Catecholamine and Second Messenger Influences on Prefrontal Cortical Networks of "Representational Knowledge": A Rational Bridge between Genetics and the Symptoms of Mental Illness

Amy F.T. Arnsten
Department of Neurobiology, Kavli Institute of Neuroscience, Yale Medical School, New Haven, CT 06510, USA

Both dopamine (DA) and norepinephrine (NE) have powerful, inverted U influences on prefrontal cortical (PFC) cognitive function. Optimal NE levels engage α2A-adrenoceptors and increase "signals" via inhibition of cAMP–HCN (cAMP–hyperpolarization-activated cyclic nucleotide-gated cation channel) signaling near preferred inputs, whereas optimal levels of DA D1 receptor stimulation decrease "noise" by increasing cAMP signaling near nonpreferred inputs. Excessive levels of catecholamine release during stress impair working memory 1) by very high levels of cAMP–HCN signaling diminishing preferred as well as nonpreferred inputs and 2) by high levels of NE engaging α1 stimulation of phosphotidyl inositol (PI) signaling that suppresses cell firing. Common mental illnesses are associated with extracellular changes in these pathways: Attention Deficit Hyperactivity Disorder is linked to genetic changes that reduce catecholamine transmission to suboptimal levels and is treated with agents that increase catecholamine transmission, whereas Post-Traumatic Stress Disorder (PTSD) is associated with amplified noradrenergic transmission that impairs PFC but strengthens amygdala function. PTSD is now treated with agents that block α1 or β adrenoceptors. In contrast, the more severe mental illnesses, schizophrenia and bipolar disorder, are associated with genetic changes in molecules regulating intracellular signaling pathways activated by stress. Specifically, DISC1 inhibits cAMP signaling whereas regulator of G-protein signaling 4 inhibits PI signaling. Loss of function in these genes may render patients vulnerable to profound stress-induced PFC dysfunction including symptoms of thought disorder.

Keywords: ADHD, bipolar, dopamine, norepinephrine, PTSD, schizophrenia, working memory

Introduction

Patricia Goldman-Rakic (1991) spoke of prefrontal cortical (PFC) network activity as a fundamental contribution to mind and the disruption of this process as a primary contribution to thought disorder in mental illness. She used the term working memory to describe a building block of cognition: the ability to represent information no longer in the environment through recurrent excitation within a network of pyramidal cells with shared stimulus properties (Fig. 1A) (Goldman-Rakic 1995). The Goldman-Rakic laboratory discovered that the persistent activity within this network is tuned by γ-aminobutyric acidergic (GABergic) interneurons activated by pyramidal cells with dissimilar stimulus properties (Rao et al. 2000). Although Goldman-Rakic used spatial working memory as a model system for examining functional circuitry, she proposed that these principles applied to other sensory and affective domains as well and described this process as representational knowledge within parallel processing streams (Goldman-Rakic 1987).

The microcircuitry supporting representational knowledge critically depends on the local neurochemical environment in PFC. In her landmark study with Brozoski et al. (1979), Goldman-Rakic (then Goldman) discovered that dopamine (DA) was essential to the spatial working memory operations of the PFC. She found that marked depletion of catecholamines from the dorsolateral PFC was as devastating as removing the cortex itself. This finding heralded a new era in neuropsychiatric research, where revealing neuromodulatory influences on PFC networks has been key to understanding and treating mental illness.

