Molecular mechanisms of stress-induced prefrontal cortical impairment: Implications for mental illness

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The symptoms of mental illness often involve weakened regulation of thought, emotion, and behavior by the prefrontal cortex. Exposure to stress exacerbates symptoms of mental illness and causes prefrontal cortical dysfunction. Studies in animals have revealed the intracellular signaling pathways activated by stress exposure that induce profound prefrontal cortical impairment: Excessive dopamine stimulation of D1 receptors impairs prefrontal function via cAMP intracellular signaling, leading to disconnection of prefrontal networks, while excessive norepinephrine stimulation of α1 receptors impairs prefrontal function via phosphatidylinositol–protein kinase C intracellular signaling. Genetic studies indicate that the genes disrupted in serious mental illness (bipolar disorder and schizophrenia) often encode for the intracellular proteins that serve as brakes on the intracellular stress pathways. For example, disrupted in schizophrenia 1 (DISC1) normally regulates cAMP levels, while regulator of G protein signaling 4 (RGS4) and diacylglycerol kinase (DGKH)—the molecule most associated with bipolar disorder—normally serve to inhibit phosphatidylinositol–protein kinase C intracellular signaling. Patients with mutations resulting in loss of adequate function of these genes likely have weaker endogenous regulation of these stress pathways. This may account for the vulnerability to stress and the severe loss of PFC regulation of behavior, thought, and affect in these illnesses. This review highlights the signaling pathways onto which genetic vulnerability and stress converge to impair PFC function and induce debilitating symptoms such as thought disorder, disinhibition, and impaired working memory.
appropriate reactions to a changing environment requires representation of information not currently in the environment, i.e., representational knowledge. The ability to represent information is often referred to as working memory or the “mental sketchpad,” and these operations allow for the maintenance and manipulation of information and control over new, incoming information processing (e.g., Goldman-Rakic 1995b). These processes ultimately regulate impulses, language, attention, decision-making, and error correction and are commonly referred to as the executive functions (e.g., Botvinick et al. 2001; Miller and Cohen 2001; Corbetta and Shulman 2002).

Given the central role of working memory and representational knowledge in the executive operations of the PFC, the majority of animal studies described below assess behavioral and physiological performance on working memory tasks. Many of the studies examining PFC functions in rats utilized the spatial delayed alternation task (T maze), a task that requires spatial working memory, but also behavioral inhibition (inhibiting the tendency to return to a rewarded location) and regulation of distractibility (the rats are picked up and returned to the start box on each trial). Thus, these data address a range of PFC cognitive operations. Electrophysiological and iontophoresis studies have been limited to recordings from dorsolateral PFC (dlPFC) in monkeys performing a spatial working memory task (described below). These findings may apply to other PFC regions and cognitive operations, especially those functions requiring complex network interactions and inhibition of prepotent responses. However, these findings may not apply to all PFC abilities, and one must be cautious in generalizing this information to other PFC functions.

Single unit recording studies in non-human primates have helped to reveal the circuitry underlying working memory. The dlPFC maintains modality-specific information via recurrent excitatory connections among local networks of pyramidal neurons (Goldman-Rakic 1990, 1995a,b). These networks, or microcircuits, remain active through a delay period, thereby holding information “online.” The strength of these network connections is dynamically modulated by NE acting at α2a adrenoceptors (α2a-ARs) (Wang et al. 2007). Conversely, selective inhibition by γ-aminobutyric acid (GABA) interneurons and dopamine (DA) receptor signaling (Vijayaraghavan et al. 2007) sculpts, or tunes, microcircuits to respond selectively, for example, to fire following cues presented in a particular portion of the visuospatial field, but not following other spatial locations (Fig. 1; for review, see Goldman-Rakic 1995b). The ability to represent information in a properly tuned manner depends on the network having the appropriate connections for the current cognitive demand. Thus, any disruption in the balance of excitation and inhibition, or inappropriate neuromodulation, can profoundly impact network actions and result in suboptimal PFC function. It is important to note that the structural and functional integrity of these working memory microcircuits is relevant to a variety of cognitive operations. For example, PFC neurons can fire in relationship to abstract rules, can maintain information not currently in the environment, i.e., representational knowledge. The ability to represent information is often referred to as working memory or the “mental sketchpad,” and these operations allow for the maintenance and manipulation of information and control over new, incoming information processing (e.g., Goldman-Rakic 1995b). These processes ultimately regulate impulses, language, attention, decision-making, and error correction and are commonly referred to as the executive functions (e.g., Botvinick et al. 2001; Miller and Cohen 2001; Corbetta and Shulman 2002).

