelevant noise are suppressed. These actions occur via receptors that influence cyclic adenosine monophosphate (cAMP) production, which in turn alters the open probability of ion channels localized near synaptic inputs on dendritic spines (Wang et al., 2007). NE and DA have complementary actions on PFC network connectivity, with NE stimulation of alpha-2A adrenoceptors increasing "signals" via suppression of cAMP production, and D1 DA receptor stimulation decreasing "noise" by increasing cAMP.

NE strengthens PFC representations by stimulating alpha-2A adrenoceptors in the PFC (Avery, Franowicz, Studholme, van Dyck, & Arnsten, 2000; Birnbaum, Podell, & Arnsten, 2000; Franowicz et al., 2002; Jakala et al., 1999; Li & Mei, 1994; Li, Mao, Wang, & Mei, 1999; Ramos, Stark, Verduzco, van Dyck, & Arnsten, 2006; Sawaguchi, 1998; Tanila, Rama, & Carlson, 1996; Wang et al., 2007) (Figures 2E, 3A). These receptors have higher affinity for NE than the alpha-1 and beta-1 adrenoceptors (O'Rourke, Blaxall, Iversen, & Bylund, 1994), which are discussed below. Much of the previous research has focused on the role of alpha-2 adrenoceptors on presynaptic terminals. However, it is now known that the majority of alpha-2 adrenoceptors in the brain are actually *post-synaptic* to NE terminals (U'Prichard, Bechtel, Rouot, & Snyder, 1979), and it is these receptors that likely mediate the beneficial effects of NE and alpha-2A agonists on PFC function (Arnsten & Cai, 1993; Arnsten, Steere, & Hunt, 1996; Wang et al., 2007). Alpha-2A adrenoceptors are localized on dendritic spines in the superficial layers of the PFC (Aoki, Go, Venkatesan, & Kurose, 1994; Aoki, Venkatesan, & Kurose, 1998; Goldman-Rakic, Lidow, & Gallager, 1990; Wang et al., 2007), allowing them to modulate PFC circuits in a synapse-specific manner.

Stimulation of alpha-2A adrenoceptors in the PFC improves working memory performance in rodents and monkeys (Arnsten & Goldman-Rakic, 1985; Cai, Ma, Xu, & Hu, 1993; Mao, Arnsten, & Li, 1999; Ramos et al., 2006). At the cellular level, stimulating alpha-2A adrenoceptors in the DLPFC of a monkey engaged in a spatial working memory task enhances recurrent network activity for the relevant cue positions, but not for other positions (Li et al., 1999; Wang et al., 2007) (Figure 3A). Blocking these receptors or depleting NE from the PFC impairs working memory performance and delay-related firing (Arnsten & Goldman-Rakic, 1985; Li & Mei, 1994; Li et al., 1999), likely because there is insufficient encoding of the working memory "signal."

Alpha-2A adrenoceptors enhance network connectivity by inhibiting cAMP production (Ramos et al., 2006; Wang et al., 2007), which strengthens synaptic connectivity by closing potassium channels, such as the hyperpolarization-activated cyclic nucleotide gated cation (HCN) channels (Wang et al., 2007) and possibly Kv7 (KCNQ) potassium channels (Delmas & Brown, 2005; George, Abbott, & Siegelbaum, 2009; Arnsten, unpublished data) (Figures 2E, 4). Alpha-2A adrenoceptors are colocalized with HCN channels at dendritic spines (Wang et al., 2007), which places them in an ideal location to interact via intracellular pathways within the spines.

Inhibition of cAMP signaling may also enhance connectivity by opening depolarizing TRPC channels (canonical transient receptor potential channels) (Hagenston, Fitzpatrick, & Yeckel, 2008; Partridge, Swandulla, & Muller, 1990) (Figure 4). These actions would depolarize the spine and increase the efficacy of nearby network inputs.

Moderate levels of DA help to "sculpt" the network firing, that is, reduce noise to focus the stimulus selectivity of PFC networks, via moderate simulation of D1/5 receptors (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007) (Figures 2E, 3B). (As there are currently no drugs that can distinguish between the D1 and D5 subtypes, we will henceforth refer to the D1/5 receptor family as "D1 receptors.") Physiological recordings from the PFC of monkeys performing a spatial working memory task show that moderate levels of D1 receptor stimulation suppress network firing for irrelevant cue positions, thus enhancing the signal-to-noise ratio (Vijayraghavan et al., 2007). D1 receptors are localized on dendritic spines of pyramidal cells, allowing DA to modulate PFC circuits in a synapse-specific manner (Bergson et al., 1995; Smiley, Levey, Ciliax, & Goldman-Rakic, 1994). D1 receptors and alpha-2A adrenoceptors appear to be on separate subsets of dendritic spines (Paspalas & Arnsten, unpublished data), which would allow them to simultaneously modulate different PFC networks.