Catecholamine Regulation of PFC Circuits in Relationship to Arousal

Goldman-Rakic focused on DA's powerful beneficial effects on PFC networks through stimulation of the D1 family of receptors (Sawaguchi and Goldman-Rakic 1991). We now know that norepinephrine (NE) as well as DA are key to PFC function (Arnsten and Goldman-Rakic 1985) and that many effects formerly attributed solely to DA involve both NE and DA actions or even predominately NE actions in PFC (e.g., low doses of methylphenidate have greater effects on NE than DA in PFC (Berridge et al. 2006). We have also learned that both DA and NE exhibit an inverted U dose/response, where either too little or too much impairs working memory (Arnsten and Robbins 2002; Arnsten and Li 2005). We first learned about the DA D1 "inverted U" from our studies of noise stress impairing PFC cognitive function in monkeys (Arnsten and Goldman-Rakic 1990, 1998), discovering that excessive D1 stimulation during stress was as detrimental to working memory performance as insufficient D1 receptor stimulation. DA and NE cell firing and PFC catecholamine release are related to the arousal state of the subject, and these in turn have dramatic effects on cognitive state. Phasic firing of DA neurons is related to expectation of reward (Schultz 1998), while stress exposure induces high levels of DA release in PFC that likely correspond to high levels of tonic firing (Deutch et al. 1990). Similarly, phasic firing of NE neurons is related to a subject’s interest in a stimulus (Rajkowski et al. 2004), whereas tonic firing of NE neurons in the locus coeruleus ranges from silent (during REM sleep), slight (nonREM sleep/drowsy), moderate (alert nonstressed) to high levels during stress (Foote et al. 1980). The levels of NE release in PFC in turn determine the type of adrenocortical engaged: moderate levels of NE during nonstressed waking engage high affinity α2A receptors that couple to Gi and inhibit cAMP signaling, whereas higher levels released during stress engage lower affinity α1 receptors coupled to phosphotidyl inositol (PI) signaling, and lowest affinity β1 receptors, likely coupled to Gs to increase cAMP signaling (Arnsten 2000). Interactions among these receptors...
have yet to be studied but likely depend upon a number of factors such as proximity and G-protein dynamics. PFC working memory function is improved by NE \(\alpha2A\) receptor stimulation and moderate levels of DA D1 receptor stimulation (Fig. 2) but impaired by high levels of D1 and by \(\alpha1\) and \(\beta1\) receptor stimulation (Fig. 3). In contrast, \(\alpha1\) and \(\beta1\) receptor stimulation promote the affective and sensorimotor functions of the amygdala and posterior cortices (reviewed in (Arnsten 2000). This reduction in PFC regulation of behavior during stress likely has survival value when we are in danger but is costly when we are faced with cognitive challenges (Arnsten 1998). These stress mechanisms also confer great vulnerability to mental illness. Thus, understanding these chemical processes can be critical for the treatment of PFC cognitive dysfunction.

As NE's actions in PFC are dissociated by receptor type, the NE system has been particularly useful for therapeutic targets. Indeed, the \(\alpha2A\) receptor agonist, guanfacine (Scahill et al. 2001; Taylor and Russo 2001), and the \(\alpha1\) receptor antagonist, prazosin (Taylor and Raskind 2002; Raskind et al. 2003), are already in widespread clinical use based on research in animals, thus validating the approach initiated by Goldman-Rakic in the 1970's.

The inverted U influence of catecholamines on PFC cognitive abilities also explains variations in cognitive abilities related to genetic variations. Specifically, alterations in catechol-O-methyltransferase (COMT) genotype—an enzyme that catabolizes catecholamines—explain some individual differences in PFC cognitive abilities in humans (Egan et al. 2001). When methionine is substituted for valine in COMT, this enzyme is weakened, allowing greater levels of catecholamines to build in PFC. Individuals with the methionine substitutions have superior PFC cognitive functions under basal conditions when catecholamine release is modest but perform more poorly under conditions of stress or amphetamine administration when catecholamine release is high (ibid). Thus, differences in cognitive ability related to catecholamines in laboratory animals can now be observed in humans.

**Optimal Regulation of PFC Networks**

Catecholamines have multiple actions on PFC circuits, and different regions of PFC have differing sensitivities to monoamine effects (see Robbins, forthcoming). The effects of NE and DA depend not only on the type of receptor engaged but also on the localization of that receptor on a specific type of neuron and on the cellular compartment within that neuron (e.g., a distal spine vs. the soma). A few examples of important catecholamine actions are illustrated in Figure 4. (Note that most examples describe DA D1 actions, as in vitro recordings have focused on this receptor.) For example, DA D1 receptors have fundamental excitatory effects on PFC pyramidal cells, enhancing persistent...
Na⁺ currents (Gorelova and Yang 2000) and potentiating N-methyl D-aspartate (NMDA) inputs (Seamans et al. 2001; Wang and O’Donnell 2001), and loss of this stimulation likely renders neurons unresponsive in vivo as well as in vitro (Sawaguchi 1998). In recordings from awake monkeys performing spatial working memory tasks, one can also observe dramatic changes in spatial tuning of delay-related firing following manipulations of catecholamines. It is likely that GABAergic interneurons provide more stable “hard-wired” spatial tuning, while changes in catecholamines induce dynamic changes in tuning based on arousal state.