The primate PFC can be divided into several subregions with specialized, but related, operations (for reviews, see Davidson and Irwin 1999; Aron et al. 2004; Pessoa 2008). The dorsal and lateral PFC project to sensory cortices, premotor cortices, striatum, and the cerebellum for the regulation of attention and action (Selemon and Goldman-Rakic 1985, 1988; Cavada and Goldman-Rakic 1989; Middleton and Strick 2000; Romanski 2004; Barbas et al. 2005). Lesions of the dlPFC in humans result in characteristic “frontal” cognitive deficits in planning and executing organized sequences of behavior or speech as well as working memory impairment (Luria 1970; Luria et al. 1970; Baddeley et al. 2000; Fuster 2001). The ventral PFC performs similar functions in the affective realm. Lesions of the ventral and orbital cortex are characterized by the inability to inhibit inappropriate emotions, and the inability to flexibly regulate behavior based on the representation of future punishment or reward (Damasio et al. 1994; Dias et al. 1996). Consistent with this, the ventromedial PFC (vmPFC) has massive projections to the amygdala, ventral striatum, and hypothalamus (Ongur et al. 1998; Price 1999; Ghashghaei and Barbas 2002; Stefanacci and Amaral 2002; Ghashghaei et al. 2007).

![Figure 1](https://example.com/figure1.png) Spatial tuning of PFC networks by DA D1 and NE α2a receptors. (A) Schematic representation of oculomotor delayed response (ODR) spatial working memory task. Monkeys are presented with a cue in a specified region of the visual field (90°). After a brief delay (0–5 sec), the monkey must move its eyes to the previous cue location. (B) Neuronal firing of a single unit in the dlPFC during the delay period of the ODR task. The unit is “tuned” to 90° (preferred direction) as indicated by increased delay-related firing following this stimulus. Firing of this unit is suppressed when the cue is presented in a nonpreferred region of the visual field (e.g., 270°). (C) Schematic representation of spatial working memory network. Pyramidal cells with shared spatial preferences mutually excite each other to create persistent firing during the delay period. These network connections are strengthened by stimulation of α2a-ARs on PFC dendritic spines, reducing cAMP production and closing nearby HCN channels. Conversely, inputs from pyramidal neurons representing non-preferred directions (particularly orthogonal directions) onto a different set of spines are suppressed via DA D1-R stimulation, which increases cAMP production. These actions likely occur through opening of HCN channels near the nonpreferred input (refer to Fig. 2B for signaling cascade). The combination of signal enhancement and noise reduction achieves precision in the network, thereby strengthening working memory.
Anterior and medial portions of the PFC, including the anterior cingulate cortex (ACC), are also of particular relevance to mental illness. These areas are specialized for error and reality monitoring, which would include the ability to decipher internal versus external sources of stimulation (Carter et al. 1998; Bush et al. 2000; Rubia et al. 2003; Lutcke and Frahm 2008; Simons et al. 2008; Turner et al. 2008). Widespread circuits within the PFC are likely involved with such high-order decision-making and categorization. The contributions of these pathways to such processes are now under investigation (Muhammad et al. 2006; Lee et al. 2007; Freedman and Miller 2008).

In humans, the PFC shows hemispheric specialization, with the left PFC being central to language production (Broca’s area), while the right PFC is especially important for behavioral inhibition. Impairments to the right inferior and lateral PFC produce a symptom profile of impaired impulse control and weaker sustained attention, while right anterior orbital lesions lead in increased engagement in risky behaviors (Woods and Knight 1986; Garavan et al. 1999; Rubia et al. 2003; Aron et al. 2004).

Neuropsychological, brain imaging, and post-mortem studies have helped to identify PFC subregions affected by specific mental illnesses. It should be noted that other brain areas, including the amygdala, hippocampus, and temporal cortices, have also been implicated in schizophrenia, bipolar disorder, and PTSD, and are reviewed elsewhere (e.g., Campbell and MacQueen 2006; Boyer et al. 2007; Frey et al. 2007; Gur et al. 2007; Libezeron and Sripada 2008). Given the scope of this review, we briefly highlight findings most relevant to PFC dysfunction in these illnesses.

Schizophrenia

Schizophrenia is a multidimensional disorder resulting in alterations to thought, mood, and behavior. Psychotic symptoms are characterized by impairments in the perception of reality including delusions and hallucinations. Disorganized thought, speech, and behavior, and flattened affect or avolition are also prominent symptoms (American Psychological Association 2000). Impaired cognitive functioning is a fundamental feature of schizophrenia, and impoverished executive abilities contribute to the poor functional outcome of patients (Ragland et al. 2007). Numerous studies indicate that dysfunction of the dlPFC underlies schizophrenia pathophysiology (e.g., Goldman-Rakic 1994, 1995a, 1999; Lewis 1995; Lewis and Anderson 1995; Goldman-Rakic and Selemon 1997; Glantz and Lewis 2000). Early studies by Weinberger and colleagues using the Wisconsin Card Sorting Task (WCST), which measures concept formation, working memory, cognitive flexibility, and feedback monitoring, found reduced cerebral blood flow to the dlPFC in schizophrenia patients compared with healthy control subjects (Berman et al. 1986, 1988; Weinberger et al. 1986, 1988). More recent fMRI studies examining distinct components of this task, such as working memory, indicate reduced activity of the dlPFC in schizophrenia patients, which may explain performance deficits in these operations (e.g., Callicott et al. 1998; Barch et al. 2001; Perlstein et al. 2001).