D1 receptors hyperpolarize dendritic spines and reduce connectivity among pyramidal cell networks by increasing cAMP production (Vijayraghavan et al., 2007; Zahrt, Taylor, Mathew, & Arnsten, 1997), which in turn opens potassium channels on dendritic spines (Gamo, Wang & Arnsten, unpublished data) (Figures 2E, 4). DA depletion or insufficient D1 stimulation impairs working memory performance (Sawaguchi & Goldman-Rakic, 1991; Sawaguchi & Goldman-Rakic, 1994; Vijayraghavan et al., 2007; Zahrt et al., 1997), and creates noisy firing patterns, where the neuron fires during the delay period to both relevant and irrelevant information (Vijayraghavan et al., 2007) (Figure 3B). In contrast, moderate levels of D1 receptor stimulation decrease firing to non-preferred directions, narrowing the spatial tuning of the neuron (Figure 3B). It is likely that these sculpting effects on neuronal firing are especially beneficial when a cognitive task requires a narrow focus of memory or attention, such as when remembering a small, specific location in space. In contrast, D1 receptor stimulation may actually be harmful when broader inputs or cognitive flexibility is required, for example, as seen with attentional set-shifting tasks (Crofts et al., 2001).

Treatments that restore optimal levels of alpha-2A and D1 receptor stimulation can help to strengthen PFC function in disorders associated with insufficient catecholamine transmission, such as ADHD. For example, the symptoms of inattentiveness, hyperactivity and impulsivity in ADHD are consistent with PFC dysfunction, and a variety of approaches have implicated weakened PFC function in patients with ADHD. Both structural and functional imaging studies show evidence of smaller PFC volume, reduced PFC activity, weaker PFC white matter connections and weaker resting connectivity in patients (Arnsten, 2006; Castellanos & Tannock, 2002; Dickstein, Bannon, Castellanos, & Milham, 2006; Kieling, Goncalves, Tannock, & Castellanos, 2008; Seidman, Valera, & Makris, 2005; Spencer, 2002). Similarly, many neuropsychological studies have shown evidence of impaired PFC function, especially on tasks that require inhibition of inappropriate actions or sustained regulation of attention (Barkley, 1997).

ADHD can be associated with abnormal catecholamine transmission (reviewed in Arnsten, 2006; Arnsten, 2009b; e.g. Greene, Bellgrove, Gill, & Robertson, 2009; Hess et al., 2009; Kieling, Genro, Hutz, & Rohde, 2008). For example, a subset of ADHD cases is associated with polymorphisms in the gene that encodes for DA beta-hydroxylase, the enzyme that converts DA to NE, which may result in insufficient noradrenergic activity (Daly, Hawi, Fitzgerald, & Gill, 1999; reviewed in Faraone et al., 2005; Kopeckova, Paclt, & Goetz, 2006; Roman et al., 2002). Approved treatments for ADHD enhance catecholamine actions in the PFC, likely restoring catecholamine activity to an optimal range (Arnsten et al., 1996). One such treatment is guanfacine (Intuniv™), an alpha-2A andrenoceptor agonist that mimics NE actions at these receptors (Biederman, Melmed, Patel, McBurnett, Konow et al., 2008; Uhlen & Wikberg, 1991) (Figures 2E, 4).

Originally marketed as an anti-hypertension drug (Sorkin & Heel, 1986), initial studies of guanfacine in animals have illustrated its beneficial effects on PFC function. Guanfacine improved performance in a delayed response task in adult (Avery et al., 2000; Mao et al., 1999; Ramos et al., 2006) and aged (Arnsten, Cai, & Goldman-Rakic, 1988; Rama, Linnankoski, Tanila, Pertovaara, & Carlson, 1996) monkeys, as well as in rats (Ramos et al., 2006). It enhanced delay-related firing in the DLPFC (Wang et al., 2007) and increased the regional cerebral blood flow in this region relative to more posterior cortical regions (Avery et al., 2000) in monkeys performing a spatial working memory task, confirming the importance of this region for the actions of guanfacine. Guanfacine also improved other PFC functions, such as reversal performance in a visual object discrimination task in aged monkeys (Steere & Arnsten, 1997), and performance in a visuomotor association task in adult monkeys (Wang, Tang, & Li, 2004). Furthermore, guanfacine protected cognitive function from distraction by irrelevant stimuli in aged monkeys (O'Neill, Fitten, Siembieda, Ortiz, & Halgren, 2000), and reduced overactivity, impulsiveness and inattentiveness in the spontaneously hypertensive rat, a model of ADHD (Sagvolden, 2006). The range of cognitive functions that benefit from guanfacine illustrate that findings from studies using spatial working memory can be generalized to other PFC functions.