Under optimal neurochemical conditions, moderate levels of NE engage α2A receptors and increase “signals” (i.e., responses to preferred spatial directions; Fig. 1B), whereas moderate levels of DA D1 receptor stimulation decrease “noise” (i.e., responses to nonpreferred spatial directions; Fig. 1C). Specifically, α2A receptor stimulation with clonidine (Li et al. 1999) or guanfacine (Wang et al. 2007) increases delay-related firing for the preferred spatial direction, whereas modest levels of D1 receptor stimulation with low doses of SKF81297 decrease delay-related firing for the nonpreferred directions (Vijayraghavan et al. 2007). In each case, tuning of delay-related firing is enhanced, corresponding with the improvements in working memory evident at the behavioral level following treatment with either guanfacine (Arnsten et al. 1988) or low doses of SKF91287 (Cai and Arnsten 1997). Persistent, highly tuned delay-related firing is key for overcoming distractors (Miller et al. 1996) or inhibiting inappropriate behaviors (Funahashi et al. 1993), and treatment with the α2A agonist guanfacine can indeed lessen distractibility (Arnsten and Contant 1992) and improve behavioral inhibition (Steere and Arnsten 1997) in aged monkeys with inadequate catecholamine transmission.

Recent research indicates that the beneficial effects of NE α2A and DA D1 receptor stimulation arise from opposing effects on the intracellular signaling mechanisms modulating spatial working memory networks in PFC under optimal conditions. It is presumed that the inhibition of cAMP by α2A adrenoceptors, and the activation of cAMP by D1 receptors, occurs on separate spines receiving inputs from neurons with shared versus dissimilar spatial properties, respectively. Molecules that are associated with ADHD are shown in red. These molecules are mostly extracellular, and the genetic changes likely weaken catecholamine transmission.

**Figure 2.** The intracellular signaling mechanisms modulating spatial working memory networks in PFC under optimal conditions. It is presumed that the inhibition of cAMP by α2A adrenoceptors, and the activation of cAMP by D1 receptors, occurs on separate spines receiving inputs from neurons with shared versus dissimilar spatial properties, respectively. Molecules that are associated with ADHD are shown in red. These molecules are mostly extracellular, and the genetic changes likely weaken catecholamine transmission.

**Figure 3.** The intracellular signaling mechanisms that impair PFC function under conditions of stress and their relationship to genetic linkages with schizophrenia and bipolar disorder. High levels of catecholamine release during stress impair PFC cognitive function through excessive cAMP-HCN and PI-PKC signaling. cAMP signaling is inhibited by DISC1, whereas PI signaling is inhibited by RGS4. Both DISC1 and RGS4 have been linked to schizophrenia and bipolar disorder, indicating that patients with these mutations likely have weaker regulation of these stress pathways. This may account for the vulnerability of patients with schizophrenia or bipolar disorder to stress exposure and the severe loss of PFC regulation of behavior, thought, and affect in these mental illnesses.
on cAMP intracellular signaling, where NE α2A receptor stimulation inhibits (Ramos et al. 2006), while DA D1 activates (Vijayaraghavan et al. 2007) cAMP production. cAMP increases the probability of hyperpolarization-activated cyclic nucleotide-gated cation channels (HCN channels) opening in response to changes in membrane potential. We have recently found high concentrations of HCN channels on the dendritic spines of PFC pyramidal cells in superficial layers where they are in the position to regulate incoming information (Wang et al. 2007). They are often found near synapses on the spine head or in spine necks, where their opening would reduce membrane resistance and decrease the efficacy of synaptic inputs onto that spine (ibid). These HCN channels are often colocalized with α2A adrenoceptors (the relationship with D1 receptors is currently under investigation) such that the local concentration of cAMP and the open state of the HCN channels can be regulated by catecholamines. The data suggest that α2A adrenoceptor stimulation results in closure of HCN channels on spines receiving inputs from neurons with similar spatial properties, thus increasing firing during the delay period for the preferred direction, whereas moderate levels of D1 receptor stimulation leads to opening of HCN channels on spines receiving inputs from neurons with dissimilar spatial properties, reducing delay-related firing to nonpreferred directions (Fig. 2). This model indicates that it is not only the amount of cAMP produced but also its subcellular location within the dendritic tree that optimizes working memory abilities. This arrangement would allow catecholamines to modulate the width of spatial tuning, adjusting the breadth of tuning according to task demands. Thus, lower levels of DA would be optimal when broad tuning was appropriate, whereas somewhat higher levels would be helpful when narrow tuning was needed. This model implies that some PFC cognitive tasks should be more sensitive to DA depletion than others, and indeed this pattern has been observed (e.g., Collins et al. 1998). Thus, optimal modulation of PFC cognitive function is dynamic and tightly regulated to focus inputs relevant to task demands.