While the dlPFC is most widely implicated with schizophrenia, recent studies indicate a role for other subregions of the PFC in symptomology. Hypoactivity of the ACC is observed in patients for a variety of inhibitory tasks (e.g., Rubia et al. 2001). In addition to impaired error monitoring (Carter et al. 2001; Kerns et al. 2005), a recent study has linked underactivity of the medial anterior and right lateral PFC to altered associative abilities and proneness to psychosis (Simons et al. 2008). Furthermore, auditory hallucinations may arise from inadequate corollary discharge from the PFC to Wernicke’s area during inner speech (Ford and Mathalon 2005), i.e., inadequate tagging that a voice is internally generated. Taken together, these new data represent increasing links between PFC dysfunction, cognitive impairment, and the so-called “positive” symptoms of psychotic illness.

Structural imaging and post-mortem studies indicate significant alterations in fundamental PFC network substrates in schizophrenia patients. Studies by Lewis and colleagues found reduced axonal cartridges of chandelier GABAergic interneurons in the dlPFC of schizophrenia patients (Woo et al. 1998; Volk and Lewis 2002) that may impair tuning of PFC networks. Reduced glutamate receptor binding is also observed in the dlPFC of schizophrenia patients (Konradi and Heckers 2003), compromising the main currency of these recurrent excitatory networks. Structural imaging studies indicate deficits in dlPFC gray matter volume in schizophrenia (Sullivan et al. 1998; Gur et al. 2000), and associations between PFC gray matter density and clinical symptom ratings in schizophrenia patients have been identified, with reduced PFC volume predicting more severe symptoms (Gur et al. 2000). Gray matter reduction is thought to reflect loss of neurit (e.g., Selemon et al. 1998; Selemon and Goldman-Rakic 1999; Selemon 2001) and, particularly, dendritic retraction and dendritic spine loss among pyramidal neurons, as post-mortem analyses indicate a pronounced reduction in dendritic spine density in superficial PFC pyramidal neurons (Lewis and Anderson 1995; Glantz and Lewis 2000, 2001). Importantly, PFC network operations are believed to be carried out within superficial layers (Goldman-Rakic 1990, 1995b). Since dendritic spines comprise the majority of excitatory cortical synapses (Gray 1959; for reviews, see Shepherd 1996; Sheng and Hoogenraad 2007), they represent a critical component of the excitatory circuitry underlying PFC operations.

Bipolar disorder

Bipolar disorder, also called manic-depressive illness, is characterized by recurrent fluctuations in affect and behavior. The clinical spectrum of bipolar disorder, as defined by the DSM-IV, includes two subtypes: Diagnosis of bipolar disorder I requires a manic episode (patients may have mixed manic and depressive episodes), and diagnosis of bipolar disorder II requires both depressive and hypomanic episodes (American Psychological Association 2000). The fluctuation in mood states within bipolar disorder provides the unique opportunity to observe changes in cognition and brain state while the same patient is in different phases of the illness. Manic patients are characterized by increased risk taking, distractibility, and reduced inhibition (American Psychological Association 2000). These deficits are associated with impaired right PFC function (Woods and Knight 1986; Garavan et al. 1999; Rubia et al. 2003; Aron et al. 2004). Neuropsychological studies indicate patients are also impaired in attention and reversal tasks during the depressed phase (Murphy et al. 1999; Murphy and Sahakian 2001), and past number of depressive episodes is predictive of poorer neurocognitive function (for review, see Bauer et al. 2003). Subsyndromal symptoms of impaired cognitive control and executive function, most notably attention and inhibition, persist during periods of remission in patients, suggesting that these impairments are inherent to the disease state (for reviews, see Phillips and Vieta 2007; Vieta and Phillips 2007).

Neuroimaging studies reveal alterations to the PFC in both the manic and depressed phases. Blumberg and colleagues (2003) have shown that during the depressive phase, patients demonstrate altered activity in the left vmPFC. This is consistent with the role of the left vmPFC in negative stimuli appraisal and depressed mood (Robinson et al. 1984), and is similar to alterations observed in patients with Major Depressive Disorder (Drevets et al. 1992). However, during the manic phase, bipolar patients exhibit underactivity of the ventral PFC, inferior PFC, and frontal...
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pole in the right hemisphere (Blumberg et al. 1999, 2003, 2006). These results are consistent with the right PFC regulating attention and inhibitory processes and fit with the disinhibited mood and behaviors that characterize mania. Similar to schizophrenia, bipolar disorder is also associated with reduced PFC gray matter volume in regions where functional alterations are observed, particularly the ventral PFC (Lopez-Larson et al. 2002; Blumberg et al. 2006). Not surprisingly, reduced PFC volume predicts impaired performance on an attention task in acutely manic bipolar patients (Sax et al. 1999).