As in animal models, guanfacine has been shown to be effective in improving PFC function in ADHD patients. Guanfacine significantly reduced symptoms in children, adolescents (Biederman, Melmed, Patel, McBurnett, Donahue et al., 2008; Biederman, Melmed, Patel, McBurnett, Konow et al., 2008; Hunt, Arnsten, & Asbell, 1995; Sallee et al., 2009; Scahill et al., 2001) and adults (Hunt et al., 1995; Taylor & Russo, 2001) with ADHD. In children with co-morbid ADHD and tic disorders, it improved sustained visual attention and motor response inhibition, and decreased the severity of tics (Chappell et al., 1995; Scahill et al., 2001). It also improved performance in tests of attention in adults with ADHD (Taylor & Russo, 2001). In addition to ADHD, guanfacine has also improved behavior in autism spectrum disorders (McCracken et al., 2010; Wink, Erickson, & McDougle, 2010). Thus,

mimicking the action of NE at alpha-2A adrenoceptors appears to be helpful in many conditions in which top-down PFC guidance of behavior is weakened.

Guanfacine provides an advantage over previously existing alpha-2 agonist treatments, such as clonidine (Catapres™), as it has less sedative and hypotensive side effects due to is greater selectivity for the alpha-2A subtype (Arnsten et al., 1988; Uhlen & Wikberg, 1991). Additional ADHD treatments, methylphenidate (Ritalin™, Concerta™) and atomoxetine (Strattera™), have recently been shown to act via similar mechanisms. These treatments improve delayed response performance in monkeys by increasing endogenous stimulation of alpha-2 adrenoceptors and D1 dopamine receptors (Gamo, Wang, & Arnsten, 2010) (Figure 2E).

Stress signaling pathways take PFC "off-line"

Under uncontrollable stress, excess levels of catecholamines are released in the PFC, and initiate a variety of intracellular pathways that rapidly impair PFC function (Aston-Jones et al., 1999; Deutch & Roth, 1990; Deutch, Clark, & Roth, 1990; Finlay et al., 1995; Roth et al., 1988) (Figure 4). As shown in Figure 4, many of the molecules that inhibit the stress pathways are genetically altered in patients with mental illness, which may explain why these disorders are often precipitated or exacerbated by stress (reviewed in Arnsten, 2009a; Breier, Wolkowitz, & Pickar, 1991; Dohrenwend, Shrout, Link, Skodol, & Stueve, 1995; Hammen & Gitlin, 1997; Mazure, 1995; Mazure & Maciejewski, 2003; Southwick, Rasmusson, Barron, & Arnsten, 2003).

High DA levels impair PFC function via excessive stimulation of D1 DA receptors and widespread increases in cAMP production (Vijayraghavan et al., 2007; Zahrt et al., 1997) (Figures 3B, 4). Physiological studies show that high levels of D1 receptor stimulation suppress all PFC network firing, reducing responses to both preferred and non-preferred inputs (Vijayraghavan et al., 2007) (Figure 3B). These reductions in neuronal firing are mimicked by compounds that increase cAMP signaling, and prevented by cAMP inhibition (Vijayraghavan et al., 2007; Wang et al., 2007). Excess D1 receptor stimulation in the PFC also results in impaired spatial working memory performance in monkeys and rodents (Arnsten & Goldman-Rakic, 1990; Sawaguchi & Goldman-Rakic, 1991; Zahrt et al., 1997). These DA actions are an important part of the stress response, as stress-induced impairments in working memory performance can be prevented by pre-treating the animals with a D1 receptor antagonist (Murphy, Arnsten, Goldman-Rakic, & Roth, 1996).

While D1 DA receptors appear to suppress PFC neuronal activity in a cognitively engaged animal, they have also been shown to enhance excitability in cortical pyramidal cells in vitro (Gorelova & Yang, 2000; Henze, Gonzalez-Burgos, Urban, Lewis, & Barrionuevo, 2000; Seamans, Durstewitz, Christie, Stevens, & Sejnowski, 2001; Wang & O'Donnell, 2001; Yang & Seamans, 1996). It is possible that in a cognitively engaged animal, these basic excitatory influences are saturated, and additional inhibitory effects are seen with higher levels of stimulation (Vijayraghavan et al., 2007), or that the inhibitory effects in vivo override the excitatory influences observed in vitro (reviewed in Arnsten et al., 2009). In this case, having no D1 receptor stimulation would prevent even the basic excitatory influences, thus suppressing all firing. Consistent with this idea, blocking D1 receptors has been shown to reduce DLPFC firing as well as impair performance in monkeys performing a spatial working memory task (Sawaguchi & Goldman-Rakic, 1991; Sawaguchi & Goldman-Rakic, 1994; Sawaguchi, 2000; Sawaguchi, 2001).

High levels of NE release during stress impairs PFC function via lower-affinity alpha-1 (Arnsten, Mathew, Ubriani, Taylor, & Li, 1999; Birnbaum, Gobeske, Auerbach, Taylor, & Arnsten, 1999; Mao et al., 1999; Mohell, Svartengren, & Cannon, 1983) and beta-1 (Aoki et

al., 1998; Ramos et al., 2005) adrenoceptors in the PFC (Arnsten, 2000) (Figure 3A). Alpha-1 adrenoceptors are concentrated in superficial layers of the cortex (Goldman-Rakic et al., 1990), while beta receptors are found mainly in the intermediate layers (Aoki et al. 1998). Beta adrenoceptors have been localized on dendritic spines (Aoki et al., 1998), such that they can modulate the PFC circuits in a synapse-specific manner.