Electrophysiological studies of monkeys performing a spatial working memory task have shown that DA also has powerful effects via D2 receptors. In contrast to D1 receptors that potently influence delay-related firing, D2 receptors modulate response-related firing (Wang et al. 2004). Intriguingly, some of the response-related firing is initiated after the monkey has made the saccadic response, suggesting that this firing may serve as corollary discharge to alert the brain that it has made a response. Disruptions in corollary discharge have been associated with hallucinations (see below), suggesting that this D2 mechanism in PFC may have important relevance to these symptoms.

Finally, it should be noted that DA also modulates GABAergic interneuron activity, and thus DA may also modulate tuning via these mechanisms. In vitro recordings from PFC slices have shown that DA can powerfully activate GABAergic interneurons via D1 receptors in rat (Seamans et al. 2001) and monkey (Kroner et al. 2006) PFC slices and inhibit these interneurons via D4 receptors (Wang et al. 2002) (the latter may involve NE as well, as NE has high affinity for D4 receptors). In summary, these varied catecholamine actions have intricate influences on PFC neurons necessary for appropriate network activity.

**Collapse of PFC Networks during Acute Stress**

In contrast to optimal arousal conditions, exposure to uncontrollable stressors (i.e., stressors for which the subject feels no control over the stress) induces high levels of DA and NE release in the PFC (Deutch et al. 1990; Finlay et al. 1995). These high levels of catecholamines engage intracellular actions that dramatically reduce PFC neuronal firing and impair working memory performance. These pathways are summarized in Figure 3.

Although moderate levels of appropriately regulated cAMP optimize working memory, excessive cAMP production impairs working memory at the behavioral level (Taylor et al. 1999) and markedly reduces the delay-related firing of PFC neurons during a working memory task (Wang et al. 2007). Impairments in working memory and spatially tuned delay-related firing induced by excessive DA D1 receptor stimulation are mediated by cAMP (Vijayaraghavan et al. 2007), and it is likely that the impairment arising from β1 receptor stimulation is mediated by cAMP as well (Ramos et al. 2005). We hypothesize that these impairments arise from cAMP opening HCN channels throughout the distal dendrite, disconnecting all cortical-cortical connections and inducing network collapse (visually represented in Fig. 5A). An example supporting this model is shown in Figure 5B, where disinhibition of cAMP signaling with the...
phosphodiesterase inhibitor, etazolate, dramatically reduces PFC neuronal firing. Similarly, blockade of α2 receptors with yohimbine markedly reduces PFC neuronal firing, whereas firing is restored by blockade of HCN channels (Wang et al. 2007). Without cortical-cortical connections, PFC neurons are unable to sustain persistent activity during the delay period, and working memory is markedly impaired.

It should be noted that the finding of high levels of cAMP impairing working memory refers to conditions where delays are relatively short, and performance can be mediated solely by PFC networks. Memory storage over long delays requires the involvement of hippocampal circuits, and this type of memory is improved by cAMP, likely via protein kinase A (Seamans et al. 1998; Runyan and Dash 2005). These pathways appear to be modulated by NE β (Tronel et al. 2004) as well as D1 receptors. It is likely that these mechanisms involve distinct cellular compartments with few HCN channels, for example, as schematically illustrated in Figure 4.