PTSD
PTSD is an anxiety disorder precipitated by an extreme stressor or traumatic event such as natural disaster, combat, or physical or sexual abuse (Francati et al. 2007). PTSD is characterized by intrusive and vivid re-experiencing of a trauma. Symptoms include enhanced memory for arousing events, flashbacks, hypervigilance, and impaired executive operations of the PFC (Yehuda et al. 1995; Orr 1997; Orr et al. 1997; Vasterberg et al. 2004; Bremer et al. 1999a,b; Southwick et al. 1999; Golier and Yehuda 2002). PTSD is commonly associated with overactivity of the noradrenergic/norepinephrine (NE) system arising from the locus coeruleus (LC), hyperactivation of the amygdala, and hypoactivation of the PFC (for reviews, see Francati et al. 2007; Bremer et al. 2008). Medial PFC volume is reduced and underactive during symptomatic states, and these medial PFC deficits are inversely proportional to symptom severity (for review, see Shin et al. 2006). Underactivity of the PFC likely contributes to patients’ inability to suppress traumatic memories and to modulate amygdala and LC activation, resulting in anxiety and hypervigilance. Since dysfunction of the medial PFC is related to impaired error and reality monitoring (Carter et al. 2001; Simons et al. 2008), these findings may also serve to explain flashbacks, where patients confabulate vivid memories with reality.

Molecular regulation of the PFC
The integrity of local working memory circuits is highly sensitive to PFC neurochemical state. Glutamate, GABA, and numerous neuromodulators critically contribute to PFC function (for review, see Arnsten and Robbins 2002). This review focuses on the influence of catecholamines on PFC function, as catecholamine signaling is directly relevant to the stress response as well as the pathophysiology and treatment of neuropsychiatric disorders.

It is well established that catecholamines exert an inverted U dose response on working memory performance, whereby too much or too little DA or NE impairs spatial working memory and delay-related neuron firing (Fig. 2: Arnsten 2007). Catecholamines are likewise important for the attentional set-shifting properties of the lateral PFC. DA is needed to establish an attentional set (Crofts et al. 2001), and NE is needed to shift set (Tait et al. 2007). NE is also important for the operations of the ventrolateral PFC, including behavioral inhibition (Chamberlain et al. 2007) and conditional motor responding (Wang et al. 2004). In contrast, studies of the reversal operations of the orbital PFC indicate that serotonin is especially important to this region (Clarke et al. 2007), although more detailed manipulations indicate that catecholamines influence some orbital functions as well (e.g., Steere and Arnsten 1997).
NE and DA are released in the PFC according to state of arousal, with low levels released during drowsy/bored conditions, moderate levels during alert conditions, and high levels during even mild, uncontrollable stress. Under optimal, alert conditions, NE and DA neurons have relatively low spontaneous firing, but fire to stimuli that are relevant and/or associated with reward, respectively (for reviews, see Berreidge and Waterhouse 2003; Aston-Jones and Cohen 2005; Schultz 2007a,b). Neurons of the PFC project to NE and DA cells in brainstem and likely regulate this firing pattern under optimal conditions (Arnsten and Goldman-Rakic 1984; Gariato and Groses 1988; Aston-Jones et al. 1991; Sesack and Pickel 1992; Sara and Herve-Minvielle 1995; Shinba et al. 2000; Bouret and Sara 2004). In contrast, under conditions of psychological stress, the amygdala activates NE and DA cells and increases catecholamine release in the PFC (Goldstein et al. 1996). The amount of NE released engages different types of receptors: NE has highest affinity for α2a-ARs, lower affinity for α1-ARs (α1-L-ARs), and lowest affinity for β-adrenoceptors (β-ARs). These receptors have opposing effects on PFC function, with α2a-ARs improving and α1-ARs and β1-ARs impairing PFC function (for review, see Ramos and Arnsten 2006). Thus, PFC function is tightly coupled to arousal state due to powerful catecholamine actions in the PFC.

Optimal regulation of working memory by catecholamines

The pioneering work of Brozoski and Goldman-Rakic revealed the powerful influences of catecholamines on the cognitive operations of the dIPFC (Brozoski et al. 1979). This early study showed that depleting catecholamines in PFC was as destructive as lesioning the PFC. Although this study focused on DA, it is now known that blockade of either NE or DA actions has deleterious effects, and moderate α2a-AR and D1 receptor (D1-R) stimulation is required for optimal working memory performance (Sawaguchi and Goldman-Rakic 1991; Li et al. 1994). Electrophysiological studies in monkeys performing working memory tasks indicate that optimal levels of catecholamines are needed for the appropriate connectivity of PFC networks engaged in cognitive operations. As illustrated in Figure 1, moderate levels of NE strengthen the connectivity of network inputs from neurons with shared properties through stimulation of post-synaptic α2a-ARs (i.e., α2a-ARs enhance “signals” within the network), while optimal DA stimulation of D1-Rs weakens network connections with inappropriate inputs (i.e., D1-Rs decrease “noise” within the network).