Beta-1 adrenoceptors stimulate cAMP production, converging onto the D1 receptor-mediated cAMP signaling to impair PFC function (reviewed in Arnsten, 2007a; Ramos et al., 2005) (Figure 4). In contrast, alpha-1 adrenoceptors activate phosphatidylinositol (PI) signaling, increasing IP_3-calcium and protein kinase C (PKC)-mediated pathways via G_q signaling (Figure 4). IP_3 receptor stimulation increases calcium release from the endoplasmic reticulum (Soulsby & Wojcikiewicz, 2005), which in turn opens small-conductance calcium-activated potassium (SK) channels (Brennan et al., 2008; Faber, 2010; Hagenston et al., 2008). Calcium can also stimulate some forms of adenylyl cyclase to increase cAMP production (Ferguson & Storm, 2004), further contributing to the collapse of PFC network activity. Finally, calcium is needed for the migration of PKC to the membrane, where it is activated by diacylglycerol (DAG). Activation of this pathway in PFC impairs working memory in rats and monkeys (Birnbaum et al., 2004; Runyan, Moore, & Dash, 2005), and suppresses PFC network firing (Birnbaum et al., 2004).

As with D1 DA receptors, alpha-1 and beta adrenoceptors have also been shown to have excitatory influences on cortical pyramidal cells in vitro (McCormick, Pape, & Williamson, 1991; Mouradian, Sessler, & Waterhouse, 1991; Waterhouse, Moises, & Woodward, 1981). In particular, alpha-1 receptors have been shown to have excitatory effects in the somatosensory cortex (Mouradian et al., 1991; Waterhouse et al., 1981). Again, these basic effects in vitro are likely fully engaged in an awake, behaving animal, and additional inhibitory effects are observed in vivo.

Chronic stress exposure leads to further changes in the cellular architecture of the PFC. There is prominent loss of dendritic spines and atrophy of dendrites in PFC pyramidal cells following chronic stress (Radley & Morrison, 2005; Radley et al., 2006), which correlates with impaired working memory (Hains et al., 2009) and attentional control (Liston, McEwen, & Casey, 2009). Dendritic spine loss appears to involve increased PKC signaling, as daily treatment with a PKC inhibitor prevents the spine loss and cognitive deficits associated with chronic stress (Hains et al., 2009). It is possible that spine loss occurs via PKC-mediated phosphorylation of myristoylated, alanine-rich C-kinase substrate (MARCKS), which leads to actin destabilization and spine collapse (Calabrese & Halpain, 2005). This mechanism may also contribute to the PFC gray matter loss associated with lead poisoning, as lead potently activates PKC by mimicking calcium actions (Markovac & Goldstein, 1988).

While DA and NE neurons project extensively throughout the brain and affect similar receptors in other regions, subsequent signaling cascades and net effects on cognition appear to be unique to the PFC. In the amygdala, stress-induced stimulation of alpha-1 (Ferry, Roozendaal, & McGaugh, 1999) and beta-1 (Cahill & McGaugh, 1996; Debiec & LeDoux, 2006; Ferry & McGaugh, 1999; Introini-Collison, Miyazaki, & McGaugh, 1991; Roozendaal, Quirarte, & McGaugh, 2002) receptors strengthens its function, for example in retaining memory for the inhibitory avoidance task or fear conditioning (reviewed in Wilensky, Schafe, & LeDoux, 2000). Furthermore, D1 receptor stimulation and increase in cAMP help to consolidate long-term memory by facilitating interactions between the hippocampus and PFC (Hopkins & Johnston, 1988; Runyan et al., 2005; Seamans, Floresco, & Phillips, 1998). Such effects may involve D1 receptors that are localized in cellular compartments with few HCN channels to disconnect the synaptic inputs (Arnsten, 2007a).

DA also stimulates D2 receptors, which are less abundant than D1 receptors in the PFC and are found mostly in layer V (Lidow, Goldman-Rakic, Gallager, & Rakic, 1991), where cortical outputs to subcortical regions are located. Consistent with this function of layer V, D2 receptors have been shown to modulate response-related firing in the DLPFC of monkeys performing a spatial working memory task (Wang, Vijayraghavan, & Goldman-Rakic, 2004). This activity may serve as a corollary discharge to indicate that the animal has made a response (Arnsten, 2007b). D2 receptors also oppose D1 receptor actions by reducing excitability in PFC pyramidal cells and interneurons (Gulledge & Jaffe, 1998; Seamans et al., 2001; Zheng, Zhang, Bunney, & Shi, 1999). It is currently not known whether mechanisms similar to those in the PFC exist in other association cortices. This unique neurochemical requirement for optimal PFC function is important when developing treatments that target PFC cognitive functions with minimal side effects.