High levels of NE release also engage α1 receptors that activate PI intracellular signaling (Fig. 3). Activation of PI signaling with the α1 agonist, phenylephrine, suppresses PFC neuronal firing, especially during the delay period following a preferred stimulus (Fig. 5C; Birnbaum et al. 2004). The ionic basis for this suppression is currently under investigation and may include intracellular calcium opening of small conductance calcium-activated potassium channels (Hagenston et al., forthcoming). Studies of working memory performance in both rodents and monkeys demonstrate that the detrimental effects of stress can be mimicked by an α1 agonist infused directly into the PFC (Mao et al. 1999) and that the detrimental effects of either stress or an α1 agonist can be blocked by inhibiting protein kinase C (PKC) in the PFC (Birnbaum et al. 2004). Conversely, direct activation of PKC in PFC markedly impairs working memory performance (Birnbaum et al. 2004). Similar effects are observed at the cellular level, where PKC inhibition restores normal patterns of delay-related firing in the PFC neurons of monkeys performing a working memory task (Birnbaum et al. 2004). The role of the IP3 arm of PI signaling in working memory firing and performance is currently under investigation and likely contributes as well.

In summary, high levels of catecholamines markedly weaken spatially tuned, delay-related firing of PFC neurons and impair PFC regulation of behavior and thought.

**Spine Loss in PFC with Chronic Stress**

This review has focused on momentary neurochemical changes with exposure to acute stress. However, these factors are likely accentuated with chronic stress. Studies of the rat PFC have shown heightened NE innervation with chronic stress (Miner et al. 2006). In addition, sustained exposure to uncontrollable...
stress in rats leads to dendritic retraction and loss of dendritic spines from PFC pyramidal cells (Radley et al. 2005, 2006). This dendritic retraction is associated with weakened PFC cognitive function (Liston et al. 2006). The distal portion of the apical dendrite is particularly vulnerable, and this is the region of the dendrite that contains dense numbers of HCN channels. Thus, chronic elevations in cAMP during chronic stress may lead to sustained opening of HCN channels, and sustained weakness of synaptic efficacy that then targets distal spines for removal. This hypothesis is currently being tested in our laboratory. These mechanisms may be especially relevant to mental disorders that are caused or worsened by prolonged stress exposure and associated with spine loss.

Altered Extracellular Changes in Common Mental Illnesses

Attention Deficit Hyperactivity Disorder (ADHD) and Post-Traumatic Stress Disorder (PTSD) are common conditions that involve prominent PFC dysfunction. The cardinal symptoms of ADHD include distractibility, impaired sustained attention and organizational abilities, poor impulse control, and locomotor hyperactivity, all of which can be produced by PFC lesions, especially of the right hemisphere (reviewed in Arnsten 2006). PTSD involves a spectrum of symptoms including hypervigilance, flashbacks and intrusive memories, and heightened conditioned fear responses. Interestingly, both of these disorders appear to involve changes in catecholamines in the extracellular compartment: with insufficient catecholamine stimulation associated with ADHD and excessive NE release associated with PTSD. Treatments for these disorders are in keeping with these changes, with ADHD medications enhancing catecholamine transmission, whereas PTSD treatments reduce catecholamine actions at α1 and β receptors.