Emerging data indicate a critical role for cAMP activation of Hyperpolarization Activation Cyclic Nucleotide Gated (HCN) cation channels in these gating functions. HCN channels are localized 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). When the HCN channels are opened by the presence of cAMP, nearby synaptic inputs are shunted due to the reduction in membrane resistance (Wang et al. 2007). Thus, activation of cAMP–HCN signaling weakens the network inputs onto that spine compartment, α2a-ARs are localized next to HCN channels on spines, and are thus ideally positioned to modulate the local concentration of cAMP near the channels via Gs inhibition of cAMP production (Fig. 2B). Electrophysiological studies have shown that α2a-AR stimulation increases network firing for preferred directions, and this improvement can be reversed by manipulations that increase or mimic cAMP (Wang et al. 2007). Conversely, blockade of α2a-ARs induces network collapse that can be rescued by blockade of HCN channels (Wang et al. 2007). Similar results have been observed at the behavioral level (Ramos et al. 2006; Wang et al. 2007).

In contrast, optimal D1-R stimulation helps to tune PFC microcircuits by suppressing cell responses to nonpreferred stimuli (e.g., spatial directions for which the microcircuit is not tuned) (Vijayraghavan et al. 2007). D1-Rs and α2a-ARs appear to be on different dendritic spines (C. Paspalas and A.F.T. Arnsten, unpubl.), suggesting they modulate different sets of network inputs. D1-R-mediated suppression of inputs occurs via stimulation of Gs proteins and subsequent increases in cAMP signaling (Fig. 2B; Vijayraghavan et al. 2007), and preliminary data indicate that this suppression occurs via opening of HCN channels (N.J. Gamo, M. Wang, and A.F.T. Arnsten, unpubl.). We have proposed that D1-R stimulation dynamically regulates the breadth of network tuning based on task demands (Vijayraghavan et al. 2007).

High levels of catecholamine release during stress impair PFC function

It is now clear that the deleterious effects of acute stress on PFC operations arise from excessive NE and DA release in the PFC (Deutch and Roth 1990; Rossetti et al. 1990; Finlay et al. 1995; Murphy et al. 1996; Birnbaum et al. 1999, 2004; Vijayraghavan et al. 2007). Under conditions of high arousal or stress, the amygdala excites brainstem nuclei to release high levels of DA and NE in the PFC (Goldstein et al. 1996). Excessive D1-R stimulation in PFC impairs working memory through cAMP signaling (Zahrt et al. 1997; Vijayraghavan et al. 2007), and electrophysiological studies show that high levels of D1-R stimulation suppress delay-related cell firing via excessive cAMP actions, consistent with network collapse (Vijayraghavan et al. 2007). Preliminary evidence indicates that these deleterious actions can be prevented by blocking HCN channels (N.J. Gamo, M. Wang, and A.F.T. Arnsten, unpubl.). High levels of NE stimulation of β1-AR may also contribute to excessive cAMP signaling and PFC cognitive dysfunction (Ramos et al. 2005).

High levels of NE released during stress impair working memory and neuronal firing through stimulation of α1-ARs (Birnbaum et al. 1999, 2004). As shown in Figure 2B, α1-AR stimulation impairs PFC function through products of the phosphatidylinositol (PI) cascade (Garcia-Sainz 1993; Birnbaum et al. 1999, 2004). Upon activation of the PI cascade, phospholipase C cleaves the phospholipid phosphatidylinositol bisphosphate (PIP2), generating membrane-bound diacylglycerol (DAG) and diisositol 1, 4, 5-trisphosphate (IP3). IP3 binds receptors on the endoplasmic reticulum, leading to release of calcium (Ca2+). Ca2+-dependent kinases negatively influence PFC cognitive functions. Activation of Ca2+-calmodulin-dependent kinase II (CaMKII) and inhibition of the Ca2+-activated phosphatase, calcineurin, impair spatial working memory in the rat (Runyan et al. 2005; Dash et al. 2007). These actions may be mediated, in part, by the opening of small-conductance Ca2+-gated potassium channels (SK channels) that suppress neuronal firing (Hagenston et al. 2007; Brennan et al. 2008). Protein kinase C (PKC) is cooperatively activated by Ca2+ and DAG. PKC activation suppresses delay-related firing of PFC neurons in monkeys performing a working memory task, and impairs spatial working memory performance in both rats and monkeys (Birnbaum et al. 2004; Runyan et al. 2005). Thus, both products of the stress-activated PI cascade have deleterious effects on PFC functioning.