Relationships to genetic alterations in mental illness

There are a variety of mechanisms that serve as "molecular brakes" to protect cognitive function under stress. Figure 4 illustrates some of these molecules: Disrupted in Schizophrenia 1 (DISC1), Regulator of G-protein Signaling 4 (RGS4) and DAG kinase-eta (DGKH). Several psychiatric disorders are associated with genetic alterations of these "molecular brakes," which may disinhibit the stress signaling pathways and lower the threshold for stress-induced PFC dysfunction.

DISC1, first identified with a translocation mutation in a Scottish family, is now associated with many psychiatric disorders in addition to schizophrenia, and in many populations worldwide (reviewed in Chubb, Bradshaw, Soares, Porteous, & Millar, 2008; Millar et al., 2000). It is a scaffold protein that is found in dendritic spines in the DLPFC of humans (Kirkpatrick et al., 2006; Paspalas & Arnsten, unpublished data), and interacts with many proteins, including phosphodiesterase 4 (PDE4) (Millar et al., 2005; Millar et al., 2007) (Figure 4). DISC1 may activate PDE4 under conditions of high cAMP production (Millar et al., 2005), as occur during stress exposure. Thus, a genetic insult to *DISC1* would prevent proper PDE4 function, leading to build-up of cAMP and collapse of PFC function. Consistent with this hypothesis, rodents with *Disc1* mutations show impaired working memory function (Gamo et al., 2010; Koike, Arguello, Kvajo, Karayiorgou, & Gogos, 2006; Kvajo et al., 2008).

RGS4 and DGKH have been shown to inhibit G_q-mediated PI-PKC signaling (Figure 4). RGS4, which inhibits G_q signaling (Berman, Wilkie, & Gilman, 1996; Hepler, Berman, Gilman, & Kozasa, 1997; Watson, Linder, Druey, Kehrl, & Blumer, 1996), is greatly reduced in the PFC of patients with schizophrenia (Erdely, Tamminga, Roberts, & Vogel, 2006; Mirnics, Middleton, Stanwood, Lewis, & Levitt, 2001; Volk, Eggan, & Lewis, 2010). Other studies have also found genetic alterations in *RGS4* in association with schizophrenia and bipolar disorder (Chowdari et al., 2002; Levitt, Ebert, Mirnics, Nimgaonkar, & Lewis, 2006; Morris et al., 2004; Talkowski et al., 2006), including evidence that *RGS4* genotype interacts with PFC volume and connectivity in patients and control subjects (Buckholtz et al., 2007; Prasad et al., 2005). DGKH hydrolyzes DAG and inhibits PKC activation (Figure 4), and mutations that affect its function are strongly associated with bipolar disorder (reviewed in Arnsten & Manji, 2008; Baum et al., 2008). Loss of DGKH function would disinhibit PKC signaling, which may contribute to the loss of PFC gray matter and impaired PFC function observed in bipolar disorder (reviewed in Arnsten & Manji, 2008). Importantly, most treatments for bipolar disorder inhibit PKC signaling, e.g. lithium and valproate (reviewed in Arnsten & Manji, 2008; Manji & Lenox, 1999; Manji, McNamara, Chen, & Lenox, 1999) (Figure 4). Other treatments for psychiatric disorders also target these G_q-mediated pathways. For example, many atypical antipsychotics block alpha-1 and serotonin 5-HT2 receptors, which are both coupled to G_q signaling (reviewed in Arnsten &

Manji, 2008;Deutch et al., 1991;Manji & Lenox, 1999), and the alpha-1 adrenoceptor antagonist, prazosin, is used to treat PTSD (Figure 4).

PTSD symptoms involve inappropriate, disinhibited fear responses to trauma-associated stimuli, which are consistent with an impaired ability of the PFC to modulate fear responses via inputs to the amygdala (reviewed in Bremner, 2007; Bremner, Elzinga, Schmahl, & Vermetten, 2008; Elzinga & Bremner, 2002; Milad, Rauch, Pitman, & Quirk, 2006; Morgan, Romanski, & LeDoux, 1993; Southwick et al., 1999). In particular, the medial PFC, which in both humans and rats is reciprocrally connected with they amygdala, is involved in the extinction of fear conditioning (Milad & Quirk, 2002; reviewed in Milad et al., 2006; Morgan et al., 1993), and may be deficient in PTSD patients (reviewed in Milad et al., 2006). Consistent with these hypotheses, studies in PTSD patients show impaired medial PFC activation in response to reminders of traumatic events (Bremner et al., 1999; Bremner, 1999; Bremner et al., 2005; Shin et al., 2004), as well as enhanced amygdala activity (Bremner et al., 2005; Liberzon et al., 1999; Rauch et al., 2000; Shin et al., 1997; Shin et al., 2004) when exposed to negative emotional material relative to normal control subjects. There is further support for impaired PFC function, as PTSD is associated with elevated catecholamine release in response to stress (reviewed in Charney, Deutch, Krystal, Southwick, & Davis, 1993; Southwick et al., 1999), and patients show deficits in working memory (Bremner et al., 1993; Bremner et al., 1995). They are also impaired in the Stroop task, which requires inhibition of habitual responses (McNally, Kaspi, Riemann, & Zeitlin, 1990; McNally, English, & Lipke, 1993; Vasterling, Brailey, Constans, & Sutker, 1998), and in object-alternation and extinction tasks, which depend on the medial PFC (reviewed in Milad et al., 2006).