ADHD: ADHD is highly heritable, and the symptoms of hyperactivity, poor impulse control, and distractibility are evident at a very young age. A large number of genetic studies of ADHD have pointed to altered catecholamine actions, as summarized in Figure 2 and reviewed in Faraone et al. (2005). For example, NE transmission may be weakened in some patients by genetic alterations in the NE synthetic enzyme, DA β hydroxylase (Daly et al. 1999; Roman et al. 2002). ADHD has also been linked to alterations in the DA transporter and the D1 receptor family (Daly et al. 1999), as well as polymorphisms in the D4 receptor that weaken D4 receptor efficacy (Sunohara et al. 2000; Tahir et al. 2000). D4 receptors are concentrated on interneurons in primate PFC (Mrzljak et al. 1996), where they appear to hold GABAergic actions in check (Wang et al. 2002). Thus, weakened D4 receptors may lead to excessive inhibition of PFC networks. Importantly, effective treatments for ADHD all act extracellularly to increase catecholamine transmission. Although much previous research has focused on the DA actions of stimulant medications such as methylphenidate, it is now known that low doses of stimulants relevant to therapeutic doses actually have a greater effect on NE than DA (Kuczenski and Segal 2002; Berridge et al. 2006). Thus, low doses of methylphenidate produce about a 400% increase in NE and a 200% increase in DA in the rodent PFC, while having only modest effects on subcortical catecholamine release (Berridge et al. 2006). These low doses of methylphenidate significantly improve PFC cognitive function in animals (Arnsten and Dudley 2005; Berridge et al. 2006), and this improvement can be blocked by either an α2 or a D1 receptor antagonist (Arnsten and Dudley 2005). Thus, stimulant medications likely have their therapeutic effects by increasing endogenous catecholamine actions to produce optimal stimulation within the PFC as depicted in Figure 2. ADHD is also treated with atomoxetine (Strattera), a nonstimulant that increases catecholamine release in the PFC (Bymaster et al. 2002), and by guanfacine, which mimics NE actions at α2A adrenoceptors in PFC (Scanhill et al. 2001; Taylor and Russo 2001). Therefore, our understanding of the genetic changes and treatment targets for ADHD are readily explained by our understanding of beneficial catecholamine actions in PFC.

PTSD: PTSD is caused by exposure to a traumatic stressor, either in the context of combat (e.g., seeing a friend killed) or a civilian setting (e.g., being raped, witnessing the horrors of the World Trade Center demise). The syndrome includes symptoms of hyperarousal, fearful responses to previously neutral stimuli, and the intrusion of traumatic memories, often as vivid flashbacks, that are thought to arise from an overactive amygdala, a weakened PFC, and weakened PFC regulation of amygdala. Specifically, PFC dysfunction is thought to contribute to the weakened inhibition of traumatic memories and to flashbacks arising from poor reality testing (Southwick et al. 2005). Weaker PFC inhibition of amygdala also likely contributes to stronger fear conditioning and the retarded extinction to neutral stimuli that were once associated with the trauma (ibid). PTSD is associated with heightened NE release (Southwick et al. 1997, 1999; Geraci et al. 2001). Indeed, when PTSD patients were given a small dose of yohimbine to amplify NE release during an imaging study in the laboratory, it induced hypofrontality associated with flashbacks and intrusive memories (Bremmer et al. 1997). This clinical profile is consistent with recent animal studies showing increased expression of the NE synthetic enzyme, tyrosine hydroxylase, within NE axons in the PFC following chronic stress exposure (Miner et al. 2006). It is likely that high levels of NE act at α1 and β receptors to weaken PFC regulation of behavior, emotion, and thought (Birmbaum et al. 1999; Ramos et al. 2005), while strengthening the affective functions of the amygdala (Ferry et al. 1999). Consistent with mechanisms uncovered in basic science research, PTSD symptoms are being successfully treated with the α1 receptor blocker, prazosin. Prazosin has been shown to be helpful in both veterans (Raskind et al. 2003) and civilians (Taylor and Raskind 2002) with PTSD, including elderly patients with longstanding illness (e.g., survivors of Auschwitz) (Peskind et al. 2003). Treatment with the β receptor blocker, propranolol (Vaiva et al. 2003), and the α2A agonist, guanfacine (Horrigan 1996), is also being tested in PTSD. Guanfacine may be helpful in a number of ways: reducing NE release via presynaptic actions, weakening amygdala function, and strengthening PFC network regulation. These agents would normalize the level of catecholamine receptor stimulation in the extracellular compartment and thus ameliorate symptoms.