The effects of chronic stress on the PFC

Studies of the effects of chronic stress may provide valuable insight regarding the consequences of sustained neurochemical disruption in mental illness. Chronic stress increases NE responsivity within the PFC (Finlay et al. 1995, 1997; Miner et al. 2006), which likely leads to sustained, elevated PI–PKC signaling and suppression of working memory networks. Conversely, chronic stress exposure has also been linked to depletions in DA within the rat PFC (Mizoguchi et al. 2000), indicating that the neuro-
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The effects of stress on amygdala function and structure are opposite to those observed in the PFC (summarized in Fig. 3). High levels of catecholamines enhance amygdala operations; e.g., catecholamines strengthen fear conditioning and memory consolidation (Debiec and LeDoux 2004, 2006). Thus, memory of an event is improved when β-AR and α1-AR agonists are infused into the amygdala immediately after its occurrence (Ferry et al. 1999a,b,c; McGaugh and Roozendaal 2002; Roozendaal et al. 2002, 2004a,b). High levels of NE also enhance memory consolidation through actions in the hippocampus (Hopkins and Johnston 1988; Roozendaal et al. 2004b). For example, β-AR stimulation increases plasticity, synapse strength, and excitability of hippocampal neurons (Hopkins and Johnston 1988; Lancaster et al. 2001; Hu et al. 2007). The effects of stress on hippocampus- and amygdala-dependent memory operations are reviewed elsewhere (e.g., Sandi and Pinelo-Nava 2007). Differences between the amygdala, hippocampus, and PFC are also evident following chronic stress. While chronic stress exposure induces dendritic retraction in PFC, it causes dendritic hypertrophy and increased spine density in principal neurons of the amygdala (Mitra et al. 2005) and facilitates fear conditioning (Conrad et al. 1999), suggesting these structural elaborations also enhance amygdala function. The hippocampus exhibits an intermediate response, with dendritic retraction observed after prolonged stress exposure (Watanabe et al. 1992; Magarinos and McEwen 1995). The PFC shows structural impairments following shorter and milder stress exposure than that required for hippocampal structural changes (Magarinos and McEwen 1995; Brown et al. 2005), indicating the profound vulnerability of the PFC to stress.

The opposing effects of stress on PFC and amygdala function may have adaptive value (Arnsten 1998). In nonstressful conditions, the PFC tonically inhibits amygdala firing, suppressing anxious behavior and supporting a state that favors goal-directed, controlled behavior (Jaskiw and Weinberger 1990; Jinks and McGregore 1997; Hariri et al. 2000, 2003). Under conditions of stress, operations of the amygdala are facilitated, increasing the likelihood that the “present danger” will be remembered and avoided in the future, and helping the animal organize and execute an efficient behavioral response to the fearful or stressful stimuli. Since stressful conditions disengage the PFC and memory retrieval mechanisms, resources can be devoted to these more instinctive, rapid responses to the immediate stressor. This stress response system can also lead to maladaptive changes (for a review of the role of the hippocampus in stress dysregulation and mental illness, see Phillips et al. 2006). The amygdala plays a critical role in stress-induced increases in catecholamine release within the PFC (Goldstein et al. 1996). This would lead to further deterioration of top-down regulation by PFC and an increasingly amygdala-centric mode of processing. Dysregulation of catecholamine signaling and PFC and amygdala structure and function are central to PTSD and reflect the deleterious consequences of this feed-forward stress response system.

Genetics of severe mental illness

Most mental illnesses are considered polygenic, where a variety of genes interact or contribute to disease pathological. This complexity has eluded attempts to find a single “key” genetic variable that substantially predicts or contributes to a psychiatric disorder. Due to the small effect of individual genes, the heterogeneity of illnesses, and methodological and statistical variations, there are many conflicting reports on the involvement of specific genes in specific disorders. Despite these limitations, uncovering genes involved in schizophrenia and bipolar disorder carry the promise of improving our understanding of these illnesses. Indeed, some of the most consistent evidence of both

Figure 3. High levels of NE release during acute stress weaken PFC but strengthen amygdala and hippocampal function. Different types of NE receptors are engaged depending on the amount of NE released. The actions of these different NE receptors help to orchestrate brain responses appropriate to environmental conditions. Under nonstressed conditions, moderate levels of NE are released, engaging high-affinity α2A-ARs, which strengthen PFC functions and weaken those of the amygdala and hippocampus. In contrast, during exposure to stress, high levels of NE are released, engaging the low-affinity α1-ARs and β-ARs. Stimulation of these receptors has opposite effects on PFC vs. subcortical functions: They weaken the higher cognitive functions of the PFC, while strengthening the functions of the amygdala and hippocampus. This likely has survival value under conditions of danger (e.g., encountering a bear in the woods), switching the control of behavior to more rapid, primitive responses mediated by the amygdala, and strengthening consolidation of the stressful event so it can be avoided in the future. However, these changes would be detrimental under stressful conditions that require the more complex regulation by the PFC (e.g., piloting an airplane or taking a difficult exam). NE transmission is greatly increased in PTSD, likely contributing to symptoms of flashbacks, intrusive traumatic memories, and heightened conditioned fear. Successful treatments for PTSD block α1-ARs or β-ARs and restore PFC regulation of brain and behavior.
genetic linkage and association in schizophrenia and bipolar disorder involve genes that may directly impact PFC function. Several of these genes play a role in cortical development, neurotransmission (BDNF), and glutamate signaling, and these important genetic factors are reviewed elsewhere (e.g., Craddock et al. 2005; Owen et al. 2005, Tan et al. 2007; van Haren et al. 2008).