Prazosin was originally used to treat hypertension and benign prostatic hypertrophy (Hieble & Ruffolo, 1996; Lund-Johansen, Hjermann, Iversen, & Thaulow, 1993), but has since been shown to improve PFC function and weaken amygdala function in animal studies (Ferry et al., 1999). While it did not affect delayed response performance in monkeys under non-stress conditions (Arnsten & Goldman-Rakic, 1985; Li & Mei, 1994), it was able to prevent impairment in spatial working memory induced by stimulation of alpha-1 adrenoceptors as in stress (Arnsten & Jentsch, 1997). Prazosin is now being tested in both civilian (Taylor & Raskind, 2002; Taylor et al., 2006; Taylor et al., 2008) and combat veterans (Raskind et al., 2000; Raskind et al., 2002; Raskind et al., 2003; Raskind et al., 2007) with PTSD, and may also reduce alcohol abuse in veterans with PTSD symptoms (Simpson et al., 2009).

The challenges of translation from animals to humans

It is no accident that the two examples of successful translation discussed above – guanfacine for ADHD and prazosin for PTSD – are drugs that had already been approved for human use to treat other conditions. This fact has allowed creative clinical researchers to directly test ideas emerging from basic research in human patients. The great challenge in drug development is when exciting mechanisms are identified in animals, but no appropriate agents are immediately available for human use. Unfortunately, developing new compounds that are safe for human use involves great expenses in time and money, and relies on the interest of large pharmaceutical companies or small biotechnology firms founded on venture capital. This "valley of death" during the drug development process has slowed or halted the progress of many burgeoning ideas. Studies in monkeys can be particularly helpful in this regard, as a drug that improves cognition following oral administration in monkeys has a high likelihood of succeeding in humans. In fact, the exact same doses of guanfacine and prazosin that have improved PFC function in young monkeys in the above studies are now used in humans. Thus, such studies in primates should help to decide which strategies are worthy of further development, and which doses would be appropriate for human trials.

Conclusion

The rich knowledge of molecular and cellular mechanisms mediating PFC function and dysfunction gained from animal models has allowed the identification of potential drug targets for psychiatric disorders. Elucidating these basic mechanisms is key to understanding the etiology of such disorders, and for the rational translation of basic research to human therapies. The present review has focused on mechanisms underlying spatial working memory. Some of these mechanisms likely extend to other PFC cognitive operations, such as impulse control (Bari, Eagle, Mar, Robinson, & Robbins, 2009; Dalley, Mar, Economidou, & Robbins, 2008) and cognitive flexibility (Kehagia, Murray, & Robbins, 2010). For example, alpha-2A adrenoceptors appear to play an important role in behavioral inhibition (reviewed in Arnsten et al., 1996). Additional neurotransmitters and signaling pathways likely play a significant role in modulating other PFC functions. For example, serotonin is involved in mediating reversal learning in the orbitofrontal cortex (Clarke, Dalley, Crofts, Robbins, & Roberts, 2004; Clarke et al., 2005; Clarke, Walker, Dalley, Robbins, & Roberts, 2007). Investigating the molecular influences on other PFC subregions may help to elucidate the etiology of a variety of neuropsychiatric symptoms, and will be an important arena for future research.