Altered Intracellular Changes in Severe Mental Illness

The psychotic disorders schizophrenia and bipolar disorder involve more profound PFC dysfunction, including thought disorder, hallucinations, and altered emotional state (mood fluctuation in bipolar disorder, emotional flattening in schizophrenia). These disorders are also associated with hypofrontality in imaging studies, with changes in dorsolateral PFC most associated with schizophrenia (Weinberger et al. 1986; Weinberger and Berman 1996) and hypofrontality of the right
ventral PFC most associated with mania (Blumberg et al. 1999). These patterns of hypofrontality correspond well to the symptoms observed in these disorders. For example, the right ventral PFC in humans is specialized for behavioral inhibition, and the state-dependent weakening of the ventral and orbital PFC in the manic versus euthymic state is consistent with the disinhibited emotions, behaviors, and attention observed in mania. The more constant bilateral weakening of the dorsolateral PFC in schizophrenia is consistent with the profound deficits in memory and attention in this disorder. Thus, patients with large bilateral PFC lesions often exhibit a deficit state, including apathy, attention deficits, and memory loss, that resembles chronic schizophrenia. 

PFC dysfunction likely contributes to some aspects of the so-called positive symptoms as well and may involve altered PFC regulation of temporal association cortices and caudate. Researchers have posited that PFC dysfunction may contribute to auditory hallucinations and to thought disorder. Imaging and electrophysiological data suggest that auditory hallucinations may involve a weakening of corollary discharge from the PFC, that is, the loss of a signal from the PFC indicating that the brain has made an action (e.g., spoken a word). In the absence of this feedback, the sensory cortices attribute the voice to an external source, that is, an auditory hallucination (Blakemore et al. 2000; Ford et al. 2002; Lawrie et al. 2002). Recordings from PFC neurons in monkeys show that response-related firing associated with corollary discharge is modulated by DA D2 receptors (Wang et al. 2004), which may be one reason why D2 blockers are effective in treating these symptoms. Severe PFC dysfunction may also contribute to the fractionation of mental experience in thought disorder. Goldman-Rakic (1991) described how profound disruptions in representational knowledge would destabilize thought. Imaging studies of patients with thought disorder suggest that symptom severity may correlate with reduced activity in Wernicke’s area (Kircher et al. 2001). Thus, as with auditory hallucinations, disrupted communications between PFC and Wernicke’s area may contribute to thought disorder. As monkeys do not have a Wernicke’s area, these hypotheses cannot be studied directly in the nonhuman primate. However, it is likely that some of the lessons learned from cortical network connectivity in PFC apply to Wernicke’s area as well, given the role of this cortex in comprehending the symbolic representations of language, and the importance of networks in creating representational knowledge.

Neuropathological studies have confirmed striking changes in the PFC in patients with schizophrenia, with qualitatively similar, but more subtle pathology in temporal cortex (Konopaske et al. 2006). These studies have revealed striking changes in the PFC neuropil (Selemon et al. 1995), including dendritic spine loss (Glantz and Lewis 1995) and reduced GABAergic transmission (Leвис 2000). These morphological changes are now being associated with genetic alterations in molecules that regulate neural development or glutamate transmission (Owen et al. 2005; Craddock et al. 2006; Ross et al. 2006). However, genetic studies have also revealed molecules linked with schizophrenia and bipolar disorder that are key to inhibiting the intracellular signaling pathways that impair PFC function during stress: Disrupted In Schizophrenia (DISC1) and RGS4.

DISC1 has been linked to serious mental illness in families in Scotland (Ishizuka et al. 2006). The function of the DISC1 protein has recently been discovered: DISC1 activates the phosphodiesterase 4B under conditions of cAMP production (Millar et al. 2005), thus providing negative feedback on cAMP signaling (Fig. 3). DISC1 is found in the dendritic spines of human PFC and thus is likely in the same compartment as HCN channels (Kirkpatrick et al. 2006). The genetic change in DISC1 confers loss of function, indicating that patients with this mutation would be less capable of inhibiting stress-induced cAMP signaling and more vulnerable to PFC network collapse. The data shown in Figure 5B show a neuron’s firing pattern in the presence of excessive cAMP levels; patients with DISC1 mutations may have a similar collapse in PFC network firing.