Another common genetic alteration, a single nucleotide polymorphism in the gene encoding for catechol-O-methyl transferase (COMT), may influence the risk for schizophrenia (for reviews, see Craddock et al. 2006; Turnbridge et al. 2006). COMT is an extracellular enzyme involved in the degradation of catecholamines, and particularly DA in the PFC (e.g., Turnbridge et al. 2006). The substitution of methionine for valine weakens the enzymatic degradation of DA, and shifts the D1 inverted U rightward (e.g., Nolan et al. 2004; Turnbridge et al. 2004, 2006; Winterer and Weinberger 2004). This substitution influences PFC cognitive abilities in both normal individuals (e.g., Nolan et al. 2004; Turnbridge et al. 2004) and patients (e.g., Egan et al. 2001). Numerous studies have investigated the association of COMT with mental illness and particularly schizophrenia. COMT is located on chromosome 22q11, a susceptibility locus for schizophrenia (Coon et al. 1994) and bipolar disorder (Badner and Ger son 2002). Indeed, there is evidence that the COMT valine variation is a weak risk factor for schizophrenia (Egan et al. 2001; Glatt et al. 2003), although such studies have produced mixed results (e.g., Munafo et al. 2005). However, given the scope of this review, it is not possible to adequately cover the progress and discrepancies within these fields. Instead, we will focus on findings relevant to the **intracellular** regulation of the PFC stress response.

Several of the genes most consistently altered in serious mental illness encode intracellular signaling molecules that inhibit stress pathways in PFC. These genes include **DISC1**, **RGS4**, and **Diacylglycerol Kinase Signaling 4**, (**DGKH**, **Schizophrenia 1**, (**DISC1**), and **PFC hypofunctioning in bipolar patients (Mirmics et al. 2001). It should be noted that there have been failed attempts to replicate an association between **RGS4** alterations and schizophrenia (e.g., Sobell et al. 2005). There are a variety of factors that may explain discrepant findings including sample size, diagnostic criteria, population structure, and statistical analysis, reporting measures, and the likelihood that schizophrenia has a heterogeneous etiology. However, subsequent findings support a role for **RGS4** in both symptomatology and pathophysiology. For example, a postmortem study found significantly lower mRNA and protein levels in the dPFC of schizophrenia patients compared with healthy controls (Erdey et al. 2006), and **RGS4** SNPs predicted poorer performance on clinical ratings scales in a recent study performed in a population of Han-Chinese schizophrenia patients (Lane et al. 2008).

While **RGS4** does not appear to be selective for a single heterotrimERIC G protein, the most consistent evidence is for **RGS4** inhibiting Gs and Ca2+ signaling (Rogers et al. 2001; Tovey and Willars 2004; Snabaitis et al. 2005; Hao et al. 2006; Ladds et al. 2007). Moreover, GAPs such as **RGS4** are critical for the regulation of PI-PKC-linked Gs proteins, which have low intrinsic GTPassive activity compared with Gs or Gi proteins (Hamm and Gilchrist 1996). Interestingly, **RGS4** is also altered following chronic and acute stress exposure and amphetamine administration in rats (Ni et al. 1999; Schwendt et al. 2006). Thus, one may speculate that the loss of **RGS4** in the PFC of patients with schizophrenia would increase PI signaling during stress exposure, leading to suppressed neuronal firing and loss of PFC cognitive abilities.

**DGKH**

**DGKH** encodes the η isoform of DAG Kinase (DGK). DGKs are family of lipid kinases that catalyze the conversion of DAG to phosphatidic acid, thereby leading to reductions in DAG. DAG is a necessary cofactor for many isoforms of PKC; thus, DGKs are key regulators of PKC activation. A genome-wide association study, which examined over 500,000 genetic polymorphisms in independent samples, found that mutations in **DGKH** are most robustly linked to bipolar disorder (Baum et al. 2008), and this finding has now been replicated in a separate, large sample (Wellcome Trust Case Control Consortium 2007). These genetic findings are consistent with numerous lines of evidence linking dysregulation of the PKC signaling cascade to bipolar disorder, and particularly mania (Friedman et al. 1993; Wang and Friedman 1996; Hahn and Friedman 1999; Manji and Lenox 1999; Manji et al. 1999; Wang et al. 1999, 2001; Arnsten and Manji 2008). Reduced DGK activity through mutations in **DGKH** provides a potential mechanism for PKC dysregulation in bipolar disorder. Weakened inhibition of PKC signaling in bipolar disorder is consistent with stress precipitating manic episodes (Hammen and Gitlin 1997), and with PFC hypofunctioning in bipolar patients in the manic state (Blumberg et al. 1999).
Treatments for mental illness normalize PFC stress pathways

Treatments for schizophrenia and bipolar disorder directly or indirectly modulate stress-related PFC signaling cascades, potentially correcting for the loss of adequate RS54, DISCI, or DKG function. Atypical antipsychotics (e.g., olanzapine, risperidone, clozapine) block α1-ARs and SHT2a receptors (Peroutka and Snyder 1980; Cohen and Lipinskit 1986; Dwivedi and Pandey 1999; Svensson 2003), thereby reducing PI–PKC signaling. DISCI is increased in the frontal cortex following antipsychotic treatment (Chiba et al. 2006; Mackie et al. 2007), suggesting antipsychotic treatment may also help to regulate cAMP. Consistent with these actions, functional imaging studies indicate that chronic treatment with atypical antipsychotics can normalize PFC function in schizophrenia patients (Surguladze et al. 2007), and both schizophrenia and bipolar patients show improvements in measures of executive functioning, including working memory, following risperidone treatment (Harvey et al. 2005, 2007).