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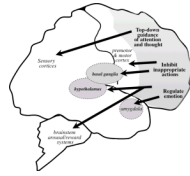
Figure 1.
The prefrontal cortex (PFC) is highly interconnected with the rest of the brain, allowing it to modulate information processing in other regions of the brain, as well as to regulate the arousal and reward systems, to appropriately modulate behavior, thought and affect.
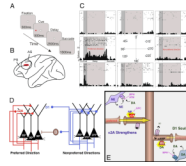
Figure 2.
Physiological recordings of PFC microcircuits in the monkey dorsolateral PFC (DLPFC), and their modulation by catecholamine signaling pathways.
A. Monkeys performed the oculomotor delayed response (ODR) task. Each trial begins when the monkey fixates on a central point on a screen (fixation period). Next, a cue briefly appears in 1 of 8 peripheral locations, followed by a 2.5-second delay period, during which the monkey continues to maintain fixation. At the end of the delay period, the monkey makes a memory-guided saccade to the remembered cue location (response period), and is rewarded with juice if correct. Each test session consists of hundreds of trials, in which the cued location randomly changes for each trial, thus requiring the monkey to update his working memory despite extensive, proactive interference.
B. Single-unit recording was performed in the DLPFC, the region associated with spatial working memory in monkeys.
C. The firing patterns of a representative neuron in the monkey DLPFC. Under optimal conditions, neurons show delay-related firing for a preferred direction, but suppress firing for non-preferred directions (Goldman-Rakic, 1995; Goldman-Rakic, 1996). This pattern is considered to be the cellular basis for spatial working memory.
D. Circuit basis for spatial working memory as proposed by Patricia Goldman-Rakic (Goldman-Rakic, 1995). Spatial working memory is maintained in the DLPFC by recurrent excitation among networks of glutamatergic pyramidal cells with shared stimulus inputs, e.g. 90° position in space. Spatial tuning is sharpened by GABAergic interneurons, such as basket cells (B) (Rao et al., 1999; Rao et al., 2000), that suppress firing for dissimilar spatial positions, e.g. 270°. The preferred inputs to the 90° neuron are shown in red; physiological data indicate that these networks are modulated by norepinephrine (NE) alpha-2A adrenoceptor stimulation. In contrast, inputs from non-preferred directions are shown in blue; physiological data indicate that these networks are sculpted by D1 dopamine (DA) receptor stimulation.
E. A working model of catecholamine influences on PFC network connectivity. Under optimal levels of PFC catecholamine release, alpha-2A adrenoceptors strengthen connectivity for the preferred direction of the PFC network by reducing cyclic adenosine monophosphate (cAMP) and closing hyperpolarizing potassium channels. Conversely, D1 DA receptors sharpen spatial tuning by weakening inputs from non-preferred directions by increasing cAMP production. Treatments for ADHD facilitate these actions to restore optimal PFC function, e.g. methylphenidate (MPH) and atomoxetine (ATM) block NE and DA transporters (NET and DAT) and enhance the endogenous stimulation of alpha-2A and D1 receptors, while guanfacine (GFC) directly stimulates alpha-2A adrenoceptors.