Gene array characterization studies of molecular differences between the PFC of patients with schizophrenia and controls first identified massive reductions in RGS4 in patients with schizophrenia (Mirmics et al. 2001). As shown in Figure 3, RGS4 normally functions to inhibit PI signaling. RGS4 mRNA and protein are both markedly reduced in the PFC of patients with schizophrenia (Erdely et al. 2006), and genetic studies have suggested a linkage between RGS4 and schizophrenia (Chowdari et al. 2002; Morris et al. 2004; Prasad et al. 2004; Williams et al. 2004; Talkowski et al. 2006) and possibly bipolar disorder (Chowdari et al. 2002). These genetic and molecular analyses indicate that PI–PKC signaling is likely disinhibited in patients with these disorders, resulting in suppression of PFC firing similar to that shown in Figure 5C.

Loss of RGS4 and/or DISC1 function would result in a greatly exaggerated stress response. It has been appreciated for many years that stress exacerbates or even precipitates schizophrenia and bipolar disorder (Mazure 1995). This is particularly evident in bipolar disorder where stress exposure can move a patient from a euthymic (normal) state into a manic state (Hammen and Gitlin 1997). Stress can also induce an acute disintegration in patients with schizophrenia (Breier et al. 1991). Our new understanding of intracellular actions suggests that these lapses into profound PFC dysfunction likely involve unregulated cAMP and PI signaling.

It is noteworthy that mutations in intracellular molecules lead to severe PFC dysfunction (e.g., thought disorder, distractibility within a sentence), whereas genetic changes in extracellular molecules weaken PFC cognitive regulation but are less severe (e.g., poor impulse control, distractibility within the classroom). Extracellular changes may be likened to a car with low levels of gas (the car itself is properly made but insufficiently powered), whereas intracellular changes may be likened to a car where the steering wheel is not properly connected to the wheels. Thus, medications for the psychotic disorders may be most effective if they work inside the cell to inhibit cAMP and PKC signaling downstream from the genetic alterations. Manji and Lenox (1999) have noted that most treatments for bipolar disorder, for example lithium and valproate (i.e., Depakote), inhibit PI–PKC signaling. Manji has found that chronic treatment with either lithium or valproate reduces PKC activity (Manji et al. 1999). Atypical antipsychotic medications also reduce PI–PKC signaling through extracellular blockade of α1, D2, and 5HT2A receptors. It is noteworthy that so-called mood stabilizers are often used to treat schizophrenia (e.g., Depakote), while antipsychotics are often given to patients with bipolar disorder (e.g., Risperidol). The efficacy of these agents across psychotic disorders and the shared genetics suggests that disinhibited PI–PKC signaling is relevant to this spectrum of illness and that direct inhibition of PKC signaling may be more effective in treating these serious disorders. Our new understanding of DISC1 actions suggests that agents that inhibit cAMP–HCN actions may also be helpful...
in treating schizophrenia and bipolar disorder. These signaling molecules may be more effective therapeutic targets than those aimed at correcting altered glutamate or GABA transmission, as both GABA and glutamate neurons provide information that is precisely timed and patterned within PFC networks. In contrast, neuromodulators work over a longer time frame and are more globally distributed and thus can be manipulated or mimicked more effectively by pharmacological treatments. Furthermore, as sustained disinhibition of these stress pathways likely induce dendritic retraction in the PFC, medications that inhibit these pathways may ameliorate gray matter loss in frontal lobe. This idea is encouraged by results from structural imaging studies of patients with bipolar disorder, showing that medications that inhibit PKC signaling increase gray matter in ventral PFC (Blumberg et al. 2006).

The Legacy of Patricia Goldman-Rakic: A Rational Approach to Neuropsychiatry

The landmark findings of Brozoski et al. remain a beacon in our field: by revealing the powerful chemical influences on PFC cognitive function, we have been able to understand why our cognitive abilities can change so dramatically over the course of a single day and why genetic alterations in molecules that regulate these chemical influences can play such havoc with our mental state. The success of guanaficine and prazosin in treating ADHD and PTSD encourage the rational pursuit of treatments for PFC dysfunction based on neuromodulatory influences on PFC networks revealed in animals performing tasks that depend on “representational knowledge.” The inspiring insights of Patricia Goldman-Rakic continue in these efforts.

Notes

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Address correspondence to amy.arnsten@yale.edu.

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