Treatments for mania inhibit PKC signaling, a finding first noted by Manji and colleagues (Manji and Lenox 1999; Manji et al. 1999). Chronic treatment with the antimanic agents lithium or valproate significantly reduce PKC activity and alter PKC distribution in bipolar patients and within the rat cortex (Manji and Lenox 1999; Manji et al. 1999, 2001; Chen et al. 2000; Wang et al. 2001; Manji and Chen 2002; Friedman et al. 2004; Hahn et al. 2005). There is indirect evidence that PKC activity plays a role in PFC structural alterations, as well. PFC gray matter loss in bipolar and schizophrenia patients is reversed by chronic lithium or valproate treatments (Blumberg et al. 2006; Bearden et al. 2007; Nakamura et al. 2007), and rodent studies indicate that chronic lithium treatment counteracts stress-induced plasticity in the hippocampus (Wood et al. 2004).

Finally, the medications used to treat PTSD are consistent with our understanding of the neurobiology of PTSD symptoms. As summarized above, PTSD is associated with high levels of NE release, which engage α1-ARs and β-ARs, thereby impairing PFC function and enhancing amygdala function (summarized in Fig. 3). Accordingly, effective treatments for PTSD include prazosin, an α1-AR antagonist, and possibly propranolol, a β-AR blocker (for review, see Strawn and Geraciotti Jr. 2007). β-AR blockade is most effective when administered immediately following the trauma (Pitman et al. 2002; Debic and LeDoux 2006). These acute effects may interfere with amygdala operations including memory consolidation and the immediate sensitization of stress pathways. In contrast, α1-AR antagonism is beneficial even in patients with established PTSD symptoms (Peskind et al. 2003; Raskind et al. 2003; Taylor et al. 2006). Prazosin improves symptoms of intrusive re-experiencing of the trauma and reduces psychological distress in response to trauma related cues (Raskind et al. 2003; Taylor et al. 2006; Strawn and Geraciotti Jr. 2007). These beneficial effects likely reflect strengthened PFC modulation of amygdala and brain activity.

Summary

Symptoms of schizophrenia, bipolar disorder, and PTSD involve weakened PFC regulation of thought, emotion, and action. Exposure to stress exacerbates these symptoms in patients and reproduces aspects of PFC cognitive impairments in animals. The last decade has seen unprecedented advancements in our understanding of the molecular mechanisms of stress as well as the molecular and genetic correlates of mental illness. It is now clear that stress-induced catecholamine elevations impair PFC integrity, and particularly working memory function, by disconnecting local networks. Excessive DA stimulation of D1-Rs disconnects PFC networks via cAMP–HCN intracellular signaling, and excessive NE stimulation of α1-AR impairs prefrontal function via PI–PKC intracellular signaling.

Emerging genetic and genomic research indicates genetic weaknesses in the endogenous regulation of cAMP–HCN and PI–PKC pathways in bipolar disorder and schizophrenia. Further studies in animals are required to assess whether such genetic weaknesses confer increased vulnerability to stress via the pathways described herein. NE overactivation is also implicated in the pathophysiology of PTSD. Dysregulation of these stress-related pathways likely explains patients’ profound vulnerability to life stressors and characteristic PFC impairments. Animal studies of chronic stress may be helpful in understanding the effects of sustained dysregulation of stress-related in pathways in these disorders. Chronic dysregulation of stress pathways may lead to further elevations in catecholamine release within the PFC via enhancing amygdala processing. Recent rodent studies also indicate that chronic exposure to stress compromises critical structural components of PFC circuitry. Similar mechanisms may underlie illness and stress-related PFC structural impairments.

It is immensely encouraging that genetic and molecular research implicates common pathways in the pathophysiology of several of the most complex, poorly understood, and debilitating psychiatric illnesses. These intersections should herald new approaches for neurobiological and translational research. The immediate implications for developing novel therapies are clear: While the mainstay treatments for bipolar disorder and schizophrenia are likely effective through inhibiting aspects of these stress-related pathways, thereby interrupting this feed-forward cycle, new treatments that directly and specifically target PKC carry the promise of increased efficacy and reduced side effects.

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References


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Hagenston, A.M., Fitzpatrick, J.S., and Yeckel, M.F. 2007. MGlut-mediated calcium waves that invade the soma regulate firing

www.learnmem.org Learning & Memory


Trends Neurosci. 27: 683–690.


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