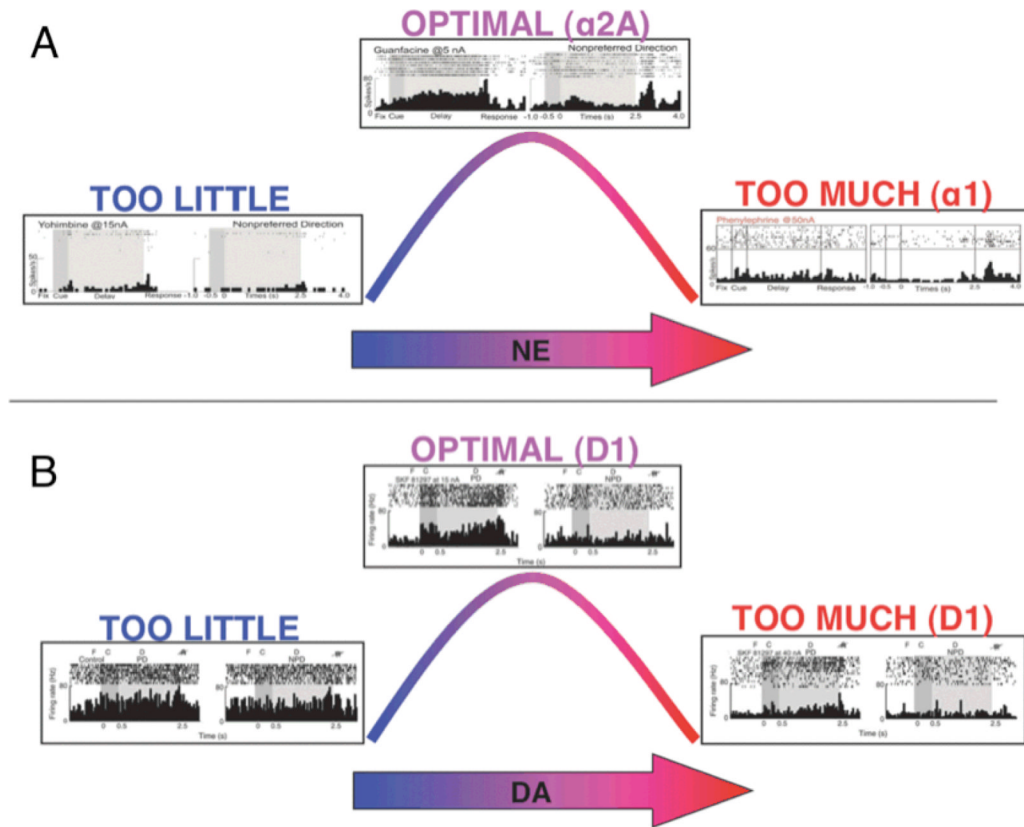
Figure 3.
NE and DA show inverted-U dose-response curves on delay-related activity in a monkey performing the ODR task.
A. Optimal levels of NE enhance delay-related activity for the preferred direction via alpha-2A adrenoceptors, while excessive levels suppress firing via alpha-1 and beta-1 adrenoceptors (Birnbaum et al., 2004; Wang et al., 2007).
B. Optimal levels of DA enhance spatial tuning by suppressing delay-related firing for the non-preferred direction, while excessive levels suppress firing for both preferred and non-preferred stimuli (Vijayraghavan et al., 2007).
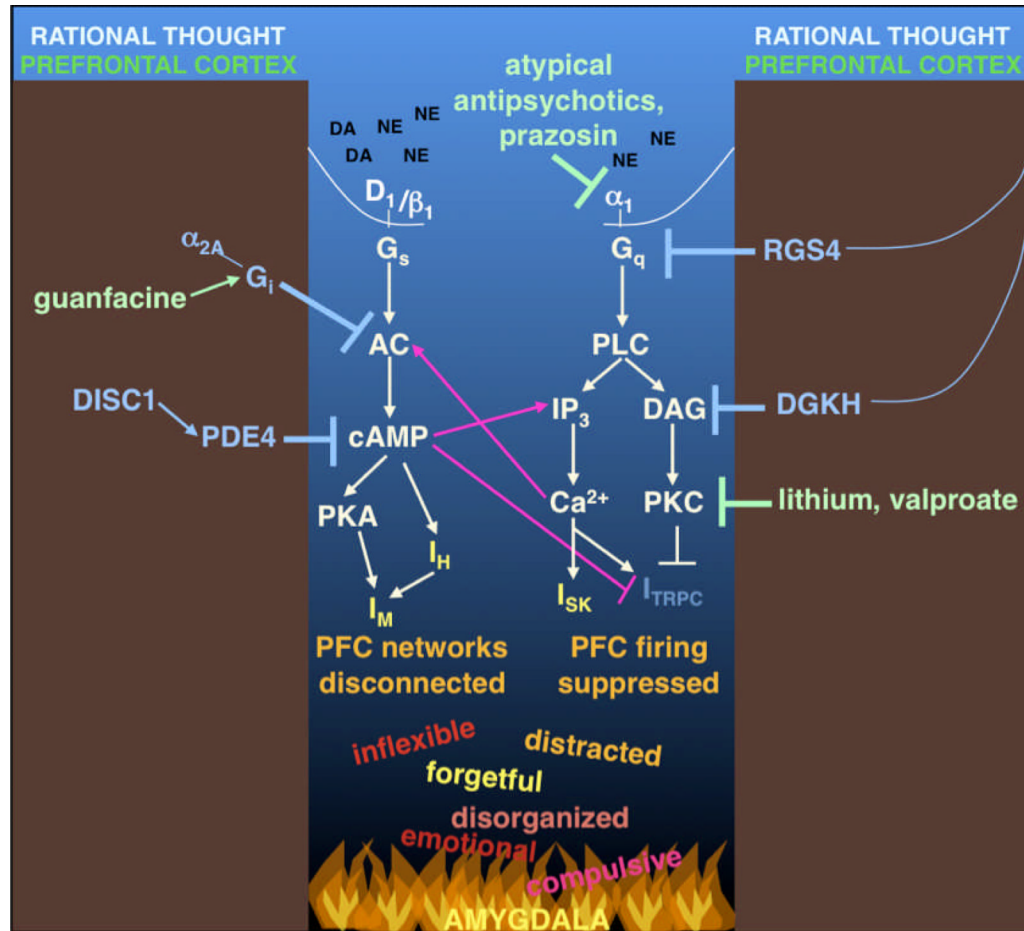
Figure 4.
During exposure to uncontrollable stress, high levels of NE and DA release initiate intracellular signaling events that increase potassium currents (I_H, I_M and I_{SK}), and decrease depolarizing currents (I_{CAN}, also called I_{TRPC}). This cascade leads to a collapse in PFC network firing and a loss of PFC regulation of behavior. Many of these signaling events appear to have feed-forward interactions, e.g. whereby cAMP facilitates IP_3 receptor signaling and vice versa, thus providing the opportunity for rapid changes in cellular physiology. In such a situation, rational control of behavior goes to "hell in a handbasket," and is replaced by instinctual reactions mediated by subcortical regions such as the amygdala, which are strengthened rather than weakened by PKA and PKC signaling. However, there are signaling pathways in the PFC that serve as "molecular brakes" to inhibit these stress-induced pathways, e.g. DISC1, RGS4 and DGK. Intriguingly, these molecules are often genetically altered in mental illness. Many treatments for psychiatric disorders inhibit these stress responses, e.g. prazosin and atypical antipsychotics block alpha-1 adrenoceptors, while the bipolar agents, lithium and valproate, reduce PKC signaling. These treatments may restore a more optimal signaling environment in the PFC. Abbreviations: AC: adenylyl cyclase; cAMP: cyclic adenosine monophosphate; DA: dopamine; DAG: diacylglycerol; DGKH: DAG kinase-η; DISC1: Disrupted In Schizophrenia 1; I_H: h-current mediated by hyperpolarization-activated cyclic nucleotide gated cation (HCN) channels; I_M: M-current mediated by KCNQ channels; IP_3: inositol triphosphate; I_{SK}: current mediated by small-conductance calcium-activated potassium (SK) channels; I_{TRPC}: current mediated by canonical transient receptor potential channels (TRPC); NE: norepinephrine; PDE4:

phosphodiesterase 4; PFC: prefrontal cortex; PKA: protein kinase A; PKC: protein kinase C; PLC: phopholipase C; RGS4: Regulator of G-protein Signaling 4.